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(54) Title: TREATMENT OF CANCER USING HUMANIZED ANTI-BCMA CHIMERIC ANTIGEN RECEPTOR

(57) Abstract: The invention provides compositions and methods for treating diseases associated with expression of BCMA. The invention also relates to chimeric antigen receptor (CAR) specific to BCMA vectors encoding the same, and recombinant T cells comprising the BCMA CAR. The invention also includes methods of administering a genetically modified T cell expressing a CAR that comprises a BCMA binding domain.

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TREATMENT OF CANCER USING HUMANIZED ANTI-BCMA CHIMERIC ANTIGEN RECEPTOR

This application claims priority to PCT Application No. PCT/CN2014/090501, filed November 6, 2014, and PCT Application No. PCT/CN2014/082586, filed July 21, 2014. The entire contents of these applications are incorporated herein by reference.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on July 15, 2015, is named N2067-7045WO3_SL.txt and is 771,026 bytes in size.

FIELD OF THE INVENTION

The present invention relates generally to the use of immune effector cells (e.g., T cells, NK cells) engineered to express a Chimeric Antigen Receptor (CAR) to treat a disease associated with expression of the B-cell maturation antigen protein (BCMA).

BACKGROUND OF THE INVENTION

B-cell maturation antigen (BCMA) is a tumor necrosis family receptor (TNFR) member expressed cells of the B-cell lineage. BCMA expression is the highest on terminally differentiated B cells. BCMA is involved in mediating the survival of plasma cells for mataining long-term humoral immunity. The expression of BCMA has been recently linked to a number of cancers, autoimmune disorders, and infectious diseases. Cancers with increased expression of BCMA include some hematological cancers, such as multiple myeloma, Hodgkin's and non-Hodgkin's lymphoma, various leukemias, and glioblastoma.

SUMMARY OF THE INVENTION

In a first aspect, the invention features an isolated nucleic acid molecule encoding a chimeric antigen receptor (CAR), wherein the CAR comprises an antibody or antibody fragment which includes a human anti-BCMA binding domain or a humanized anti-BCMA

binding domain, a transmembrane domain, and an intracellular signaling domain (e.g., an intracellular signaling domain comprising a costimulatory domain and/or a primary signaling domain). In one embodiment, the CAR comprises an antibody or antibody fragment which includes a human anti-BCMA binding domain described herein or a humanized anti-BCMA binding domain, described herein, a transmembrane domain described herein, and an intracellular signaling domain described herein (e.g., an intracellular signaling domain comprising a costimulatory domain and/or a primary signaling domain).

In one embodiment, the encoded BCMA binding domain (e.g., human or humanized anti-BCMA binding domain) comprises one or more (e.g., all three) light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and light chain complementary determining region 3 (LC CDR3) of a human or humanized anti-BCMA binding domain described herein, and/or one or more (e.g., all three) heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of an anti-BCMA binding domain described herein, e.g., a human or humanized anti-BCMA binding domain comprising one or more, e.g., all three, LC CDRs and one or more, e.g., all three, HC CDRs. In one embodiment, the encoded human anti-BCMA binding domain comprises a light chain variable region described herein (e.g., in Table 1) and/or a heavy chain variable region described herein (e.g., in Table 1). In one embodiment, the encoded humanized anti-BCMA binding domain comprises a light chain variable region provided in SEQ ID NO: 271 or 273 and/or a heavy chain variable region provided in SEQ ID NO: 271 or 273. In one embodiment, the encoded human anti-BCMA binding domain is a scFv comprising a light chain and a heavy chain of an amino acid sequence of Table 1. In one embodiment, the encoded humanized anti-BCMA binding domain is a scFv comprising a light chain and a heavy chain of an amino acid sequence of SEQ ID NO: 271 or 273. In an embodiment, the human or humanized anti-BCMA binding domain (e.g., an scFv) comprises: a light chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a light chain variable region provided in Table 1 or SEQ ID NO: 271 or 273, or a sequence with 95-99% identity with an amino acid sequence of Table 1 or SEQ ID NO: 271 or 273; and/or a heavy

chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a heavy chain variable region provided in Table 1 or SEQ ID NO: 271 or 273, or a sequence with 95-99% identity to an amino acid sequence of Table 1. In one embodiment, the encoded human anti-BCMA binding domain comprises a sequence selected from a group consisting of SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, and SEQ ID NO: 149, or a sequence with 95-99% identity thereof. In one embodiment, the encoded humanized anti-BCMA binding domain comprises a sequence selected from a group consisting of SEQ ID NO: 271 or SEQ ID NO: 273, or a sequence with 95-99% identity thereof. In one embodiment, the encoded human or humanized anti-BCMA binding domain includes a (Gly4-Ser)n linker, wherein n is 1, 2, 3, 4, 5, or 6, preferably 3 or 4 (SEQ ID NO:26). The light chain variable region and heavy chain variable region of a scFv can be, e.g., in any of the following orientations: light chain variable region-linker-heavy chain variable region or heavy chain variable region-linker-light chain variable region.

In other embodiments, the encoded BCMA binding domain comprises a HC CDR1, a HC CDR2, and a HC CDR3 of any BCMA heavy chain binding domain amino acid sequences listed in Table 1 or 16. In embodiments, the BCMA binding domain further comprises a LC CDR1, a LC CDR2, and a LC CDR3. In embodiments, the BCMA binding domain comprises a LC CDR1, a LC CDR2, and a LC CDR3 of any BCMA light chain binding domain amino acid sequences listed in Table 1 or 16.

In some embodiments, the encoded BCMA binding domain comprises one, two or all of LC CDR1, LC CDR2, and LC CDR3 of any BCMA light chain binding domain amino acid sequences listed in Table 1 or 16, and one, two or all of HC CDR1, HC CDR2, and HC CDR3 of any BCMA heavy chain binding domain amino acid sequences listed in Table 1 or 16.

In one embodiment, the encoded anti-BCMA binding domain comprises a light chain variable region described herein (e.g., in Table 16) and/or a heavy chain variable region described herein (e.g., in Table 16). In one embodiment, the encoded humanized anti-BCMA binding domain comprises a light chain variable region provided in SEQ ID NO: 259, SEQ ID NO: 260, SEQ ID NO: 261, SEQ ID NO: 262, and/or a heavy chain variable region provided in SEQ ID NO: 255, SEQ ID NO: 256, SEQ ID NO: 257, SEQ ID NO: 258. In one embodiment, the encoded anti-BCMA binding domain is a scFv comprising a light chain and a heavy chain of an amino acid sequence of Table 16. In an embodiment, the human or humanized anti-BCMA binding domain (e.g., an scFv) comprises: a light chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a light chain variable region provided in SEQ ID NO: 259, SEQ ID NO: 260, SEQ ID NO: 261, SEQ ID NO: 262, or a sequence with 95-99% identity thereof; and/or a heavy chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a heavy chain variable region provided in SEQ ID NO: 255, SEQ ID NO: 256, SEQ ID NO: 257, SEQ ID NO: 258, or a sequence with 95-99% identity thereof. In one embodiment, the encoded anti-BCMA binding domain includes a (Gly4-Ser)n linker, wherein n is 1, 2, 3, 4, 5, or 6, preferably 3 or 4 (SEQ ID NO:26). The light chain variable region and heavy chain variable region of a scFv can be, e.g., in any of the following orientations: light chain variable region-linker-heavy chain variable region or heavy chain variable region-linker-light chain variable region.

In one embodiment, the encoded human anti-BCMA binding domain comprises a sequence selected from a group consisting of SEQ ID NO: 263, SEQ ID NO: 264, SEQ ID NO: 265, and SEQ ID NO: 266, or a sequence with 95-99% identity thereof.

In one embodiment, the encoded CAR includes a transmembrane domain that comprises a transmembrane domain of a protein, e.g., described herein, e.g., selected from the group consisting of the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 and CD154. In one embodiment, the encoded transmembrane domain comprises the sequence of

SEQ ID NO: 6. In one embodiment, the encoded transmembrane domain comprises an amino acid sequence comprising at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:6, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO:6. In one embodiment, the nucleic acid sequence encoding the transmembrane domain comprises the sequence of SEQ ID NO: 17, or a sequence with 95-99% identity thereof.

In one embodiment, the encoded anti-BCMA binding domain is connected to the transmembrane domain by a hinge region, e.g., a hinge region described herein. In one embodiment, the encoded hinge region comprises SEQ ID NO:2, or a sequence with 95-99% identity thereof. In one embodiment, the nucleic acid sequence encoding the hinge region comprises the sequence of SEQ ID NO: 13, or a sequence with 95-99% identity thereof.

In one embodiment, the isolated nucleic acid molecule further comprises a sequence encoding a costimulatory domain, e.g., a costimulatory domain described herein. In embodiments, the intracellular signaling domain comprises a costimulatory domain. In embodiments, the intracellular signaling domain comprises a primary signaling domain. In embodiments, the intracellular signaling domain comprises one or more (e.g., one or more, two or more, or three or more) of a costimulatory domain and a primary signaling domain.

In one embodiment, the encoded costimulatory domain is a functional signaling domain obtained from a protein, e.g., described herein, e.g., selected from the group consisting of MHC class I molecule, TNF receptor proteins, Immunoglobulin-like proteins, cytokine receptors, integrins, signaling lymphocytic activation molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT,

GADS, SLP-76, PAG/Cbp, CD19a, and a ligand that specifically binds with CD83.. In embodiments, the encoded costimulatory domain comprises 4-1BB, CD27, CD28, or ICOS.

In one embodiment, the encoded costimulatory domain of 4-1BB comprises the amino acid sequence of SEQ ID NO:7. In one embodiment, the encoded costimulatory domain comprises an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO:7, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO:7. In one embodiment, the nucleic acid sequence encoding the costimulatory domain comprises the nucleotide sequence of SEQ ID NO:18, or a sequence with 95-99% identity thereof. In another embodiment, the encoded costimulatory domain of CD28 comprises the amino acid sequence of SEQ ID NO:1104. In one embodiment, the encoded costimulatory domain comprises an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO:1104, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO:1104. In one embodiment, the nucleic acid sequence encoding the costimulatory domain of CD28 comprises the nucleotide sequence of SEQ ID NO:1105 or a sequence with 95-99% identity thereof. In another embodiment, the encoded costimulatory domain of CD27 comprises the amino acid sequence of SEQ ID NO:8. In one embodiment, the encoded costimulatory domain comprises an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO:8, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO:8. In one embodiment, the nucleic acid sequence encoding the costimulatory domain of CD27 comprises the nucleotide sequence of SEQ ID NO:19, or a sequence with 95-99% identity thereof. In another embodiment, the encoded costimulatory domain of ICOS comprises the amino acid sequence of SEQ ID NO:1106. In one embodiment, the encoded costimulatory domain comprises an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO:1106, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO:1106. In one embodiment, the nucleic acid sequence encoding the costimulatory domain of ICOS comprises the nucleotide sequence of SEQ ID NO:1107 or a sequence with 95-99% identity thereof.

In embodiments, the encoded primary signaling domain comprises a functional signaling domain of CD3 zeta. In embodiments, the functional signaling domain of CD3 zeta comprises the amino acid sequence of SEQ ID NO: 9 (mutant CD3zeta) or SEQ ID NO: 10 (wild type human CD3zeta), or a sequence with 95-99% identity thereof.

In one embodiment, the encoded intracellular signaling domain comprises a functional signaling domain of 4-1BB and/or a functional signaling domain of CD3 zeta. In one embodiment, the encoded intracellular signaling domain of 4-1BB comprises the amino acid sequence of SEQ ID NO: 7 and/or the CD3 zeta amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10. In one embodiment, the intracellular signaling domain comprises an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO:7 and/or an amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO:7 and/or an amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10. In one embodiment, the encoded intracellular signaling domain comprises the sequence of SEQ ID NO:7 and the sequence of SEQ ID NO:9 or SEQ ID NO:10, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain. In one embodiment, the nucleic acid sequence encoding the intracellular signaling domain of 4-1BB comprises the nucleotide sequence of SEQ ID NO:18, or a sequence with 95-99% identity thereof, and/or the CD3 zeta nucleotide sequence of SEQ ID NO:20 or SEQ ID NO:21, or a sequence with 95-99% identity thereof.

In one embodiment, the encoded intracellular signaling domain comprises a functional signaling domain of CD27 and/or a functional signaling domain of CD3 zeta. In one embodiment, the encoded intracellular signaling domain of CD27 comprises the amino acid sequence of SEQ ID NO: 8 and/or the CD3 zeta amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10. In one embodiment, the intracellular signaling domain comprises an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO:8 and/or an amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO:8 and/or an amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10. In one embodiment, the encoded intracellular signaling domain comprises the sequence of SEQ ID NO:8 and the sequence of SEQ ID NO:9 or SEQ ID NO:10, wherein the sequences

comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain. In one embodiment, the nucleic acid sequence encoding the intracellular signaling domain of CD27 comprises the nucleotide sequence of SEQ ID NO:19, or a sequence with 95-99% identity thereof, and/or the CD3 zeta nucleotide sequence of SEQ ID NO:20 or SEQ ID NO:21, or a sequence with 95-99% identity thereof.

In one embodiment, the encoded intracellular signaling domain comprises a functional signaling domain of CD28 and/or a functional signaling domain of CD3 zeta. In one embodiment, the encoded intracellular signaling domain of CD28 comprises the amino acid sequence of SEQ ID NO: 1104 and/or the CD3 zeta amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10. In one embodiment, the intracellular signaling domain comprises an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO:1104 and/or an amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO:1104 and/or an amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10. In one embodiment, the encoded intracellular signaling domain comprises the sequence of SEQ ID NO:1104 and the sequence of SEQ ID NO:9 or SEQ ID NO:10, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain. In one embodiment, the nucleic acid sequence encoding the intracellular signaling domain of CD28 comprises the nucleotide sequence of SEQ ID NO:1105, or a sequence with 95-99% identity thereof, and/or the CD3 zeta nucleotide sequence of SEQ ID NO:20 or SEQ ID NO:21, or a sequence with 95-99% identity thereof.

In one embodiment, the encoded intracellular signaling domain comprises a functional signaling domain of ICOS and/or a functional signaling domain of CD3 zeta. In one embodiment, the encoded intracellular signaling domain of ICOS comprises the amino acid sequence of SEQ ID NO: 1106 and/or the CD3 zeta amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10. In one embodiment, the intracellular signaling domain comprises an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO:1106 and/or an amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO:1106 and/or an amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10. In one embodiment, the encoded intracellular signaling domain comprises the

sequence of SEQ ID NO:1106 and the sequence of SEQ ID NO:9 or SEQ ID NO:10, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain. In one embodiment, the nucleic acid sequence encoding the intracellular signaling domain of ICOS comprises the nucleotide sequence of SEQ ID NO:1107, or a sequence with 95-99% identity thereof, and/or the CD3 zeta nucleotide sequence of SEQ ID NO:20 or SEQ ID NO:21, or a sequence with 95-99% identity thereof.

In another aspect, the invention pertains to an isolated nucleic acid molecule encoding a CAR construct comprising a leader sequence, e.g., a leader sequence described herein, e.g., the amino acid sequence of SEQ ID NO: 1; an anti-BCMA binding domain described herein, e.g., human anti-BCMA binding domain comprising a LC CDR1, a LC CDR2, a LC CDR3, a HC CDR1, a HC CDR2 and a HC CDR3 described herein (e.g., a human anti-BCMA binding domain described in Table 1 or 16), or a sequence with 95-99% identify thereof; a hinge region described herein, e.g., the amino acid sequence of SEQ ID NO:2; a transmembrane domain described herein, e.g., having a sequence of SEQ ID NO: 6; and an intracellular signaling domain, e.g., an intracellular signaling domain described herein. In one embodiment, the encoded intracellular signaling domain comprises a costimulatory domain, e.g., a costimulatory domain described herein (e.g., a 4-1BB costimulatory domain having the amino acid sequence of SEQ ID NO:7 or a CD27 costimulatory domain having the amino acid sequence of SEQ ID NO:8), and/or a primary signaling domain, e.g., a primary signaling domain described herein, (e.g., a CD3 zeta stimulatory domain having a sequence of SEQ ID NO:9 or SEQ ID NO:10). In one embodiment, the isolated nucleic acid molecule encoding the CAR construct includes a leader sequence encoded by the nucleic acid sequence of SEQ ID NO:1, or a sequence with 95-99% identity thereto.

In another aspect, the invention pertains to an isolated nucleic acid molecule encoding a CAR construct comprising a leader sequence, e.g., a leader sequence described herein, e.g., the amino acid sequence of SEQ ID NO: 1; an anti-BCMA binding domain described herein (e.g., humanized anti-BCMA binding domain comprising a LC CDR1, a LC CDR2, a LC CDR3, a HC CDR1, a HC CDR2 and/or a HC CDR3 described herein, e.g., a humanized anti-BCMA

binding domain described herein (e.g., a humanized anti-BCMA binding domain comprising a sequence selected from a group consisting of SEQ ID NO: 271 or SEQ ID NO: 273), or a sequence with 95-99% identify thereof); a hinge region described herein, e.g., the amino acid sequence of SEQ ID NO:2; a transmembrane domain described herein, e.g., having a sequence of SEQ ID NO: 6, and an intracellular signaling domain, e.g., an intracellular signaling domain described herein. In one embodiment, the encoded intracellular signaling domain comprises a costimulatory domain, e.g., a costimulatory domain described herein (e.g., a 4-1BB costimulatory domain having a sequence of SEQ ID NO:7), and/or a primary signaling domain, e.g., a primary signaling domain described herein (e.g., a CD3 zeta stimulatory domain having a sequence of SEQ ID NO:9 or SEQ ID NO:10). In one embodiment, the isolated nucleic acid molecule encoding the CAR construct includes a leader sequence encoded by the nucleic acid sequence of SEQ ID NO:1, or a sequence with 95-99% identity thereto.

In one embodiment, the isolated nucleic acid molecule encoding the CAR construct includes a human anti-BCMA binding domain sequence encoded by the nucleic acid sequence of SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 150, SEQ ID NO: 151, SEQ ID NO: 152, SEQ ID NO: 153, SEQ ID NO: 154, SEQ ID NO: 155, SEQ ID NO: 156, SEQ ID NO: 157, SEQ ID NO: 158, SEQ ID NO: 159, SEQ ID NO: 160, SEQ ID NO: 161, SEQ ID NO: 162, SEQ ID NO: 163, SEQ ID NO: 164, SEQ ID NO: 165, SEQ ID NO: 166, SEQ ID NO: 167, SEQ ID NO: 168, SEQ ID NO: 169, or SEQ ID NO: 170, or a sequence with 95-99% identity thereto. In one embodiment, the isolated nucleic acid molecule encoding the CAR construct includes a humanized anti-BCMA binding domain sequence encoded by the nucleic acid sequence of SEQ ID NO: 272, SEQ ID NO: 274, or a sequence with 95-99% identity thereto.

In one embodiment, the isolated nucleic acid molecule comprises (e.g., consists of) a nucleic acid encoding a CAR amino acid sequence of SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO: 105, SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 213, SEQ ID NO: 214, SEQ ID NO: 215, SEQ ID NO: 216, SEQ ID NO: 217, SEQ ID NO: 218, SEQ ID NO: 219, SEQ ID

NO: 220, SEQ ID NO: 221, SEQ ID NO: 222, SEQ ID NO: 223, SEQ ID NO: 224, SEQ ID NO: 225, SEQ ID NO: 226, SEQ ID NO: 227, SEQ ID NO: 228, SEQ ID NO: 229, SEQ ID NO: 230, SEQ ID NO: 231, SEQ ID NO: 232, or SEQ ID NO: 233, or an amino acid sequence having 85%, 90%, 95%, 96%, 97%, 98% or 99% identity to or having one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of an amino acid sequence of SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO: 105, SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 213, SEQ ID NO: 214, SEQ ID NO: 215, SEQ ID NO: 216, SEQ ID NO: 217, SEQ ID NO: 218, SEQ ID NO: 219, SEQ ID NO: 220, SEQ ID NO: 221, SEQ ID NO: 222, SEQ ID NO: 223, SEQ ID NO: 224, SEQ ID NO: 225, SEQ ID NO: 226, SEQ ID NO: 227, SEQ ID NO: 228, SEQ ID NO: 229, SEQ ID NO: 230, SEQ ID NO: 231, SEQ ID NO: 232, or SEQ ID NO: 233.

In one embodiment, the isolated nucleic acid molecule comprises (e.g., consists of) a nucleic acid sequence of SEQ ID NO: 114, SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 119, SEQ ID NO: 120, SEQ ID NO: 121, SEQ ID NO: 122, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 234, SEQ ID NO: 235, SEQ ID NO: 236, SEQ ID NO: 237, SEQ ID NO: 238, SEQ ID NO: 239, SEQ ID NO: 240, SEQ ID NO: 241, SEQ ID NO: 242, SEQ ID NO: 243, SEQ ID NO: 244, SEQ ID NO: 245, SEQ ID NO: 246, SEQ ID NO: 247, SEQ ID NO: 248, SEQ ID NO: 249, SEQ ID NO: 250, SEQ ID NO: 251, SEQ ID NO: 252, SEQ ID NO: 253, or SEQ ID NO: 254, or a nucleic acid sequence having 85%, 90%, 95%, 96%, 97%, 98% or 99% identity to or having one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a nucleic acid sequence of SEQ ID NO: 114, SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 119, SEQ ID NO: 120, SEQ ID NO: 121, SEQ ID NO: 122, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 234, SEQ ID NO: 235, SEQ ID NO: 236, SEQ ID NO: 237, SEQ ID NO: 238, SEQ ID NO: 239, SEQ ID NO: 240, SEQ ID NO: 241, SEQ ID NO: 242, SEQ ID

NO: 243, SEQ ID NO: 244, SEQ ID NO: 245, SEQ ID NO: 246, SEQ ID NO: 247, SEQ ID NO: 248, SEQ ID NO: 249, SEQ ID NO: 250, SEQ ID NO: 251, SEQ ID NO: 252, SEQ ID NO: 253, or SEQ ID NO: 254.

In one aspect, the invention pertains to an isolated nucleic acid molecule encoding an anti-BCMA binding domain, wherein the anti-BCMA binding domain comprises one or more (e.g., all three) light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and/or light chain complementary determining region 3 (LC CDR3) of an anti-BCMA binding domain described herein, and one or more (e.g., all three) heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and/or heavy chain complementary determining region 3 (HC CDR3) of an anti-BCMA binding domain described herein, e.g., a human anti-BCMA binding domain comprising one or more, e.g., all three, LC CDRs and one or more, e.g., all three, HC CDRs. In one embodiment, the encoded anti-BCMA binding domain comprises a light chain variable region described herein (e.g., in SEQ ID NO: 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 259, 260, 261, or 262) and/or a heavy chain variable region described herein (e.g., in SEQ ID NO: 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 81, 82, 83, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 255, 256, 257, or 258). In one embodiment, the encoded anti-BCMA binding domain is a scFv comprising a light chain and a heavy chain of an amino acid sequence of in SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, SEQ ID NO: 149, SEQ ID NO: 263, SEQ ID NO: 264, SEQ ID NO: 265, or SEQ ID NO: 266, or a sequence with 95-99% identity thereof. In an embodiment, the anti-BCMA binding domain (e.g., an scFv) comprises: a light chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative

substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a light chain variable region provided in SEQ ID NO: 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 259, 260, 261, or 262 or a sequence with 95-99% identity with an amino acid sequence of SEQ ID NO: 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 259, 260, 261, or 262; and/or a heavy chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a heavy chain variable region provided in SEQ ID NO: 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 81, 82, 83, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 255, 256, 257, or 258 or a sequence with 95-99% identity to an amino acid sequence in SEQ ID NO: 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 81, 82, 83, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 255, 256, 257, or 258. In one embodiment, the anti-BCMA binding domain comprises a sequence selected from the group consisting of SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, and SEQ ID NO: 149, SEQ ID NO: 263, SEQ ID NO: 264, SEQ ID NO: 265, or SEQ ID NO: 266, or a sequence with 95-99% identify thereof. In one embodiment, the encoded anti-BCMA binding domain is a scFv, and a light chain variable region comprising an amino acid sequence described herein, e.g., in Table 1 or 16, is attached to a heavy chain variable region comprising an amino acid sequence described herein, e.g., in Table 1 or 16, via a linker, e.g., a linker described herein. In one embodiment, the encoded anti-BCMA binding domain includes a $(Gly_4\text{-}Ser)n$ linker, wherein n is 1, 2, 3, 4, 5, or 6, preferably 4 (SEQ ID NO: 26). The light chain variable region and heavy chain variable region of a scFv can be, e.g., in any of the following orientations: light chain variable region-linker-

heavy chain variable region or heavy chain variable region-linker-light chain variable region. In one embodiment, the isolated nucleic acid sequence encoding the human anti-BCMA binding domain comprises a sequence selected from a group consisting of SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 150, SEQ ID NO: 151, SEQ ID NO: 152, SEQ ID NO: 153, SEQ ID NO: 154, SEQ ID NO: 155, SEQ ID NO: 156, SEQ ID NO: 157, SEQ ID NO: 158, SEQ ID NO: 159, SEQ ID NO: 160, SEQ ID NO: 161, SEQ ID NO: 162, SEQ ID NO: 163, SEQ ID NO: 164, SEQ ID NO: 165, SEQ ID NO: 166, SEQ ID NO: 167, SEQ ID NO: 168, SEQ ID NO: 169, and SEQ ID NO: 170, or a sequence with 95-99% identity thereof.

In other embodiments, the encoded BCMA binding domain comprises a HC CDR1, a HC CDR2, and a HC CDR3 of any BCMA heavy chain binding domain amino acid sequences listed in Table 1 or 16. In embodiments, the BCMA binding domain further comprises a LC CDR1, a LC CDR2, and a LC CDR3. In embodiments, the BCMA binding domain comprises a LC CDR1, a LC CDR2, and a LC CDR3 of any BCMA light chain binding domain amino acid sequences listed in Table 1or 16.

In some embodiments, the encoded BCMA binding domain comprises one, two or all of LC CDR1, LC CDR2, and LC CDR3 of any BCMA light chain binding domain amino acid sequences listed in Table 1 or 16, and one, two or all of HC CDR1, HC CDR2, and HC CDR3 of any BCMA heavy chain binding domain amino acid sequences listed in Table 1 or 16.

In an embodiment, the anti-BCMA binding domain (e.g., an scFv) comprises: a light chain variable region comprising an amino acid sequence comprising (or consisting of) a light chain variable region of SEQ ID NO: 271 or 273; and amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a light chain variable region provided in SEQ ID NO: 271 or 273, or a sequence with 95-99% identify thereof; and/or a heavy chain variable region comprising an amino acid sequence comprising (or consisting of) a heavy chain variable region of SEQ ID NO: 271 or 273; and amino acid sequence having at least one, two or three modifications (e.g.,

substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a heavy chain variable region provided in SEQ ID NO: 271 or 273, or a sequence with 95-99% identify thereof. In one embodiment, the encoded humanized anti-BCMA binding domain is a scFv, and a light chain variable region comprising an amino acid sequence described herein, e.g., provided in SEQ ID NO: 271 or 273, is attached to a heavy chain variable region comprising an amino acid sequence described herein, e.g., provided in SEQ ID NO: 271 or 273, via a linker, e.g., a linker described herein. In one embodiment, the encoded anti-BCMA binding domain includes a $(Gly_4$-Ser)n linker, wherein n is 1, 2, 3, 4, 5, or 6, preferably 4 (SEQ ID NO: 26).

In another aspect, the invention pertains to an isolated polypeptide molecule, e.g., isolated chimeric antigen receptor (CAR) molecule, encoded by the nucleic acid molecule. In one embodiment, the isolated polypeptide molecule comprises a sequence selected from the group consisting of SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO: 105, SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 213, SEQ ID NO: 214, SEQ ID NO: 215, SEQ ID NO: 216, SEQ ID NO: 217, SEQ ID NO: 218, SEQ ID NO: 219, SEQ ID NO: 220, SEQ ID NO: 221, SEQ ID NO: 222, SEQ ID NO: 223, SEQ ID NO: 224, SEQ ID NO: 225, SEQ ID NO: 226, SEQ ID NO: 227, SEQ ID NO: 228, SEQ ID NO: 229, SEQ ID NO: 230, SEQ ID NO: 231, SEQ ID NO: 232, and SEQ ID NO: 233, or a sequence with 95-99% identify thereof.

In another aspect, the invention pertains to an isolated chimeric antigen receptor (CAR) molecule (e.g., polypeptide) comprising an anti-BCMA binding domain (e.g., a human or humanized antibody or antibody fragment that specifically binds to BCMA), a transmembrane domain, and an intracellular signaling domain (e.g., an intracellular signaling domain comprising a costimulatory domain and/or a primary signaling domain). In one embodiment, the CAR comprises an antibody or antibody fragment which includes an anti-BCMA binding domain described herein (e.g., a human antibody or antibody fragment that specifically binds to BCMA as described herein), a transmembrane domain described herein, and an intracellular signaling domain described herein (e.g., an intracellular signaling domain comprising a costimulatory domain and/or a primary signaling domain described herein).

In one embodiment, the anti-BCMA binding domain comprises one or more (e.g., all three) light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and light chain complementary determining region 3 (LC CDR3) of an anti-BCMA binding domain described herein, and one or more (e.g., all three) heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of an anti-BCMA binding domain described herein, e.g., a human or humanized anti-BCMA binding domain comprising one or more, e.g., all three, LC CDRs and one or more, e.g., all three, HC CDRs. In one embodiment, the anti-BCMA binding domain comprises a light chain variable region described herein (e.g., in Table 1 or SEQ ID NO: 271 or 273) and/or a heavy chain variable region described herein (e.g., in Table 1 or SEQ ID NO: 271 or 273). In one embodiment, the anti-BCMA binding domain is a scFv comprising a light chain and a heavy chain of an amino acid sequence listed in Table 1, SEQ ID NO: 271 or 273. In an embodiment, the anti-BCMA binding domain (e.g., an scFv) comprises: a light chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a light chain variable region provided in Table 1 or SEQ ID NO: 271 or 273, or a sequence with 95-99% identity with an amino acid sequence provided in Table 1 or SEQ ID NO: 271 or 273; and/or a heavy chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a heavy chain variable region provided in Table 1 or SEQ ID NO: 271 or 273, or a sequence with 95-99% identity to an amino acid sequence provided in Table 1 or SEQ ID NO: 271 or 273. In one embodiment, the anti-BCMA binding domain comprises a sequence selected from a group consisting of SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO:

148, SEQ ID NO: 149, SEQ ID NO: 263, SEQ ID NO: 264, SEQ ID NO: 265, or SEQ ID NO: 266; or an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) to any of the aforesaid sequences; or a sequence with 95-99% identify to any of the aforesaid sequences. In one embodiment, the anti-BCMA binding domain comprises a sequence selected from a group consisting of SEQ ID NO: 271 or SEQ ID NO: 273, or a sequence with 95-99% identify thereof. In one embodiment, the anti-BCMA binding domain is a scFv, and a light chain variable region comprising an amino acid sequence described herein, e.g., in Table 1 or 16, SEQ ID NO: 271 or SEQ ID NO: 273, is attached to a heavy chain variable region comprising an amino acid sequence described herein, e.g., in Table 1 or 16, SEQ ID NO: 271 or SEQ ID NO: 273, via a linker, e.g., a linker described herein. In one embodiment, the anti-BCMA binding domain includes a $(Gly_4\text{-}Ser)n$ linker, wherein n is 1, 2, 3, 4, 5, or 6, preferably 4 (SEQ ID NO: 26). The light chain variable region and heavy chain variable region of a scFv can be, e.g., in any of the following orientations: light chain variable region-linker-heavy chain variable region or heavy chain variable region-linker-light chain variable region.

In other embodiments, the BCMA binding domain comprises a HC CDR1, a HC CDR2, and a HC CDR3 of any BCMA heavy chain binding domain amino acid sequences listed in Table 1 or 16. In embodiments, the BCMA binding domain further comprises a LC CDR1, a LC CDR2, and a LC CDR3. In embodiments, the BCMA binding domain comprises a LC CDR1, a LC CDR2, and a LC CDR3 of any BCMA light chain binding domain amino acid sequences listed in Table 1or 16.

In some embodiments, the BCMA binding domain comprises one, two or all of LC CDR1, LC CDR2, and LC CDR3 of any BCMA light chain binding domain amino acid sequences listed in Table 1 or 16, and one, two or all of HC CDR1, HC CDR2, and HC CDR3 of any BCMA heavy chain binding domain amino acid sequences listed in Table 1 or 16.

In one embodiment, the isolated CAR molecule comprises a transmembrane domain of a protein, e.g., described herein, e.g., selected from the group consisting of the the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16,

CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 and CD154. In one embodiment, the transmembrane domain comprises a sequence of SEQ ID NO: 6. In one embodiment, the transmembrane domain comprises an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 20, 10 or 5 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of SEQ ID NO: 6, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO: 6.

In one embodiment, the anti-BCMA binding domain is connected to the transmembrane domain by a hinge region, e.g., a hinge region described herein. In one embodiment, the encoded hinge region comprises SEQ ID NO:2, or a sequence with 95-99% identity thereof.

In one embodiment, the isolated CAR molecule further comprises a sequence encoding a costimulatory domain, e.g., a costimulatory domain described herein. In embodiments, the intracellular signaling domain of the isolated CAR molecule comprises a costimulatory domain. In embodiments, the intracellular signaling domain of the isolated CAR molecule comprises a primary signaling domain. In embodiments, the intracellular signaling domain of the isolated CAR molecule comprises a costimulatory domain and a primary signaling domain.

In one embodiment, the costimulatory domain comprises a functional signaling domain of a protein selected from the group consisting of MHC class I molecule, TNF receptor proteins, Immunoglobulin-like proteins, cytokine receptors, integrins, signaling lymphocytic activation molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150,

IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, and a ligand that specifically binds with CD83.

In one embodiment, the costimulatory domain comprises a sequence of SEQ ID NO:7. In one embodiment, the costimulatory domain comprises an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 20, 10 or 5 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of SEQ ID NO:7, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO:7. In another embodiment, the costimulatory domain of CD28 comprises the amino acid sequence of SEQ ID NO:1104. In one embodiment, the costimulatory domain comprises an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO:1104, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO:1104. In another embodiment, the costimulatory domain of CD27 comprises the amino acid sequence of SEQ ID NO:8. In one embodiment, the costimulatory domain comprises an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO:8, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO:8. In another embodiment, the costimulatory domain of ICOS comprises the amino acid sequence of SEQ ID NO:1106. In one embodiment, the costimulatory domain comprises an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO:1106, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO:1106.

In embodiments, the primrary signaling domain comprises a signaling domain or CD3 zeta. In embodiments, the functional dignaling domain of CD3 zeta comprises SEQ ID NO: 9 (mutant CD3 zeta) or SEQ ID NO: 10 (wild type human CD3 zeta), or a sequence with 95-99% identity thereof.

In one embodiment, the intracellular signaling domain comprises a functional signaling domain of 4-1BB and/or a functional signaling domain of CD3 zeta. In one embodiment, the intracellular signaling domain comprises the sequence of SEQ ID NO: 7 and/or the sequence of SEQ ID NO:9 or SEQ ID NO:10. In one embodiment, the intracellular signaling domain comprises an amino acid sequence having at least one, two or three modifications (e.g.,

substitutions, e.g., conservative substitutions) but not more than 20, 10 or 5 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of SEQ ID NO: 7 and/or the sequence of SEQ ID NO:9 or SEQ ID NO:10., or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO: 7 and/or the sequence of SEQ ID NO:9 or SEQ ID NO:10. In one embodiment, the intracellular signaling domain comprises the sequence of SEQ ID NO: 7 and/or the sequence of SEQ ID NO:9 or SEQ ID NO:10, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain.

In one embodiment, the intracellular signaling domain comprises a functional signaling domain of CD27 and/or a functional signaling domain of CD3 zeta. In one embodiment, the intracellular signaling domain of CD27 comprises the amino acid sequence of SEQ ID NO: 8 and/or the CD3 zeta amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10. In one embodiment, the intracellular signaling domain comprises an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO:8 and/or an amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO:8 and/or an amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10. In one embodiment, the intracellular signaling domain comprises the sequence of SEQ ID NO:8 and the sequence of SEQ ID NO:9 or SEQ ID NO:10, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain.

In one embodiment, the intracellular signaling domain comprises a functional signaling domain of CD28 and/or a functional signaling domain of CD3 zeta. In one embodiment, the encoded intracellular signaling domain of CD28 comprises the amino acid sequence of SEQ ID NO: 1104 and/or the CD3 zeta amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10. In one embodiment, the intracellular signaling domain comprises an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO: 1104 and/or an amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO: 379 and/or an amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10. In one embodiment, the intracellular signaling domain comprises the sequence of SEQ ID NO: 1104 and the sequence

of SEQ ID NO:9 or SEQ ID NO:10, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain.

In one embodiment, the intracellular signaling domain comprises a functional signaling domain of ICOS and/or a functional signaling domain of CD3 zeta. In one embodiment, the intracellular signaling domain of ICOS comprises the amino acid sequence of SEQ ID NO: 1106 and/or the CD3 zeta amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10. In one embodiment, the intracellular signaling domain comprises an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO:1106 and/or an amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO:1106 and/or an amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10. In one embodiment, the encoded intracellular signaling domain comprises the sequence of SEQ ID NO:1106 and the sequence of SEQ ID NO:9 or SEQ ID NO:10, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain.

In one embodiment, the isolated CAR molecule further comprises a leader sequence, e.g., a leader sequence described herein. In one embodiment, the leader sequence comprises an amino acid sequence of SEQ ID NO: 1, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO:1

In another aspect, the invention pertains to an isolated CAR molecule comprising a leader sequence, e.g., a leader sequence described herein, e.g., a leader sequence of SEQ ID NO: 1, or having 95-99% identity thereof, an anti-BCMA binding domain described herein, e.g., an anti-BCMA binding domain comprising a LC CDR1, a LC CDR2, a LC CDR3, a HC CDR1, a HC CDR2 and a HC CDR3 described herein, e.g., an anti-BCMA binding domain described in Table 1 or 16, SEQ ID NO: 271 or SEQ ID NO: 273, or a sequence with 95-99% identify thereof, a hinge region, e.g., a hinge region described herein, e.g., a hinge region of SEQ ID NO:2, or having 95-99% identity thereof, a transmembrane domain, e.g., a transmembrane domain described herein, e.g., a transmembrane domain having a sequence of SEQ ID NO: 6 or a sequence having 95-99% identity thereof, an intracellular signaling domain, e.g., an intracellular signaling domain described herein (e.g., an intracellular signaling domain comprising a costimulatory domain and/or a primary signaling domain). In one embodiment,

the intracellular signaling domain comprises a costimulatory domain, e.g., a costimulatory domain described herein, e.g., a 4-1BB costimulatory domain having a sequence of SEQ ID NO:7, or having 95-99%identity thereof, and/or a primary signaling domain, e.g., a primary signaling domain described herein, e.g., a CD3 zeta stimulatory domain having a sequence of SEQ ID NO:9 or SEQ ID NO:10, or having 95-99% identity thereof. In one embodiment, the intracellular signaling domain comprises a costimulatory domain, e.g., a costimulatory domain described herein, e.g., a 4-1BB costimulatory domain having a sequence of SEQ ID NO:7, and/or a primary signaling domain, e.g., a primary signaling domain described herein, e.g., a CD3 zeta stimulatory domain having a sequence of SEQ ID NO:9 or SEQ ID NO:10.

In one embodiment, the isolated CAR molecule comprises (e.g., consists of) an amino acid sequence of SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO: 105, SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 213, SEQ ID NO: 214, SEQ ID NO: 215, SEQ ID NO: 216, SEQ ID NO: 217, SEQ ID NO: 218, SEQ ID NO: 219, SEQ ID NO: 220, SEQ ID NO: 221, SEQ ID NO: 222, SEQ ID NO: 223, SEQ ID NO: 224, SEQ ID NO: 225, SEQ ID NO: 226, SEQ ID NO: 227, SEQ ID NO: 228, SEQ ID NO: 229, SEQ ID NO: 230, SEQ ID NO: 231, SEQ ID NO: 232, or SEQ ID NO: 233, or an amino acid sequence having at least one, two, three, four, five, 10, 15, 20 or 30 modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 60, 50 or 40 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO: 105, SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 213, SEQ ID NO: 214, SEQ ID NO: 215, SEQ ID NO: 216, SEQ ID NO: 217, SEQ ID NO: 218, SEQ ID NO: 219, SEQ ID NO: 220, SEQ ID NO: 221, SEQ ID NO: 222, SEQ ID NO: 223, SEQ ID NO: 224, SEQ ID NO: 225, SEQ ID NO: 226, SEQ ID NO: 227, SEQ ID NO: 228, SEQ ID NO: 229, SEQ ID NO: 230, SEQ ID NO: 231, SEQ ID NO: 232, or SEQ ID NO: 233, or an amino acid sequence having 85%, 90%, 95%, 96%, 97%, 98% or 99% identity to an amino acid sequence of SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO: 105, SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID

NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 213, SEQ ID NO: 214, SEQ ID NO: 215, SEQ ID NO: 216, SEQ ID NO: 217, SEQ ID NO: 218, SEQ ID NO: 219, SEQ ID NO: 220, SEQ ID NO: 221, SEQ ID NO: 222, SEQ ID NO: 223, SEQ ID NO: 224, SEQ ID NO: 225, SEQ ID NO: 226, SEQ ID NO: 227, SEQ ID NO: 228, SEQ ID NO: 229, SEQ ID NO: 230, SEQ ID NO: 231, SEQ ID NO: 232, or SEQ ID NO: 233.

In other embodiments, the anti-BCMA binding domain comprises a HC CDR1, a HC CDR2, and a HC CDR3 of any BCMA heavy chain binding domain amino acid sequences listed in Table 1 or 16. In embodiments, the BCMA binding domain further comprises a LC CDR1, a LC CDR2, and a LC CDR3. In embodiments, the BCMA binding domain comprises a LC CDR1, a LC CDR2, and a LC CDR3 of any BCMA light chain binding domain amino acid sequences listed in Table 1or 16.

In some embodiments, the anti-BCMA binding domain comprises one, two or all of LC CDR1, LC CDR2, and LC CDR3 of any BCMA light chain binding domain amino acid sequences listed in Table 1 or 16, and one, two or all of HC CDR1, HC CDR2, and HC CDR3 of any BCMA heavy chain binding domain amino acid sequences listed in Table 1 or 16.

In one aspect, the invention pertains to a BCMA binding domain comprising one or more (e.g., all three) light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and light chain complementary determining region 3 (LC CDR3) of a BCMA binding domain described herein, and/or one or more (e.g., all three) heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of a BCMA binding domain described herein, e.g., a BCMA binding domain comprising one or more, e.g., all three, LC CDRs and one or more, e.g., all three, HC CDRs.

In other embodiments, the BCMA binding domain comprises a HC CDR1, a HC CDR2, and a HC CDR3 of any BCMA heavy chain binding domain amino acid sequences listed in Table 1 or 16. In embodiments, the BCMA binding domain further comprises a LC CDR1, a LC CDR2, and a LC CDR3. In embodiments, the BCMA binding domain comprises

a LC CDR1, a LC CDR2, and a LC CDR3 of any BCMA light chain binding domain amino acid sequences listed in Table 1or 16.

In some embodiments, the BCMA binding domain comprises one, two or all of LC CDR1, LC CDR2, and LC CDR3 of any BCMA light chain binding domain amino acid sequences listed in Table 1 or 16, and one, two or all of HC CDR1, HC CDR2, and HC CDR3 of any BCMA heavy chain binding domain amino acid sequences listed in Table 1 or 16.

In one embodiment, the BCMA binding domain comprises one or more (e.g., all three) light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and light chain complementary determining region 3 (LC CDR3) of an BCMA binding domain described herein, and one or more (e.g., all three) heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of an BCMA binding domain described herein, e.g., a human or humanized anti-BCMA binding domain comprising one or more, e.g., all three, LC CDRs and one or more, e.g., all three, HC CDRs. In one embodiment, the BCMA binding domain comprises a light chain variable region described herein (e.g., in Table 1 or SEQ ID NO: 271 or 273) and/or a heavy chain variable region described herein (e.g., in Table 1 or SEQ ID NO: 271 or 273). In one embodiment, the BCMA binding domain is a scFv comprising a light chain and a heavy chain of an amino acid sequence listed in Table 1, SEQ ID NO: 271 or 273. In an embodiment, the BCMA binding domain (e.g., an scFv) comprises: a light chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a light chain variable region provided in Table 1 or SEQ ID NO: 271 or 273, or a sequence with 95-99% identity with an amino acid sequence provided in Table 1 or SEQ ID NO: 271 or 273; and/or a heavy chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a heavy chain variable region provided in Table 1 or SEQ ID NO: 271 or 273, or a sequence with 95-99% identity to an amino acid sequence provided in Table 1 or SEQ ID NO: 271 or 273. In one embodiment, the BCMA binding domain comprises a sequence selected from a

group consisting of SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, SEQ ID NO: 149, SEQ ID NO: 263, SEQ ID NO: 264, SEQ ID NO: 265, or SEQ ID NO: 266; or an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) to any of the aforesaid sequences; or a sequence with 95-99% identify to any of the aforesaid sequences. In one embodiment, the BCMA binding domain comprises a sequence selected from a group consisting of SEQ ID NO: 271 or SEQ ID NO: 273, or a sequence with 95-99% identify thereof. In one embodiment, the anti-BCMA binding domain is a scFv, and a light chain variable region comprising an amino acid sequence described herein, e.g., in Table 1 or 16, SEQ ID NO: 271 or SEQ ID NO: 273, is attached to a heavy chain variable region comprising an amino acid sequence described herein, e.g., in Table 1 or 16, SEQ ID NO: 271 or SEQ ID NO: 273, via a linker, e.g., a linker described herein. In one embodiment, the BCMA binding domain includes a $(Gly_4\text{-}Ser)n$ linker, wherein n is 1, 2, 3, 4, 5, or 6, preferably 4 (SEQ ID NO: 26). The light chain variable region and heavy chain variable region of a scFv can be, e.g., in any of the following orientations: light chain variable region-linker-heavy chain variable region or heavy chain variable region-linker-light chain variable region.

In another aspect, the invention pertains to a vector comprising a nucleic acid molecule described herein, e.g., a nucleic acid molecule encoding a CAR described herein. In one embodiment, the vector is selected from the group consisting of a DNA, a RNA, a plasmid, a lentivirus vector, adenoviral vector, or a retrovirus vector.

In one embodiment, the vector is a lentivirus vector. In one embodiment, the vector further comprises a promoter. In one embodiment, the promoter is an EF-1 promoter. In one embodiment, the EF-1 promoter comprises a sequence of SEQ ID NO: 11. In another

embodiment, the promoter is a PGK promoter, e.g., a truncated PGK promoter as described herein.

In one embodiment, the vector is an in vitro transcribed vector, e.g., a vector that transcribes RNA of a nucleic acid molecule described herein. In one embodiment, the nucleic acid sequence in the vector further comprises a poly(A) tail, e.g., a poly A tail described herein, e.g., comprising about 150 adenosine bases (SEQ ID NO: 382). In one embodiment, the nucleic acid sequence in the vector further comprises a 3'UTR, e.g., a 3' UTR described herein, e.g., comprising at least one repeat of a 3'UTR derived from human beta-globulin. In one embodiment, the nucleic acid sequence in the vector further comprises promoter, e.g., a T2A promoter.

In another aspect, the invention pertains to a cell comprising a vector described herein. In one embodiment, the cell is a cell described herein, e.g., an immune effector cell, e.g., a human T cell or a human NK cell, e.g., a human T cell described herein or a human NK cell described herein. In one embodiment, the human T cell is a CD8+ T cell.

In another embodiment, the CAR-expressing cell described herein can further express another agent, e.g., an agent which enhances the activity of a CAR-expressing cell. For example, in one embodiment, the agent can be an agent which inhibits an inhibitory molecule. Examples of inhibitory molecules include PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGFR beta. In embodiments, the agent is an agent that inhibits PD1. In embodiments, the agent is an agent that inhibits PD-L1. In one embodiment, the agent which inhibits an inhibitory molecule can be an agent described herein, such as, e.g., an agent that comprises a first polypeptide, e.g., an inhibitory molecule, associated with a second polypeptide that provides a positive signal to the cell, e.g., an intracellular signaling domain described herein. In one embodiment, the agent comprises a first polypeptide, e.g., of an inhibitory molecule such as PD1, PD-L1, PD-L2, LAG3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), CTLA4, VISTA, CD160, BTLA, LAIR1, TIM3, 2B4, TGFR beta, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TIGIT, or a fragment of any of these (e.g., at least a portion of the extracellular

domain of any of these), and a second polypeptide which is an intracellular signaling domain described herein (e.g., comprising a costimulatory domain (e.g., 41BB, CD27 or CD28, e.g., as described herein) and/or a primary signaling domain (e.g., a CD3 zeta signaling domain described herein). In one embodiment, the agent comprises a first polypeptide of PD1 or a fragment thereof (e.g., at least a portion of the extracellular domain of PD1), and a second polypeptide of an intracellular signaling domain described herein (e.g., a CD28 signaling domain described herein and/or a CD3 zeta signaling domain described herein).

In another aspect, the invention pertains to a method of making a cell comprising transducing a cell described herein, e.g., an immune effector cell described herein, e.g., a T cell or NK cell described herein, with a vector of comprising a nucleic acid encoding a CAR, e.g., a CAR described herein.

The present invention also provides a method of generating a population of RNA-engineered cells, e.g., cells described herein, e.g., immune effector cells, e.g., T cells or NK cells, transiently expressing exogenous RNA. The method comprises introducing an in vitro transcribed RNA or synthetic RNA into a cell, where the RNA comprises a nucleic acid encoding a CAR molecule described herein.

In another aspect, the invention pertains to a method of providing an anti-tumor immunity in a mammal comprising administering to the mammal an effective amount of a cell expressing a CAR molecule, e.g., a cell expressing a CAR molecule described herein. In one embodiment, the cell is an autologous immune effector cell, e.g., T cell or an autologous NK cell. In one embodiment, the cell is an immune effector cell, e.g., allogeneic T cell or an allogeneic NK cell. In one embodiment, the mammal is a human, e.g., a patient with a hematologic cancer.

In another aspect, the invention pertains to a method of treating a mammal having a disease associated with expression of BCMA (*e.g.*, a proliferative disease, a precancerous condition, and a noncancer related indication associated with the expression of BCMA) comprising administering to the mammal an effective amount of the cells expressing a CAR molecule, e.g., a CAR molecule described herein. In one embodiment, the mammal is a human, e.g., a patient with a hematologic cancer.

In one embodiment, the disease is a disease described herein. In one embodiment, the disease associated with BCMA expression is selected from a hematologic cancer such as acute leukemias including but not limited to acute myeloid leukemia (AML); myelodysplastic syndrome; myeloproliferative neoplasms; chronic myeloid leukemia (CML); Blastic plasmacytoid dendritic cell neoplasm; and to disease associated with BCMA expression including, but not limited to atypical and/or non-classical cancers, malignancies, precancerous conditions or proliferative diseases expressing BCMA; and combinations thereof. In one embodiment,the disease associated with BCMA expression is a hematologic cancer selected from the group consisting of one or more acute leukemias including but not limited to B-cell acute lymphoid leukemia ("BALL"), T-cell acute lymphoid leukemia ("TALL"), acute lymphoid leukemia (ALL); one or more chronic leukemias including but not limited to chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL); additional hematologic cancers or hematologic conditions including, but not limited to B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, and "preleukemia" which are a diverse collection of hematological conditions united by ineffective production (or dysplasia) of myeloid blood cells, and to disease associated with BCMA expression include, but not limited to atypical and/or non-classical cancers, malignancies, precancerous conditions or proliferative diseases expressing BCMA; and combinations thereof.

In embodiments, a disease associated with expression of BCMA includes a plasma cell proliferative disorder, e.g., asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), monoclonal gammapathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia, plasmacytomas (e.g., plasma cell dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, and POEMS syndrome (also known as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome).

In embodiments, a disease associated with expression of BCMA includes a cancer, e.g., a cancer described herein, e.g., a prostate cancer (e.g., castrate-resistant or therapy-resistant prostate cancer, or metastatic prostate cancer), pancreatic cancer, or lung cancer.

In one embodiment of the therapeutic methods, the cell expressing a CAR molecule described herein (e.g., a BCMA CAR molecule) is administered in combination with a cell comprising a CD19 CAR molecule. In one embodiment, the cell expressing the BCMA CAR molecule is administered before, subsequent to, or simultaneously with administration of the cell expressing the CD19 CAR. In one embodiment, the cell expressing the BCMA CAR molecule and the cell expressing the CD19 CAR molecule are part of a single composition, and in other embodiments the cell expressing the BCMA CAR molecule and the cell expressing the CD19 CAR molecule are part of separate compositions. In one embodiment, the cell expressing a CAR molecule described herein (e.g., a BCMA CAR molecule) also express a CD19 CAR molecule. In one embodiment, the disease associated with BCMA is multiple myeloma, e.g., CD19-negative multiple myeloma. In one embodiment, the disease associated with expression of BCMA is multiple myeloma e.g., a multiple myeloma that is CD19-negative, e.g., having a vast majority (e.g., 99.95%) of the neoplastic plasma cells with a CD19-negative phenotype, e.g., as detected by both flow cytometry and RT-PCR.

In one embodiment, the cells expressing a CAR molecule, e.g., a CAR molecule described herein, are administered in combination with an agent that increases the efficacy of a cell expressing a CAR molecule, e.g., an agent described herein.

In one embodiment, the cells expressing a CAR molecule, e.g., a CAR molecule described herein, are administered in combination with a low, immune enhancing dose of an mTOR inhibitor. While not wishing to be bound by theory, it is believed that treatment with a low, immune enhancing, dose (e.g., a dose that is insufficient to completely suppress the immune system but sufficient to improve immune function) is accompanied by a decrease in PD-1 positive immune effector cells, e.g., T cells or NK cells, or an increase in PD-1 negative cells. PD-1 positive immune effector cells, e.g., T cells or NK cells, but not PD-1 negative immune effector cells (e.g., T cells or NK cells), can be exhausted by engagement with cells which express a PD-1 ligand, e.g., PD-L1 or PD-L2.

In an embodiment this approach can be used to optimize the performance of CAR cells described herein in the subject. While not wishing to be bound by theory, it is believed that, in

an embodiment, the performance of endogenous, non-modified immune effector cells, e.g., T cells or NK cells, is improved. While not wishing to be bound by theory, it is believed that, in an embodiment, the performance of a BCMA CAR expressing cell is improved. In other embodiments, cells, e.g., immune effector cells (e.g., T cells or NK cells), which have, or will be engineered to express a CAR, can be treated ex vivo by contact with an amount of an mTOR inhibitor that increases the number of PD1 negative immune effector cells, e.g., T cells or NK cells, or increases the ratio of PD1 negative immune effector cells, e.g., T cells or NK cells / PD1 positive immune effector cells, e.g., T cells or NK cells.

In an embodiment, administration of a low, immune enhancing, dose of an mTOR inhibitor, e.g., an allosteric inhibitor, e.g., RAD001, or a catalytic inhibitor, is initiated prior to administration of an CAR expressing cell described herein, e.g., immune effector cells (e.g., T cells or NK cells). In an embodiment, the CAR cells are administered after a sufficient time, or sufficient dosing, of an mTOR inhibitor, such that the level of PD1 negative immune effector cells, e.g., T cells or NK cells, or the ratio of PD1 negative immune effector cells, e.g., T cells or NK cells/ PD1 positive immune effector cells, e.g., T cells or NK cells, has been, at least transiently, increased.

In an embodiment, the cell, e.g., immune effector cell (e.g., T cell or NK cell), to be engineered to express a CAR, is harvested after a sufficient time, or after sufficient dosing of the low, immune enhancing, dose of an mTOR inhibitor, such that the level of PD1 negative immune effector cells, e.g., T cells or NK cells, or the ratio of PD1 negative immune effector cells, e.g., T cells or NK cells/ PD1 positive immune effector cells, e.g., T cells or NK cells, in the subject or harvested from the subject has been, at least transiently, increased.

In an embodiment, the invention provides an mTOR inhibitor for use in the treatment of a subject, wherein said mTOR inhibitor enhances an immune response of said subject, and wherein said subject has received, is receiving or is about to receive an immune effector cell that expresses a BCMA CAR as described herein.In one embodiment, the cells expressing a CAR molecule, e.g., a CAR molecule described herein, are administered in combination with an agent that ameliorates one or more side effect associated with administration of a cell expressing a CAR molecule, e.g., an agent described herein.

In one embodiment, the cells expressing a CAR molecule, e.g., a CAR molecule described herein, are administered in combination with an agent that treats the disease associated with BCMA, e.g., an agent described herein.

In certain embodiments, the disease associated with BCMA is a proliferative disease such as a cancer or malignancy or a precancerous condition such as a myelodysplasia, a myelodysplastic syndrome or a preleukemia, or is a non-cancer related indication associated with expression of BCMA.

In certain embodiments, the disease associated with BCMA is a hematologic cancer selected from the group consisting of one or more acute leukemias including but not limited to acute myeloid leukemia (AML); myelodysplastic syndrome; myeloproliferative neoplasms; chronic myeloid leukemia (CML); Blastic plasmacytoid dendritic cell neoplasm; multiple myeloma; and to disease associated with BMCA expression including, but not limited to atypical and/or non-classical cancers, malignancies, precancerous conditions or proliferative diseases expressing BCMA; and combinations thereof. In one embodiment, the disease associated with BCMA is multiple myeloma. In embodiments, a disease associated with expression of BCMA includes a plasma cell proliferative disorder, e.g., asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), monoclonal gammapathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia, plasmacytomas (e.g., plasma cell dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, and POEMS syndrome (also known as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome). In embodiments, a disease associated with expression of BCMA includes a cancer, e.g., a cancer described herein, e.g., a prostate cancer (e.g., castrate-resistant or therapy-resistant prostate cancer, or metastatic prostate cancer), pancreatic cancer, or lung cancer.

In embodiments, a BCMA CAR-expressing cell, e.g., a BCMA CAR-expressing cell described herein, is used to treat a subject having multiple myeloma. In embodiments, a BCMA CAR-expressing cell, e.g., BCMA CAR-expressing cell described herein, is used to treat a subject having a plasma cell proliferative disorder, e.g., asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), monoclonal gammapathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia, plasmacytomas (e.g., plasma cell dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma,

and multiple plasmacytoma), systemic amyloid light chain amyloidosis, and POEMS syndrome (also known as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome). In embodiments, a BCMA CAR-expressing cell, e.g., BCMA CAR-expressing cell described herein, is used to treat a subject having a cancer, e.g., a cancer described herein, e.g., a prostate cancer (e.g., castrate-resistant or therapy-resistant prostate cancer, or metastatic prostate cancer), pancreatic cancer, or lung cancer.

In embodiments, a BCMA CAR-expressing cell, e.g., a BCMA CAR-expressing cell described herein, is administered to the subject according to a dosing regimen comprising a total dose of cells administered to the subject by dose fractionation, e.g., one, two, three or more separate administration of a partial dose. In embodiments, a first percentage of the total dose is administered on a first day of treatment, a second percentage of the total dose is administered on a subsequent (e.g., second, third, fourth, fifth, sixth, or seventh or later) day of treatment, and optionally, a third percentage (e.g., the remaining percentage) of the total dose is administered on a yet subsequent (e.g., third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, or later) day of treatment. For example, 10% of the total dose of cells is delivered on the first day, 30% of the total dose of cells is delivered on the second day, and the remaining 60% of the total dose of cells is delivered on the third day of treatment. For example, a total cell dose includes 1 to 5 x 10^7 or 1 to 5 x 10^8 BCMA-CART cells.

In embodiments, a lympho-depleting therapy (e.g., Cytoxan, e.g., at 1.5 g/m^2) is administered to the subject before CAR-expressing cell administration. In embodiments, no lympho-depleting therapy (e.g., cytoxan) is administered to the subject before CAR-expressing cell administration.

In embodiments, no lympho-depleting chemotherapy is administered, and a total BCMA-CART cell dose of 1 to 5 x 10^7 is administered (e.g., by infusion) with 10% of the cell dose on day 1 of treatment, 30% on day 2 of treatment, and 60% on day 3 of treatment. In another embodiment, no lympho-depleting chemotherapy is administered, and a total BCMA-CART cell dose of 1 to 5 x 10^8 is administered (e.g., by infusion) with 10% of the cell dose on day 1 of treatment, 30% on day 2 of treatment, and 60% on day 3 of treatment. In embodiments, , a lympho-depleting chemotherapy (cytoxan at 1.5 g/m^2) is administered three days before BCMA-CART cell administration, and then a total BCMA-CART cell dose of 1 to 5 x 10^7 is administered (e.g., by infusion) with 10% of the cell dose on day 1 of treatment, 30%

on day 2 of treatment, and 60% on day 3 of treatment. In embodiments, a lympho-depleting chemotherapy (cytoxan at 1.5 g/m^2) is administered three days before BCMA-CART cell administration, and then a total BCMA-CART cell dose of 1 to 5 x 10^8 is administered (e.g., by infusion) with 10% of the cell dose on day 1 of treatment, 30% on day 2 of treatment, and 60% on day 3 of treatment.

In another aspect, the invention pertains to a method of conditioning a subject prior to cell transplantation comprising administering to the subject an effective amount of the cell of comprising a CAR molecule described herein. In one embodiment, the cell transplantation is a stem cell transplantation. The stem cell transplantation is a hematopoietic stem cell stransplantation or a bone marrow transplantation. In one embodiment, the cell transplantation is allogeneic or autologous.

In one embodiment, the conditioning a subject prior to cell transplantation comprises reducing the number of BCMA-expressing cells in a subject. The BCMA-expressing cells in the subject are BCMA-expressing normal cells or BCMA-expressing cancer cells, and in some cases, the condition in the subject will reduce both BCMA-expressing normal and cancer cells prior to a cell transplantation.

In another aspect, the invention pertains to the isolated nucleic acid molecule encoding a CAR of the invention, the isolated polypeptide molecule of a CAR of the invention, the vector comprising a CAR of the invention, and the cell comprising a CAR of the invention for use as a medicament, e.g., as described herein.

In another aspect, the invention pertains to a the isolated nucleic acid molecule encoding a CAR of the invention, the isolated polypeptide molecule of a CAR of the invention, the vector comprising a CAR of the invention, and the cell comprising a CAR of the invention for use in the treatment of a disease expressing BCMA, e.g., a disease expressing BCMA as described herein.

Additional features and embodiments of the aforesaid compositions and methods include one or more of the following:

In certain embodiments, the BCMA CAR molecule (e.g., a BCMA CAR nucleic acid or a BCMA CAR polypeptide as described herein), or the BCMA binding domain as described

herein, includes one, two or three CDRs from the heavy chain variable region (e.g., HC CDR1, HC CDR2 and/or HC CDR3), provided in Table 20; and/or one, two or three CDRs from the light chain variable region (e.g., LC CDR1, LC CDR2 and/or LC CDR3) of BCMA-1, BCMA-2, BCMA-3, BCMA-4, BCMA-5, BCMA-6, BCMA-7, BCMA-8, BCMA-9, BCMA-10, BCMA-11, BCMA-12, BCMA-13, BCMA-14, BCMA-15, 149362, 149363, 149364, 149365, 149366, 149367, 149368, 149369, BCMA_EBB-C1978-A4, BCMA_EBB-C1978-G1, BCMA_EBB-C1979-C1, BCMA_EBB-C1978-C7, BCMA_EBB-C1978-D10, BCMA_EBB-C1979-C12, BCMA_EBB-C1980-G4, BCMA_EBB-C1980-D2, BCMA_EBB-C1978-A10, BCMA_EBB-C1978-D4, BCMA_EBB-C1980-A2, BCMA_EBB-C1981-C3, BCMA_EBB-C1978-G4, A7D12.2, C11D5.3, C12A3.2, C13F12.1, provided in Table 21; or a sequence substantially identical (e.g., 95-99% identical, or up to 5, 4, 3, 2, or 1 amino acid changes, e.g., substitutions (e.g., conservative substitutions)) to any of the aforesaid sequences.

In certain embodiments, the BCMA CAR molecule (e.g., a BCMA CAR nucleic acid or a BCMA CAR polypeptide as described herein), or the anti-BCMA antigen binding domain as described herein, includes one, two or three CDRs from the heavy chain variable region (e.g., HC CDR1, HC CDR2 and/or HC CDR3), provided in Table 22; and/or one, two or three CDRs from the light chain variable region (e.g., LC CDR1, LC CDR2 and/or LC CDR3) of BCMA-1, BCMA-2, BCMA-3, BCMA-4, BCMA-5, BCMA-6, BCMA-7, BCMA-8, BCMA-9, BCMA-10, BCMA-11, BCMA-12, BCMA-13, BCMA-14, BCMA-15, 149362, 149363, 149364, 149365, 149366, 149367, 149368, 149369, BCMA_EBB-C1978-A4, BCMA_EBB-C1978-G1, BCMA_EBB-C1979-C1, BCMA_EBB-C1978-C7, BCMA_EBB-C1978-D10, BCMA_EBB-C1979-C12, BCMA_EBB-C1980-G4, BCMA_EBB-C1980-D2, BCMA_EBB-C1978-A10, BCMA_EBB-C1978-D4, BCMA_EBB-C1980-A2, BCMA_EBB-C1981-C3, BCMA_EBB-C1978-G4, A7D12.2, C11D5.3, C12A3.2, C13F12.1, provided in Table 23; or a sequence substantially identical (e.g., 95-99% identical, or up to 5, 4, 3, 2, or 1 amino acid changes, e.g., substitutions (e.g., conservative substitutions)) to any of the aforesaid sequences.In certain embodiments, the BCMA CAR molecule, or the anti-BCMA antigen binding domain, includes one, two or three CDRs from the heavy chain variable region (e.g., HCDR1, HCDR2 and/or HCDR3), provided in Table 24; and/or one, two or three CDRs from the light chain variable region (e.g., LC CDR1, LC CDR2 and/or LC CDR3) of BCMA-1, BCMA-2, BCMA-3, BCMA-4, BCMA-5, BCMA-6, BCMA-7, BCMA-8, BCMA-9, BCMA-10, BCMA-11, BCMA-12, BCMA-13, BCMA-14, BCMA-15, 149362, 149363, 149364, 149365, 149366,

149367, 149368, 149369, BCMA_EBB-C1978-A4, BCMA_EBB-C1978-G1, BCMA_EBB-C1979-C1, BCMA_EBB-C1978-C7, BCMA_EBB-C1978-D10, BCMA_EBB-C1979-C12, BCMA_EBB-C1980-G4, BCMA_EBB-C1980-D2, BCMA_EBB-C1978-A10, BCMA_EBB-C1978-D4, BCMA_EBB-C1980-A2, BCMA_EBB-C1981-C3, BCMA_EBB-C1978-G4, A7D12.2, C11D5.3, C12A3.2, C13F12.1, provided in Table 25; or a sequence substantially identical (e.g., 95-99% identical, or up to 5, 4, 3, 2, or 1 amino acid changes, e.g., substitutions (e.g., conservative substitutions)) to any of the aforesaid sequences.

In certain embodiments, the BCMA CAR molecule, or the anti-BCMA antigen binding domain, includes

(i) a LC CDR1, LC CDR2 and LC CDR3 of any BCMA light chain binding domain amino acid sequences listed in Table 1 or 16, in SEQ ID NO: 271 or 273, or in the LC CDRs in Table 21, , 23 or 25; and/or.

(ii) a HC CDR1, HC CDR2 and HC CDR3 of any BCMA heavy chain binding domain amino acid sequences listed in Table 1 or 16, in SEQ ID NO: 271 or 273, or in the HC CDRs in Table 20, 22, or 24.

In certain embodiments, the BCMA molecule (e.g., a BCMA CAR nucleic acid or a BCMA CAR polypeptide as described herein), or the anti-BCMA antigen binding domain as described herein, includes:

(1) three light chain (LC) CDRs chosen from one of the following:

(i) a LC CDR1 of SEQ ID NO: 504, LC CDR2 of SEQ ID NO: 544 and LC CDR3 of SEQ ID NO: 584 of BCMA-4 CAR (139103);

(ii) a LC CDR1 of SEQ ID NO: 514, LC CDR2 of SEQ ID NO: 554 and LC CDR3 of SEQ ID NO: 594 of BCMA-10 CAR (139109);

(iii) a LC CDR1 of SEQ ID NO: 516, LC CDR2 of SEQ ID NO: 556 and LC CDR3 of SEQ ID NO: 596 of BCMA-13 CAR (139112); or

(iv) a LC CDR1 of SEQ ID NO: 518, LC CDR2 of SEQ ID NO: 558 and LC CDR3 of SEQ ID NO: 598 of BCMA-15 CAR (139114); and/or

(2) three heavy chain (HC) CDRs chosen from one of the following:

(i) a HC CDR1 of SEQ ID NO: 384, HC CDR2 of SEQ ID NO: 424 and HC CDR3 of SEQ ID NO: 464 of BCMA-4 CAR (139103);

(ii) a HC CDR1 of SEQ ID NO: 394, HC CDR2 of SEQ ID NO: 434 and HC CDR3 of SEQ ID NO: 474 of BCMA-10 CAR (139109);

(iii) a HC CDR1 of SEQ ID NO: 396, HC CDR2 of SEQ ID NO: 436 and HC CDR3 of SEQ ID NO: 476 of BCMA-13 CAR (139112); or

(iv) a HC CDR1 of SEQ ID NO: 398, HC CDR2 of SEQ ID NO: 438 and HC CDR3 of SEQ ID NO: 478 of BCMA-15 (139114).

In certain embodiments, the BCMA CAR molecule (e.g., a BCMA CAR nucleic acid or a BCMA CAR polypeptide as described herein), or the anti-BCMA antigen binding domain as described herein, includes:

(1) three light chain (LC) CDRs chosen from one of the following:

(i) a LC CDR1 of SEQ ID NO: 744, LC CDR2 of SEQ ID NO: 784 and LC CDR3 of SEQ ID NO: 824 of BCMA-4 CAR (139103);

(ii) a LC CDR1 of SEQ ID NO: 754, LC CDR2 of SEQ ID NO: 794 and LC CDR3 of SEQ ID NO: 834 of BCMA-10 CAR (139109);

(iii) a LC CDR1 of SEQ ID NO: 756, LC CDR2 of SEQ ID NO: 796 and LC CDR3 of SEQ ID NO: 836 of BCMA-13 CAR (139112); or

(iv) a LC CDR1 of SEQ ID NO: 758, LC CDR2 of SEQ ID NO: 798 and LC CDR3 of SEQ ID NO: 838 of BCMA-15 CAR (139114); and/or

(2) three heavy chain (HC) CDRs chosen from one of the following:

(i) a HC CDR1 of SEQ ID NO: 624, HC CDR2 of SEQ ID NO: 664 and HC CDR3 of SEQ ID NO: 704 of BCMA-4 CAR (139103);

(ii) a HC CDR1 of SEQ ID NO: 634, HC CDR2 of SEQ ID NO: 674 and HC CDR3 of SEQ ID NO: 714 of BCMA-10 CAR (139109);

(iii) a HC CDR1 of SEQ ID NO: 636, HC CDR2 of SEQ ID NO: 676 and HC CDR3 of SEQ ID NO: 716 of BCMA-13 CAR (139112); or

(iv) a HC CDR1 of SEQ ID NO: 638, HC CDR2 of SEQ ID NO: 678 and HC CDR3 of SEQ ID NO: 718 of BCMA-15 CAR (139114).

In certain embodiments, the BCMA CAR molecule (e.g., a BCMA CAR nucleic acid or a BCMA CAR polypeptide as described herein), or the anti-BCMA antigen binding domain as described herein, includes:

(1) three light chain (LC) CDRs chosen from one of the following:

(i) a LC CDR1 of SEQ ID NO: 984 LC CDR2 of SEQ ID NO: 1024 and LC CDR3 of SEQ ID NO: 1064 of BCMA-4 CAR (139103);

(ii) a LC CDR1 of SEQ ID NO: 994, LC CDR2 of SEQ ID NO: 1034 and LC CDR3 of SEQ ID NO: 1074 of BCMA-10 CAR (139109);

(iii) a LC CDR1 of SEQ ID NO: 996, LC CDR2 of SEQ ID NO: 1036 and LC CDR3 of SEQ ID NO: 1076 of BCMA-13 CAR (139112); or

(iv) a LC CDR1 of SEQ ID NO: 998, LC CDR2 of SEQ ID NO: 1038 and LC CDR3 of SEQ ID NO: 1078 of BCMA-15 CAR (139114); and/or

(2) three heavy chain (HC) CDRs chosen from one of the following:

(i) a HC CDR1 of SEQ ID NO: 864, HC CDR2 of SEQ ID NO: 904 and HC CDR3 of SEQ ID NO: 944 of BCMA-4 CAR (139103);

(ii) a HC CDR1 of SEQ ID NO: 874, HC CDR2 of SEQ ID NO: 914 and HC CDR3 of SEQ ID NO: 954 of BCMA-10 CAR (139109);

(iii) a HC CDR1 of SEQ ID NO: 876, HC CDR2 of SEQ ID NO: 916 and HC CDR3 of SEQ ID NO: 956 of BCMA-13 CAR (139112);

(iv) a HC CDR1 of SEQ ID NO: 878, HC CDR2 of SEQ ID NO: 918 and HC CDR3 of SEQ ID NO: 958 of BCMA-15 CAR (139114).

In certain embodiments, the BCMA CAR molecule (e.g., a BCMA CAR nucleic acid or a BCMA CAR polypeptide as described herein), or the anti-BCMA antigen binding domain as described herein, includes the humanized scFv amino acid sequence of SEQ ID NO: 271 or 273 or a nucleotide sequence encoding scFv (SEQ ID NO: 272 or 274), or an antigen binding domain thereof (e.g., a VH, VL or one or more CDRs thereof).

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned

herein are incorporated by reference in their entirety. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting. Headings, sub-headings or numbered or lettered elements, e.g., (a), (b), (i) etc, are presented merely for ease of reading. The use of headings or numbered or lettered elements in this document does not require the steps or elements be performed in alphabetical order or that the steps or elements are necessarily discrete from one another. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1, comprising Figures 1A and 1B, is two graphical representations of BCMA expression in myeloma samples as determined by quantitative PCR. BCMA expression was determined in different myeloma cell lines (Fig. 1A). BCMA expression was compared between normal plasma cells and myeloma patient samples (Fig. 1B)

Figure 2, comprising Figures 2A, 2B, 2C, 2D, and 2E, is a series of graphical representations of BCMA expression in multiple myeloma cell lines and primary samples by flow cytometry. BCMA was detected on the surface of cell lines U266 (Fig. 2A), H929 (Fig. 2B), and 8226 (Fig. 2C). BCMA was also homogenously expressed on the majority of clonal plasma cells in 9 out of 10 multiple myeloma patients analyzed (Figs. 2D and 2E).

Figure 3, comprising Figures 3A and 3B, is a series of graphical representations demonstrating the lack of BCMA expression in normal peripheral blood cells and after CD3/CD28 expansion (Fig. 3A) and on normal bone marrow cells (Fig. 3B).

Figure 4, comprising Figures 4A, 4B, 4C, 4D, 4E,and 4F, is a series of pictures and a graph showing BCMA expression in normal tissues. Tissues that stained positive for BCMA expression in immunohistochemical analysis were lymph node (Fig. 4A) and tonsil (Fig. 4B). Representative tissues that did not stain for BCMA expression (BCMA negative) included lung (Fig. 4C), pancreas (Fig. 4D), and thyroid (Fig. 4E). RNA in situ hybridization analysis in different tissues was also performed (Fig. 4F).

Figure 5 is a schematic representation of the four CAR constructs containing humanized murine anti-BCMA scFvs, designated pBCMA1, pBCMA2, pBCMA3, and pBCMA4.

Figure 6 is a series of flow cytometry plots showing the transduction efficiency and expression of the BMCA-CAR constructs on T cells. SS1-BBz represents anti-mesothelin CAR, which serves as a negative control.

Figure 7, comprising Figure 7A and Figure 7B, is two graphs demonstrating the antigen-specific cytokine production of BCMA-CARTs, as measured by ELISA assays. IL2 (Fig. 7A) and interferon-gamma (IFNg) (Fig. 7B) production was assessed.

Figure 8, comprising Figure 8A, Figure 8B, Figure 8C, and Figure 8D, is a series of graphs demonstrating the cyotoxic activity BCMA-CARTs on the indicated myeloma cell lines: K562-expressing BCMA (Fig. 8A); 8226 (Fig. 8B); NCI H929 (Fig. 8C); and OPM2 (Fig. 8D).

Figure 9, comprising Figure 9A and Figure 9B, is a graph and a series of pictures showing the anti-tumor activity of the BCMA-CARTs in a preclinical multiple myeloma animal model. Figure 9A shows the quantification of mean bioluminescence representing disease burden in the whole animal (represented by photons /second). Figure 9B shows pictures of the bioluminescence detected in the treated mice at 5, 15, and 20 days after treatment.

Figure 10, comprising Figures 10A and 10B, is a series of schematic representations of tool BCMA CAR constructs containing humanized murine anti-BCMA scFvs.

Figure11 is a series of graphs demonstrating target-specific activation of tool BCMA CAR constructs tranduced in a reporter cell line by luciferase reporter assay.

Figure 12 is a flow cytometry plot showing the distribution of CD4+ and CD8+ populations of T cells after CD3/CD28 expansion prior to transduction with tool BCMA CAR constructs.

Figure 13 is a series of plots showing CART transduction efficiency by detection of the BCMA-Fc antigen 10 days after transduction by flow cytometry analysis and corresponding histograms.

Figure 14 is a series of histogram plots showing proliferation of the tool BCMA CART cells by CFSE staining after stimulation with the indicated target cells (e.g., K562, K562 expressing BCMA, KMS11-luc, MM1-S-luc, NCI-H929, KMs26, RPMI 8226, and CD3/CD28 beads).

Figure 15, comprising Figures 15A and 15B, are two graphs showing the proliferation of the tool BCMA CART cells by cell count (as measured by flow cytometry) for CART-expressing cells (Fig. 15A) and the total number of cells (Fig. 15B), after stimulation with the indicated target cells.

Figure 16 is a graph showing the tool BCMA CART killing in response to BCMA-expressing target cells KMS11-luciferase cells (left) and MM1-S-luciferase cells (right) by luciferase assay.

Figure 17 is a series of graphs showing tool BCMA CART killing in response to BCMA-expressing target cells by CFSE cell killing assay.

Figure 18 is a series of graphs demonstrating target-specific activation of BCMA CARs containing human anti-BCMA scFvs tranduced in a reporter cell line by luciferase reporter assay.

Figure 19 is a flow cytometry plot showing the distribution of CD4+ and CD8+ T cell populations after CD3/CD28 expansion, and before CAR transduction.

Figure 20 is a series of flow cytometry plots and corresponding histogram plots showing the transduction efficiency by assessing CAR expression on the transduced T cells.

Figure 21 is a series of histogram plots showing the cell proliferation of BCMA CART cells in response to stimulation with the indicated target cells (K562, K562 expressing BCMA, RPMI 8226, KM11-luc, and NCI-H929), as measured by CFSE staining.

Figure 22, comprising Figure 22A, Figure 22B, and Figure 22C, is a series of graphs that demonstrate BCMA CART cell proliferation in response to stimulation with the indicated target cells (K562, K562 expressing BCMA, RPMI 8226, KMS11-luc, and NCI-H929), as measured by flow cytometry analysis. Proliferation of the CART cells was independently analyzed for each T cell populations expressing CD3 (Fig. 22A), CD4 (Fig. 22B), and CD8 (Fig. 22C).

Figure 23, comprising Figures 23A, 23B, and 23C, is a series of graphs showing BCMA CART killing in response to BCMA-expressing KMS11-luciferase target cells, by luciferase assay. Killing capacity (percent of target cells killed) of each BCMA CAR construct is compared to BCMA-3NP and BCMA-4NP in each graph in Figure 23A. In Figure 23B, select

BCMA CAR constructs were compared to each other. In Figure 23C, the effector:target ratio was normalized to the CAR-expressing cells. X-axis represents the percent of target cells killed; Y-axis represents effector:target (E:T) ratio.

Figure 24 is a graph showing that treatment with BCMA CARTs results in control of disease progression in the KMS-11-luc human multiple myeloma xenograft in NSG mice. Mean bioluminescence (+/- SEM) of the tumor cells shows the disease burden in the whole animal, as represented in the graph as photons/second (p/s) of the ROI (region of interest, e.g., the whole mouse). Significance calculated by ANOVA versus the vehicle; * denotes P<0.01.

Figure 25, comprising Figures 25A and 25B, is two graphs demonstrating anti-tumor activity of BCMA CAR T cells in the KMS-11 human multiple myeloma model in two independent experiments. Mean bioluminescence (+/- SEM) of the tumor cells shows the disease burden in the whole animal, represented in the graph as photons/second (p/s) (or total flux or BLI) of the whole mouse. Significance calculated by ANOVA versus the vehicle on day 28; * denotes P<0.01 in Figure 25A. In Figure 25B, BCMA-4NP* denotes the BCMA-4NP results from the first experiment (results shown in Figure 25A).

Figure 26, comprising Figures 26A, 26B, 26C, and 26D, is graphs showing the proliferation of BCMA-CART cells by quantification of BCMA-CART cell number in the peripheral blood of KMS-11-luc tumor-bearing mice. Peripheral blood T cells were analyzed on days 1, 3, 7, 10, 14 and weekly thereafter following CAR T cell treatment. From the first tumor experiment (results shown in Figure 25A), the CD4+ CART population was assessed in Figure 26A and the CD8+ CART population was assessed in Figure 26B. From the second tumor experiment (results shown in Figure 25B), the CD4+ CART population was assessed in Figure 26C and the CD8+ CART population was assessed in Figure 26D.

Figure 27, comprising Figures 27A, 27B, 27C, and 27D, is graphs showing the expansion of BCMA CAR-expressing T cells in the bone marrow and spleen at the end of the first tumor experiment (results shown in Figure 25A). The average number of CD4+ BCMA CAR-expressing T cells in the bone marrow (Fig. 27A) and the spleen (Fig. 27B) was calculated. The average number of CD4=8+ BCMA CAR-expressing T cells in the bone marrow (Fig. 27C) and the spleen (Fig. 27D) was calculated. J6MO sample represents CAR T cells expressing the BCMA-4NP CAR construct.

Figure 28, comprising Figures 28A and 28B, is graphs showing the lentiviral titer for select BCMA CAR constructs in two independent lentiviral experiments. In the first test run, two different DNA preps of the BCMA CAR constructs were tested (A and B) (Fig. 28A). In the second test run, three different DNA preps of the BCMA CAR constructs were tested (A, B, and C) (Fig. 28B).

Figure 29 is a graph showing the competition assay between BCMA-4NP and select BCMA CAR constructs, BCMA-4 (B4), BCMA-10 (B10), BCMA-13 (B13) and BCMA-15 (B15).

Figure 30, comprising Figures 30A, 30B, 30C, 30D, and 30E, is graphs showing the results of affinity assays for select BCMA constructs: BMCA-10 (Fig. 30A); BCMA-13 (Fig. 30B), BCMA-15 (Fig. 30C), BCMA-4 (Fig. 30D), and BCMA-4NP (Fig. 30E).

Figure 31 is a graph showing the selective binding of select BCMA CAR-expressing T cells for recombinant BCMA. Recombinant forms of BCMA and closely related family members BAFFR and TACI comprising the proteins fused to Fc domains were incubated with T cells expressing BCMA-4, BCMA-10, BCMA-13, and BCMA-15. The percentage of cells that bound to the recombinant proteins (% positive cells) was detected.

Figure 32, comprising Figures 32A, 32B, 32C, 32D, 32E, and 32F, is a series of images depicting the immunohistochemical staining of BCMA in brain tissue. BCMA-staining in climbing fibers of the cerebellum of cynomolgus macaque (Fig. 32A). BCMA-staining in the neuronal cell bodies in the inferior olivary nucleus of cynomolgus macaque (Fig. 32B). BCMA-staining (Fig. 32C) and Ig staining (control) (Fig. 32E) in cynomolgus macaque medulla oblongata. BCMA-staining (Fig. 32D) and Ig staining (control) (Fig. 32F) in human medulla oblongata.

Figure 33, comprising Figures 33A, 33B, 33C, 33D, and 33E, is a series of images and a graph that depicts RNA analysis of BCMA expression in brain tissue. BCMA, DAPB, and PPIB RNA in situ hybridization of non-human primate cerebellum (Fig. 33A). BCMA, DAPB, and PPIB RNA in situ hybridization of non-human primate medulla oblongata (Fig. 33B). Quantitative PCR analysis of BCMA in cerebellum, medulla oblongata, stomach, and kidney in human (Fig. 33C). Quantitative PCR analysis of BCMA in white matter, grey matter, medulla

oblongata, stomach, and kidney in cynomolgus macaque (Fig. 33D). RNAseq analysis of normal tissue in human (Fig. 33E); the box indicates BCMA-expression in cerebellum.

Figure 34 is a schematic diagram showing the timeline of the study to assess the safety and feasibility of BCMA CART cell therapy in relapsed and/or refractory myeloma.

Figures 35A and 35B are graphs showing the concentration of cytokines secreted by BCMA-10 CARTs when co-cultured with target cells. Figure 35A is a graph showing the concentration of interleukin-2 (IL-2) and interferon-gamma (IFNγ) secreted by BCMA-10 CARTs. Figure 35B is a graph showing the concentration of tumor necrosis factor-alpha (TNF-α) secreted by BCMA-10 CARTs.

Figures 36A and 36B are graphs/plots showing the growth curve and efficiency of huBCMA-BBz lentiviral transduction of T cells. Figure 36A is a graph showing the number of T cell transduced with huBCMA-BBz vector on several days after expansion. Figure 36B is a panel of flow cytometry plots showing the expression on day 6 of ex vivo expansion of BCMA on CART-BCMA cells (T cells transduced with huBCMA-BBz vector) compared to non-transduced NTD cells.

Figure 37 is a panel of flow cytometry histograms showing the BCMA surface expression on various cell lines, including K562- BCMA cells and multiple myeloma cell lines NCI H929, U266, RPMI 8226, OPM2 and MM1S. For all plots, the orange solid peak represents isotype control and the blue solid peak staining with BCMA antibody.

Figures 38A and 38B are graphs showing the concentration of cytokines produced by CART-BCMA cells in response to myeloma cell lines. Figure 38A shows the concentration of IL-2 produced, and Figure 38B shows the concentration of IFN-γ produced. Values represent cytokine concentration in pg/mL.

Figures 39A, 39B, and 39C are graphs showing the antigen-specific killing of $BCMA^+$ multiple myeloma cell lines by CART-BCMA cells. Figure 39A shows the antigen-specific killing of K562-BCMA cells, Figure 39B shows the antigen specific killing of RPMI 8226 cells, and Figure 39C shows the antigen specific killing of MM1S cells.

Figures 40A, 40B, and 40C are graphs showing that CART-BCMA cells displayed effective anti-myeloma activity *in vivo*. Figure 40A is a graph showing total radiance in non-transduced mice, and Figure 40B is a graph showing total radiance in CART-BCMA mice.

Figure 40C is a graph showing percent survival of NTD or CART-BCMA mice after T cell injection. Dorsal photon emission from RPMI 8226 CBG+ tumors are shown with individual animals depicted in grey and median total radiance shown in red. n=10 for each group. Time is shown in weeks following T cell injection.

Figure 41A-41D show the various configurations on a single vector, e.g., where the U6 regulated shRNA is upstream or downstream of the EF1 alpha regulated CAR encoding elements. In the exemplary constructs depicted in Fig. 41A and 41B, the transcription occurs through the U6 and EF1 alpha promoters in the same direction. In the exemplary constructs depicted in Fig. 41C and 41D, the transcription occurs through the U6 and EF1 alpha promoters in different directions. In Figure 41E, the shRNA (and corresponding U6 promoter) is on a first vector, and the CAR (and corresponding EF1 alpha promoter) is on a second vector.

Figure 42 depicts the structures of two exemplary RCAR configurations. The antigen binding members comprise an antigen binding domain, a transmembrane domain, and a switch domain. The intracellular binding members comprise a switch domain, a co-stimulatory signaling domain and a primary signaling domain. The two configurations demonstrate that the first and second switch domains described herein can be in different orientations with respect to the antigen binding member and the intracellular binding member. Other RCAR configurations are further described herein.

Figure 43 shows that the proliferation of CAR-expressing, transduced T cells is enhanced by low doses of RAD001 in a cell culture system. CARTs were co-cultured with Nalm-6 cells in the presence of different concentrations of RAD001. The number of CAR-positive CD3-positive T cells (black) and total T cells (gray) was assessed after 4 days of co-culture.

Figure 44 depicts tumor growth measurements of NALM6-luc cells with daily RAD001 dosing at 0.3, 1, 3, and 10 mg/kg (mpk) or vehicle dosing. Circles denote the vehicle; squares denote the 10 mg/kg dose of RAD001; triangles denote the 3 mg/kg dose of RAD001, inverted triangles denote the 1 mg/kg dose of RAD001; and diamonds denote the 0.3 mg/kg dose of RAD001.

Figures 45A and 45B show pharmacokinetic curves showing the amount of RAD001 in the blood of NSG mice with NALM6 tumors. FIG. 45A shows day 0 PK following the first

dose of RAD001. FIG. 45B shows Day 14 PK following the final RAD001 dose. Diamonds denote the 10 mg/kg dose of RAD001; squares denote the 1 mg/kg dose of RAD001; triangles denote the 3 mg/kg dose of RAD001; and x's denote the 10 mg/kg dose of RAD001.

Figures 46A and 46B show *in vivo* proliferation of humanized CD19 CART cells with and without RAD001 dosing. Low doses of RAD001 (0.003 mg/kg) daily lead to an enhancement in CAR T cell proliferation, above the normal level of huCAR19 proliferation. Figures 46A shows $CD4^+$ CAR T cells; FIG. 46B shows $CD8^+$ CAR T cells. Circles denote PBS; squares denote huCTL019; triangles denote huCTL019 with 3 mg/kg RAD001; inverted triangles denote huCTL019 with 0.3 mg/kg RAD001; diamonds denote huCTL019 with 0.03 mg/kg RAD001; and circles denote huCTL019 with 0.003 mg/kg RAD001.

FIG. 47 depicts CD19 expression in a patient's tumor cells. $CD138^+$ $CD45^{dim}$ tumor cells were stained for CD19 (x-axis) and CD38 (y-axis). Approximately 1-2% of the tumor cells expressed the CD19 antigen.

DETAILED DESCRIPTION

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains.

The term "a" and "an" refers to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

The term "about" when referring to a measurable value such as an amount, a temporal duration, and the like, is meant to encompass variations of ±20% or in some instances ±10%, or in some instances ±5%, or in some instances ±1%, or in some instances ±0.1% from the specified value, as such variations are appropriate to perform the disclosed methods.

The term "Chimeric Antigen Receptor" or alternatively a "CAR" refers to a recombinant polypeptide construct comprising at least an extracellular antigen binding domain,

a transmembrane domain and a cytoplasmic signaling domain (also referred to herein as "an intracellular signaling domain") comprising a functional signaling domain derived from a stimulatory molecule as defined below. In some embodiments, the domains in the CAR polypeptide construct are in the same polypeptide chain, e.g., comprise a chimeric fusion protein. In some embodiments, the domains in the CAR polypeptide construct are not contiguous with each other, e.g., are in different polypeptide chains, e.g., as provided in an RCAR as described herein.

In one aspect, the stimulatory molecule of the CAR is the zeta chain associated with the T cell receptor complex. In one aspect, the cytoplasmic signaling domain comprises a primary signaling domain (e.g., a primary signaling domain of CD3-zeta). In one aspect, the cytoplasmic signaling domain further comprises one or more functional signaling domains derived from at least one costimulatory molecule as defined below. In one aspect, the costimulatory molecule is chosen from 4-1BB (i.e., CD137), CD27, ICOS, and/or CD28. In one aspect, the CAR comprises a chimeric fusion protein comprising an extracellular antigen recognition domain, a transmembrane domain and an intracellular signaling domain comprising a functional signaling domain derived from a stimulatory molecule. In one aspect, the CAR comprises a chimeric fusion protein comprising an extracellular antigen recognition domain, a transmembrane domain and an intracellular signaling domain comprising a functional signaling domain derived from a co-stimulatory molecule and a functional signaling domain derived from a stimulatory molecule. In one aspect, the CAR comprises a chimeric fusion protein comprising an extracellular antigen recognition domain, a transmembrane domain and an intracellular signaling domain comprising two functional signaling domains derived from one or more co-stimulatory molecule(s) and a functional signaling domain derived from a stimulatory molecule. In one aspect, the CAR comprises a chimeric fusion protein comprising an extracellular antigen recognition domain, a transmembrane domain and an intracellular signaling domain comprising at least two functional signaling domains derived from one or more co-stimulatory molecule(s) and a functional signaling domain derived from a stimulatory molecule. In one aspect the CAR comprises an optional leader sequence at the amino-terminus (N-ter) of the CAR fusion protein. In one aspect, the CAR further comprises a leader sequence at the N-terminus of the extracellular antigen recognition domain, wherein the leader sequence is optionally cleaved from the antigen recognition domain (e.g., aa scFv) during cellular processing and localization of the CAR to the cellular membrane.

A CAR that comprises an antigen binding domain (e.g., a scFv, a single domain antibody, or TCR (e.g., a TCR alpha binding domain or TCR beta binding domain)) that targets a specific tumor marker X, wherein X can be a tumor marker as described herein, is also referred to as XCAR. For example, a CAR that comprises an antigen binding domain that targets BCMA is referred to as BCMACAR. The CAR can be expressed in any cell, e.g., an immune effector cell as described herein (e.g., a T cell or an NK cell).

The term "signaling domain" refers to the functional portion of a protein which acts by transmitting information within the cell to regulate cellular activity via defined signaling pathways by generating second messengers or functioning as effectors by responding to such messengers.

As used herein, the term "BCMA" refers to B-cell maturation antigen. BCMA (also known as TNFRSF17, BCM or CD269) is a member of the tumor necrosis receptor (TNFR) family and is predominantly expressed on terminally differentiated B cells, e.g., memory B cells, and plasma cells. Its ligand is called B-cell activator of the TNF family (BAFF) and a proliferation inducing ligand (APRIL). BCMA is involved in mediating the survival of plasma cells for mataining long-term humoral immunity. The gene for BCMA is encoded on chromosome 16 producing a primary mRNA transcript of 994 nucleotides in length (NCBI accession NM_001192.2) that encodes a protein of 184 amino acids (NP_001183.2). A second antisense transcript derived from the BCMA locus has been described, which may play a role in regulating BCMA expression. (Laabi Y. et al., Nucleic Acids Res., 1994, 22:1147-1154). Additional transcript variants have been described with unknown significance (Smirnova AS et al. Mol Immunol., 2008, 45(4):1179-1183. A second isoform, also known as TV4, has been identified (Uniprot identifier Q02223-2). As used herein, "BCMA" includes proteins comprising mutations, e.g., point mutations, fragments, insertions, deletions and splice variants of full length wild-type BCMA.

The term "antibody," as used herein, refers to a protein, or polypeptide sequence derived from an immunoglobulin molecule, which specifically binds with an antigen. Antibodies can be polyclonal or monoclonal, multiple or single chain, or intact immunoglobulins, and may be derived from natural sources or from recombinant sources. Antibodies can be tetramers of immunoglobulin molecules.

The term "antibody fragment" refers to at least one portion of an intact antibody, or recombinant variants thereof, and refers to the antigen binding domain, e.g., an antigenic determining variable region of an intact antibody, that is sufficient to confer recognition and specific binding of the antibody fragment to a target, such as an antigen. Examples of antibody fragments include, but are not limited to, Fab, Fab', $F(ab')_2$, and Fv fragments, scFv antibody fragments, linear antibodies, single domain antibodies such as sdAb (either VL or VH), camelid VHH domains, and multi-specific molecules formed from antibody fragments such as a bivalent fragment comprising two or more, e.g., two, Fab fragments linked by a disulfide brudge at the hinge region, or two or more, e.g., two isolated CDR or other epitope binding fragments of an antibody linked. An antibody fragment can also be incorporated into single domain antibodies, maxibodies, minibodies, nanobodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR and bis-scFv (see, e.g., Hollinger and Hudson, Nature Biotechnology 23:1126-1136, 2005). Antibody fragments can also be grafted into scaffolds based on polypeptides such as a fibronectin type III (Fn3)(see U.S. Patent No.: 6,703,199, which describes fibronectin polypeptide minibodies).

The term "scFv" refers to a fusion protein comprising at least one antibody fragment comprising a variable region of a light chain and at least one antibody fragment comprising a variable region of a heavy chain, wherein the light and heavy chain variable regions are contiguously linked via a short flexible polypeptide linker, and capable of being expressed as a single chain polypeptide, and wherein the scFv retains the specificity of the intact antibody from which it is derived. Unless specified, as used herein an scFv may have the VL and VH variable regions in either order, e.g., with respect to the N-terminal and C-terminal ends of the polypeptide, the scFv may comprise VL-linker-VH or may comprise VH-linker-VL.

The terms "complementarity determining region" or "CDR," as used herein, refer to the sequences of amino acids within antibody variable regions which confer antigen specificity and binding affinity. For example, in general, there are three CDRs in each heavy chain variable region (e.g., HCDR1, HCDR2, and HCDR3) and three CDRs in each light chain variable region (LCDR1, LCDR2, and LCDR3). The precise amino acid sequence boundaries of a given CDR can be determined using any of a number of well-known schemes, including those described by Kabat et al. (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD ("Kabat" numbering scheme), Al-Lazikani et al., (1997) JMB 273,927-948 ("Chothia" numbering scheme), or a

combination thereof. Under the Kabat numbering scheme, in some embodiments, the CDR amino acid residues in the heavy chain variable domain (VH) are numbered 31-35 (HCDR1), 50-65 (HCDR2), and 95-102 (HCDR3); and the CDR amino acid residues in the light chain variable domain (VL) are numbered 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3). Under the Chothia numbering scheme, in some embodiments, the CDR amino acids in the VH are numbered 26-32 (HCDR1), 52-56 (HCDR2), and 95-102 (HCDR3); and the CDR amino acid residues in the VL are numbered 26-32 (LCDR1), 50-52 (LCDR2), and 91-96 (LCDR3). In a combined Kabat and Chothia numbering scheme, in some embodiments, the CDRs correspond to the amino acid residues that are part of a Kabat CDR, a Chothia CDR, or both. For instance, in some embodiments, the CDRs correspond to amino acid residues 26-35 (HCDR1), 50-65 (HCDR2), and 95-102 (HCDR3) in a VH, e.g., a mammalian VH, e.g., a human VH; and amino acid residues 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3) in a VL, e.g., a mammalian VL, e.g., a human VL.

The portion of the CAR composition of the invention comprising an antibody or antibody fragment thereof may exist in a variety of forms, for example, where the antigen binding domain is expressed as part of a polypeptide chain including, for example, a single domain antibody fragment (sdAb), a single chain antibody (scFv), or e.g., a humanized antibody (Harlow et al., 1999, In: Using Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press, NY; Harlow et al., 1989, In: Antibodies: A Laboratory Manual, Cold Spring Harbor, New York; Houston et al., 1988, Proc. Natl. Acad. Sci. USA 85:5879-5883; Bird et al., 1988, Science 242:423-426). In one aspect, the antigen binding domain of a CAR composition of the invention comprises an antibody fragment. In a further aspect, the CAR comprises an antibody fragment that comprises a scFv.

As used herein, the term “binding domain” or "antibody molecule" (also referred to herein as “anti-target (e.g., BCMA) binding domain”) refers to a protein, e.g., an immunoglobulin chain or fragment thereof, comprising at least one immunoglobulin variable domain sequence. The term “binding domain” or “antibody molecule” encompasses antibodies and antibody fragments. In an embodiment, an antibody molecule is a multispecific antibody molecule, e.g., it comprises a plurality of immunoglobulin variable domain sequences, wherein a first immunoglobulin variable domain sequence of the plurality has binding specificity for a

first epitope and a second immunoglobulin variable domain sequence of the plurality has binding specificity for a second epitope. In an embodiment, a multispecific antibody molecule is a bispecific antibody molecule. A bispecific antibody has specificity for no more than two antigens. A bispecific antibody molecule is characterized by a first immunoglobulin variable domain sequence which has binding specificity for a first epitope and a second immunoglobulin variable domain sequence that has binding specificity for a second epitope. The term "antibody heavy chain," refers to the larger of the two types of polypeptide chains present in antibody molecules in their naturally occurring conformations, and which normally determines the class to which the antibody belongs.

The term "antibody light chain," refers to the smaller of the two types of polypeptide chains present in antibody molecules in their naturally occurring conformations. Kappa (κ) and lambda (λ) light chains refer to the two major antibody light chain isotypes.

The term "recombinant antibody" refers to an antibody which is generated using recombinant DNA technology, such as, for example, an antibody expressed by a bacteriophage or yeast expression system. The term should also be construed to mean an antibody which has been generated by the synthesis of a DNA molecule encoding the antibody and which DNA molecule expresses an antibody protein, or an amino acid sequence specifying the antibody, wherein the DNA or amino acid sequence has been obtained using recombinant DNA or amino acid sequence technology which is available and well known in the art.

The term "antigen" or "Ag" refers to a molecule that provokes an immune response. This immune response may involve either antibody production, or the activation of specific immunologically-competent cells, or both. The skilled artisan will understand that any macromolecule, including virtually all proteins or peptides, can serve as an antigen. Furthermore, antigens can be derived from recombinant or genomic DNA. A skilled artisan will understand that any DNA, which comprises a nucleotide sequences or a partial nucleotide sequence encoding a protein that elicits an immune response therefore encodes an "antigen" as that term is used herein. Furthermore, one skilled in the art will understand that an antigen need not be encoded solely by a full length nucleotide sequence of a gene. It is readily apparent that the present invention includes, but is not limited to, the use of partial nucleotide sequences of more than one gene and that these nucleotide sequences are arranged in various combinations to encode polypeptides that elicit the desired immune response. Moreover, a skilled artisan will

understand that an antigen need not be encoded by a "gene" at all. It is readily apparent that an antigen can be generated synthesized or can be derived from a biological sample, or might be macromolecule besides a polypeptide. Such a biological sample can include, but is not limited to a tissue sample, a tumor sample, a cell or a fluid with other biological components.

The term "anti-tumor effect" refers to a biological effect which can be manifested by various means, including but not limited to, e.g., a decrease in tumor volume, a decrease in the number of tumor cells, a decrease in the number of metastases, an increase in life expectancy, decrease in tumor cell proliferation, decrease in tumor cell survival, or amelioration of various physiological symptoms associated with the cancerous condition. An "anti-tumor effect" can also be manifested by the ability of the peptides, polynucleotides, cells and antibodies of the invention in prevention of the occurrence of tumor in the first place.

The term "anti-cancer effect" refers to a biological effect which can be manifested by various means, including but not limited to, e.g., a decrease in tumor volume, a decrease in the number of cancer cells, a decrease in the number of metastases, an increase in life expectancy, decrease in cancer cell proliferation, decrease in cancer cell survival, or amelioration of various physiological symptoms associated with the cancerous condition. An "anti-cancer effect" can also be manifested by the ability of the peptides, polynucleotides, cells and antibodies in prevention of the occurrence of cancer in the first place. The term "anti-tumor effect" refers to a biological effect which can be manifested by various means, including but not limited to, e.g., a decrease in tumor volume, a decrease in the number of tumor cells, a decrease in tumor cell proliferation, or a decrease in tumor cell survival.The term "autologous" refers to any material derived from the same individual to whom it is later to be re-introduced into the individual.

The term "allogeneic" refers to any material derived from a different animal of the same species as the individual to whom the material is introduced. Two or more individuals are said to be allogeneic to one another when the genes at one or more loci are not identical. In some aspects, allogeneic material from individuals of the same species may be sufficiently unlike genetically to interact antigenically

The term "xenogeneic" refers to a graft derived from an animal of a different species.

The term "apheresis" as used herein refers to the art-recognized extracorporeal process by which the blood of a donor or patient is removed from the donor or patient and

passed through an apparatus that separates out selected particular constituent(s) and returns the remainder to the circulation of the donor or patient, e.g., by retransfusion. Thus, in the context of "an apheresis sample" refers to a sample obtained using apheresis.

The term "combination" refers to either a fixed combination in one dosage unit form, or a combined administration where a compound of the present invention and a combination partner (e.g. another drug as explained below, also referred to as "therapeutic agent" or "co-agent") may be administered independently at the same time or separately within time intervals, especially where these time intervals allow that the combination partners show a cooperative, e.g. synergistic effect. The single components may be packaged in a kit or separately. One or both of the components (e.g., powders or liquids) may be reconstituted or diluted to a desired dose prior to administration. The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected combination partner to a single subject in need thereof (e.g. a patient), and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time. The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of the present invention and a combination partner, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of the present invention and a combination partner, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

The term "cancer" refers to a disease characterized by the rapid and uncontrolled growth of aberrant cells. Cancer cells can spread locally or through the bloodstream and lymphatic system to other parts of the body. Examples of various cancers are described herein and include but are not limited to, breast cancer, prostate cancer, ovarian cancer, cervical cancer, skin cancer, pancreatic cancer, colorectal cancer, renal cancer, liver cancer, brain cancer, lymphoma, leukemia, lung cancer and the like. Preferred cancers treated by the

methods described herein include multiple myeloma, Hodgkin's lymphoma or non-Hodgkin's lymphoma.

The terms "tumor" and "cancer" are used interchangeably herein, e.g., both terms encompass solid and liquid, e.g., diffuse or circulating, tumors. As used herein, the term "cancer" or "tumor" includes premalignant, as well as malignant cancers and tumors.

"Derived from" as that term is used herein, indicates a relationship between a first and a second molecule. It generally refers to structural similarity between the first molecule and a second molecule and does not connotate or include a process or source limitation on a first molecule that is derived from a second molecule. For example, in the case of an intracellular signaling domain that is derived from a CD3zeta molecule, the intracellular signaling domain retains sufficient CD3zeta structure such that is has the required function, namely, the ability to generate a signal under the appropriate conditions. It does not connotate or include a limitation to a particular process of producing the intracellular signaling domain, e.g., it does not mean that, to provide the intracellular signaling domain, one must start with a CD3zeta sequence and delete unwanted sequence, or impose mutations, to arrive at the intracellular signaling domain.

The phrase "disease associated with expression of BCMA" includes, but is not limited to, a disease associated with a cell which expresses BCMA (e.g., wild-type or mutant BCMA) or condition associated with a cell which expresses BCMA (e.g., wild-type or mutant BCMA) including, e.g., proliferative diseases such as a cancer or malignancy or a precancerous condition such as a myelodysplasia, a myelodysplastic syndrome or a preleukemia; or a noncancer related indication associated with a cell which expresses BCMA (e.g., wild-type or mutant BCMA). For the avoidance of doubt, a disease associated with expression of BCMA may include a condition associated with a cell which does not presently express BCMA, e.g., because BCMA expression has been downregulated, e.g., due to treatment with a molecule targeting BCMA, e.g., a BCMA inhibitor described herein, but which at one time expressed BCMA. In one aspect, a cancer associated with expression of BCMA (e.g., wild-type or mutant BCMA) is a hematological cancer. In one aspect, the hematogical cancer is a leukemia or a lymphoma. In one aspect, a cancer associated with expression of BCMA (e.g., wild-type or mutant BCMA) is a malignancy of differentiated plasma B cells. In one aspect, a cancer associated with expression of BCMA(e.g., wild-type or mutant BCMA) includes cancers and

malignancies including, but not limited to, e.g., one or more acute leukemias including but not limited to, e.g., B-cell acute Lymphoid Leukemia ("BALL"), T-cell acute Lymphoid Leukemia ("TALL"), acute lymphoid leukemia (ALL); one or more chronic leukemias including but not limited to, e.g., chronic myelogenous leukemia (CML), Chronic Lymphoid Leukemia (CLL). Additional cancers or hematologic conditions associated with expression of BMCA (e.g., wild-type or mutant BCMA) comprise, but are not limited to, e.g., B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, Follicular lymphoma, Hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, and "preleukemia" which are a diverse collection of hematological conditions united by ineffective production (or dysplasia) of myeloid blood cells, and the like. In some embodiments, the cancer is multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, or glioblastoma. In embodiments, a disease associated with expression of BCMA includes a plasma cell proliferative disorder, e.g., asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), monoclonal gammapathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia, plasmacytomas (e.g., plasma cell dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, and POEMS syndrome (also known as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome). Further diseases associated with expression of BCMA (e.g., wild-type or mutant BCMA) expression include, but not limited to, e.g., atypical and/or non-classical cancers, malignancies, precancerous conditions or proliferative diseases associated with expression of BCMA (e.g., wild-type or mutant BCMA), e.g., a cancer described herein, e.g., a prostate cancer (e.g., castrate-resistant or therapy-resistant prostate cancer, or metastatic prostate cancer), pancreatic cancer, or lung cancer.

Non-cancer related conditions that are associated with BCMA (e.g., wild-type or mutant BCMA) include viral infections; e.g., HIV, fungal invections, e.g., *C. neoformans*; autoimmune disease; e.g. rheumatoid arthritis, system lupus erythematosus (SLE or lupus), pemphigus vulgaris, and Sjogren's syndrome; inflammatory bowel disease, ulcerative colitis; transplant-

related allospecific immunity disorders related to mucosal immunity; and unwanted immune responses towards biologics (e.g., Factor VIII) where humoral immunity is important. In embodiments, a non-cancer related indication associated with expression of BCMA includes but is not limited to, e.g., autoimmune disease, (e.g., lupus), inflammatory disorders (allergy and asthma) and transplantation. In some embodiments, the tumor antigen-expressing cell expresses, or at any time expressed, mRNA encoding the tumor antigen. In an embodiment, the tumor antigen -expressing cell produces the tumor antigen protein (e.g., wild-type or mutant), and the tumor antigen protein may be present at normal levels or reduced levels. In an embodiment, the tumor antigen -expressing cell produced detectable levels of a tumor antigen protein at one point, and subsequently produced substantially no detectable tumor antigen protein.

The term "conservative sequence modifications" refers to amino acid modifications that do not significantly affect or alter the binding characteristics of the antibody or antibody fragment containing the amino acid sequence. Such conservative modifications include amino acid substitutions, additions and deletions. Modifications can be introduced into an antibody or antibody fragment of the invention by standard techniques known in the art, such as site-directed mutagenesis and PCR-mediated mutagenesis. Conservative substitutions are ones in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, one or more amino acid residues within a CAR of the invention can be replaced with other amino acid residues from the same side chain family and the altered CAR can be tested using the functional assays described herein.

The term "stimulation," refers to a primary response induced by binding of a stimulatory molecule (e.g., a TCR/CD3 complex) with its cognate ligand thereby mediating a signal transduction event, such as, but not limited to, signal transduction via the TCR/CD3

complex. Stimulation can mediate altered expression of certain molecules, such as downregulation of TGF-β, and/or reorganization of cytoskeletal structures, and the like.

The term "stimulatory molecule," refers to a molecule expressed by a T cell that provides the primary cytoplasmic signaling sequence(s) that regulate primary activation of the TCR complex in a stimulatory way for at least some aspect of the T cell signaling pathway. In some embodiments, the ITAM-containing domain within the CAR recapitulates the signaling of the primary TCR independently of endogenous TCR complexes. In one aspect, the primary signal is initiated by, for instance, binding of a TCR/CD3 complex with an MHC molecule loaded with peptide, and which leads to mediation of a T cell response, including, but not limited to, proliferation, activation, differentiation, and the like. A primary cytoplasmic signaling sequence (also referred to as a "primary signaling domain") that acts in a stimulatory manner may contain a signaling motif which is known as immunoreceptor tyrosine-based activation motif or ITAM. Examples of an ITAM containing primary cytoplasmic signaling sequence that is of particular use in the invention includes, but is not limited to, those derived from TCR zeta, FcR gamma, FcR beta, CD3 gamma, CD3 delta , CD3 epsilon, CD5, CD22, CD79a, CD79b, CD278 (also known as "ICOS") , FcεRI and CD66d, DAP10 and DAP12. In a specific CAR of the invention, the intracellular signaling domain in any one or more CARS of the invention comprises an intracellular signaling sequence, e.g., a primary signaling sequence of CD3-zeta. In a specific CAR of the invention, the primary signaling sequence of CD3-zeta is the sequence provided as SEQ ID NO:9, or the equivalent residues from a non-human species, e.g., mouse, rodent, monkey, ape and the like. In a specific CAR of the invention, the primary signaling sequence of CD3-zeta is the sequence as provided in SEQ ID NO:10, or the equivalent residues from a non-human species, e.g., mouse, rodent, monkey, ape and the like. The term "antigen presenting cell" or "APC" refers to an immune system cell such as an accessory cell (e.g., a B-cell, a dendritic cell, and the like) that displays a foreign antigen complexed with major histocompatibility complexes (MHC's) on its surface. T-cells may recognize these complexes using their T-cell receptors (TCRs). APCs process antigens and present them to T-cells.

An "intracellular signaling domain," as the term is used herein, refers to an intracellular portion of a molecule. In embodiments, the intracellular signal domain transduces the effector function signal and directs the cell to perform a specialized function. While the entire

intracellular signaling domain can be employed, in many cases it is not necessary to use the entire chain. To the extent that a truncated portion of the intracellular signaling domain is used, such truncated portion may be used in place of the intact chain as long as it transduces the effector function signal. The term intracellular signaling domain is thus meant to include any truncated portion of the intracellular signaling domain sufficient to transduce the effector function signal.

The intracellular signaling domain generates a signal that promotes an immune effector function of the CAR containing cell, e.g., a CART cell. Examples of immune effector function, e.g., in a CART cell, include cytolytic activity and helper activity, including the secretion of cytokines.

In an embodiment, the intracellular signaling domain can comprise a primary intracellular signaling domain. Exemplary primary intracellular signaling domains include those derived from the molecules responsible for primary stimulation, or antigen dependent simulation. In an embodiment, the intracellular signaling domain can comprise a costimulatory intracellular domain. Exemplary costimulatory intracellular signaling domains include those derived from molecules responsible for costimulatory signals, or antigen independent stimulation. For example, in the case of a CART, a primary intracellular signaling domain can comprise a cytoplasmic sequence of a T cell receptor, and a costimulatory intracellular signaling domain can comprise cytoplasmic sequence from co-receptor or costimulatory molecule.

A primary intracellular signaling domain can comprise a signaling motif which is known as an immunoreceptor tyrosine-based activation motif or ITAM. Examples of ITAM containing primary cytoplasmic signaling sequences include, but are not limited to, those derived from CD3 zeta, FcR gamma, FcR beta, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, CD278 (also known as "ICOS"), FcεRI, CD66d, DAP10 and DAP12.

The term "zeta" or alternatively "zeta chain", "CD3-zeta" or "TCR-zeta" is defined as the protein provided as GenBan Acc. No. BAG36664.1, or the equivalent residues from a non-human species, e.g., mouse, rodent, monkey, ape and the like, and a "zeta stimulatory domain" or alternatively a "CD3-zeta stimulatory domain" or a "TCR-zeta stimulatory domain" is defined as the amino acid residues from the cytoplasmic domain of the zeta chain that are sufficient to functionally transmit an initial signal necessary for T cell activation. In one aspect

the cytoplasmic domain of zeta comprises residues 52 through 164 of GenBank Acc. No. BAG36664.1 or the equivalent residues from a non-human species, e.g., mouse, rodent, monkey, ape and the like, that are functional orthologs thereof. In one aspect, the "zeta stimulatory domain" or a "CD3-zeta stimulatory domain" is the sequence provided as SEQ ID NO:9. In one aspect, the "zeta stimulatory domain" or a "CD3-zeta stimulatory domain" is the sequence provided as SEQ ID NO:10.

The term "costimulatory molecule" refers to the cognate binding partner on a T cell that specifically binds with a costimulatory ligand, thereby mediating a costimulatory response by the T cell, such as, but not limited to, proliferation. Costimulatory molecules are cell surface molecules other than antigen receptors or their ligands that are required for an efficient immune response. Costimulatory molecules include, but are not limited to an MHC class I molecule, TNF receptor proteins, Immunoglobulin-like proteins, cytokine receptors, integrins, signaling lymphocytic activation molecules (SLAM proteins), activating NK cell receptors, BTLA, Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, and a ligand that specifically binds with CD83.

A costimulatory intracellular signaling domain refers to the intracellular portion of a costimulatory molecule.

The intracellular signaling domain can comprise the entire intracellular portion, or the entire native intracellular signaling domain, of the molecule from which it is derived, or a functional fragment thereof.

The term "4-1BB" refers to a member of the TNFR superfamily with an amino acid sequence provided as GenBank Acc. No. AAA62478.2, or the equivalent residues from a non-

human species, e.g., mouse, rodent, monkey, ape and the like; and a "4-1BB costimulatory domain" is defined as amino acid residues 214-255 of GenBank Acc. No. AAA62478.2, or the equivalent residues from a non-human species, e.g., mouse, rodent, monkey, ape and the like. In one aspect, the "4-1BB costimulatory domain" is the sequence provided as SEQ ID NO:7 or the equivalent residues from a non-human species, e.g., mouse, rodent, monkey, ape and the like.

"Immune effector cell," as that term is used herein, refers to a cell that is involved in an immune response, e.g., in the promotion of an immune effector response. Examples of immune effector cells include T cells, e.g., alpha/beta T cells and gamma/delta T cells, B cells, natural killer (NK) cells, natural killer T (NKT) cells, mast cells, and myeloic-derived phagocytes.

"Immune effector function or immune effector response," as that term is used herein, refers to function or response, e.g., of an immune effector cell, that enhances or promotes an immune attack of a target cell. E.g., an immune effector function or response refers a property of a T or NK cell that promotes killing or the inhibition of growth or proliferation, of a target cell. In the case of a T cell, primary stimulation and co-stimulation are examples of immune effector function or response.

The term "effector function" refers to a specialized function of a cell. Effector function of a T cell, for example, may be cytolytic activity or helper activity including the secretion of cytokines.

The term "encoding" refers to the inherent property of specific sequences of nucleotides in a polynucleotide, such as a gene, a cDNA, or an mRNA, to serve as templates for synthesis of other polymers and macromolecules in biological processes having either a defined sequence of nucleotides (e.g., rRNA, tRNA and mRNA) or a defined sequence of amino acids and the biological properties resulting therefrom. Thus, a gene, cDNA, or RNA, encodes a protein if transcription and translation of mRNA corresponding to that gene produces the protein in a cell or other biological system. Both the coding strand, the nucleotide sequence of which is identical to the mRNA sequence and is usually provided in sequence listings, and the non-coding strand, used as the template for transcription of a gene or cDNA, can be referred to as encoding the protein or other product of that gene or cDNA.

Unless otherwise specified, a "nucleotide sequence encoding an amino acid sequence" includes all nucleotide sequences that are degenerate versions of each other and that encode the same amino acid sequence. The phrase nucleotide sequence that encodes a protein or a RNA may also include introns to the extent that the nucleotide sequence encoding the protein may in some version contain an intron(s).

The term "effective amount" or "therapeutically effective amount" are used interchangeably herein, and refer to an amount of a compound, formulation, material, or composition, as described herein effective to achieve a particular biological result.

The term "endogenous" refers to any material from or produced inside an organism, cell, tissue or system.

The term "exogenous" refers to any material introduced from or produced outside an organism, cell, tissue or system.

The term "expression" refers to the transcription and/or translation of a particular nucleotide sequence driven by a promoter.

The term "transfer vector" refers to a composition of matter which comprises an isolated nucleic acid and which can be used to deliver the isolated nucleic acid to the interior of a cell. Numerous vectors are known in the art including, but not limited to, linear polynucleotides, polynucleotides associated with ionic or amphiphilic compounds, plasmids, and viruses. Thus, the term "transfer vector" includes an autonomously replicating plasmid or a virus. The term should also be construed to further include non-plasmid and non-viral compounds which facilitate transfer of nucleic acid into cells, such as, for example, a polylysine compound, liposome, and the like. Examples of viral transfer vectors include, but are not limited to, adenoviral vectors, adeno-associated virus vectors, retroviral vectors, lentiviral vectors, and the like.

The term "expression vector" refers to a vector comprising a recombinant polynucleotide comprising expression control sequences operatively linked to a nucleotide sequence to be expressed. An expression vector comprises sufficient cis-acting elements for expression; other elements for expression can be supplied by the host cell or in an in vitro expression system. Expression vectors include all those known in the art, including cosmids,

plasmids (e.g., naked or contained in liposomes) and viruses (e.g., lentiviruses, retroviruses, adenoviruses, and adeno-associated viruses) that incorporate the recombinant polynucleotide.

The term "lentivirus" refers to a genus of the Retroviridae family. Lentiviruses are unique among the retroviruses in being able to infect non-dividing cells; they can deliver a significant amount of genetic information into the DNA of the host cell, so they are one of the most efficient methods of a gene delivery vector. HIV, SIV, and FIV are all examples of lentiviruses.

The term "lentiviral vector" refers to a vector derived from at least a portion of a lentivirus genome, including especially a self-inactivating lentiviral vector as provided in Milone et al., Mol. Ther. 17(8): 1453–1464 (2009). Other examples of lentivirus vectors that may be used in the clinic, include but are not limited to, e.g., the LENTIVECTOR® gene delivery technology from Oxford BioMedica, the LENTIMAX™ vector system from Lentigen and the like. Nonclinical types of lentiviral vectors are also available and would be known to one skilled in the art.

The term "homologous" or "identity" refers to the subunit sequence identity between two polymeric molecules, e.g., between two nucleic acid molecules, such as, two DNA molecules or two RNA molecules, or between two polypeptide molecules. When a subunit position in both of the two molecules is occupied by the same monomeric subunit; e.g., if a position in each of two DNA molecules is occupied by adenine, then they are homologous or identical at that position. The homology between two sequences is a direct function of the number of matching or homologous positions; e.g., if half (e.g., five positions in a polymer ten subunits in length) of the positions in two sequences are homologous, the two sequences are 50% homologous; if 90% of the positions (e.g., 9 of 10), are matched or homologous, the two sequences are 90% homologous.

"Humanized" forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')2 or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies and antibody fragments thereof are human immunoglobulins (recipient antibody or antibody fragment) in which residues from a complementary-determining region (CDR) of the recipient are replaced

by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, a humanized antibody/antibody fragment can comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. These modifications can further refine and optimize antibody or antibody fragment performance. In general, the humanized antibody or antibody fragment thereof will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or a significant portion of the FR regions are those of a human immunoglobulin sequence. The humanized antibody or antibody fragment can also comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones et al., Nature, 321: 522-525, 1986; Reichmann et al., Nature, 332: 323-329, 1988; Presta, Curr. Op. Struct. Biol., 2: 593-596, 1992.

"Fully human" refers to an immunoglobulin, such as an antibody or antibody fragment, where the whole molecule is of human origin or consists of an amino acid sequence identical to a human form of the antibody or immunoglobulin.

The term "isolated" means altered or removed from the natural state. For example, a nucleic acid or a peptide naturally present in a living animal is not "isolated," but the same nucleic acid or peptide partially or completely separated from the coexisting materials of its natural state is "isolated." An isolated nucleic acid or protein can exist in substantially purified form, or can exist in a non-native environment such as, for example, a host cell.

In the context of the present invention, the following abbreviations for the commonly occurring nucleic acid bases are used. "A" refers to adenosine, "C" refers to cytosine, "G" refers to guanosine, "T" refers to thymidine, and "U" refers to uridine.

The term "operably linked" or "transcriptional control" refers to functional linkage between a regulatory sequence and a heterologous nucleic acid sequence resulting in expression of the latter. For example, a first nucleic acid sequence is operably linked with a second nucleic acid sequence when the first nucleic acid sequence is placed in a functional relationship with the second nucleic acid sequence. For instance, a promoter is operably linked to a coding

sequence if the promoter affects the transcription or expression of the coding sequence. Operably linked DNA sequences can be contiguous with each other and, e.g., where necessary to join two protein coding regions, are in the same reading frame.

The term "parenteral" administration of an immunogenic composition includes, e.g., subcutaneous (s.c.), intravenous (i.v.), intramuscular (i.m.), or intrasternal injection, intratumoral, or infusion techniques.

The term "nucleic acid" or "polynucleotide" refers to deoxyribonucleic acids (DNA) or ribonucleic acids (RNA) and polymers thereof in either single- or double-stranded form. Unless specifically limited, the term encompasses nucleic acids containing known analogues of natural nucleotides that have similar binding properties as the reference nucleic acid and are metabolized in a manner similar to naturally occurring nucleotides. Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (e.g., degenerate codon substitutions, e.g., conservative substitutions), alleles, orthologs, SNPs, and complementary sequences as well as the sequence explicitly indicated. Specifically, degenerate codon substitutions, e.g., conservative substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzer et al., Nucleic Acid Res. 19:5081 (1991); Ohtsuka et al., J. Biol. Chem. 260:2605-2608 (1985); and Rossolini et al., Mol. Cell. Probes 8:91-98 (1994)).

The terms "peptide," "polypeptide," and "protein" are used interchangeably, and refer to a compound comprised of amino acid residues covalently linked by peptide bonds. A protein or peptide must contain at least two amino acids, and no limitation is placed on the maximum number of amino acids that can comprise a protein's or peptide's sequence. Polypeptides include any peptide or protein comprising two or more amino acids joined to each other by peptide bonds. As used herein, the term refers to both short chains, which also commonly are referred to in the art as peptides, oligopeptides and oligomers, for example, and to longer chains, which generally are referred to in the art as proteins, of which there are many types. "Polypeptides" include, for example, biologically active fragments, substantially homologous polypeptides, oligopeptides, homodimers, heterodimers, variants of polypeptides, modified polypeptides, derivatives, analogs, fusion proteins, among others. A polypeptide includes a natural peptide, a recombinant peptide, or a combination thereof.

The term "promoter" refers to a DNA sequence recognized by the synthetic machinery of the cell, or introduced synthetic machinery, required to initiate the specific transcription of a polynucleotide sequence.

The term "promoter/regulatory sequence" refers to a nucleic acid sequence which is required for expression of a gene product operably linked to the promoter/regulatory sequence. In some instances, this sequence may be the core promoter sequence and in other instances, this sequence may also include an enhancer sequence and other regulatory elements which are required for expression of the gene product. The promoter/regulatory sequence may, for example, be one which expresses the gene product in a tissue specific manner.

The term "constitutive" promoter refers to a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a cell under most or all physiological conditions of the cell.

The term "inducible" promoter refers to a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a cell substantially only when an inducer which corresponds to the promoter is present in the cell.

The term "tissue-specific" promoter refers to a nucleotide sequence which, when operably linked with a polynucleotide encodes or specified by a gene, causes the gene product to be produced in a cell substantially only if the cell is a cell of the tissue type corresponding to the promoter.

The terms "cancer associated antigen" or "tumor antigen" interchangeably refers to a molecule (typically a protein, carbohydrate or lipid) that is expressed on the surface of a cancer cell, either entirely or as a fragment (e.g., MHC/peptide), and which is useful for the preferential targeting of a pharmacological agent to the cancer cell. In some embodiments, a tumor antigen is a marker expressed by both normal cells and cancer cells, e.g., a lineage marker, e.g., CD19 on B cells. In some embodiments, a tumor antigen is a cell surface molecule that is overexpressed in a cancer cell in comparison to a normal cell, for instance, 1-fold over expression, 2-fold overexpression, 3-fold overexpression or more in comparison to a normal cell. In some enbodiments, a tumor antigen is a cell surface molecule that is inappropriately synthesized in the cancer cell, for instance, a molecule that contains deletions,

additions or mutations in comparison to the molecule expressed on a normal cell. In some embodiments, a tumor antigen will be expressed exclusively on the cell surface of a cancer cell, entirely or as a fragment (e.g., MHC/peptide), and not synthesized or expressed on the surface of a normal cell. In some embodiments, the CARs of the present invention includes CARs comprising an antigen binding domain (e.g., antibody or antibody fragment) that binds to a MHC presented peptide. Normally, peptides derived from endogenous proteins fill the pockets of Major histocompatibility complex (MHC) class I molecules, and are recognized by T cell receptors (TCRs) on CD8 + T lymphocytes. The MHC class I complexes are constitutively expressed by all nucleated cells. In cancer, virus-specific and/or tumor-specific peptide/MHC complexes represent a unique class of cell surface targets for immunotherapy. TCR-like antibodies targeting peptides derived from viral or tumor antigens in the context of human leukocyte antigen (HLA)-A1 or HLA-A2 have been described (see, e.g., Sastry et al., J Virol. 2011 85(5):1935-1942; Sergeeva et al., Blood, 2011 117(16):4262-4272; Verma et al., J Immunol 2010 184(4):2156-2165; Willemsen et al., Gene Ther 2001 8(21) :1601-1608 ; Dao et al., Sci Transl Med 2013 5(176) :176ra33 ; Tassev et al., Cancer Gene Ther 2012 19(2):84-100). For example, TCR-like antibody can be identified from screening a library, such as a human scFv phage displayed library.

The term "tumor-supporting antigen" or "cancer-supporting antigen" interchangeably refer to a molecule (typically a protein, carbohydrate or lipid) that is expressed on the surface of a cell that is, itself, not cancerous, but supports the cancer cells, e.g., by promoting their growth or survival e.g., resistance to immune cells. Exemplary cells of this type include stromal cells and myeloid-derived suppressor cells (MDSCs). The tumor-supporting antigen itself need not play a role in supporting the tumor cells so long as the antigen is present on a cell that supports cancer cells.

The term "flexible polypeptide linker" or "linker" as used in the context of a scFv refers to a peptide linker that consists of amino acids such as glycine and/or serine residues used alone or in combination, to link variable heavy and variable light chain regions together. In one embodiment, the flexible polypeptide linker is a Gly/Ser linker and comprises the amino acid sequence $(Gly\text{-}Gly\text{-}Gly\text{-}Ser)_n$ (SEQ ID NO: 38)., where n is a positive integer equal to or greater than 1. For example, n=1, n=2, n=3. n=4, n=5 and n=6, n=7, n=8, n=9 and n=10 In one embodiment, the flexible polypeptide linkers include, but are not limited to, $(Gly_4\ Ser)_4$ (SEQ

ID NO:27) or $(Gly_4 Ser)_3$ (SEQ ID NO:28). In another embodiment, the linkers include multiple repeats of (Gly_2Ser), (GlySer) or (Gly_3Ser) (SEQ ID NO:29). Also included within the scope of the invention are linkers described in WO2012/138475, incorporated herein by reference).

As used herein, a 5' cap (also termed an RNA cap, an RNA 7-methylguanosine cap or an RNA m^7G cap) is a modified guanine nucleotide that has been added to the "front" or 5' end of a eukaryotic messenger RNA shortly after the start of transcription. The 5' cap consists of a terminal group which is linked to the first transcribed nucleotide. Its presence is critical for recognition by the ribosome and protection from RNases. Cap addition is coupled to transcription, and occurs co-transcriptionally, such that each influences the other. Shortly after the start of transcription, the 5' end of the mRNA being synthesized is bound by a cap-synthesizing complex associated with RNA polymerase. This enzymatic complex catalyzes the chemical reactions that are required for mRNA capping. Synthesis proceeds as a multi-step biochemical reaction. The capping moiety can be modified to modulate functionality of mRNA such as its stability or efficiency of translation.

As used herein, "in vitro transcribed RNA" refers to RNA, preferably mRNA, that has been synthesized in vitro. Generally, the in vitro transcribed RNA is generated from an in vitro transcription vector. The in vitro transcription vector comprises a template that is used to generate the in vitro transcribed RNA.

As used herein, a "poly(A)" is a series of adenosines attached by polyadenylation to the mRNA. In the preferred embodiment of a construct for transient expression, the polyA is between 50 and 5000 (SEQ ID NO: 30), preferably greater than 64, more preferably greater than 100, most preferably greater than 300 or 400. poly(A) sequences can be modified chemically or enzymatically to modulate mRNA functionality such as localization, stability or efficiency of translation.

As used herein, "polyadenylation" refers to the covalent linkage of a polyadenylyl moiety, or its modified variant, to a messenger RNA molecule. In eukaryotic organisms, most messenger RNA (mRNA) molecules are polyadenylated at the 3' end. The 3' poly(A) tail is a long sequence of adenine nucleotides (often several hundred) added to the pre-mRNA through the action of an enzyme, polyadenylate polymerase. In higher eukaryotes, the poly(A) tail is added onto transcripts that contain a specific sequence, the polyadenylation signal. The poly(A)

tail and the protein bound to it aid in protecting mRNA from degradation by exonucleases. Polyadenylation is also important for transcription termination, export of the mRNA from the nucleus, and translation. Polyadenylation occurs in the nucleus immediately after transcription of DNA into RNA, but additionally can also occur later in the cytoplasm. After transcription has been terminated, the mRNA chain is cleaved through the action of an endonuclease complex associated with RNA polymerase. The cleavage site is usually characterized by the presence of the base sequence AAUAAA near the cleavage site. After the mRNA has been cleaved, adenosine residues are added to the free 3' end at the cleavage site.

As used herein, "transient" refers to expression of a non-integrated transgene for a period of hours, days or weeks, wherein the period of time of expression is less than the period of time for expression of the gene if integrated into the genome or contained within a stable plasmid replicon in the host cell.

As used herein, the terms "treat", "treatment" and "treating" refer to the reduction or amelioration of the progression, severity and/or duration of a proliferative disorder, or the amelioration of one or more symptoms (preferably, one or more discernible symptoms) of a proliferative disorder resulting from the administration of one or more therapies (e.g., one or more therapeutic agents such as a CAR of the invention). In specific embodiments, the terms "treat", "treatment" and "treating" refer to the amelioration of at least one measurable physical parameter of a proliferative disorder, such as growth of a tumor, not necessarily discernible by the patient. In other embodiments the terms "treat", "treatment" and "treating" -refer to the inhibition of the progression of a proliferative disorder, either physically by, e.g., stabilization of a discernible symptom, physiologically by, e.g., stabilization of a physical parameter, or both. In other embodiments the terms "treat", "treatment" and "treating" refer to the reduction or stabilization of tumor size or cancerous cell count.

The term "signal transduction pathway" refers to the biochemical relationship between a variety of signal transduction molecules that play a role in the transmission of a signal from one portion of a cell to another portion of a cell. The phrase "cell surface receptor" includes molecules and complexes of molecules capable of receiving a signal and transmitting signal across the membrane of a cell.

The term "subject" is intended to include living organisms in which an immune response can be elicited (e.g., mammals, human).

The term, a "substantially purified" cell refers to a cell that is essentially free of other cell types. A substantially purified cell also refers to a cell which has been separated from other cell types with which it is normally associated in its naturally occurring state. In some instances, a population of substantially purified cells refers to a homogenous population of cells. In other instances, this term refers simply to cell that have been separated from the cells with which they are naturally associated in their natural state. In some aspects, the cells are cultured in vitro. In other aspects, the cells are not cultured in vitro.

The term "therapeutic" as used herein means a treatment. A therapeutic effect is obtained by reduction, suppression, remission, or eradication of a disease state.

The term "prophylaxis" as used herein means the prevention of or protective treatment for a disease or disease state.

In the context of the present invention, "tumor antigen" or "hyperproliferative disorder antigen" or "antigen associated with a hyperproliferative disorder" refers to antigens that are common to specific hyperproliferative disorders. In certain aspects, the hyperproliferative disorder antigens of the present invention are derived from, cancers including but not limited to primary or metastatic melanoma, thymoma, lymphoma, sarcoma, lung cancer, liver cancer, non-Hodgkin lymphoma, Hodgkin lymphoma, leukemias, uterine cancer, cervical cancer, bladder cancer, kidney cancer and adenocarcinomas such as breast cancer, prostate cancer (e.g., castrate-resistant or therapy-resistant prostate cancer, or metastatic prostate cancer), ovarian cancer, pancreatic cancer, and the like, or a plasma cell proliferative disorder, e.g., asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), monoclonal gammapathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia, plasmacytomas (e.g., plasma cell dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, and POEMS syndrome (also known as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome).

The term "transfected" or "transformed" or "transduced" refers to a process by which exogenous nucleic acid is transferred or introduced into the host cell. A "transfected" or

"transformed" or "transduced" cell is one which has been transfected, transformed or transduced with exogenous nucleic acid. The cell includes the primary subject cell and its progeny.

The term "specifically binds," refers to an antibody, or a ligand, which recognizes and binds with a cognate binding partner (e.g., a stimulatory and/or costimulatory molecule present on a T cell) protein present in a sample, but which antibody or ligand does not substantially recognize or bind other molecules in the sample.

"Regulatable chimeric antigen receptor (RCAR)," as used herein, refers to a set of polypeptides, typically two in the simplest embodiments, which when in an immune effector cell, provides the cell with specificity for a target cell, typically a cancer cell, and with intracellular signal generation. In some embodiments, an RCAR comprises at least an extracellular antigen binding domain, a transmembrane domain and a cytoplasmic signaling domain (also referred to herein as "an intracellular signaling domain") comprising a functional signaling domain derived from a stimulatory molecule and/or costimulatory molecule as defined herein in the context of a CAR molecule. In some embodiments, the set of polypeptides in the RCAR are not contiguous with each other, e.g., are in different polypeptide chains. In some embodiments, the RCAR includes a dimerization switch that, upon the presence of a dimerization molecule, can couple the polypeptides to one another, e.g., can couple an antigen binding domain to an intracellular signaling domain. In some embodiments, the RCAR is expressed in a cell (e.g., an immune effector cell) as described herein, e.g., an RCAR-expressing cell (also referred to herein as "RCARX cell"). In an embodiment the RCARX cell is a T cell, and is referred to as a RCART cell. In an embodiment the RCARX cell is an NK cell, and is referred to as a RCARN cell. The RCAR can provide the RCAR-expressing cell with specificity for a target cell, typically a cancer cell, and with regulatable intracellular signal generation or proliferation, which can optimize an immune effector property of the RCAR-expressing cell. In embodiments, an RCAR cell relies at least in part, on an antigen binding domain to provide specificity to a target cell that comprises the antigen bound by the antigen binding domain.

"Membrane anchor" or "membrane tethering domain", as that term is used herein, refers to a polypeptide or moiety, e.g., a myristoyl group, sufficient to anchor an extracellular or intracellular domain to the plasma membrane.

"Switch domain," as that term is used herein, e.g., when referring to an RCAR, refers to an entity, typically a polypeptide-based entity, that, in the presence of a dimerization molecule, associates with another switch domain. The association results in a functional coupling of a first entity linked to, e.g., fused to, a first switch domain, and a second entity linked to, e.g., fused to, a second switch domain. A first and second switch domain are collectively referred to as a dimerization switch. In embodiments, the first and second switch domains are the same as one another, e.g., they are polypeptides having the same primary amino acid sequence, and are referred to collectively as a homodimerization switch. In embodiments, the first and second switch domains are different from one another, e.g., they are polypeptides having different primary amino acid sequences, and are referred to collectively as a heterodimerization switch. In embodiments, the switch is intracellular. In embodiments, the switch is extracellular. In embodiments, the switch domain is a polypeptide-based entity, e.g., FKBP or FRB-based, and the dimerization molecule is small molecule, e.g., a rapalogue. In embodiments, the switch domain is a polypeptide-based entity, e.g., an scFv that binds a myc peptide, and the dimerization molecule is a polypeptide, a fragment thereof, or a multimer of a polypeptide, e.g., a myc ligand or multimers of a myc ligand that bind to one or more myc scFvs. In embodiments, the switch domain is a polypeptide-based entity, e.g., myc receptor, and the dimerization molecule is an antibody or fragments thereof, e.g., myc antibody.

"Dimerization molecule," as that term is used herein, e.g., when referring to an RCAR, refers to a molecule that promotes the association of a first switch domain with a second switch domain. In embodiments, the dimerization molecule does not naturally occur in the subject, or does not occur in concentrations that would result in significant dimerization. In embodiments, the dimerization molecule is a small molecule, e.g., rapamycin or a rapalogue, e.g, RAD001.

The term "bioequivalent" refers to an amount of an agent other than the reference compound (e.g., RAD001), required to produce an effect equivalent to the effect produced by the reference dose or reference amount of the reference compound (e.g., RAD001). In an embodiment the effect is the level of mTOR inhibition, e.g., as measured by P70 S6 kinase inhibition, e.g., as evaluated in an *in vivo* or *in vitro* assay, e.g., as measured by an assay described herein, e.g., the Boulay assay, or measurement of phosphorylated S6 levels by

western blot. In an embodiment, the effect is alteration of the ratio of PD-1 positive/PD-1 negative T cells, as measured by cell sorting. In an embodiment a bioequivalent amount or dose of an mTOR inhibitor is the amount or dose that achieves the same level of P70 S6 kinase inhibition as does the reference dose or reference amount of a reference compound. In an embodiment, a bioequivalent amount or dose of an mTOR inhibitor is the amount or dose that achieves the same level of alteration in the ratio of PD-1 positive/PD-1 negative T cells as does the reference dose or reference amount of a reference compound.

The term "low, immune enhancing, dose" when used in conjuction with an mTOR inhibitor, e.g., an allosteric mTOR inhibitor, e.g., RAD001 or rapamycin, or a catalytic mTOR inhibitor, refers to a dose of mTOR inhibitor that partially, but not fully, inhibits mTOR activity, e.g., as measured by the inhibition of P70 S6 kinase activity. Methods for evaluating mTOR activity, e.g., by inhibition of P70 S6 kinase, are discussed herein. The dose is insufficient to result in complete immune suppression but is sufficient to enhance the immune response. In an embodiment, the low, immune enhancing, dose of mTOR inhibitor results in a decrease in the number of PD-1 positive immune effector cells, e.g., T cells or NK cells, and/or an increase in the number of PD-1 negative immune effector cells, e.g., T cells or NK cells, or an increase in the ratio of PD-1 negative immune effector cells (e.g., T cells or NK cells) /PD-1 positive immune effector cells (e.g., T cells or NK cells).

In an embodiment, the low, immune enhancing, dose of mTOR inhibitor results in an increase in the number of naive T cells. In an embodiment, the low, immune enhancing, dose of mTOR inhibitor results in one or more of the following:

an increase in the expression of one or more of the following markers: $CD62L^{high}$, $CD127^{high}$, $CD27^{+}$, and BCL2, e.g., on memory T cells, e.g., memory T cell precursors;

a decrease in the expression of KLRG1, e.g., on memory T cells, e.g., memory T cell precursors; and

an increase in the number of memory T cell precursors, e.g., cells with any one or combination of the following characteristics: increased $CD62L^{high}$, increased $CD127^{high}$, increased $CD27^{+}$, decreased KLRG1, and increased BCL2;

wherein any of the changes described above occurs, e.g., at least transiently, e.g., as compared to a non-treated subject.

"Refractory" as used herein refers to a disease, e.g., cancer, that does not respond to a treatment. In embodiments, a refractory cancer can be resistant to a treatment before or at the beginning of the treatment. In other embodiments, the refractory cancer can become resistant during a treatment. A refractory cancer is also called a resistant cancer.

"Relapsed" or a "relapse" as used herein refers to the reappearance of a disease (e.g., cancer) or the signs and symptoms of a disease such as cancer after a period of improvement or responsiveness, e.g., after prior treatment of a therapy, e.g., cancer therapy. For example, the period of responsiveness may involve the level of cancer cells falling below a certain threshold, e.g., below 20%, 1%, 10%, 5%, 4%, 3%, 2%, or 1%. The reappearance may involve the level of cancer cells rising above a certain threshold, e.g., above 20%, 1%, 10%, 5%, 4%, 3%, 2%, or 1%.

Ranges: throughout this disclosure, various aspects of the invention can be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 2.7, 3, 4, 5, 5.3, and 6. As another example, a range such as 95-99% identity, includes something with 95%, 96%, 97%, 98% or 99% identity, and includes subranges such as 96-99%, 96-98%, 96-97%, 97-99%, 97-98% and 98-99% identity. This applies regardless of the breadth of the range.

Description

Provided herein are compositions of matter and methods of use for the treatment of a disease such as cancer using cells expressing BCMA chimeric antigen receptors (CAR), e.g., CART-BCMA.

In one aspect, the invention provides a number of chimeric antigen receptors (CAR) comprising an antibody or antibody fragment engineered for enhanced binding to a BCMA protein. In one aspect, the invention provides a cell (e.g., an immune effector cell, e.g., T cell or NK cell) engineered to express a CAR, wherein the CAR T cell ("CART") or CAR NK cell

exhibits an antitumor property. In one aspect a cell is transformed with the CAR and the CAR is expressed on the cell surface. In some embodiments, the cell (e.g., an immune effector cell, e.g., T cell or NK cell) is transduced with a viral vector encoding a CAR. In some embodiments, the viral vector is a retroviral vector. In some embodiments, the viral vector is a lentiviral vector. In some such embodiments, the cell may stably express the CAR. In another embodiment, the cell (e.g., an immune effector cell, e.g., T cell or NK cell) is transfected with a nucleic acid, e.g., mRNA, cDNA, DNA, encoding a CAR. In some such embodiments, the cell may transiently express the CAR.

In one aspect, the anti-BCMA antigen binding portion of the CAR is a scFv antibody fragment. In one aspect such antibody fragments are functional in that they retain the equivalent binding affinity, e.g., they bind the same antigen with comparable efficacy, as the IgG antibody from which it is derived. In other embodiments, the antibody fragment has a lower binding affinity, e.g., it binds the same antigen with a lower binding affinity than the antibody from which it is derived, but is functional in that it provides a biological response described herein. In one embodiment, the CAR molecule comprises an antibody fragment that has a binding affinity KD of 10^{-4} M to 10^{-8} M, e.g., 10^{-5} M to 10^{-7} M, e.g., 10^{-6} M or 10^{-7} M, for the target antigen. In one embodiment, the antibody fragment has a binding affinity that is at least five-fold, 10-fold, 20-fold, 30-fold, 50-fold, 100-fold or 1,000-fold less than a reference antibody, e.g., an antibody described herein.

In one aspect such antibody fragments are functional in that they provide a biological response that can include, but is not limited to, activation of an immune response, inhibition of signal-transduction origination from its target antigen, inhibition of kinase activity, and the like, as will be understood by a skilled artisan. In one aspect, the anti-BCMA antigen binding domain of the CAR is a scFv antibody fragment that is humanized compared to the murine sequence of the scFv from which it is derived. In one embodiment, the anti-BCMA antigen binding domain is a human anti-BCMA antigen binding domain. In one embodiment, the anti-BCMA antigen binding domain is a humanized anti-BCMA antigen binding domain.

In some aspects, the antibodies of the invention are incorporated into a chimeric antigen receptor (CAR). In one aspect, the CAR comprises a BCMA binding domain comprising a sequence of SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ

ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ ID NO:134, SEQ ID NO: 135, SEQ ID NO:136, SEQ ID NO: 137, SEQ ID NO:138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, SEQ ID NO: 149, SEQ ID NO: 263, SEQ ID NO: 264, SEQ ID NO: 265, or SEQ ID NO: 266. In one aspect, the scFv domains are human. In another aspect, the scFv domains are humanized variants of the scFv domain of the antibodies or antibody fragments described in PCT Publication No. WO 2012/163805, US Patent No. 7,083,785, EP Patent No. 1975231B1, or PCT Publication No. WO 13/154760 (the contents of each are hereby incorporated by reference in their entireties), which disclose antibodies or scFv fragments of murine origin that specifically binds to human BCMA. Humanization of these mouse antibodies and/or scFvs may be desired for the clinical setting, where the mouse-specific residues may induce a human-anti-mouse antigen (HAMA) response in patients who receive CART-BCMA treatment, e.g., treatment with immune effector cells, e.g., T cells or NK cells, transduced with the anti-BCMA CAR construct.

In one aspect, the anti-BCMA binding domain, e.g., human or humanized scFv, portion of a CAR of the invention is encoded by a transgene whose sequence has been codon optimized for expression in a mammalian cell. In one aspect, entire CAR construct of the invention is encoded by a transgene whose entire sequence has been codon optimized for expression in a mammalian cell. Codon optimization refers to the discovery that the frequency of occurrence of synonymous codons (i.e., codons that code for the same amino acid) in coding DNA is biased in different species. Such codon degeneracy allows an identical polypeptide to be encoded by a variety of nucleotide sequences. A variety of codon optimization methods is known in the art, and include, e.g., methods disclosed in at least US Patent Numbers 5,786,464 and 6,114,148.

In one aspect, the human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 39. In one aspect, the human anti-BCMA CAR comprises the scFv portion provided in SEQ ID NO: 40. In one aspect, the human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 41. In one aspect, the human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 42. In one aspect, the

human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 43. In one aspect, the human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 44. In one aspect, the human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 45. In one aspect, the human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 46. In one aspect, the human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 47. In one aspect, the human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 48. In one aspect, the human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 49. In one aspect, the human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 50. In one aspect, the human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 51. In one aspect, the human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 52. In one aspect, the human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 53. In one aspect, the human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 129. In one aspect, the human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 130. In one aspect, the human anti-BCMA CAR comprises the scFv portion provided in SEQ ID NO: 131. In one aspect, the human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 132. In one aspect, the human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 133. In one aspect, the human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 134. In one aspect, the human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 135. In one aspect, the human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 136. In one aspect, the human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 137. In one aspect, the human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 138. In one aspect, the human anti-BCMA binding domaincomprises the scFv portion provided in SEQ ID NO: 139. In one aspect, the human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 140. In one aspect, the human anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 141. In one aspect, the human anti-BCMA CAR comprises the scFv portion provided in SEQ ID NO: 142. In one aspect, the human anti-BCMA CAR comprises the scFv portion provided in SEQ ID NO: 143. In one aspect, the human anti-BCMA CAR comprises the scFv portion provided in SEQ ID NO: 144. In one aspect, the

human anti-BCMA CAR comprises the scFv portion provided in SEQ ID NO: 145. In one aspect, the human anti-BCMA CAR comprises the scFv portion provided in SEQ ID NO: 146. In one aspect, the human anti-BCMA CAR comprises the scFv portion provided in SEQ ID NO: 147. In one aspect, the human anti-BCMA CAR comprises the scFv portion provided in SEQ ID NO: 148. In one aspect, the human anti-BCMA CAR comprises the scFv portion provided in SEQ ID NO: 149. In one aspect, the humanized anti-BCMA binding domain comprises the scFv portion provided in SEQ ID NO: 255. In one aspect, the humanized anti-BCMA CAR comprises the scFv portion provided in SEQ ID NO: 257.

In one aspect, the human anti-BCMA CAR comprises the scFv portion provided in SEQ ID NO: 263. In one aspect, the human anti-BCMA CAR comprises the scFv portion provided in SEQ ID NO: 264. In one aspect, the human anti-BCMA CAR comprises the scFv portion provided in SEQ ID NO: 265. In one aspect, the human anti-BCMA CAR comprises the scFv portion provided in SEQ ID NO: 266.

In one aspect, the CARs of the invention combine an antigen binding domain of a specific antibody with an intracellular signaling molecule. For example, in some aspects, the intracellular signaling molecule includes, but is not limited to, CD3-zeta chain, 4-1BB and CD28 signaling modules and combinations thereof. In one aspect, the antigen binding domain binds to BCMA. In one aspect, the BCMA CAR comprises a CAR selected from the sequence provided in one or more of SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO: 105, SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 213, SEQ ID NO: 214, SEQ ID NO: 215, SEQ ID NO: 216, SEQ ID NO: 217, SEQ ID NO: 218, SEQ ID NO: 219, SEQ ID NO: 220, SEQ ID NO: 221, SEQ ID NO: 222, SEQ ID NO: 223, SEQ ID NO: 224, SEQ ID NO: 225, SEQ ID NO: 226, SEQ ID NO: 227, SEQ ID NO: 228, SEQ ID NO: 229, SEQ ID NO: 230, SEQ ID NO: 231, SEQ ID NO: 232, and SEQ ID NO: 233. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:99. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:100. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:101. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:102. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:103. In one aspect, the BCMA CAR comprises the sequence

provided in SEQ ID NO:104. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:105. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:106. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:107. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:108. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:109. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:110. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:111. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:112. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:213. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:214. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:215. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:216. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:217. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:218. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:219. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:220. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:221. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:222. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:223. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:224. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:225. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:226. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:227. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:228. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:229. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:230. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:231. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:232. In one aspect, the BCMA CAR comprises the sequence provided in SEQ ID NO:233.

Furthermore, the present invention provides BCMA CAR compositions and their use in medicaments or methods for treating, among other diseases, cancer or any malignancy or autoimmune diseases involving cells or tissues which express BCMA

In one aspect, the CAR of the invention can be used to eradicate BCMA-expressing normal cells, thereby applicable for use as a cellular conditioning therapy prior to cell transplantation. In one aspect, the BCMA-expressing normal cell is a BCMA-expressing normal stem cell and the cell transplantation is a stem cell transplantation.

In one aspect, the invention provides a cell (e.g., T cell or NK cell) engineered to express a chimeric antigen receptor (CAR), wherein the CAR T cell ("CART") or the CAR NK cell exhibits an antitumor property. A preferred antigen is BCMA. In one aspect, the antigen binding domain of the CAR comprises a human anti-BCMA antibody fragment or a partially humanized anti-BCMA antibody fragment. In one aspect, the antigen binding domain of the CAR comprises human anti-BCMA antibody fragment or a partially humanized anti-BCMA antibody fragment comprising an scFv. Accordingly, the invention provides a BCMA-CAR that comprises a humanized anti-BCMA binding domain and is engineered into a cell, e.g., a T cell or NK cell, and methods of their use for adoptive therapy.

In one aspect, the BCMA-CAR comprises at least one intracellular domain selected from the group of a CD137 (4-1BB) signaling domain, a CD28 signaling domain, a CD3zeta signal domain, and any combination thereof. In one aspect, the BCMA-CAR comprises at least one intracellular signaling domain is from one or more co-stimulatory molecule(s) other than a CD137 (4-1BB) or CD28.

Chimeric Antigen Receptor (CAR)

The present invention provides a CAR (e.g., a CAR polypeptide) that comprises an anti-BCMA binding domain (e.g., human or humanized BCMA binding domain as described herein), a transmembrane domain, and an intracellular signaling domain, and wherein said anti-BCMA binding domain comprises a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of any anti-BMCA heavy chain binding domain amino acid sequences listed in Table 1 or 16. The anti-BCMA binding domain of the

CAR can further comprise a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of any anti-BMCA heavy chain binding domain amino acid sequences listed in Table 1 or 16.

The present invention also provides nucleic acid molecules encoding the CAR as described herein, e.g., encoding a CAR that comprises an anti-BCMA binding domain (e.g., human or humanized BCMA binding domain as described herein), a transmembrane domain, and an intracellular signaling domain, and wherein said anti-BCMA binding domain comprises a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of any anti-BMCA heavy chain binding domain amino acid sequences listed in Table 1 or 16 . In one embodiment, the encoded anti-BCMA binding domain of the CAR can further comprise a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of any anti-BMCA heavy chain binding domain amino acid sequences listed in Table 1 or 16.

In specific aspects, a CAR construct of the invention comprises a scFv domain selected from the group consisting of SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, SEQ ID NO: 149, SEQ ID NO: 263, SEQ ID NO: 264, SEQ ID NO: 265, and SEQ ID NO: 266, wherein the scFv may be preceded by an optional leader sequence such as provided in SEQ ID NO: 1, and followed by an optional hinge sequence such as provided in SEQ ID NO:2 or SEQ ID NO:3 or SEQ ID NO:4 or SEQ ID NO:5, a transmembrane region such as provided in SEQ ID NO:6, an intracellular signalling domain that includes SEQ ID NO:7 or SEQ ID NO:8 and a CD3 zeta sequence that includes SEQ ID NO:9 or SEQ ID NO:10, wherein the domains are contiguous with and in the same reading frame to form a single fusion protein.

Also included in the invention is a nucleotide sequence that encodes the polypeptide of each of the scFv fragments selected from the group consisting of SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, SEQ ID NO: 149, SEQ ID NO: 263, SEQ ID NO: 264, SEQ ID NO: 265, and SEQ ID NO: 266.

Also included in the invention is a nucleotide sequence that encodes the polypeptide of each of the scFv fragments selected from the group consisting of SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, SEQ ID NO: 149, SEQ ID NO: 263, SEQ ID NO: 264, SEQ ID NO: 265, and SEQ ID NO: 266, and each of the domains of SEQ ID NOS: 1,2, and 6-9, plus the encoded BCMA CAR fusion protein of the invention.

In one aspect, an exemplary BCMA CAR constructs comprise an optional leader sequence, an extracellular antigen binding domain, a hinge, a transmembrane domain, and an intracellular stimulatory domain. In one aspect an exemplary BCMA CAR construct comprises an optional leader sequence, an extracellular antigen binding domain, a hinge, a transmembrane domain, an intracellular costimulatory domain and an intracellular stimulatory domain. Specific BCMA CAR constructs containing human scFv domains of the invention are provided as SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO:

134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, and SEQ ID NO: 149. Full-length CAR sequences are also provided herein as SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, and SEQ ID NO: 149 as shown in Table 1.

An exemplary leader sequence is provided as SEQ ID NO: 1. An exemplary hinge/spacer sequence is provided as SEQ ID NO:2 or SEQ ID NO:3 or SEQ ID NO:4 or SEQ ID NO:5. An exemplary transmembrane domain sequence is provided as SEQ ID NO:6. An exemplary sequence of the intracellular signaling domain of the 4-1BB protein is provided as SEQ ID NO: 7. An exemplary sequence of the intracellular signaling domain of CD27 is provided as SEQ ID NO:8. An exemplary CD3zeta domain sequence is provided as SEQ ID NO: 9 or SEQ ID NO:10.

In one aspect, the present invention encompasses a recombinant nucleic acid construct comprising a nucleic acid molecule encoding a CAR, wherein the nucleic acid molecule comprises the nucleic acid sequence encoding an anti-BCMA binding domain, e.g., described herein, that is contiguous with and in the same reading frame as a nucleic acid sequence encoding an intracellular signaling domain. In one aspect, the anti-BCMA binding domain is selected from one or more of SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 150, SEQ ID NO: 151, SEQ ID NO: 152, SEQ ID NO: 153, SEQ ID NO: 154, SEQ ID NO: 155, SEQ ID NO: 156, SEQ ID NO: 157, SEQ ID NO: 158, SEQ ID NO: 159, SEQ ID NO: 160, SEQ ID NO: 161, SEQ ID NO: 162, SEQ ID NO: 163, SEQ ID NO: 164, SEQ ID NO: 165, SEQ ID NO: 166, SEQ ID NO: 167, SEQ ID NO: 168, SEQ ID NO: 169, and SEQ ID NO: 170. In one aspect, the anti-BCMA binding domain comprises SEQ ID

NO: 54.In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 55. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 56. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 57. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 58. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 59. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 60. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 61. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 62. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 63. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 64. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 65. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 66. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 67. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 68. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 150. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 151. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 152. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 153. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 154. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 155. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 156. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 157. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 158. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 159. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 160. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 161. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 162. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 163. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 164. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 165. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 166. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 167. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 168. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 169. In one aspect, the anti-BCMA binding domain comprises SEQ ID NO: 170.

In one aspect, the present invention encompasses a recombinant nucleic acid construct comprising a nucleic acid molecule encoding a CAR, wherein the nucleic acid molecule comprises a nucleic acid sequence encoding an anti- BCMA binding domain selected from one or more of SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 150, SEQ ID NO: 151, SEQ ID NO: 152, SEQ ID NO: 153, SEQ ID NO: 154, SEQ ID NO: 155, SEQ ID NO: 156, SEQ ID NO: 157, SEQ ID NO: 158, SEQ ID NO: 159, SEQ ID NO: 160, SEQ ID NO: 161, SEQ ID NO: 162, SEQ ID NO: 163, SEQ ID NO: 164, SEQ ID NO: 165, SEQ ID NO: 166, SEQ ID NO: 167, SEQ ID NO: 168, SEQ ID NO: 169, and SEQ ID NO: 170, e.g., wherein the sequence is contiguous with and in the same reading frame as the nucleic acid sequence encoding an intracellular signaling domain. An exemplary intracellular signaling domain that can be used in the CAR includes, but is not limited to, one or more intracellular signaling domains of, e.g., CD3-zeta, CD28, 4-1BB, and the like. In some instances, the CAR can comprise any combination of CD3-zeta, CD28, 4-1BB, and the like. In one aspect the nucleic acid sequence of a CAR construct of the invention is selected from one or more of SEQ ID NO: 114, SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 119, SEQ ID NO: 120, SEQ ID NO: 121, SEQ ID NO: 122, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 234, SEQ ID NO: 235, SEQ ID NO: 236, SEQ ID NO: 237, SEQ ID NO: 238, SEQ ID NO: 239, SEQ ID NO: 240, SEQ ID NO: 241, SEQ ID NO: 242, SEQ ID NO: 243, SEQ ID NO: 244, SEQ ID NO: 245, SEQ ID NO: 246, SEQ ID NO: 247, SEQ ID NO: 248, SEQ ID NO: 249, SEQ ID NO: 250, SEQ ID NO: 251, SEQ ID NO: 252, SEQ ID NO: 253, or SEQ ID NO: 254. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 114. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 115. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 116. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 117. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 118. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 119. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 120. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 121. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 122. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO:

123. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 124. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 125. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 126. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 127. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 128. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 234. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 235. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 236. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 237. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 238. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 239. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 240. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 241. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 242. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 243. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 244. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 245. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 246. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 247. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 248. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 249. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 250. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 251. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 252. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 253. In one aspect the nucleic acid sequence of a CAR construct is SEQ ID NO: 254.

The nucleic acid sequences coding for the desired molecules can be obtained using recombinant methods known in the art, such as, for example by screening libraries from cells expressing the gene, by deriving the gene from a vector known to include the same, or by isolating directly from cells and tissues containing the same, using standard techniques. Alternatively, the nucleic acid of interest can be produced synthetically, rather than cloned.

The present invention includes retroviral and lentiviral vector constructs expressing a CAR that can be directly transduced into a cell.

The present invention also includes an RNA construct that can be directly transfected into a cell. A method for generating mRNA for use in transfection involves in vitro transcription (IVT) of a template with specially designed primers, followed by polyA addition, to produce a construct containing 3' and 5' untranslated sequence ("UTR"), a 5' cap and/or Internal Ribosome Entry Site (IRES), the nucleic acid to be expressed, and a polyA tail, typically 50-2000 bases in length (SEQ ID NO:35). RNA so produced can efficiently transfect different kinds of cells. In one embodiment, the template includes sequences for the CAR. In an embodiment, an RNA CAR vector is transduced into a cell, e.g., T cell or NK cell, by electroporation.

Antigen binding domain

The CARs of the present invention comprise a target-specific binding domain. The choice of moiety depends upon the type and number of ligands that define the surface of a target cell. For example, the antigen binding domain may be chosen to recognize an antigen that acts as a cell surface marker on target cells associated with a particular disease state.

In one aspect, the CAR-mediated T-cell response can be directed to an antigen of interest by way of engineering an antigen binding domain that specifically binds a desired antigen into the CAR.

In one aspect, the CAR of the present invention comprises a binding domain that specifically binds BCMA. In one aspect, the CAR of the present invention comprises an antigen binding domain that specifically binds human BCMA.

The antigen binding domain can be any protein that binds to the antigen including but not limited to a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a human antibody, a humanized antibody, and a functional fragment thereof, including but not limited to a single-domain antibody such as a heavy chain variable domain (VH), a light chain variable domain (VL) and a variable domain (VHH) of camelid derived nanobody, and to an alternative scaffold known in the art to function as antigen binding domain, such as a recombinant fibronectin domain, and the like. In some instances, it is beneficial for the antigen binding domain to be derived from the same species in which the CAR will ultimately be used in. For example, for use in humans, it may be beneficial for the antigen binding domain of the CAR to

comprise human or humanized residues for the antigen binding domain of an antibody or antibody fragment.

Thus, in one aspect, the antigen binding domain comprises a human or a humanized antibody or an antibody fragment. In one embodiment, the human anti-BCMA binding domain comprises one or more (e.g., all three) light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and light chain complementary determining region 3 (LC CDR3) of a human anti-BCMA binding domain described herein, and/or one or more (e.g., all three) heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of a human anti-BCMA binding domain described herein, e.g., a human anti-BCMA binding domain comprising one or more, e.g., all three, LC CDRs and one or more, e.g., all three, HC CDRs. In one embodiment, the human anti-BCMA binding domain comprises one or more (e.g., all three) heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of a human anti-BCMA binding domain described herein, e.g., the human anti-BCMA binding domain has two variable heavy chain regions, each comprising a HC CDR1, a HC CDR2 and a HC CDR3 described herein. In one embodiment, the human anti-BCMA binding domain comprises a human light chain variable region described herein (e.g., in Table 1) and/or a human heavy chain variable region described herein (e.g., in Table 1). In one embodiment, the human anti-BCMA binding domain comprises a human heavy chain variable region described herein (e.g., in Table 1), e.g., at least two human heavy chain variable regions described herein (e.g., in Table 1). In one embodiment, the anti-BCMA binding domain is a scFv comprising a light chain and a heavy chain of an amino acid sequence of Table 1. In an embodiment, the anti-BCMA binding domain (e.g., an scFv) comprises: a light chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a light chain variable region provided in Table 1, or a sequence with 95-99% identity with an amino acid sequence of Table 11; and/or a heavy chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not

more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a heavy chain variable region provided in Table 1, or a sequence with 95-99% identity to an amino acid sequence of Table 1.

In one embodiment, the human anti-BCMA binding domain comprises a sequence selected from a group consisting of SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, and SEQ ID NO: 149, or a sequence with 95-99% identify thereof. In one embodiment, the nucleic acid sequence encoding the human anti-BCMA binding domain comprises a sequence selected from a group consisting of SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 150, SEQ ID NO: 151, SEQ ID NO: 152, SEQ ID NO: 153, SEQ ID NO: 154, SEQ ID NO: 155, SEQ ID NO: 156, SEQ ID NO: 157, SEQ ID NO: 158, SEQ ID NO: 159, SEQ ID NO: 160, SEQ ID NO: 161, SEQ ID NO: 162, SEQ ID NO: 163, SEQ ID NO: 164, SEQ ID NO: 165, SEQ ID NO: 166, SEQ ID NO: 167, SEQ ID NO: 168, SEQ ID NO: 169, and SEQ ID NO: 170, or a sequence with 95-99% identify thereof. In one embodiment, the human anti-BCMA binding domain is a scFv, and a light chain variable region comprising an amino acid sequence described herein, e.g., in Table 1, is attached to a heavy chain variable region comprising an amino acid sequence described herein, e.g., in Table 1, via a linker, e.g., a linker described herein. In one embodiment, the human anti-BCMA binding domain includes a $(Gly_4\text{-}Ser)n$ linker, wherein n is 1, 2, 3, 4, 5, or 6, preferably 3 or 4 (SEQ ID NO:26). The light chain variable region and heavy chain variable region of a scFv can be, e.g., in any of the following orientations: light chain variable region-linker-heavy chain variable region or heavy chain variable region-linker-light chain variable region. In one aspect, the antigen binding domain portion comprises one or more sequence selected from SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44,

SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, and SEQ ID NO: 149. In one aspect the CAR is selected from one or more sequence selected from SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO: 105, SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 213, SEQ ID NO: 214, SEQ ID NO: 215, SEQ ID NO: 216, SEQ ID NO: 217, SEQ ID NO: 218, SEQ ID NO: 219, SEQ ID NO: 220, SEQ ID NO: 221, SEQ ID NO: 222, SEQ ID NO: 223, SEQ ID NO: 224, SEQ ID NO: 225, SEQ ID NO: 226, SEQ ID NO: 227, SEQ ID NO: 228, SEQ ID NO: 229, SEQ ID NO: 230, SEQ ID NO: 231, SEQ ID NO: 232, and SEQ ID NO: 233.

In one embodiment, the anti- BCMA binding domain comprises a light chain variable region described herein (e.g., in Table 16) and/or a heavy chain variable region described herein (e.g., in Table 16). In one embodiment, the encoded humanized anti-BCMA binding domain comprises a light chain variable region provided in SEQ ID NO: 259, SEQ ID NO: 260, SEQ ID NO: 261, SEQ ID NO: 262, and/or a heavy chain variable region provided in SEQ ID NO: 255, SEQ ID NO: 256, SEQ ID NO: 257, SEQ ID NO: 258. In one embodiment, the encoded anti- BCMA binding domain is a scFv comprising a light chain and a heavy chain of an amino acid sequence of Table 16. In an embodiment, the human or humanized anti-BCMA binding domain (e.g., an scFv) comprises: a light chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a light chain variable region provided in SEQ ID NO: 259, SEQ ID NO: 260, SEQ ID NO: 261, SEQ ID NO: 262, or a sequence with 95-99% identity thereof; and/or a heavy chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a heavy chain

variable region provided in SEQ ID NO: 255, SEQ ID NO: 256, SEQ ID NO: 257, SEQ ID NO: 258, or a sequence with 95-99% identity thereof. In one embodiment, the encoded anti-BCMA binding domain includes a (Gly4-Ser)n linker, wherein n is 1, 2, 3, 4, 5, or 6, preferably 3 or 4 (SEQ ID NO:26). The light chain variable region and heavy chain variable region of a scFv can be, e.g., in any of the following orientations: light chain variable region-linker-heavy chain variable region or heavy chain variable region-linker-light chain variable region.

In one embodiment, the human anti- BCMA binding domain comprises a sequence selected from a group consisting of SEQ ID NO: 263, SEQ ID NO: 264, SEQ ID NO: 265, and SEQ ID NO: 266, or a sequence with 95-99% identity thereof.

In some aspects, a non-human antibody is humanized, where specific sequences or regions of the antibody are modified to increase similarity to an antibody naturally produced in a human or fragment thereof. In one aspect, the antigen binding domain is humanized.

A humanized antibody can be produced using a variety of techniques known in the art, including but not limited to, CDR-grafting (see, e.g., European Patent No. EP 239,400; International Publication No. WO 91/09967; and U.S. Pat. Nos. 5,225,539, 5,530,101, and 5,585,089, each of which is incorporated herein in its entirety by reference), veneering or resurfacing (see, e.g., European Patent Nos. EP 592,106 and EP 519,596; Padlan, 1991, Molecular Immunology, 28(4/5):489-498; Studnicka et al., 1994, Protein Engineering, 7(6):805-814; and Roguska et al., 1994, PNAS, 91:969-973, each of which is incorporated herein by its entirety by reference), chain shuffling (see, e.g., U.S. Pat. No. 5,565,332, which is incorporated herein in its entirety by reference), and techniques disclosed in, e.g., U.S. Patent Application Publication No. US2005/0042664, U.S. Patent Application Publication No. US2005/0048617, U.S. Pat. No. 6,407,213, U.S. Pat. No. 5,766,886, International Publication No. WO 9317105, Tan et al., J. Immunol., 169:1119-25 (2002), Caldas et al., Protein Eng., 13(5):353-60 (2000), Morea et al., Methods, 20(3):267-79 (2000), Baca et al., J. Biol. Chem., 272(16):10678-84 (1997), Roguska et al., Protein Eng., 9(10):895-904 (1996), Couto et al., Cancer Res., 55 (23 Supp):5973s-5977s (1995), Couto et al., Cancer Res., 55(8):1717-22 (1995), Sandhu J S, Gene, 150(2):409-10 (1994), and Pedersen et al., J. Mol. Biol., 235(3):959-73 (1994), each of which is incorporated herein in its entirety by reference. Often, framework residues in the framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, for example improve, antigen binding. These framework

substitutions, e.g., conservative substitutions are identified by methods well-known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Pat. No. 5,585,089; and Riechmann et al., 1988, Nature, 332:323, which are incorporated herein by reference in their entireties.)

A humanized antibody or antibody fragment has one or more amino acid residues remaining in it from a source which is nonhuman. These nonhuman amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. As provided herein, humanized antibodies or antibody fragments comprise one or more CDRs from nonhuman immunoglobulin molecules and framework regions wherein the amino acid residues comprising the framework are derived completely or mostly from human germline. Multiple techniques for humanization of antibodies or antibody fragments are well-known in the art and can essentially be performed following the method of Winter and co-workers (Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-327 (1988); Verhoeyen et al., Science, 239:1534-1536 (1988)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody, i.e., CDR-grafting (EP 239,400; PCT Publication No. WO 91/09967; and U.S. Pat. Nos. 4,816,567; 6,331,415; 5,225,539; 5,530,101; 5,585,089; 6,548,640, the contents of which are incorporated herein by reference herein in their entirety). In such humanized antibodies and antibody fragments, substantially less than an intact human variable domain has been substituted by the corresponding sequence from a nonhuman species. Humanized antibodies are often human antibodies in which some CDR residues and possibly some framework (FR) residues are substituted by residues from analogous sites in rodent antibodies. Humanization of antibodies and antibody fragments can also be achieved by veneering or resurfacing (EP 592,106; EP 519,596; Padlan, 1991, Molecular Immunology, 28(4/5):489-498; Studnicka et al., Protein Engineering, 7(6):805-814 (1994); and Roguska et al., PNAS, 91:969-973 (1994)) or chain shuffling (U.S. Pat. No. 5,565,332), the contents of which are incorporated herein by reference herein in their entirety.

The choice of human variable domains, both light and heavy, to be used in making the humanized antibodies is to reduce antigenicity. According to the so-called "best-fit" method,

the sequence of the variable domain of a rodent antibody is screened against the entire library of known human variable-domain sequences. The human sequence which is closest to that of the rodent is then accepted as the human framework (FR) for the humanized antibody (Sims et al., J. Immunol., 151:2296 (1993); Chothia et al., J. Mol. Biol., 196:901 (1987), the contents of which are incorporated herein by reference herein in their entirety). Another method uses a particular framework derived from the consensus sequence of all human antibodies of a particular subgroup of light or heavy chains. The same framework may be used for several different humanized antibodies (see, e.g., Nicholson et al. Mol. Immun. 34 (16-17): 1157-1165 (1997); Carter et al., Proc. Natl. Acad. Sci. USA, 89:4285 (1992); Presta et al., J. Immunol., 151:2623 (1993), the contents of which are incorporated herein by reference herein in their entirety). In some embodiments, the framework region, e.g., all four framework regions, of the heavy chain variable region are derived from a VH4_4-59 germline sequence. In one embodiment, the framework region can comprise, one, two, three, four or five modifications, e.g., substitutions, e.g., conservative substitutions, e.g., from the amino acid at the corresponding murine sequence. In one embodiment, the framework region, e.g., all four framework regions of the light chain variable region are derived from a VK3_1.25 germline sequence. In one embodiment, the framework region can comprise, one, two, three, four or five modifications, e.g., substitutions, e.g., conservative substitutions, e.g., from the amino acid at the corresponding murine sequence.

In some aspects, the portion of a CAR composition of the invention that comprises an antibody fragment is humanized with retention of high affinity for the target antigen and other favorable biological properties. According to one aspect of the invention, humanized antibodies and antibody fragments are prepared by a process of analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, e.g., the analysis of residues that influence the ability of the candidate immunoglobulin to bind the target antigen. In this way, FR residues can be selected and combined from the recipient and import sequences

so that the desired antibody or antibody fragment characteristic, such as increased affinity for the target antigen, is achieved. In general, the CDR residues are directly and most substantially involved in influencing antigen binding.

A humanized antibody or antibody fragment may retain a similar antigenic specificity as the original antibody, e.g., in the present invention, the ability to bind human BCMA In some embodiments, a humanized antibody or antibody fragment may have improved affinity and/or specificity of binding to human BCMA.

In one embodiment, the humanized anti-BCMA binding domain of the CAR, comprises one or more (e.g., all three) light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and light chain complementary determining region 3 (LC CDR3) of a humanized anti-BCMA binding domain described herein, and/or one or more (e.g., all three) heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of a humanized anti-BCMA binding domain described herein, e.g., a humanized anti-BCMA binding domain comprising one or more, e.g., all three, LC CDRs and one or more, e.g., all three, HC CDRs. In one embodiment, the humanized anti-BCMA binding domain comprises one or more (e.g., all three) heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of a humanized anti-BCMA binding domain described herein, e.g., the humanized anti-BCMA binding domain has two variable heavy chain regions, each comprising a HC CDR1, a HC CDR2 and a HC CDR3 described herein. In one embodiment, the humanized anti-BCMA binding domain comprises a humanized light chain variable region described herein (e.g., SEQ ID NO:255 or 257) and/or a human heavy chain variable region described herein (e.g., SEQ ID NO:255 or 257).

In one aspect, the anti-BCMA binding domain is characterized by particular functional features or properties of an antibody or antibody fragment. For example, in one aspect, the portion of a CAR composition of the invention that comprises an antigen binding domain specifically binds human BCMA

In one aspect, the antigen binding domain has the same or a similar binding specificity to human BCMA as mouse BCMA. In one aspect, the invention relates to an antigen binding domain comprising an antibody or antibody fragment, wherein the antibody binding domain specifically binds to a BCMA protein or fragment thereof, wherein the antibody or antibody fragment comprises a variable light chain and/or a variable heavy chain that includes an amino acid sequence of SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, or SEQ ID NO: 149. In one aspect, the antigen binding domain comprises an amino acid sequence of an scFv selected from SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, or SEQ ID NO: 149. In certain aspects, the scFv is contiguous with and in the same reading frame as a leader sequence. In one aspect the leader sequence is the polypeptide sequence provided as SEQ ID NO:1.

In one aspect, the anti-BCMA binding domain is a fragment, e.g., a single chain variable fragment (scFv). In one aspect, the anti-BCMA binding domain is a Fv, a Fab, a (Fab')2, or a bi-functional (e.g. bi-specific) hybrid antibody (e.g., Lanzavecchia et al., Eur. J. Immunol. 17, 105 (1987)). In one aspect, the antibodies and fragments thereof of the invention binds a BCMA protein with wild-type or enhanced affinity.

In some instances, scFvs can be prepared according to method known in the art (see, for example, Bird et al., (1988) Science 242:423-426 and Huston et al., (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883). ScFv molecules can be produced by linking VH and VL regions

together using flexible polypeptide linkers. The scFv molecules comprise a linker (e.g., a Ser-Gly linker) with an optimized length and/or amino acid composition. The linker length can greatly affect how the variable regions of a scFv fold and interact. In fact, if a short polypeptide linker is employed (e.g., between 5-10 amino acids) intrachain folding is prevented. Interchain folding is also required to bring the two variable regions together to form a functional epitope binding site. For examples of linker orientation and size see, e.g., Hollinger et al. 1993 Proc Natl Acad. Sci. U.S.A. 90:6444-6448, U.S. Patent Application Publication Nos. 2005/0100543, 2005/0175606, 2007/0014794, and PCT publication Nos. WO2006/020258 and WO2007/024715, is incorporated herein by reference.

An scFv can comprise a linker of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, or more amino acid residues between its VL and VH regions. The linker sequence may comprise any naturally occurring amino acid. In some embodiments, the linker sequence comprises amino acids glycine and serine. In another embodiment, the linker sequence comprises sets of glycine and serine repeats such as $(Gly_4Ser)n$, where n is a positive integer equal to or greater than 1 (SEQ ID NO:25). In one embodiment, the linker can be $(Gly_4Ser)_4$ (SEQ ID NO:27) or $(Gly_4Ser)_3$(SEQ ID NO:28). Variation in the linker length may retain or enhance activity, giving rise to superior efficacy in activity studies.

Exemplary Human BCMA CAR Constructs and Antigen Binding Domains

Exemplary BCMA CAR constructs disclose herein comprise an scFv (e.g., a scFv as disclosed in Tables 1 or 16, optionally preceded with an optional leader sequence (e.g., SEQ ID NO:1 and SEQ ID NO:12 for exemplary leader amino acid and nucleotide sequences, respectively). The sequences of the scFv fragments (SEQ ID NOs: 39-53, 129-149, or 263-266, not including the optional leader sequence) are provided herein in Tables 1 or 16. The BCMA CAR construct can further include an optional hinge domain, e.g., a CD8 hinge domain (e.g., including the amino acid sequence of SEQ ID NO: 2 or encoded by a nucleic acid sequence of SEQ ID NO:13); a transmembrane domain, e.g., a CD8 transmembrane domain (e.g., including the amino acid sequence of SEQ ID NO: 6 or encoded by the nucleotide sequence of SEQ ID NO: 17); an intracellular domain, e.g., a 4-1BB intracellular domain (e.g., including the amino acid sequence of SEQ ID NO: 7 or encoded by the nucleotide sequence of SEQ ID NO: 18; and a functional signaling domain, e.g., a CD3 zeta domain (e.g., including

amino acid sequence of SEQ ID NO: 9 or 10, or encoded by the nucleotide sequence of SEQ ID NO: 20 or 21). In certain embodiments, the domains are contiguous with and in the same reading frame to form a single fusion protein. In other embodiments, the domain are in separate polypeptides, e.g., as in an RCAR molecule as described herein.

In certain embodiments, the full length BCMA CAR molecule includes the amino acid sequence of, or is encoded by the nucleotide sequence of, BCMA-1, BCMA-2, BCMA-3, BCMA-4, BCMA-5, BCMA-6, BCMA-7, BCMA-8, BCMA-9, BCMA-10, BCMA-11, BCMA-12, BCMA-13, BCMA-14, BCMA-15, 149362, 149363, 149364, 149365, 149366, 149367, 149368, 149369, BCMA_EBB-C1978-A4, BCMA_EBB-C1978-G1, BCMA_EBB-C1979-C1, BCMA_EBB-C1978-C7, BCMA_EBB-C1978-D10, BCMA_EBB-C1979-C12, BCMA_EBB-C1980-G4, BCMA_EBB-C1980-D2, BCMA_EBB-C1978-A10, BCMA_EBB-C1978-D4, BCMA_EBB-C1980-A2, BCMA_EBB-C1981-C3, BCMA_EBB-C1978-G4, A7D12.2, C11D5.3, C12A3.2, or C13F12.1 provided in Table 1 or 16, or a sequence substantially (e.g., 95-99%) identical thereto.

In certain embodiments, the BCMA CAR molecule, or the anti-BCMA antigen binding domain, includes the scFv amino acid sequence of BCMA-1, BCMA-2, BCMA-3, BCMA-4, BCMA-5, BCMA-6, BCMA-7, BCMA-8, BCMA-9, BCMA-10, BCMA-11, BCMA-12, BCMA-13, BCMA-14, BCMA-15, 149362, 149363, 149364, 149365, 149366, 149367, 149368, 149369, BCMA_EBB-C1978-A4, BCMA_EBB-C1978-G1, BCMA_EBB-C1979-C1, BCMA_EBB-C1978-C7, BCMA_EBB-C1978-D10, BCMA_EBB-C1979-C12, BCMA_EBB-C1980-G4, BCMA_EBB-C1980-D2, BCMA_EBB-C1978-A10, BCMA_EBB-C1978-D4, BCMA_EBB-C1980-A2, BCMA_EBB-C1981-C3, BCMA_EBB-C1978-G4, A7D12.2, C11D5.3, C12A3.2, or C13F12.1 provided in Table 1 or 16 (with or without the leader sequence), or a sequence substantially identical (e.g., 95-99% identical, or up to 20, 15, 10, 8, 6, 5, 4, 3, 2, or 1 amino acid changes, e.g., substitutions (e.g., conservative substitutions)) to any of the aforesaid sequences.

In certain embodiments, the BCMA CAR molecule, or the anti-BCMA antigen binding domain, includes the heavy chain variable region and/or the light chain variable region of BCMA-1, BCMA-2, BCMA-3, BCMA-4, BCMA-5, BCMA-6, BCMA-7, BCMA-8, BCMA-9, BCMA-10, BCMA-11, BCMA-12, BCMA-13, BCMA-14, BCMA-15, 149362, 149363, 149364, 149365, 149366, 149367, 149368, 149369, BCMA_EBB-C1978-A4, BCMA_EBB-C1978-G1, BCMA_EBB-C1979-C1, BCMA_EBB-C1978-C7, BCMA_EBB-C1978-D10, BCMA_EBB-C1979-C12, BCMA_EBB-C1980-G4, BCMA_EBB-C1980-D2, BCMA_EBB-C1978-A10, BCMA_EBB-C1978-D4, BCMA_EBB-C1980-A2, BCMA_EBB-C1981-C3, BCMA_EBB-

C1978-G4, A7D12.2, C11D5.3, C12A3.2, or C13F12.1 provided in Table 1 or 16, or a sequence substantially identical (e.g., 95-99% identical, or up to 20, 15, 10, 8, 6, 5, 4, 3, 2, or 1 amino acid changes, e.g., substitutions (e.g., conservative substitutions)) to any of the aforesaid sequences.

In certain embodiments, the BCMA CAR molecule, or the anti-BCMA antigen binding domain, includes one, two or three CDRs from the heavy chain variable region (e.g., HCDR1, HCDR2 and/or HCDR3), provided in Table 20; and/or one, two or three CDRs from the light chain variable region (e.g., LCDR1, LCDR2 and/or LCDR3) of BCMA-1, BCMA-2, BCMA-3, BCMA-4, BCMA-5, BCMA-6, BCMA-7, BCMA-8, BCMA-9, BCMA-10, BCMA-11, BCMA-12, BCMA-13, BCMA-14, BCMA-15, 149362, 149363, 149364, 149365, 149366, 149367, 149368, 149369, BCMA_EBB-C1978-A4, BCMA_EBB-C1978-G1, BCMA_EBB-C1979-C1, BCMA_EBB-C1978-C7, BCMA_EBB-C1978-D10, BCMA_EBB-C1979-C12, BCMA_EBB-C1980-G4, BCMA_EBB-C1980-D2, BCMA_EBB-C1978-A10, BCMA_EBB-C1978-D4, BCMA_EBB-C1980-A2, BCMA_EBB-C1981-C3, BCMA_EBB-C1978-G4, A7D12.2, C11D5.3, C12A3.2, or C13F12.1, provided in Table 21; or a sequence substantially identical (e.g., 95-99% identical, or up to 20, 15, 10, 8, 6, 5, 4, 3, 2, or 1 amino acid changes, e.g., substitutions (e.g., conservative substitutions)) to any of the aforesaid sequences.

In certain embodiments, the BCMA CAR molecule, or the anti-BCMA antigen binding domain, includes one, two or three CDRs from the heavy chain variable region (e.g., HCDR1, HCDR2 and/or HCDR3), provided in Table 22; and/or one, two or three CDRs from the light chain variable region (e.g., LCDR1, LCDR2 and/or LCDR3) of BCMA-1, BCMA-2, BCMA-3, BCMA-4, BCMA-5, BCMA-6, BCMA-7, BCMA-8, BCMA-9, BCMA-10, BCMA-11, BCMA-12, BCMA-13, BCMA-14, BCMA-15, 149362, 149363, 149364, 149365, 149366, 149367, 149368, 149369, BCMA_EBB-C1978-A4, BCMA_EBB-C1978-G1, BCMA_EBB-C1979-C1, BCMA_EBB-C1978-C7, BCMA_EBB-C1978-D10, BCMA_EBB-C1979-C12, BCMA_EBB-C1980-G4, BCMA_EBB-C1980-D2, BCMA_EBB-C1978-A10, BCMA_EBB-C1978-D4, BCMA_EBB-C1980-A2, BCMA_EBB-C1981-C3, BCMA_EBB-C1978-G4, A7D12.2, C11D5.3, C12A3.2, or C13F12.1, provided in Table 23; or a sequence substantially identical (e.g., 95-99% identical, or up to 20, 15, 10, 8, 6, 5, 4, 3, 2, or 1 amino acid changes, e.g., substitutions (e.g., conservative substitutions)) to any of the aforesaid sequences.

In certain embodiments, the BCMA CAR molecule, or the anti-BCMA antigen binding domain, includes one, two or three CDRs from the heavy chain variable region (e.g., HCDR1,

HCDR2 and/or HCDR3), provided in Table 24; and/or one, two or three CDRs from the light chain variable region (e.g., LCDR1, LCDR2 and/or LCDR3) of BCMA-1, BCMA-2, BCMA-3, BCMA-4, BCMA-5, BCMA-6, BCMA-7, BCMA-8, BCMA-9, BCMA-10, BCMA-11, BCMA-12, BCMA-13, BCMA-14, BCMA-15, 149362, 149363, 149364, 149365, 149366, 149367, 149368, 149369, BCMA_EBB-C1978-A4, BCMA_EBB-C1978-G1, BCMA_EBB-C1979-C1, BCMA_EBB-C1978-C7, BCMA_EBB-C1978-D10, BCMA_EBB-C1979-C12, BCMA_EBB-C1980-G4, BCMA_EBB-C1980-D2, BCMA_EBB-C1978-A10, BCMA_EBB-C1978-D4, BCMA_EBB-C1980-A2, BCMA_EBB-C1981-C3, BCMA_EBB-C1978-G4, A7D12.2, C11D5.3, C12A3.2, or C13F12.1, provided in Table 25; or a sequence substantially identical (e.g., 95-99% identical, or up to 20, 15, 10, 8, 6, 5, 4, 3, 2, or 1 amino acid changes, e.g., substitutions (e.g., conservative substitutions)) to any of the aforesaid sequences.

The sequences of human CDR sequences of the scFv domains are shown in Tables 20, 22, and 24 for the heavy chain variable domains and in Tables 21, 23, and 25 for the light chain variable domains. "ID" stands for the respective SEQ ID NO for each CDR.

Table 20: Heavy Chain Variable Domain CDRs according to the Kabat numbering scheme (Kabat et al. (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD)

Candidate	HCDR1	ID	HCDR2	ID	HCDR3	ID
139109	NHGMS	394	GIVYSGSTYYAASVKG	434	HGGESDV	474
139103	NYAMS	384	GISRSGENTYYADSVKG	424	SPAHYYGGMDV	464
139105	DYAMH	385	GISWNSGSIGYADSVKG	425	HSFLAY	465
139111	NHGMS	386	GIVYSGSTYYAASVKG	426	HGGESDV	466
139100	NFGIN	387	WINPKNNNTNYAQKFQG	427	GPYYYQSYMDV	467
139101	SDAMT	388	VISGSGGTTYYADSVKG	428	LDSSGYYYARGPRY	468
139102	NYGIT	389	WISAYNGNTNYAQKFQG	429	GPYYYYMDV	469
139104	NHGMS	390	GIVYSGSTYYAASVKG	430	HGGESDV	470
139106	NHGMS	391	GIVYSGSTYYAASVKG	431	HGGESDV	471
139107	NHGMS	392	GIVYSGSTYYAASVKG	432	HGGESDV	472
139108	DYYMS	393	YISSSGSTIYYADSVKG	433	ESGDGMDV	473

139110	DYYMS	395	YISSSGNTIYYADSVKG	435	STMVREDY	475
139112	NHGMS	396	GIVYSGSTYYAASVKG	436	HGGESDV	476
139113	NHGMS	397	GIVYSGSTYYAASVKG	437	HGGESDV	477
139114	NHGMS	398	GIVYSGSTYYAASVKG	438	HGGESDV	478
149362	SSYYYWG	399	SIYYSGSAYYNPSLKS	439	HWQEWPDAFDI	479
149363	TSGMCVS	400	RIDWDEDKFYSTSLKT	440	SGAGGTSATAFDI	480
149364	SYSMN	401	SISSSSSYIYYADSVKG	441	TIAAVYAFDI	481
149365	DYYMS	402	YISSSGSTIYYADSVKG	442	DLRGAFDI	482
149366	SHYIH	403	MINPSGGVTAYSQTLQG	443	EGSGSGWYFDF	483
149367	SGGYYWS	404	YIYYSGSTYYNPSLKS	444	AGIAARLRGAFDI	484
149368	SYAIS	405	GIIPIFGTANYAQKFQG	445	RGGYQLLRWDVGLLRSAFDI	485
149369	SNSAAWN	406	RTYYRSKWYSFYAISLKS	446	SSPEGLFLYWFDP	486
BCMA_EBB-C1978-A4	SYAMS	407	AISGSGGSTYYADSVKG	447	VEGSGSLDY	487
BCMA_EBB-C1978-G1	RYPMS	408	GISDSGVSTYYADSAKG	448	RAGSEASDI	488
BCMA_EBB-C1979-C1	SYAMS	409	AISGSGGSTYYADSVKG	449	ATYKRELRYYYGMDV	489
BCMA_EBB-C1978-C7	SYAMS	410	AISGSGGSTYYADSVKG	450	ATYKRELRYYYGMDV	490
BCMA_EBB-C1978-D10	DYAMH	411	GISWNSGSIGYADSVKG	451	VGKAVPDV	491
BCMA_EBB-C1979-C12	DYAMH	412	SINWKGNSLAYGDSVKG	452	HQGVAYYNYAMDV	492
BCMA_EBB-C1980-G4	SYAMS	413	AISGSGGSTYYADSVKG	453	VVRDGMDV	493
BCMA_EBB-C1980-D2	SYAMS	414	AISGSGGSTYYADSVKG	454	IPQTGTFDY	494
BCMA_EBB-C1978-A10	SYAMS	415	AISGSGGSTYYADSVKG	455	ANYKRELRYYYGMDV	495
BCMA_EBB-C1978-D4	SYAMS	416	AISGSGGSTYYADSVKG	456	ALVGATGAFDI	496
BCMA_EBB-C1980-A2	SYAMS	417	AISGSGGSTYYADSVKG	457	WFGEGFDP	497
BCMA_EBB-C1981-C3	SYAMS	418	AISGSGGSTYYADSVKG	458	VGYDSSGYYRDYYGMDV	498
BCMA_EBB-C1978-G4	SYAMS	419	AISGSGGSTYYADSVKG	459	MGWSSGYLGAFDI	499
A7D12.2	NFGMN	420	WINTYTGESYFADDFKG	460	GEIYYGYDGGFAY	500
C11D5.3	DYSIN	421	WINTETREPAYAYDFRG	461	DYSYAMDY	501
C12A3.2	HYSMN	422	RINTESGVPIYADDF	462	DYLYSLDF	502

			KG			
C13F12.1	HYSMN	423	RINTETGEPLYADDFKG	463	DYLYSCDY	503

Table 21: Light Chain Variable Domain CDRs according to the Kabat numbering scheme (Kabat et al. (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD)

Candidate	LCDR1	ID	LCDR2	ID	LCDR3	ID
139109	RASQSISSYLN	514	AASSLQS	554	QQSYSTPYT	594
139103	RASQSISSSFLA	504	GASRRAT	544	QQYHSSPSWT	584
139105	RSSQSLLHSNGYNYLD	505	LGSNRAS	545	MQALQTPYT	585
139111	KSSQSLLRNDGKTPLY	506	EVSNRFS	546	MQNIQFPS	586
139100	RSSQSLLHSNGYNYLN	507	LGSKRAS	547	MQALQTPYT	587
139101	RASQSISSYLN	508	GASTLAS	548	QQSYKRAS	588
139102	RSSQSLLYSNGYNYVD	509	LGSNRAS	549	MQGRQFPYS	589
139104	RASQSVSSNLA	510	GASTRAS	550	QQYGSSLT	590
139106	RASQSVSSKLA	511	GASIRAT	551	QQYGSSSWT	591
139107	RASQSVGSTNLA	512	DASNRAT	552	QQYGSSPPWT	592
139108	RASQSISSYLN	513	AASSLQS	553	QQSYTLA	593
139110	KSSESLVHNSGKTYLN	515	EVSNRDS	555	MQGTHWPGT	595
139112	QASEDINKFLN	516	DASTLQT	556	QQYESLPLT	596
139113	RASQSVGSNLA	517	GASTRAT	557	QQYNDWLPVT	597
139114	RASQSIGSSSLA	518	GASSRAS	558	QQYAGSPPFT	598
149362	KASQDIDDAMN	519	SATSPVP	559	LQHDNFPLT	599
149363	RASQDIYNNLA	520	AANKSQS	560	QHYYRFPYS	600
149364	RSSQSLLHSNGYNYLD	521	LGSNRAS	561	MQALQTPYT	601
149365	GGNNIGTKSVH	522	DDSVRPS	562	QVWDSDSEHVV	602
149366	SGDGLSKKYVS	523	RDKERPS	563	QAWDDTTVV	603
149367	RASQGIRNWLA	524	AASNLQS	564	QKYNSAPFT	604
149368	GGNNIGSKSVH	525	GKNNRPS	565	SSRDSSGDHLRV	605
149369	QGDSLGNYYAT	526	GTNNRPS	566	NSRDSSGHHLL	606
BCMA_EBB-C1978-A4	RASQSVSSAYLA	527	GASTRAT	567	QHYGSSFNGSSLFT	607
BCMA_EBB-C1978-G1	RASQSVSNSLA	528	DASSRAT	568	QQFGTSSGLT	608
BCMA_EBB-C1979-C1	RASQSVSSSFLA	529	GASSRAT	569	QQYHSSPSWT	609
BCMA_EBB-C1978-C7	RASQSVSTTFLA	530	GSSNRAT	570	QQYHSSPSWT	610
BCMA_EBB-C1978-D10	RASQSISSYLN	531	AASSLQS	571	QQSYSTPYS	611
BCMA_EBB-C1979-C12	RATQSIGSSFLA	532	GASQRAT	572	QHYESSPSWT	612

BCMA_EBB-C1980-G4	RASQSVSSSYLA	533	GASSRAT	573	QQYGSPPRFT	613
BCMA_EBB-C1980-D2	RASQSVSSSYLA	534	GASSRAT	574	QHYGSSPSWT	614
BCMA_EBB-C1978-A10	RASQRVASNYLA	535	GASSRAT	575	QHYDSSPSWT	615
BCMA_EBB-C1978-D4	RASQSLSSNFLA	536	GASNWAT	576	QYYGTSPMYT	616
BCMA_EBB-C1980-A2	RSSQSLLHSNGYNYLD	537	LGSNRAS	577	MQALQTPLT	617
BCMA_EBB-C1981-C3	RASQSVSSSYLA	538	GTSSRAT	578	QHYGNSPPKFT	618
BCMA_EBB-C1978-G4	RASQSVASSFLA	539	GASGRAT	579	QHYGGSPRLT	619
A7D12.2	RASQDVNTAVS	540	SASYRYT	580	QQHYSTPWT	620
C11D5.3	RASESVSVIGAHLIH	541	LASNLET	581	LQSRIFPRT	621
C12A3.2	RASESVTILGSHLIY	542	LASNVQT	582	LQSRTIPRT	622
C13F12.1	RASESVTILGSHLIY	543	LASNVQT	583	LQSRTIPRT	623

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Table 22: Heavy Chain Variable Domain CDRs according to the Chothia numbering scheme (Al-Lazikani et al., (1997) JMB 273,927-948)

Candidate	**HCDR1**	**ID**	**HCDR2**	**ID**	**HCDR3**	**ID**
139109	GFALSNH	634	VYSGS	674	HGGESDV	714
139103	GFTFSNY	624	SRSGEN	664	SPAHYYGGMDV	704
139105	GFTFDDY	625	SWNSGS	665	HSFLAY	705
139111	GFALSNH	626	VYSGS	666	HGGESDV	706
139100	GYIFDNF	627	NPKNNN	667	GPYYYQSYMDV	707
139101	GFTFSSD	628	SGSGGT	668	LDSSGYYYARGPRY	708
139102	GYTFSNY	629	SAYNGN	669	GPYYYYMDV	709
139104	GFALSNH	630	VYSGS	670	HGGESDV	710
139106	GFALSNH	631	VYSGS	671	HGGESDV	711
139107	GFALSNH	632	VYSGS	672	HGGESDV	712
139108	GFTFSDY	633	SSSGST	673	ESGDGMDV	713
139110	GFTFSDY	635	SSSGNT	675	STMVREDY	715
139112	GFALSNH	636	VYSGS	676	HGGESDV	716
139113	GFALSNH	637	VYSGS	677	HGGESDV	717
139114	GFALSNH	638	VYSGS	678	HGGESDV	718
149362	GGSISSSYY	639	YYSGS	679	HWQEWPDAFDI	719
149363	GFSLRTSGM	640	DWDED	680	SGAGGTSATAFDI	720
149364	GFTFSSY	641	SSSSSY	681	TIAAVYAFDI	721
149365	GFTFSDY	642	SSSGST	682	DLRGAFDI	722
149366	GYTVTSH	643	NPSGGV	683	EGSGSGWYFDF	723
149367	GGSISSGGY	644	YYSGS	684	AGIAARLRGAFDI	724
149368	GGTFSSY	645	IPIFGT	685	RGGYQLLRWDVGLLRSAFDI	725

149369	GDSVSSNSA	646	YYRSKWY	686	SSPEGLFLYWFDP	726
BCMA_EBB-C1978-A4	GFTFSSY	647	SGSGGS	687	VEGSGSLDY	727
BCMA_EBB-C1978-G1	GITFSRY	648	SDSGVS	688	RAGSEASDI	728
BCMA_EBB-C1979-C1	GFTFSSY	649	SGSGGS	689	ATYKRELRYYYGMDV	729
BCMA_EBB-C1978-C7	GFTFSSY	650	SGSGGS	690	ATYKRELRYYYGMDV	730
BCMA_EBB-C1978-D10	GFTFDDY	651	SWNSGS	691	VGKAVPDV	731
BCMA_EBB-C1979-C12	GFTFDDY	652	NWKGNS	692	HQGVAYYNYAMDV	732
BCMA_EBB-C1980-G4	GFTFSSY	653	SGSGGS	693	VVRDGMDV	733
BCMA_EBB-C1980-D2	GFTFSSY	654	SGSGGS	694	IPQTGTFDY	734
BCMA_EBB-C1978-A10	GFTFSSY	655	SGSGGS	695	ANYKRELRYYYGMDV	735
BCMA_EBB-C1978-D4	GFSFSSY	656	SGSGGS	696	ALVGATGAFDI	736
BCMA_EBB-C1980-A2	GFTFSSY	657	SGSGGS	697	WFGEGFDP	737
BCMA_EBB-C1981-C3	GFTFSSY	658	SGSGGS	698	VGYDSSGYYRDYYGMDV	738
BCMA_EBB-C1978-G4	GFTFSSY	659	SGSGGS	699	MGWSSGYLGAFDI	739
A7D12.2	GYTFTNF	660	NTYTGE	700	GEIYYGYDGGFAY	740
C11D5.3	GYTFTDY	661	NTETRE	701	DYSYAMDY	741
C12A3.2	GYTFRHY	662	NTESGV	702	DYLYSLDF	742
C13F12.1	GYTFTHY	663	NTETGE	703	DYLYSCDY	743

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Table 23: Light Chain Variable Domain CDRs according to the Chothia numbering scheme (Al-Lazikani et al., (1997) JMB 273,927-948)

Candidate	**LCDR1**	**ID**	**LCDR2**	**ID**	**LCDR3**	**ID**
139109	SQSISSY	754	AAS	794	SYSTPY	834
139103	SQSISSSF	744	GAS	784	YHSSPSW	824
139105	SQSLLHSNGYNY	745	LGS	785	ALQTPY	825
139111	SQSLLRNDGKTP	746	EVS	786	NIQFP	826
139100	SQSLLHSNGYNY	747	LGS	787	ALQTPY	827
139101	SQSISSY	748	GAS	788	SYKRA	828
139102	SQSLLYSNGYNY	749	LGS	789	GRQFPY	829
139104	SQSVSSN	750	GAS	790	YGSSL	830
139106	SQSVSSK	751	GAS	791	YGSSSW	831
139107	SQSVGSTN	752	DAS	792	YGSSPPW	832
139108	SQSISSY	753	AAS	793	SYTL	833
139110	SESLVHNSGKTY	755	EVS	795	GTHWPG	835

139112	SEDINKF	756	DAS	796	YESLPL	836
139113	SQSVGSN	757	GAS	797	YNDWLPV	837
139114	SQSIGSSS	758	GAS	798	YAGSPPF	838
149362	SQDIDDA	759	SAT	799	HDNFPL	839
149363	SQDIYNN	760	AAN	800	YYRFPY	840
149364	SQSLLHSNGYNY	761	LGS	801	ALQTPY	841
149365	NNIGTKS	762	DDS	802	WDSDSEHV	842
149366	DGLSKKY	763	RDK	803	WDDTTV	843
149367	SQGIRNW	764	AAS	804	YNSAPF	844
149368	NNIGSKS	765	GKN	805	RDSSGDHLR	845
149369	DSLGNYY	766	GTN	806	RDSSGHHL	846
BCMA_EBB-C1978-A4	SQSVSSAY	767	GAS	807	YGSSFNGSSLF	847
BCMA_EBB-C1978-G1	SQSVSNS	768	DAS	808	FGTSSGL	848
BCMA_EBB-C1979-C1	SQSVSSSF	769	GAS	809	YHSSPSW	849
BCMA_EBB-C1978-C7	SQSVSTTF	770	GSS	810	YHSSPSW	850
BCMA_EBB-C1978-D10	SQSISSY	771	AAS	811	SYSTPY	851
BCMA_EBB-C1979-C12	TQSIGSSF	772	GAS	812	YESSPSW	852
BCMA_EBB-C1980-G4	SQSVSSSY	773	GAS	813	YGSPPRF	853
BCMA_EBB-C1980-D2	SQSVSSSY	774	GAS	814	YGSSPSW	854
BCMA_EBB-C1978-A10	SQRVASNY	775	GAS	815	YDSSPSW	855
BCMA_EBB-C1978-D4	SQSLSSNF	776	GAS	816	YGTSPMY	856
BCMA_EBB-C1980-A2	SQSLLHSNGYNY	777	LGS	817	ALQTPL	857
BCMA_EBB-C1981-C3	SQSVSSSY	778	GTS	818	YGNSPPKF	858
BCMA_EBB-C1978-G4	SQSVASSF	779	GAS	819	YGGSPRL	859
A7D12.2	SQDVNTA	780	SAS	820	HYSTPW	860
C11D5.3	SESVSVIGAHL	781	LAS	821	SRIFPR	861
C12A3.2	SESVTILGSHL	782	LAS	822	SRTIPR	862
C13F12.1	SESVTILGSHL	783	LAS	823	SRTIPR	863

Table 24. Heavy Chain Variable Domain CDRs according to a combination of the Kabat numbering scheme (Kabat et al. (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD) and the Chothia numbering scheme (Al-Lazikani et al., (1997) JMB 273,927-948).

Candidate	HCDR1	ID	HCDR2	ID	HCDR3	ID
139109	GFALSNHGMS	874	GIVYSGSTYYAASVKG	914	HGGESDV	954
139103	GFTFSNYAMS	864	GISRSGENTYYADSVKG	904	SPAHYYGGMDV	944
139105	GFTFDDYAMH	865	GISWNSGSIGYADSVKG	905	HSFLAY	945
139111	GFALSNHGMS	866	GIVYSGSTYYAASVKG	906	HGGESDV	946
139100	GYIFDNFGIN	867	WINPKNNNTNYAQKFQG	907	GPYYYQSYMDV	947
139101	GFTFSSDAMT	868	VISGSGGTTYYADSVKG	908	LDSSGYYYARGPRY	948
139102	GYTFSNYGIT	869	WISAYNGNTNYAQKFQG	909	GPYYYYMDV	949
139104	GFALSNHGMS	870	GIVYSGSTYYAASVKG	910	HGGESDV	950
139106	GFALSNHGMS	871	GIVYSGSTYYAASVKG	911	HGGESDV	951
139107	GFALSNHGMS	872	GIVYSGSTYYAASVKG	912	HGGESDV	952
139108	GFTFSDYYMS	873	YISSSGSTIYYADSVKG	913	ESGDGMDV	953
139110	GFTFSDYYMS	875	YISSSGNTIYYADSVKG	915	STMVREDY	955
139112	GFALSNHGMS	876	GIVYSGSTYYAASVKG	916	HGGESDV	956
139113	GFALSNHGMS	877	GIVYSGSTYYAASVKG	917	HGGESDV	957
139114	GFALSNHGMS	878	GIVYSGSTYYAASVKG	918	HGGESDV	958
149362	GGSISSSYYYWG	879	SIYYSGSAYYNPSLKS	919	HWQEWPDAFDI	959
149363	GFSLRTSGMCVS	880	RIDWDEDKFYSTSLKT	920	SGAGGTSATAFDI	960
149364	GFTFSSYSMN	881	SISSSSSYIYYADSVKG	921	TIAAVYAFDI	961
149365	GFTFSDYYMS	882	YISSSGSTIYYADSVKG	922	DLRGAFDI	962
149366	GYTVTSHYIH	883	MINPSGGVTAYSQTLQG	923	EGSGSGWYFDF	963
149367	GGSISSGGYYWS	884	YIYYSGSTYYNPSLKS	924	AGIAARLRGAFDI	964
149368	GGTFSSYAIS	885	GIIPIFGTANYAQKFQG	925	RGGYQLLRWDVGLLRSAFDI	965
149369	GDSVSSNSAAWN	886	RTYYRSKWYSFYAISLKS	926	SSPEGLFLYWFDP	966
BCMA_EBB-C1978-A4	GFTFSSYAMS	887	AISGSGGSTYYADSVKG	927	VEGSGSLDY	967
BCMA_EBB-C1978-G1	GITFSRYPMS	888	GISDSGVSTYYADSAKG	928	RAGSEASDI	968
BCMA_EBB-C1979-C1	GFTFSSYAMS	889	AISGSGGSTYYADSVKG	929	ATYKRELRYYYGMDV	969
BCMA_EBB-C1978-C7	GFTFSSYAMS	890	AISGSGGSTYYADSVKG	930	ATYKRELRYYYGMDV	970

BCMA_EBB-C1978-D10	GFTFDDYAMH	891	GISWNSGSIGYADSVKG	931	VGKAVPDV	971
BCMA_EBB-C1979-C12	GFTFDDYAMH	892	SINWKGNSLAYGDSVKG	932	HQGVAYYNYAMDV	972
BCMA_EBB-C1980-G4	GFTFSSYAMS	893	AISGSGGSTYYADSVKG	933	VVRDGMDV	973
BCMA_EBB-C1980-D2	GFTFSSYAMS	894	AISGSGGSTYYADSVKG	934	IPQTGTFDY	974
BCMA_EBB-C1978-A10	GFTFSSYAMS	895	AISGSGGSTYYADSVKG	935	ANYKRELRYYYGMDV	975
BCMA_EBB-C1978-D4	GFSFSSYAMS	896	AISGSGGSTYYADSVKG	936	ALVGATGAFDI	976
BCMA_EBB-C1980-A2	GFTFSSYAMS	897	AISGSGGSTYYADSVKG	937	WFGEGFDP	977
BCMA_EBB-C1981-C3	GFTFSSYAMS	898	AISGSGGSTYYADSVKG	938	VGYDSSGYYRDYYGMDV	978
BCMA_EBB-C1978-G4	GFTFSSYAMS	899	AISGSGGSTYYADSVKG	939	MGWSSGYLGAFDI	979
A7D12.2	GYTFTNFGMN	900	WINTYTGESYFADDFKG	940	GEIYYGYDGGFAY	980
C11D5.3	GYTFTDYSIN	901	WINTETREPAYAYDFRG	941	DYSYAMDY	981
C12A3.2	GYTFRHYSMN	902	RINTESGVPIYADDFKG	942	DYLYSLDF	982
C13F12.1	GYTFTHYSMN	903	RINTETGEPLYADDFKG	943	DYLYSCDY	983

Table 25. Light Chain Variable Domain CDRs according to a combination of the Kabat numbering scheme (Kabat et al. (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD) and the Chothia numbering scheme (Al-Lazikani et al., (1997) JMB 273,927-948).

Candidate	**LCDR1**	**ID**	**LCDR2**	**ID**	**LCDR3**	**ID**
139109	RASQSISSYLN	994	AASSLQS	1034	QQSYSTPYT	1074
139103	RASQSISSSFLA	984	GASRRAT	1024	QQYHSSPSWT	1064
139105	RSSQSLLHSNGYNYLD	985	LGSNRAS	1025	MQALQTPYT	1065
139111	KSSQSLLRNDGKTPLY	986	EVSNRFS	1026	MQNIQFPS	1066
139100	RSSQSLLHSNGYNYLN	987	LGSKRAS	1027	MQALQTPYT	1067
139101	RASQSISSYLN	988	GASTLAS	1028	QQSYKRAS	1068
139102	RSSQSLLYSNGYNYVD	989	LGSNRAS	1029	MQGRQFPYS	1069
139104	RASQSVSSNLA	990	GASTRAS	1030	QQYGSSLT	1070
139106	RASQSVSSKLA	991	GASIRAT	1031	QQYGSSSWT	1071
139107	RASQSVGSTNLA	992	DASNRAT	1032	QQYGSSPPWT	1072
139108	RASQSISSYLN	993	AASSLQS	1033	QQSYTLA	1073
139110	KSSESLVHNSGKTYLN	995	EVSNRDS	1035	MQGTHWPGT	1075
139112	QASEDINKFLN	996	DASTLQT	1036	QQYESLPLT	1076
139113	RASQSVGSNLA	997	GASTRAT	1037	QQYNDWLPVT	1077
139114	RASQSIGSSSLA	998	GASSRAS	1038	QQYAGSPPFT	1078

149362	KASQDIDDAMN	999	SATSPVP	1039	LQHDNFPLT	1079
149363	RASQDIYNNLA	1000	AANKSQS	1040	QHYYRFPYS	1080
149364	RSSQSLLHSNGYNYLD	1001	LGSNRAS	1041	MQALQTPYT	1081
149365	GGNNIGTKSVH	1002	DDSVRPS	1042	QVWDSDSEHVV	1082
149366	SGDGLSKKYVS	1003	RDKERPS	1043	QAWDDTTVV	1083
149367	RASQGIRNWLA	1004	AASNLQS	1044	QKYNSAPFT	1084
149368	GGNNIGSKSVH	1005	GKNNRPS	1045	SSRDSSGDHLRV	1085
149369	QGDSLGNYYAT	1006	GTNNRPS	1046	NSRDSSGHHLL	1086
BCMA_EBB-C1978-A4	RASQSVSSAYLA	1007	GASTRAT	1047	QHYGSSFNGSSLFT	1087
BCMA_EBB-C1978-G1	RASQSVSNSLA	1008	DASSRAT	1048	QQFGTSSGLT	1088
BCMA_EBB-C1979-C1	RASQSVSSSFLA	1009	GASSRAT	1049	QQYHSSPSWT	1089
BCMA_EBB-C1978-C7	RASQSVSTTFLA	1010	GSSNRAT	1050	QQYHSSPSWT	1090
BCMA_EBB-C1978-D10	RASQSISSYLN	1011	AASSLQS	1051	QQSYSTPYS	1091
BCMA_EBB-C1979-C12	RATQSIGSSFLA	1012	GASQRAT	1052	QHYESSPSWT	1092
BCMA_EBB-C1980-G4	RASQSVSSSYLA	1013	GASSRAT	1053	QQYGSPPRFT	1093
BCMA_EBB-C1980-D2	RASQSVSSSYLA	1014	GASSRAT	1054	QHYGSSPSWT	1094
BCMA_EBB-C1978-A10	RASQRVASNYLA	1015	GASSRAT	1055	QHYDSSPSWT	1095
BCMA_EBB-C1978-D4	RASQSLSSNFLA	1016	GASNWAT	1056	QYYGTSPMYT	1096
BCMA_EBB-C1980-A2	RSSQSLLHSNGYNYLD	1017	LGSNRAS	1057	MQALQTPLT	1097
BCMA_EBB-C1981-C3	RASQSVSSSYLA	1018	GTSSRAT	1058	QHYGNSPPKFT	1098
BCMA_EBB-C1978-G4	RASQSVASSFLA	1019	GASGRAT	1059	QHYGGSPRLT	1099
A7D12.2	RASQDVNTAVS	1020	SASYRYT	1060	QQHYSTPWT	1100
C11D5.3	RASESVSVIGAHLIH	1021	LASNLET	1061	LQSRIFPRT	1101
C12A3.2	RASESVTILGSHLIY	1022	LASNVQT	1062	LQSRTIPRT	1102
C13F12.1	RASESVTILGSHLIY	1023	LASNVQT	1063	LQSRTIPRT	1103

In certain embodiments, the CAR molecule described herein (*e.g.*, the CAR nucleic acid or the CAR polypeptide) or a BCMA binding domain includes:

(1) one, two, or three light chain (LC) CDRs chosen from one of the following:

(i) a LC CDR1 of SEQ ID NO: 504, LC CDR2 of SEQ ID NO: 544 and LC CDR3 of SEQ ID NO: 584 of BCMA-4 CAR (139103);

(ii) a LC CDR1 of SEQ ID NO: 514, LC CDR2 of SEQ ID NO: 554 and LC CDR3 of SEQ ID NO: 594 of BCMA-10 CAR (139109);

(iii) a LC CDR1 of SEQ ID NO: 516, LC CDR2 of SEQ ID NO: 556 and LC CDR3 of SEQ ID NO: 596 of BCMA-13 CAR (139112); or

(iv) a LC CDR1 of SEQ ID NO: 518, LC CDR2 of SEQ ID NO: 558 and LC CDR3 of SEQ ID NO: 598 of BCMA-15 CAR (139114), and/or

(2) one, two, or three heavy chain (HC) CDRs from one of the following:

(i) a HC CDR1 of SEQ ID NO: 384, HC CDR2 of SEQ ID NO: 424 and HC CDR3 of SEQ ID NO: 464 of BCMA-4 CAR (139103);

(ii) a HC CDR1 of SEQ ID NO: 394, HC CDR2 of SEQ ID NO: 434 and HC CDR3 of SEQ ID NO: 474 of BCMA-10 CAR (139109);

(iii) a HC CDR1 of SEQ ID NO: 396, HC CDR2 of SEQ ID NO: 436 and HC CDR3 of SEQ ID NO: 476 of BCMA-13 CAR (139112); or

(iv) a HC CDR1 of SEQ ID NO: 398, HC CDR2 of SEQ ID NO: 438 and HC CDR3 of SEQ ID NO: 478 of BCMA-15 (139114).

In certain embodiments, the CAR molecule described herein (*e.g.*, the CAR nucleic acid or the CAR polypeptide) includes:

(1) one, two, or three light chain (LC) CDRs chosen from one of the following:

(i) a LC CDR1 of SEQ ID NO: 744, LC CDR2 of SEQ ID NO: 784 and LC CDR3 of SEQ ID NO: 824 of BCMA-4 CAR (139103);

(ii) a LC CDR1 of SEQ ID NO: 754, LC CDR2 of SEQ ID NO: 794 and LC CDR3 of SEQ ID NO: 834 of BCMA-10 CAR (139109);

(iii) a LC CDR1 of SEQ ID NO: 756, LC CDR2 of SEQ ID NO: 796 and LC CDR3 of SEQ ID NO: 836 of BCMA-13 CAR (139112); or

(iv) a LC CDR1 of SEQ ID NO: 758, LC CDR2 of SEQ ID NO: 798 and LC CDR3 of SEQ ID NO: 838 of BCMA-15 CAR (139114); and/or

(2) one, two, or three heavy chain (HC) CDRs chosen from one of the following:

(i) a HC CDR1 of SEQ ID NO: 624, HC CDR2 of SEQ ID NO: 664 and HC CDR3 of SEQ ID NO: 704 of BCMA-4 CAR (139103);

(ii) a HC CDR1 of SEQ ID NO: 634, HC CDR2 of SEQ ID NO: 674 and HC CDR3 of SEQ ID NO: 714 of BCMA-10 CAR (139109);

(iii) a HC CDR1 of SEQ ID NO: 636, HC CDR2 of SEQ ID NO: 676 and HC CDR3 of SEQ ID NO: 716 of BCMA-13 CAR (139112); or

(iv) a HC CDR1 of SEQ ID NO: 638, HC CDR2 of SEQ ID NO: 678 and HC CDR3 of SEQ ID NO: 718 of BCMA-15 CAR (139114).

In certain embodiments, the CAR molecule described herein (*e.g.*, the CAR nucleic acid or the CAR polypeptide) includes:

(1) one, two, or three light chain (LC) CDRs chosen from one of the following:

(i) a LC CDR1 of SEQ ID NO: 984 LC CDR2 of SEQ ID NO: 1024 and LC CDR3 of SEQ ID NO: 1064 of BCMA-4 CAR (139103);

(ii) a LC CDR1 of SEQ ID NO: 994, LC CDR2 of SEQ ID NO: 1034 and LC CDR3 of SEQ ID NO: 1074 of BCMA-10 CAR (139109);

(iii) a LC CDR1 of SEQ ID NO: 996, LC CDR2 of SEQ ID NO: 1036 and LC CDR3 of SEQ ID NO: 1076 of BCMA-13 CAR (139112); or

(iv) a LC CDR1 of SEQ ID NO: 998, LC CDR2 of SEQ ID NO: 1038 and LC CDR3 of SEQ ID NO: 1078 of BCMA-15 CAR (139114); and/or

(2) one, two, or three heavy chain (HC) CDRs chosen from one of the following:

(i) a HC CDR1 of SEQ ID NO: 864, HC CDR2 of SEQ ID NO: 904 and HC CDR3 of SEQ ID NO: 944 of BCMA-4 CAR (139103);

(ii) a HC CDR1 of SEQ ID NO: 874, HC CDR2 of SEQ ID NO: 914 and HC CDR3 of SEQ ID NO: 954 of BCMA-10 CAR (139109);

(iii) a HC CDR1 of SEQ ID NO: 876, HC CDR2 of SEQ ID NO: 916 and HC CDR3 of SEQ ID NO: 956 of BCMA-13 CAR (139112);

(iv) a HC CDR1 of SEQ ID NO: 878, HC CDR2 of SEQ ID NO: 918 and HC CDR3 of SEQ ID NO: 958 of BCMA-15 CAR (139114).

In embodiments, anti-BCMA CAR constructs, e.g., human or humanized anti-BCMA CAR constructs, are generated using a method described herein, e.g., as described in Example 4. Exemplary anti-BCMA scFvs include but are not limited to BCMA-1, BCMA-2, BCMA-3, BCMA-4, BCMA-5, BCMA-6, BCMA-7, BCMA-8, BCMA-9, BCMA-10, BCMA-11, BCMA-12, BCMA-13, BCMA-14, and BCMA-15. The sequences of human anti-BCMA scFv

fragments (SEQ ID NOS: 39-52), are provided in Table 1 (and the name designations are provided in Table 2).

In embodiments, full BCMA CAR constructs (e.g., SEQ ID NOs: 99-113) are generated using scFv fragments, e.g., the human scFv fragments (e.g., SEQ ID NOs: 39-52), in combination with additional sequences, such as those shown below.

It is noted that the scFv fragments described herein, e.g., in Tables 1 and 16 or in SEQ ID NOS: 39-53, 129-149, 263-266, 271 or 273, without a leader sequence (e.g., without the amino acid sequence of SEQ ID NO: 1 or the nucleotide sequence of SEQ ID NO:12), are encompassed by the present invention. In other embodiments, scFv fragments described herein, e.g., in Tables 1 and 16 or in SEQ ID NOS: 39-53, 129-149, 263-266, 271 or 273 with a leader sequence (e.g., without the amino acid sequence of SEQ ID NO: 1 or the nucleotide sequence of SEQ ID NO:12), are also encompassed by the present invention.

leader (amino acid sequence) (SEQ ID NO: 1)

MALPVTALLLPLALLLHAARP

leader (nucleic acid sequence) (SEQ ID NO: 12)

ATGGCCCTGCCTGTGACAGCCCTGCTGCTGCCTCTGGCTCTGCTGCTGCATGCCGCTAGACC
C

CD8 hinge (amino acid sequence) (SEQ ID NO: 2)

TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD

CD8 hinge (nucleic acid sequence) (SEQ ID NO: 13)

ACCACGACGCCAGCGCCGCGACCACCAACACCGGCGCCCACCATCGCGTCGCAGCCCCTG
TCCCTGCGCCCAGAGGCGTGCCGGCCAGCGGCGGGGGGCGCAGTGCACACGAGGGGGCTG
GACTTCGCCTGTGAT

CD8 transmembrane (amino acid sequence) (SEQ ID NO: 6)

IYIWAPLAGTCGVLLLSLVITLYC

CD8 transmembrane (nucleic acid sequence) (SEQ ID NO: 17)

ATCTACATCTGGGCGCCCTTGGCCGGGACTTGTGGGGTCCTTCTCCTGTCACTGGTTATCAC
CCTTTACTGC

4-1BB Intracellular domain (amino acid sequence) (SEQ ID NO: 7)
KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL

4-1BB Intracellular domain (nucleic acid sequence) (SEQ ID NO: 18)
AAACGGGGCAGAAAGAAACTCCTGTATATATTCAAACAACCATTTATGAGACCAGTACAA
ACTACTCAAGAGGAAGATGGCTGTAGCTGCCGATTTCCAGAAGAAGAAGAAGGAGGATGT
GAACTG

CD28 Intracellular domain (amino acid sequence) (SEQ ID NO: 1104)
RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS (SEQ ID NO: 1104)

CD28 Intracellular domain (nucleotide sequence) (SEQ ID NO: 1105)
AGGAGTAAGAGGAGCAGGCTCCTGCACAGTGACTACATGAACATGACTCCCCG
CCGCCCCGGGCCCACCCGCAAGCATTACCAGCCCTATGCCCCACCACGCGACTTCG
CAGCCTATCGCTCC (SEQ ID NO: 1105)

ICOS Intracellular domain (amino acid sequence) (SEQ ID NO: 1106)
T K K K Y S S S V H D P N G E Y M F M R A V N T A K K S R L T D V T L
(SEQ ID NO: 1106)

ICOS Intracellular domain (nucleotide sequence) (SEQ ID NO: 1107)
ACAAAAAAGAAGTATTCATCCAGTGTGCACGACCCTAACGGTGAATACATGTTCATGA
GAGCAGTGAACACAGCCAAAAAATCCAGACTCACAGATGTGACCCTA (SEQ ID NO: 1107)

CD3 zeta domain (amino acid sequence) (SEQ ID NO: 9)
RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNE
LQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

CD3 zeta (nucleic acid sequence) (SEQ ID NO: 20)
AGAGTGAAGTTCAGCAGGAGCGCAGACGCCCCCGCGTACAAGCAGGGCCAGAACCAGCTC
TATAACGAGCTCAATCTAGGACGAAGAGAGGAGTACGATGTTTTGGACAAGAGACGTGGC
CGGGACCCTGAGATGGGGGGAAAGCCGAGAAGGAAGAACCCTCAGGAAGGCCTGTACAA
TGAACTGCAGAAAGATAAGATGGCGGAGGCCTACAGTGAGATTGGGATGAAAGGCGAGCG
CCGGAGGGGCAAGGGGCACGATGGCCTTTACCAGGGTCTCAGTACAGCCACCAAGGACAC
CTACGACGCCCTTCACATGCAGGCCCTGCCCCCTCGC

CD3 zeta domain (amino acid sequence; NCBI Reference Sequence NM_000734.3) (SEQ ID NO:10)

RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNE
LQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

CD3 zeta (nucleic acid sequence; NCBI Reference Sequence NM_000734.3); (SEQ ID NO:21)

AGAGTGAAGTTCAGCAGGAGCGCAGACGCCCCCGCGTACCAGCAGGGCCAG
AACCAGCTCTATAACGAGCTCAATCTAGGACGAAGAGAGGAGTACGATGTTT
TGGACAAGAGACGTGGCCGGGACCCTGAGATGGGGGGAAAGCCGAGAAGGA
AGAACCCTCAGGAAGGCCTGTACAATGAACTGCAGAAAGATAAGATGGCGG
AGGCCTACAGTGAGATTGGGATGAAAGGCGAGCGCCGGAGGGGCAAGGGGC
ACGATGGCCTTTACCAGGGTCTCAGTACAGCCACCAAGGACACCTACGACGC
CCTTCACATGCAGGCCCTGCCCCCTCGC

IgG4 Hinge (amino acid sequence) (SEQ ID NO:36)

ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGV
EVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE
PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR
LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKM

IgG4 Hinge (nucleotide sequence) (SEQ ID NO:37)

GAGAGCAAGTACGGCCCTCCCTGCCCCCCTTGCCCTGCCCCCGAGTTCCTGGGCGGACCCA
GCGTGTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCCGGACCCCCGAGGT
GACCTGTGTGGTGGTGGACGTGTCCCAGGAGGACCCCGAGGTCCAGTTCAACTGGTACGTG
GACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCCCGGGAGGAGCAGTTCAATAGCACC
TACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAATAC
AAGTGTAAGGTGTCCAACAAGGGCCTGCCCAGCAGCATCGAGAAAACCATCAGCAAGGCC
AAGGGCCAGCCTCGGGAGCCCCAGGTGTACACCCTGCCCCCTAGCCAAGAGGAGATGACC
AAGAACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGG
AGTGGGAGAGCAACGGCCAGCCCGAGAACAACTACAAGACCACCCCCCCTGTGCTGGACA
GCGACGGCAGCTTCTTCCTGTACAGCCGGCTGACCGTGGACAAGAGCCGGTGGCAGGAGG
GCAACGTCTTTAGCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGAG
CCTGAGCCTGTCCCTGGGCAAGATG

In embodiments, the CAR scFv fragments are cloned into lentiviral vectors to create a full length CAR construct in a single coding frame, and using a promoter, e.g., EF1 alpha promoter, for expression (SEQ ID NO: 11).

EF1 alpha promoter

CGTGAGGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCCACAGTCCCCGAGAAGTTGGGGGGAGGGGTCGG
CAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAAAGTGATGTCGTGTACTGGCTCCGCCTTTTT
CCCGAGGGTGGGGGAGAACCGTATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTCGCAACGGGTTTGCCGCCA
GAACACAGGTAAGTGCCGTGTGTGGTTCCCGCGGGCCTGGCCTCTTTACGGGTTATGGCCCTTGCGTGCCTTGAAT
TACTTCCACCTGGCTGCAGTACGTGATTCTTGATCCCGAGCTTCGGGTTGGAAGTGGGTGGGAGAGTTCGAGGCCT
TGCGCTTAAGGAGCCCCTTCGCCTCGTGCTTGAGTTGAGGCCTGGCCTGGGCGCTGGGGCCGCCGCGTGCGAATCT
GGTGGCACCTTCGCGCCTGTCTCGCTGCTTTCGATAAGTCTCTAGCCATTTAAAATTTTTGATGACCTGCTGCGAC
GCTTTTTTTCTGGCAAGATAGTCTTGTAAATGCGGGCCAAGATCTGCACACTGGTATTTCGGTTTTTGGGGCCGCG
GGCGGCGACGGGGCCCGTGCGTCCCAGCGCACATGTTCGGCGAGGCGGGGCCTGCGAGCGCGGCCACCGAGAATCG
GACGGGGGTAGTCTCAAGCTGGCCGGCCTGCTCTGGTGCCTGGCCTCGCGCCGCCGTGTATCGCCCCGCCCTGGGC
GGCAAGGCTGGCCCGGTCGGCACCAGTTGCGTGAGCGGAAAGATGGCCGCTTCCCGGCCCTGCTGCAGGGAGCTCA
AAATGGAGGACGCGGCGCTCGGGAGAGCGGGCGGGTGAGTCACCCACACAAAGGAAAAGGGCCTTTCCGTCCTCAG
CCGTCGCTTCATGTGACTCCACGGAGTACCGGGCGCCGTCCAGGCACCTCGATTAGTTCTCGAGCTTTTGGAGTAC
GTCGTCTTTAGGTTGGGGGGAGGGGTTTTATGCGATGGAGTTTCCCCACACTGAGTGGGTGGAGACTGAAGTTAGG
CCAGCTTGGCACTTGATGTAATTCTCCTTGGAATTTGCCCTTTTTGAGTTTGGATCTTGGTTCATTCTCAAGCCTC
AGACAGTGGTTCAAAGTTTTTTTCTTCCATTTCAGGTGTCGTGA (SEQ ID NO: 11).

Gly/Ser (SEQ ID NO:25)

GGGGS

Gly/Ser (SEQ ID NO:26): This sequence may encompass 1-6 "Gly Gly Gly Gly Ser" repeating units

GGGGSGGGGS GGGGSGGGGS GGGGSGGGGS

Gly/Ser (SEQ ID NO:27)

GGGGSGGGGS GGGGSGGGGS

Gly/Ser (SEQ ID NO:28)

GGGGSGGGGS GGGGS

Gly/Ser (SEQ ID NO:29)

GGGS

PolyA: $(A)_{5000}$ (SEQ ID NO:30)

PolyA: $(T)_{100}$ (SEQ ID NO:31)

PolyA: $(T)_{5000}$ (SEQ ID NO:32)

PolyA: $(A)_{5000}$ (SEQ ID NO:33)

PolyA: $(A)_{400}$ (SEQ ID NO:34)

PolyA: $(A)_{2000}$ (SEQ ID NO:35)

Gly/Ser (SEQ ID NO:38): This sequence may encompass 1-10 "Gly Gly Gly Ser" repeating units

GGGSGGGSGG GSGGGSGGGS GGGSGGGSGG GSGGGSGGGS

The amino acid and nucleic acid sequences of exemplary BCMA scFv domains and exemplary BCMA CAR molecules are provided in Table 1.

Table 2 below designates the nicknames for the BCMA CAR constructs with respect to the DNA ID number, also listed in Table 1.

Table 2: CAR construct IDs

Nickname	Novartis ID	DNA2.0 ID
BCMA-1	ER95-03VA	139100
BCMA-2	UR96-08PA	139101
BCMA-3	KR98-03KA	139102
BCMA-4	JF32-78IB	139103
BCMA-5	AR99-08FA	139104
BCMA-6	ZF34-73CB	139105
BCMA-7	QR91-12ZA	139106
BCMA-8	GR92-17UA	139107
BCMA-9	OG62-93QB	139108
BCMA-10	EG63-98LB	139109
BCMA-11	UG65-93FB	139110
BCMA-12	HU13-58ZB	139111
BCMA-13	KG66-98AB	139112
BCMA-14	HJ64-62PB	139113

BCMA-15	PY43-48LB	139114

Table 1. Amino Acid and Nucleic Acid Sequences of exemplary anti-BCMA scFv domains and BCMA CAR molecules

The amino acid sequences variable heavy chain and variable light chain sequences for each scFv is also provided. Table 2 lists names and CAR construct IDs for several BCMA CARs.

Name/ Description	SEQ ID NO:	Sequence
139109		
139109- aa ScFv domain	49	EVQLVESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSGIVY SGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGGESDVWG QGTTVTVSSASGGGGSGGRASGGGGSDIQLTQSPSSLSASVGDRVTITCRASQ SISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQP EDFATYYCQQSYSTPYTFGQGTKVEIK
139109- nt ScFv domain	64	GAAGTGCAATTGGTGGAATCAGGGGGAGGACTTGTGCAGCCTGGAGGATCGCT GAGACTGTCATGTGCCGTGTCCGGCTTTGCCCTGTCCAACCACGGGATGTCCT GGGTCCGCCGCGCGCCTGGAAAGGGCCTCGAATGGGTGTCGGGTATTGTGTAC AGCGGTAGCACCTACTATGCCGCATCCGTGAAGGGGAGATTCACCATCAGCCG GGACAACTCCAGGAACACTCTGTACCTCCAAATGAATTCGCTGAGGCCAGAGG ACACTGCCATCTACTACTGCTCCGCGCATGGCGGAGAGTCCGACGTCTGGGGA CAGGGGACCACCGTGACCGTGTCTAGCGCGTCCGGCGGAGGCGGCAGCGGGGG TCGGGCATCAGGGGGCGGCGGATCGGACATCCAGCTCACCCAGTCCCCGAGCT CGCTGTCCGCCTCCGTGGGAGATCGGGTCACCATCACGTGCCGCGCCAGCCAG TCGATTTCCTCCTACCTGAACTGGTACCAACAGAAGCCCGGAAAAGCCCCGAA GCTTCTCATCTACGCCGCCTCGAGCCTGCAGTCAGGAGTGCCCTCACGGTTCT CCGGCTCCGGTTCCGGTACTGATTTCACCCTGACCATTTCCTCCCTGCAACCG GAGGACTTCGCTACTTACTACTGCCAGCAGTCGTACTCCACCCCCTACACTTT CGGACAAGGCACCAAGGTCGAAATCAAG
139109- aa VH	79	EVQLVESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSGIVY SGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGGESDVWG QGTTVTVSS
139109- aa VL	94	DIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASS LQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPYTFGQGTKVEI K
139109- aa Full CAR	109	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAVSGFALSNH GMSWVRRAPGKGLEWVSGIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSL RPEDTAIYYCSAHGGESDVWGQGTTVTVSSASGGGGSGGRASGGGGSDIQLTQ SPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVP SRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPYTFGQGTKVEIKTTTPA PRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGV LLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKN PQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
139109- nt	124	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC

Full CAR		CGCTCGGCCCGAAGTGCAATTGGTGGAATCAGGGGGAGGACTTGTGCAGCCTG GAGGATCGCTGAGACTGTCATGTGCCGTGTCCGGCTTTGCCCTGTCCAACCAC GGGATGTCCTGGGTCCGCCGCGCGCCTGGAAAGGGCCTCGAATGGGTGTCGGG TATTGTGTACAGCGGTAGCACCTACTATGCCGCATCCGTGAAGGGGAGATTCA CCATCAGCCGGGACAACTCCAGGAACACTCTGTACCTCCAAATGAATTCGCTG AGGCCAGAGGACACTGCCATCTACTACTGCTCCGCGCATGGCGGAGAGTCCGA CGTCTGGGGACAGGGGACCACCGTGACCGTGTCTAGCGCGTCCGGCGGAGGCG GCAGCGGGGGTCGGGCATCAGGGGGCGGCGGATCGGACATCCAGCTCACCCAG TCCCCGAGCTCGCTGTCCGCCTCCGTGGGAGATCGGGTCACCATCACGTGCCG CGCCAGCCAGTCGATTTCCTCCTACCTGAACTGGTACCAACAGAAGCCCGGAA AAGCCCCGAAGCTTCTCATCTACGCCGCCTCGAGCCTGCAGTCAGGAGTGCCC TCACGGTTCTCCGGCTCCGGTTCCGGTACTGATTTCACCCTGACCATTTCCTC CCTGCAACCGGAGGACTTCGCTACTTACTACTGCCAGCAGTCGTACTCCACCC CCTACACTTTCGGACAAGGCACCAAGGTCGAAATCAAGACCACTACCCCAGCA CCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCG TCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTG ACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTC CTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCT GCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGG AGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTG CGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAA CCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGG ACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAAT CCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCCTA TAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACGACGGAC TGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTTCACATG CAGGCCCTGCCGCCTCGG
139103		
139103- aa ScFv domain	39	QVQLVESGGGLVQPGRSLRLSCAASGFTFSNYAMSWVRQAPGKGLGWVSGISR SGENTYYADSVKGRFTISRDNSKNTLYLQMNSLRDEDTAVYYCARSPAHYYGG MDVWGQGTTVTVSSASGGGGSGGRASGGGGSDIVLTQSPGTLSLSPGERATLS CRASQSISSSFLAWYQQKPGQAPRLLIYGASRRATGIPDRFSGSGSGTDFTLT ISRLEPEDSAVYYCQQYHSSPSWTFGQGTKLEIK
139103- nt ScFv domain	54	CAAGTGCAACTCGTGGAATCTGGTGGAGGACTCGTGCAACCCGGAAGATCGCT TAGACTGTCGTGTGCCGCCAGCGGGTTCACTTTCTCGAACTACGCGATGTCCT GGGTCCGCCAGGCACCCGGAAAGGGACTCGGTTGGGTGTCCGGCATTTCCCGG TCCGGCGAAAATACCTACTACGCCGACTCCGTGAAGGGCCGCTTCACCATCTC AAGGGACAACAGCAAAAACACCCTGTACTTGCAAATGAACTCCCTGCGGGATG AAGATACAGCCGTGTACTATTGCGCCCGGTCGCCTGCCCATTACTACGGCGGA ATGGACGTCTGGGGACAGGGAACCACTGTGACTGTCAGCAGCGCGTCGGGTGG CGGCGGCTCAGGGGGTCGGGCCTCCGGGGGGGGAGGGTCCGACATCGTGCTGA CCCAGTCCCCGGGAACCCTGAGCCTGAGCCCGGGAGAGCGCGCGACCCTGTCA TGCCGGGCATCCCAGAGCATTAGCTCCTCCTTTCTCGCCTGGTATCAGCAGAA GCCCGGACAGGCCCCGAGGCTGCTGATCTACGGCGCTAGCAGAAGGGCTACCG GAATCCCAGACCGGTTCTCCGGCTCCGGTTCCGGGACCGATTTCACCCTTACT ATCTCGCGCCTGGAACCTGAGGACTCCGCCGTCTACTACTGCCAGCAGTACCA CTCATCCCCGTCGTGGACGTTCGGACAGGGCACCAAGCTGGAGATTAAG
139103- aa VH	69	QVQLVESGGGLVQPGRSLRLSCAASGFTFSNYAMSWVRQAPGKGLGWVSGISR SGENTYYADSVKGRFTISRDNSKNTLYLQMNSLRDEDTAVYYCARSPAHYYGG MDVWGQGTTVTVSS
139103- aa VL	84	DIVLTQSPGTLSLSPGERATLSCRASQSISSSFLAWYQQKPGQAPRLLIYGAS RRATGIPDRFSGSGSGTDFTLTISRLEPEDSAVYYCQQYHSSPSWTFGQGTKL

		EIK
139103- aa Full CAR	99	MALPVTALLLPLALLLHAARPQVQLVESGGGLVQPGRSLRLSCAASGFTFSNY AMSWVRQAPGKGLGWVSGISRSGENTYYADSVKGRFTISRDNSKNTLYLQMNS LRDEDTAVYYCARSPAHYYGGMDVWGQGTTVTVSSASGGGGSGGRASGGGGSD IVLTQSPGTLSLSPGERATLSCRASQSISSSFLAWYQQKPGQAPRLLIYGASR RATGIPDRFSGSGSGTDFTLTISRLEPEDSAVYYCQQYHSSPSWTFGQGTKLE IKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAP LAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEE EEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKD TYDALHMQALPPR
139103- nt Full CAR	114	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCCAAGTGCAACTCGTGGAATCTGGTGGAGGACTCGTGCAACCCG GAAGATCGCTTAGACTGTCGTGTGCCGCCAGCGGGTTCACTTTCTCGAACTAC GCGATGTCCTGGGTCCGCCAGGCACCCGGAAAGGGACTCGGTTGGGTGTCCGG CATTTCCCGGTCCGGCGAAAATACCTACTACGCCGACTCCGTGAAGGGCCGCT TCACCATCTCAAGGGACAACAGCAAAAACACCCTGTACTTGCAAATGAACTCC CTGCGGGATGAAGATACAGCCGTGTACTATTGCGCCCGGTCGCCTGCCCATTA CTACGGCGGAATGGACGTCTGGGGACAGGGAACCACTGTGACTGTCAGCAGCG CGTCGGGTGGCGGCGGCTCAGGGGGTCGGGCCTCCGGGGGGGGGAGGGTCCGAC ATCGTGCTGACCCAGTCCCCGGGAACCCTGAGCCTGAGCCCGGGAGAGCGCGC GACCCTGTCATGCCGGGCATCCCAGAGCATTAGCTCCTCCTTTCTCGCCTGGT ATCAGCAGAAGCCCGGACAGGCCCCGAGGCTGCTGATCTACGGCGCTAGCAGA AGGGCTACCGGAATCCCAGACCGGTTCTCCGGCTCCGGTTCCGGGACCGATTT CACCCTTACTATCTCGCGCCTGGAACCTGAGGACTCCGCCGTCTACTACTGCC AGCAGTACCACTCATCCCCGTCGTGGACGTTCGGACAGGGCACCAAGCTGGAG ATTAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGC CTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGG CCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCT CTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTG TAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGC CTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAG GAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCC AGCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGA GAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGC GGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAA GGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAA GAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGAC ACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
139105		
139105- aa ScFv domain	40	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISW NSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCSVHSFLAYWG QGTLVTVSSASGGGGSGGRASGGGGSDIVMTQTPLSLPVTPGEPASISCRSSQ SLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCMQALQTPYTFGQGTKVEIK
139105- nt ScFv domain	55	CAAGTGCAACTCGTCGAATCCGGTGGAGGTCTGGTCCAACCTGGTAGAAGCCT GAGACTGTCGTGTGCGGCCAGCGGATTCACCTTTGATGACTATGCTATGCACT GGGTGCGGCAGGCCCCAGGAAAGGGCCTGGAATGGGTGTCGGGAATTAGCTGG AACTCCGGGTCCATTGGCTACGCCGACTCCGTGAAGGGCCGCTTCACCATCTC CCGCGACAACGCAAAGAACTCCCTGTACTTGCAAATGAACTCGCTCAGGGCTG AGGATACCGCGCTGTACTACTGCTCCGTGCATTCCTTCCTGGCCTACTGGGGA CAGGGAACTCTGGTCACCGTGTCGAGCGCCTCCGGCGGCGGGGGCTCGGGTGG

		ACGGGCCTCGGGCGGAGGGGGGTCCGACATCGTGATGACCCAGACCCCGCTGA GCTTGCCCGTGACTCCCGGAGAGCCTGCATCCATCTCCTGCCGGTCATCCCAG TCCCTTCTCCACTCCAACGGATACAACTACCTCGACTGGTACCTCCAGAAGCC GGGACAGAGCCCTCAGCTTCTGATCTACCTGGGGTCAAATAGAGCCTCAGGAG TGCCGGATCGGTTCAGCGGATCTGGTTCGGGAACTGATTTCACTCTGAAGATT TCCCGCGTGGAAGCCGAGGACGTGGGCGTCTACTACTGTATGCAGGCGCTGCA GACCCCCTATACCTTCGGCCAAGGGACGAAAGTGGAGATCAAG
139105- aa VH	70	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISW NSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCSVHSFLAYWG QGTLVTVSS
139105- aa VL	85	DIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLI YLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPYTFGQG TKVEIK
139105- aa Full CAR	100	MALPVTALLLPLALLLHAARPQVQLVESGGGLVQPGRSLRLSCAASGFTFDDY AMHWVRQAPGKGLEWVSGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTALYYCSVHSFLAYWGQGTLVTVSSASGGGGSGGRASGGGGSDIVMTQ TPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNR ASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPYTFGQGTKVEIK TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLA GTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEE GGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGK PRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTY DALHMQALPPR
139105- nt Full CAR	115	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCCAAGTGCAACTCGTCGAATCCGGTGGAGGTCTGGTCCAACCTG GTAGAAGCCTGAGACTGTCGTGTGCGGCCAGCGGATTCACCTTTGATGACTAT GCTATGCACTGGGTGCGGCAGGCCCCAGGAAAGGGCCTGGAATGGGTGTCGGG AATTAGCTGGAACTCCGGGTCCATTGGCTACGCCGACTCCGTGAAGGGCCGCT TCACCATCTCCCGCGACAACGCAAAGAACTCCCTGTACTTGCAAATGAACTCG CTCAGGGCTGAGGATACCGCGCTGTACTACTGCTCCGTGCATTCCTTCCTGGC CTACTGGGGACAGGGAACTCTGGTCACCGTGTCGAGCGCCTCCGGCGGCGGGG GCTCGGGTGGACGGGCCTCGGGCGGAGGGGGGTCCGACATCGTGATGACCCAG ACCCCGCTGAGCTTGCCCGTGACTCCCGGAGAGCCTGCATCCATCTCCTGCCG GTCATCCCAGTCCCTTCTCCACTCCAACGGATACAACTACCTCGACTGGTACC TCCAGAAGCCGGGACAGAGCCCTCAGCTTCTGATCTACCTGGGGTCAAATAGA GCCTCAGGAGTGCCGGATCGGTTCAGCGGATCTGGTTCGGGAACTGATTTCAC TCTGAAGATTTCCCGCGTGGAAGCCGAGGACGTGGGCGTCTACTACTGTATGC AGGCGCTGCAGACCCCCTATACCTTCGGCCAAGGGACGAAAGTGGAGATCAAG ACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCA GCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGC ATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCT GGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCG CGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGC AGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAA GGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTA CAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGG AGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAG CCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAA GATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCA AAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTAT GACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
139111		

139111- aa ScFv domain	41	EVQLLESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSGIVY SGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGGESDVWG QGTTVTVSSASGGGGSGGRASGGGGSDIVMTQTPLSLSVTPGQPASISCKSSQ SLLRNDGKTPLYWYLQKAGQPPQLLIYEVSNRFSGVPDRFSGSGSGTDFTLKI SRVEAEDVGAYYCMQNIQFPSFGGGTKLEIK
139111- nt ScFv domain	56	GAAGTGCAATTGTTGGAATCTGGAGGAGGACTTGTGCAGCCTGGAGGATCACT GAGACTTTCGTGTGCGGTGTCAGGCTTCGCCCTGAGCAACCACGGCATGAGCT GGGTGCGGAGAGCCCCGGGGAAGGGTCTGGAATGGGTGTCCGGGATCGTCTAC TCCGGTTCAACTTACTACGCCGCAAGCGTGAAGGGTCGCTTCACCATTTCCCG CGATAACTCCCGGAACACCCTGTACCTCCAAATGAACTCCCTGCGGCCCGAGG ACACCGCCATCTACTACTGTTCCGCGCATGGAGGAGAGTCCGATGTCTGGGGA CAGGGCACTACCGTGACCGTGTCGAGCGCCTCGGGGGGGAGGAGGCTCCGGCGG TCGCGCCTCCGGGGGGGGGTGGCAGCGACATTGTGATGACGCAGACTCCACTCT CGCTGTCCGTGACCCCGGGACAGCCCGCGTCCATCTCGTGCAAGAGCTCCCAG AGCCTGCTGAGGAACGACGGAAAGACTCCTCTGTATTGGTACCTCCAGAAGGC TGGACAGCCCCCGCAACTGCTCATCTACGAAGTGTCAAATCGCTTCTCCGGGGG TGCCGGATCGGTTTTCCGGCTCGGGATCGGGCACCGACTTCACCCTGAAAATC TCCAGGGTCGAGGCCGAGGACGTGGGAGCCTACTACTGCATGCAAAACATCCA GTTCCCTTCCTTCGGCGGCGGCACAAAGCTGGAGATTAAG
139111- aa VH	71	EVQLLESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSGIVY SGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGGESDVWG QGTTVTVSS
139111- aa VL	86	DIVMTQTPLSLSVTPGQPASISCKSSQSLLRNDGKTPLYWYLQKAGQPPQLLI YEVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGAYYCMQNIQFPSFGGGT KLEIK
139111- aa Full CAR	101	MALPVTALLLPLALLLHAARPEVQLLESGGGLVQPGGSLRLSCAVSGFALSNH GMSWVRRAPGKGLEWVSGIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSL RPEDTAIYYCSAHGGESDVWGQGTTVTVSSASGGGGSGGRASGGGGSDIVMTQ TPLSLSVTPGQPASISCKSSQSLLRNDGKTPLYWYLQKAGQPPQLLIYEVSNR FSGVPDRFSGSGSGTDFTLKISRVEAEDVGAYYCMQNIQFPSFGGGTKLEIKT TTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAG TCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEG GCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKP RRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYD ALHMQALPPR
139111- nt Full CAR	116	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCGAAGTGCAATTGTTGGAATCTGGAGGAGGACTTGTGCAGCCTG GAGGATCACTGAGACTTTCGTGTGCGGTGTCAGGCTTCGCCCTGAGCAACCAC GGCATGAGCTGGGTGCGGAGAGCCCCGGGGAAGGGTCTGGAATGGGTGTCCGG GATCGTCTACTCCGGTTCAACTTACTACGCCGCAAGCGTGAAGGGTCGCTTCA CCATTTCCCGCGATAACTCCCGGAACACCCTGTACCTCCAAATGAACTCCCTG CGGCCCGAGGACACCGCCATCTACTACTGTTCCGCGCATGGAGGAGAGTCCGA TGTCTGGGGACAGGGCACTACCGTGACCGTGTCGAGCGCCTCGGGGGGAGGAG GCTCCGGCGGTCGCGCCTCCGGGGGGGGTGGCAGCGACATTGTGATGACGCAG ACTCCACTCTCGCTGTCCGTGACCCCGGGACAGCCCGCGTCCATCTCGTGCAA GAGCTCCCAGAGCCTGCTGAGGAACGACGGAAAGACTCCTCTGTATTGGTACC TCCAGAAGGCTGGACAGCCCCCGCAACTGCTCATCTACGAAGTGTCAAATCGC TTCTCCGGGGTGCCGGATCGGTTTTCCGGCTCGGGATCGGGCACCGACTTCAC CCTGAAAATCTCCAGGGTCGAGGCCGAGGACGTGGGAGCCTACTACTGCATGC AAAACATCCAGTTCCCTTCCTTCGGCGGCGGCACAAAGCTGGAGATTAAGACC ACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCC TCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATA

		CCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGT ACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGG TCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGA CTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGC GGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAA GCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGT ACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCG CGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGAT GGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAG GCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGAC GCTCTTCACATGCAGGCCCTGCCGCCTCGG
139100		
139100- aa ScFv domain	42	QVQLVQSGAEVRKTGASVKVSCKASGYIFDNFGINWVRQAPGQGLEWMGWINP KNNNTNYAQKFQGRVTITADESTNTAYMEVSSLRSEDTAVYYCARGPYYYQSY MDVWGQGTMVTVSSASGGGGSGGRASGGGGSDIVMTQTPLSLPVTPGEPASIS CRSSQSLLHSNGYNYLNWYLQKPGQSPQLLIYLGSKRASGVPDRFSGSGSGTD FTLHITRVGAEDVGVYYCMQALQTPYTFGQGTKLEIK
139100- nt ScFv domain	57	CAAGTCCAACTCGTCCAGTCCGGCGCAGAAGTCAGAAAAACCGGTGCTAGCGT GAAAGTGTCCTGCAAGGCCTCCGGCTACATTTTCGATAACTTCGGAATCAACT GGGTCAGACAGGCCCCGGGCCAGGGGCTGGAATGGATGGGATGGATCAACCCC AAGAACAACAACACCAACTACGCACAGAAGTTCCAGGGCCGCGTGACTATCAC CGCCGATGAATCGACCAATACCGCCTACATGGAGGTGTCCTCCCTGCGGTCGG AGGACACTGCCGTGTATTACTGCGCGAGGGGCCCATACTACTACCAAAGCTAC ATGGACGTCTGGGGACAGGGAACCATGGTGACCGTGTCATCCGCCTCCGGTGG TGGAGGCTCCGGGGGGCGGGCTTCAGGAGGCGGAGGAAGCGATATTGTGATGA CCCAGACTCCGCTTAGCCTGCCCGTGACTCCTGGAGAACCGGCCTCCATTTCC TGCCGGTCCTCGCAATCACTCCTGCATTCCAACGGTTACAACTACCTGAATTG GTACCTCCAGAAGCCTGGCCAGTCGCCCCAGTTGCTGATCTATCTGGGCTCGA AGCGCGCCTCCGGGGTGCCTGACCGGTTTAGCGGATCTGGGAGCGGCACGGAC TTCACTCTCCACATCACCCGCGTGGGAGCGGAGGACGTGGGAGTGTACTACTG TATGCAGGCGCTGCAGACTCCGTACACATTCGGACAGGGCACCAAGCTGGAGA TCAAG
139100- aa VH	72	QVQLVQSGAEVRKTGASVKVSCKASGYIFDNFGINWVRQAPGQGLEWMGWINP KNNNTNYAQKFQGRVTITADESTNTAYMEVSSLRSEDTAVYYCARGPYYYQSY MDVWGQGTMVTVSS
139100- aa VL	87	DIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGYNYLNWYLQKPGQSPQLLI YLGSKRASGVPDRFSGSGSGTDFTLHITRVGAEDVGVYYCMQALQTPYTFGQG TKLEIK
139100- aa Full CAR	102	MALPVTALLLPLALLLHAARPQVQLVQSGAEVRKTGASVKVSCKASGYIFDNF GINWVRQAPGQGLEWMGWINPKNNNTNYAQKFQGRVTITADESTNTAYMEVSS LRSEDTAVYYCARGPYYYQSYMDVWGQGTMVTVSSASGGGGSGGRASGGGGSD IVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGYNYLNWYLQKPGQSPQLLIY LGSKRASGVPDRFSGSGSGTDFTLHITRVGAEDVGVYYCMQALQTPYTFGQGT KLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRF PEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDP EMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTA TKDTYDALHMQALPPR
139100- nt Full CAR	117	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCCAAGTCCAACTCGTCCAGTCCGGCGCAGAAGTCAGAAAAACCG GTGCTAGCGTGAAAGTGTCCTGCAAGGCCTCCGGCTACATTTTCGATAACTTC GGAATCAACTGGGTCAGACAGGCCCCGGGCCAGGGGCTGGAATGGATGGGATG

		GATCAACCCCAAGAACAACAACACCAACTACGCACAGAAGTTCCAGGGCCGCG TGACTATCACCGCCGATGAATCGACCAATACCGCCTACATGGAGGTGTCCTCC CTGCGGTCGGAGGACACTGCCGTGTATTACTGCGCGAGGGGCCCATACTACTA CCAAAGCTACATGGACGTCTGGGGACAGGGAACCATGGTGACCGTGTCATCCG CCTCCGGTGGTGGAGGCTCCGGGGGGCGGGCTTCAGGAGGCGGAGGAAGCGAT ATTGTGATGACCCAGACTCCGCTTAGCCTGCCCGTGACTCCTGGAGAACCGGC CTCCATTTCCTGCCGGTCCTCGCAATCACTCCTGCATTCCAACGGTTACAACT ACCTGAATTGGTACCTCCAGAAGCCTGGCCAGTCGCCCCAGTTGCTGATCTAT CTGGGCTCGAAGCGCGCCTCCGGGGTGCCTGACCGGTTTAGCGGATCTGGGAG CGGCACGGACTTCACTCTCCACATCACCCGCGTGGGAGCGGAGGACGTGGGAG TGTACTACTGTATGCAGGCGCTGCAGACTCCGTACACATTCGGACAGGGCACC AAGCTGGAGATCAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCC TACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAG CTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATT TGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCAC TCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCT TCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTC CCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGC AGATGCTCCAGCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATC TTGGTCGGAGAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCA GAAATGGGCGGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGA GCTCCAAAAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGG AACGCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCC ACCAAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
139101		
139101- aa ScFv domain	43	QVQLQESGGGLVQPGGSLRLSCAASGFTFSSDAMTWVRQAPGKGLEWVSVISG SGGTTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKLDSSGYYY ARGPRYWGQGTLVTVSSASGGGGSGGRASGGGGSDIQLTQSPSSLSASVGDRV TITCRASQSISSYLNWYQQKPGKAPKLLIYGASTLASGVPARFSGSGSGTHFT LTINSLQSEDSATYYCQQSYKRASFGQGTKVEIK
139101- nt ScFv domain	58	CAAGTGCAACTTCAAGAATCAGGCGGAGGACTCGTGCAGCCCGGAGGATCATT GCGGCTCTCGTGCGCCGCCTCGGGCTTCACCTTCTCGAGCGACGCCATGACCT GGGTCCGCCAGGCCCCGGGGAAGGGGCTGGAATGGGTGTCTGTGATTTCCGGC TCCGGGGGAACTACGTACTACGCCGATTCCGTGAAAGGTCGCTTCACTATCTC CCGGGACAACAGCAAGAACACCCTTTATCTGCAAATGAATTCCCTCCGCGCCG AGGACACCGCCGTGTACTACTGCGCCAAGCTGGACTCCTCGGGCTACTACTAT GCCCGGGGTCCGAGATACTGGGGACAGGGAACCCTCGTGACCGTGTCCTCCGC GTCCGGCGGAGGAGGGTCGGGAGGGCGGGCCTCCGGCGGCGGCGGTTCGGACA TCCAGCTGACCCAGTCCCCATCCTCACTGAGCGCAAGCGTGGGCGACAGAGTC ACCATTACATGCAGGGCGTCCCAGAGCATCAGCTCCTACCTGAACTGGTACCA ACAGAAGCCTGGAAAGGCTCCTAAGCTGTTGATCTACGGGGCTTCGACCCTGG CATCCGGGGTGCCCGCGAGGTTTAGCGGAAGCGGTAGCGGCACTCACTTCACT CTGACCATTAACAGCCTCCAGTCCGAGGATTCAGCCACTTACTACTGTCAGCA GTCCTACAAGCGGGCCAGCTTCGGACAGGGCACTAAGGTCGAGATCAAG
139101- aa VH	73	QVQLQESGGGLVQPGGSLRLSCAASGFTFSSDAMTWVRQAPGKGLEWVSVISG SGGTTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKLDSSGYYY ARGPRYWGQGTLVTVSS
139101- aa VL	88	DIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYGAST LASGVPARFSGSGSGTHFTLTINSLQSEDSATYYCQQSYKRASFGQGTKVEIK
139101- aa Full CAR	103	MALPVTALLLPLALLLHAARPQVQLQESGGGLVQPGGSLRLSCAASGFTFSSD AMTWVRQAPGKGLEWVSVISGSGGTTYYADSVKGRFTISRDNSKNTLYLQMNS LRAEDTAVYYCAKLDSSGYYYARGPRYWGQGTLVTVSSASGGGGSGGRASGGG

		GSDIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYGA STLASGVPARFSGSGSGTHFTLTINSLQSEDSATYYCQQSYKRASFGQGTKVE IKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAP LAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEE EEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKD TYDALHMQALPPR
139101- nt Full CAR	118	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCCAAGTGCAACTTCAAGAATCAGGCGGAGGACTCGTGCAGCCCG GAGGATCATTGCGGCTCTCGTGCGCCGCCTCGGGCTTCACCTTCTCGAGCGAC GCCATGACCTGGGTCCGCCAGGCCCCGGGGAAGGGGCTGGAATGGGTGTCTGT GATTTCCGGCTCCGGGGGAACTACGTACTACGCCGATTCCGTGAAAGGTCGCT TCACTATCTCCCGGGACAACAGCAAGAACACCCTTTATCTGCAAATGAATTCC CTCCGCGCCGAGGACACCGCCGTGTACTACTGCGCCAAGCTGGACTCCTCGGG CTACTACTATGCCCGGGGTCCGAGATACTGGGGACAGGGAACCCTCGTGACCG TGTCCTCCGCGTCCGGCGGAGGAGGGTCGGGAGGGCGGGCCTCCGGCGGCGGC GGTTCGGACATCCAGCTGACCCAGTCCCCATCCTCACTGAGCGCAAGCGTGGG CGACAGAGTCACCATTACATGCAGGGCGTCCCAGAGCATCAGCTCCTACCTGA ACTGGTACCAACAGAAGCCTGGAAAGGCTCCTAAGCTGTTGATCTACGGGGCT TCGACCCTGGCATCCGGGGTGCCCGCGAGGTTTAGCGGAAGCGGTAGCGGCAC TCACTTCACTCTGACCATTAACAGCCTCCAGTCCGAGGATTCAGCCACTTACT ACTGTCAGCAGTCCTACAAGCGGGCCAGCTTCGGACAGGGCACTAAGGTCGAG ATCAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGC CTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGG CCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCT CTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTG TAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGC CTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAG GAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCC AGCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGA GAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGC GGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAA GGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAA GAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGAC ACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
139102		
139102- aa ScFv domain	44	QVQLVQSGAEVKKPGASVKVSCKASGYTFSNYGITWVRQAPGQGLEWMGWISA YNGNTNYAQKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYYCARGPYYYYMD VWGKGTMVTVSSASGGGGSGGRASGGGGSEIVMTQSPLSLPVTPGEPASISCR SSQSLLYSNGYNYVDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFK LQISRVEAEDVGIYYCMQGRQFPYSFGQGTKVEIK
139102- nt ScFv domain	59	CAAGTCCAACTGGTCCAGAGCGGTGCAGAAGTGAAGAAGCCCGGAGCGAGCGT GAAAGTGTCCTGCAAGGCTTCCGGGTACACCTTCTCCAACTACGGCATCACTT GGGTGCGCCAGGCCCCGGGACAGGGCCTGGAATGGATGGGGTGGATTTCCGCG TACAACGGCAATACGAACTACGCTCAGAAGTTCCAGGGTAGAGTGACCATGAC TAGGAACACCTCCATTTCCACCGCCTACATGGAACTGTCCTCCCTGCGGAGCG AGGACACCGCCGTGTACTATTGCGCCCGGGGACCATACTACTACTACATGGAT GTCTGGGGGAAGGGGACTATGGTCACCGTGTCATCCGCCTCGGGAGGCGGCGG ATCAGGAGGACGCGCCTCTGGTGGTGGAGGATCGGAGATCGTGATGACCCAGA GCCCTCTCTCCTTGCCCGTGACTCCTGGGGAGCCCGCATCCATTTCATGCCGG AGCTCCCAGTCACTTCTCTACTCCAACGGCTATAACTACGTGGATTGGTACCT CCAAAAGCCGGGCCAGAGCCCGCAGCTGCTGATCTACCTGGGCTCGAACAGGG

		CCAGCGGAGTGCCTGACCGGTTCTCCGGGTCGGGAAGCGGGACCGACTTCAAG CTGCAAATCTCGAGAGTGGAGGCCGAGGACGTGGGAATCTACTACTGTATGCA GGGCCGCCAGTTTCCGTACTCGTTCGGACAGGGCACCAAAGTGGAAATCAAG
139102- aa VH	74	QVQLVQSGAEVKKPGASVKVSCKASGYTFSNYGITWVRQAPGQGLEWMGWISA YNGNTNYAQKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYYCARGPYYYYMD VWGKGTMVTVSS
139102- aa VL	89	EIVMTQSPLSLPVTPGEPASISCRSSQSLLYSNGYNYVDWYLQKPGQSPQLLI YLGSNRASGVPDRFSGSGSGTDFKLQISRVEAEDVGIYYCMQGRQFPYSFGQG TKVEIK
139102- aa Full CAR	104	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFSNY GITWVRQAPGQGLEWMGWISAYNGNTNYAQKFQGRVTMTRNTSISTAYMELSS LRSEDTAVYYCARGPYYYYMDVWGKGTMVTVSSASGGGGSGGRASGGGGSEIV MTQSPLSLPVTPGEPASISCRSSQSLLYSNGYNYVDWYLQKPGQSPQLLIYLG SNRASGVPDRFSGSGSGTDFKLQISRVEAEDVGIYYCMQGRQFPYSFGQGTKV EIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWA PLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPE EEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEM GGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATK DTYDALHMQALPPR
139102- nt Full CAR	119	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCCAAGTCCAACTGGTCCAGAGCGGTGCAGAAGTGAAGAAGCCCG GAGCGAGCGTGAAAGTGTCCTGCAAGGCTTCCGGGTACACCTTCTCCAACTAC GGCATCACTTGGGTGCGCCAGGCCCCGGGACAGGGCCTGGAATGGATGGGGTG GATTTCCGCGTACAACGGCAATACGAACTACGCTCAGAAGTTCCAGGGTAGAG TGACCATGACTAGGAACACCTCCATTTCCACCGCCTACATGGAACTGTCCTCC CTGCGGAGCGAGGACACCGCCGTGTACTATTGCGCCCGGGGACCATACTACTA CTACATGGATGTCTGGGGGAAGGGGACTATGGTCACCGTGTCATCCGCCTCGG GAGGCGGCGGATCAGGAGGACGCGCCTCTGGTGGTGGAGGATCGGAGATCGTG ATGACCCAGAGCCCTCTCTCCTTGCCCGTGACTCCTGGGGAGCCCGCATCCAT TTCATGCCGGAGCTCCCAGTCACTTCTCTACTCCAACGGCTATAACTACGTGG ATTGGTACCTCCAAAAGCCGGGCCAGAGCCCGCAGCTGCTGATCTACCTGGGC TCGAACAGGGCCAGCGGAGTGCCTGACCGGTTCTCCGGGTCGGGAAGCGGGAC CGACTTCAAGCTGCAAATCTCGAGAGTGGAGGCCGAGGACGTGGGAATCTACT ACTGTATGCAGGGCCGCCAGTTTCCGTACTCGTTCGGACAGGGCACCAAAGTG GAAATCAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCAT CGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTG GGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCC CCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTA CTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGA GGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAG GAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGC TCCAGCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTC GGAGAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATG GGCGGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCA AAAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCA GAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAG GACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
139104		
139104- aa ScFv domain	45	EVQLLETGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSGIVY SGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGGESDVWG QGTTVTVSSASGGGGSGGRASGGGGSEIVLTQSPATLSVSPGESATLSCRASQ SVSSNLAWYQQKPGQAPRLLIYGASTRASGIPDRFSGSGSGTDFTLTISSLQA

		EDVAVYYCQQYGSSLTFGGGTKVEIK
139104- nt ScFv domain	60	GAAGTGCAATTGCTCGAAACTGGAGGAGGTCTGGTGCAACCTGGAGGATCACT TCGCCTGTCCTGCGCCGTGTCGGGCTTTGCCCTGTCCAACCATGGAATGAGCT GGGTCCGCCGCGCGCCGGGGAAGGGCCTCGAATGGGTGTCCGGCATCGTCTAC TCCGGCTCCACCTACTACGCCGCGTCCGTGAAGGGCCGGTTCACGATTTCACG GGACAACTCGCGGAACACCCTGTACCTCCAAATGAATTCCCTTCGGCCGGAGG ATACTGCCATCTACTACTGCTCCGCCCACGGTGGCGAATCCGACGTCTGGGGC CAGGGAACCACCGTGACCGTGTCCAGCGCGTCCGGGGGAGGAGGAAGCGGGGG TAGAGCATCGGGTGGAGGCGGATCAGAGATCGTGCTGACCCAGTCCCCCGCCA CCTTGAGCGTGTCACCAGGAGAGTCCGCCACCCTGTCATGCCGCGCCAGCCAG TCCGTGTCCTCCAACCTGGCTTGGTACCAGCAGAAGCCGGGGCAGGCCCCTAG ACTCCTGATCTATGGGGCGTCGACCCGGGCATCTGGAATTCCCGATAGGTTCA GCGGATCGGGCTCGGGCACTGACTTCACTCTGACCATCTCCTCGCTGCAAGCC GAGGACGTGGCTGTGTACTACTGTCAGCAGTACGGAAGCTCCCTGACTTTCGG TGGCGGGACCAAAGTCGAGATTAAG
139104- aa VH	75	EVQLLETGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSGIVY SGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGGESDVWG QGTTVTVSS
139104- aa VL	90	EIVLTQSPATLSVSPGESATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGAST RASGIPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYGSSLTFGGGTKVEIK
139104- aa Full CAR	105	MALPVTALLLPLALLLHAARPEVQLLETGGGLVQPGGSLRLSCAVSGFALSNH GMSWVRRAPGKGLEWVSGIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSL RPEDTAIYYCSAHGGESDVWGQGTTVTVSSASGGGGSGGRASGGGGSEIVLTQ SPATLSVSPGESATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGASTRASGIP DRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYGSSLTFGGGTKVEIKTTTPAP RPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVL LLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELR VKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNP QEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQ ALPPR
139104- nt Full CAR	120	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCGAAGTGCAATTGCTCGAAACTGGAGGAGGTCTGGTGCAACCTG GAGGATCACTTCGCCTGTCCTGCGCCGTGTCGGGCTTTGCCCTGTCCAACCAT GGAATGAGCTGGGTCCGCCGCGCGCCGGGGAAGGGCCTCGAATGGGTGTCCGG CATCGTCTACTCCGGCTCCACCTACTACGCCGCGTCCGTGAAGGGCCGGTTCA CGATTTCACGGGACAACTCGCGGAACACCCTGTACCTCCAAATGAATTCCCTT CGGCCGGAGGATACTGCCATCTACTACTGCTCCGCCCACGGTGGCGAATCCGA CGTCTGGGGCCAGGGAACCACCGTGACCGTGTCCAGCGCGTCCGGGGGAGGAG GAAGCGGGGGTAGAGCATCGGGTGGAGGCGGATCAGAGATCGTGCTGACCCAG TCCCCCGCCACCTTGAGCGTGTCACCAGGAGAGTCCGCCACCCTGTCATGCCG CGCCAGCCAGTCCGTGTCCTCCAACCTGGCTTGGTACCAGCAGAAGCCGGGGC AGGCCCCTAGACTCCTGATCTATGGGGCGTCGACCCGGGCATCTGGAATTCCC GATAGGTTCAGCGGATCGGGCTCGGGCACTGACTTCACTCTGACCATCTCCTC GCTGCAAGCCGAGGACGTGGCTGTGTACTACTGTCAGCAGTACGGAAGCTCCC TGACTTTCGGTGGCGGGACCAAAGTCGAGATTAAGACCACTACCCCAGCACCG AGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCC GGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACT TCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTG CTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCT GTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGG ACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGC GTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCA

		GCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGGACA AGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAATCCC CAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCCTATAG CGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACGACGGACTGT ACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTTCACATGCAG GCCCTGCCGCCTCGG
139106		
139106- aa ScFv domain	46	EVQLVETGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSGIVY SGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGGESDVWG QGTTVTVSSASGGGGSGGRASGGGGSEIVMTQSPATLSVSPGERATLSCRASQ SVSSKLAWYQQKPGQAPRLLMYGASIRATGIPDRFSGSGSGTEFTLTISSLEP EDFAVYYCQQYGSSSWTFGQGTKVEIK
139106- nt ScFv domain	61	GAAGTGCAATTGGTGGAAACTGGAGGAGGACTTGTGCAACCTGGAGGATCATT GAGACTGAGCTGCGCAGTGTCGGGATTCGCCCTGAGCAACCATGGAATGTCCT GGGTCAGAAGGGCCCCTGGAAAAGGCCTCGAATGGGTGTCAGGGATCGTGTAC TCCGGTTCCACTTACTACGCCGCCTCCGTGAAGGGGCGCTTCACTATCTCACG GGATAACTCCCGCAATACCCTGTACCTCCAAATGAACAGCCTGCGGCCGGAGG ATACCGCCATCTACTACTGTTCCGCCCACGGTGGAGAGTCTGACGTCTGGGGC CAGGGAACTACCGTGACCGTGTCCTCCGCGTCCGGCGGTGGAGGGAGCGGCGG CCGCGCCAGCGGCGGCGGAGGCTCCGAGATCGTGATGACCCAGAGCCCCGCTA CTCTGTCGGTGTCGCCCGGAGAAAGGGCGACCCTGTCCTGCCGGGCGTCGCAG TCCGTGAGCAGCAAGCTGGCTTGGTACCAGCAGAAGCCGGGCCAGGCACCACG CCTGCTTATGTACGGTGCCTCCATTCGGGCCACCGGAATCCCGGACCGGTTCT CGGGGTCGGGGTCCGGTACCGAGTTCACACTGACCATTTCCTCGCTCGAGCCC GAGGACTTTGCCGTCTATTACTGCCAGCAGTACGGCTCCTCCTCATGGACGTT CGGCCAGGGGACCAAGGTCGAAATCAAG
139106- aa VH	76	EVQLVETGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSGIVY SGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGGESDVWG QGTTVTVSS
139106- aa VL	91	EIVMTQSPATLSVSPGERATLSCRASQSVSSKLAWYQQKPGQAPRLLMYGASI RATGIPDRFSGSGSGTEFTLTISSLEPEDFAVYYCQQYGSSSWTFGQGTKVEI K
139106- aa Full CAR	106	MALPVTALLLPLALLLHAARPEVQLVETGGGLVQPGGSLRLSCAVSGFALSNH GMSWVRRAPGKGLEWVSGIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSL RPEDTAIYYCSAHGGESDVWGQGTTVTVSSASGGGGSGGRASGGGGSEIVMTQ SPATLSVSPGERATLSCRASQSVSSKLAWYQQKPGQAPRLLMYGASIRATGIP DRFSGSGSGTEFTLTISSLEPEDFAVYYCQQYGSSSWTFGQGTKVEIKTTTPA PRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGV LLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKN PQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
139106- nt Full CAR	121	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCGAAGTGCAATTGGTGGAAACTGGAGGAGGACTTGTGCAACCTG GAGGATCATTGAGACTGAGCTGCGCAGTGTCGGGATTCGCCCTGAGCAACCAT GGAATGTCCTGGGTCAGAAGGGCCCCTGGAAAAGGCCTCGAATGGGTGTCAGG GATCGTGTACTCCGGTTCCACTTACTACGCCGCCTCCGTGAAGGGGCGCTTCA CTATCTCACGGGATAACTCCCGCAATACCCTGTACCTCCAAATGAACAGCCTG CGGCCGGAGGATACCGCCATCTACTACTGTTCCGCCCACGGTGGAGAGTCTGA CGTCTGGGGCCAGGGAACTACCGTGACCGTGTCCTCCGCGTCCGGCGGTGGAG GGAGCGGCGGCCGCGCCAGCGGCGGCGGAGGCTCCGAGATCGTGATGACCCAG AGCCCCGCTACTCTGTCGGTGTCGCCCGGAGAAAGGGCGACCCTGTCCTGCCG

		GGCGTCGCAGTCCGTGAGCAGCAAGCTGGCTTGGTACCAGCAGAAGCCGGGCC AGGCACCACGCCTGCTTATGTACGGTGCCTCCATTCGGGCCACCGGAATCCCG GACCGGTTCTCGGGGTCGGGGTCCGGTACCGAGTTCACACTGACCATTTCCTC GCTCGAGCCCGAGGACTTTGCCGTCTATTACTGCCAGCAGTACGGCTCCTCCT CATGGACGTTCGGCCAGGGGACCAAGGTCGAAATCAAGACCACTACCCCAGCA CCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCG TCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTG ACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTC CTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCT GCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGG AGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTG CGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAA CCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGG ACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAAT CCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCCTA TAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACGACGGAC TGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTTCACATG CAGGCCCTGCCGCCTCGG
139107		
139107- aa ScFv domain	47	EVQLVETGGGVVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSGIVY SGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGGESDVWG QGTTVTVSSASGGGGSGGRASGGGGSEIVLTQSPGTLSLSPGERATLSCRASQ SVGSTNLAWYQQKPGQAPRLLIYDASNRATGIPDRFSGGGSGTDFTLTISRLE PEDFAVYYCQQYGSSPPWTFGQGTKVEIK
139107- nt ScFv domain	62	GAAGTGCAATTGGTGGAGACTGGAGGAGGAGTGGTGCAACCTGGAGGAAGCCT GAGACTGTCATGCGCGGTGTCGGGCTTCGCCCTCTCCAACCACGGAATGTCCT GGGTCCGCCGGGCCCCTGGGAAAGGACTTGAATGGGTGTCCGGCATCGTGTAC TCGGGTTCCACCTACTACGCGGCCTCAGTGAAGGGCCGGTTTACTATTAGCCG CGACAACTCCAGAAACACACTGTACCTCCAAATGAACTCGCTGCGGCCGGAAG ATACCGCTATCTACTACTGCTCCGCCCATGGGGGAGAGTCGGACGTCTGGGGA CAGGGCACCACTGTCACTGTGTCCAGCGCTTCCGGCGGTGGTGGAAGCGGGGG ACGGGCCTCAGGAGGCGGTGGCAGCGAGATTGTGCTGACCCAGTCCCCCGGGA CCCTGAGCCTGTCCCCGGGAGAAAGGGCCACCCTCTCCTGTCGGGCATCCCAG TCCGTGGGGTCTACTAACCTTGCATGGTACCAGCAGAAGCCCGGCCAGGCCCC TCGCCTGCTGATCTACGACGCGTCCAATAGAGCCACCGGCATCCCGGATCGCT TCAGCGGAGGCGGATCGGGCACCGACTTCACCCTCACCATTTCAAGGCTGGAA CCGGAGGACTTCGCCGTGTACTACTGCCAGCAGTATGGTTCGTCCCCACCCTG GACGTTCGGCCAGGGGACTAAGGTCGAGATCAAG
139107- aa VH	77	EVQLVETGGGVVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSGIVY SGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGGESDVWG QGTTVTVSS
139107- aa VL	92	EIVLTQSPGTLSLSPGERATLSCRASQSVGSTNLAWYQQKPGQAPRLLIYDAS NRATGIPDRFSGGGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPWTFGQGTKV EIK
139107- aa Full CAR	107	MALPVTALLLPLALLLHAARPEVQLVETGGGVVQPGGSLRLSCAVSGFALSNH GMSWVRRAPGKGLEWVSGIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSL RPEDTAIYYCSAHGGESDVWGQGTTVTVSSASGGGGSGGRASGGGGSEIVLTQ SPGTLSLSPGERATLSCRASQSVGSTNLAWYQQKPGQAPRLLIYDASNRATGI PDRFSGGGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPWTFGQGTKVEIKTTT PAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTC GVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGC ELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRR

		KNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDAL HMQALPPR
139107- nt Full CAR	122	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCGAAGTGCAATTGGTGGAGACTGGAGGAGGAGTGGTGCAACCTG GAGGAAGCCTGAGACTGTCATGCGCGGTGTCGGGCTTCGCCCTCTCCAACCAC GGAATGTCCTGGGTCCGCCGGGCCCCTGGGAAAGGACTTGAATGGGTGTCCGG CATCGTGTACTCGGGTTCCACCTACTACGCGGCCTCAGTGAAGGGCCGGTTTA CTATTAGCCGCGACAACTCCAGAAACACACTGTACCTCCAAATGAACTCGCTG CGGCCGGAAGATACCGCTATCTACTACTGCTCCGCCCATGGGGGAGAGTCGGA CGTCTGGGGACAGGGCACCACTGTCACTGTGTCCAGCGCTTCCGGCGGTGGTG GAAGCGGGGGACGGGCCTCAGGAGGCGGTGGCAGCGAGATTGTGCTGACCCAG TCCCCCGGGACCCTGAGCCTGTCCCCGGGAGAAAGGGCCACCCTCTCCTGTCG GGCATCCCAGTCCGTGGGGTCTACTAACCTTGCATGGTACCAGCAGAAGCCCG GCCAGGCCCCTCGCCTGCTGATCTACGACGCGTCCAATAGAGCCACCGGCATC CCGGATCGCTTCAGCGGAGGCGGATCGGGCACCGACTTCACCCTCACCATTTC AAGGCTGGAACCGGAGGACTTCGCCGTGTACTACTGCCAGCAGTATGGTTCGT CCCCACCCTGGACGTTCGGCCAGGGGACTAAGGTCGAGATCAAGACCACTACC CCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTC CCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGG GTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGC GGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAA GAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTC AAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGC GAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGG GCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACG TGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGA AAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGA AGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACG ACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTT CACATGCAGGCCCTGCCGCCTCGG
139108		
139108- aa ScFv domain	48	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVSYISS SGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARESGDGMDV WGQGTTVTVSSASGGGGSGGRASGGGGSDIQMTQSPSSLSASVGDRVTITCRA SQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQSYTLAFGQGTKVDIK
139108- nt ScFv domain	63	CAAGTGCAACTCGTGGAATCTGGTGGAGGACTCGTGAAACCTGGAGGATCATT GAGACTGTCATGCGCGGCCTCGGGATTCACGTTCTCCGATTACTACATGAGCT GGATTCGCCAGGCTCCGGGGAAGGGACTGGAATGGGTGTCCTACATTTCCTCA TCCGGCTCCACCATCTACTACGCGGACTCCGTGAAGGGGAGATTCACCATTAG CCGCGATAACGCCAAGAACAGCCTGTACCTTCAGATGAACTCCCTGCGGGCTG AAGATACTGCCGTCTACTACTGCGCAAGGGAGAGCGGAGATGGGATGGACGTC TGGGGACAGGGTACCACTGTGACCGTGTCGTCGGCCTCCGGCGGAGGGGGTTC GGGTGGAAGGGCCAGCGGCGGCGGAGGCAGCGACATCCAGATGACCCAGTCCC CCTCATCGCTGTCCGCCTCCGTGGGCGACCGCGTCACCATCACATGCCGGGCC TCACAGTCGATCTCCTCCTACCTCAATTGGTATCAGCAGAAGCCCGGAAAGGC CCCTAAGCTTCTGATCTACGCAGCGTCCTCCCTGCAATCCGGGGTCCCATCTC GGTTCTCCGGCTCGGGCAGCGGTACCGACTTCACTCTGACCATCTCGAGCCTG CAGCCGGAGGACTTCGCCACTTACTACTGTCAGCAAAGCTACACCCTCGCGTT TGGCCAGGGCACCAAAGTGGACATCAAG
139108- aa VH	78	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVSYISS SGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARESGDGMDV

		WGQGTTVTVSS
139108- aa VL	93	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASS LQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYTLAFGQGTKVDIK
139108- aa Full CAR	108	MALPVTALLLPLALLLHAARPQVQLVESGGGLVKPGGSLRLSCAASGFTFSDY YMSWIRQAPGKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARESGDGMDVWGQGTTVTVSSASGGGGSGGRASGGGGSDIQM TQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYTLAFGQGTKVDIKTTTPA PRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGV LLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKN PQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
139108- nt Full CAR	123	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCCAAGTGCAACTCGTGGAATCTGGTGGAGGACTCGTGAAACCTG GAGGATCATTGAGACTGTCATGCGCGGCCTCGGGATTCACGTTCTCCGATTAC TACATGAGCTGGATTCGCCAGGCTCCGGGGAAGGGACTGGAATGGGTGTCCTA CATTTCCTCATCCGGCTCCACCATCTACTACGCGGACTCCGTGAAGGGGAGAT TCACCATTAGCCGCGATAACGCCAAGAACAGCCTGTACCTTCAGATGAACTCC CTGCGGGCTGAAGATACTGCCGTCTACTACTGCGCAAGGGAGAGCGGAGATGG GATGGACGTCTGGGGACAGGGTACCACTGTGACCGTGTCGTCGGCCTCCGGCG GAGGGGGTTCGGGTGGAAGGGCCAGCGGCGGCGGAGGCAGCGACATCCAGATG ACCCAGTCCCCCTCATCGCTGTCCGCCTCCGTGGGCGACCGCGTCACCATCAC ATGCCGGGCCTCACAGTCGATCTCCTCCTACCTCAATTGGTATCAGCAGAAGC CCGGAAAGGCCCCTAAGCTTCTGATCTACGCAGCGTCCTCCCTGCAATCCGGG GTCCCATCTCGGTTCTCCGGCTCGGGCAGCGGTACCGACTTCACTCTGACCAT CTCGAGCCTGCAGCCGGAGGACTTCGCCACTTACTACTGTCAGCAAAGCTACA CCCTCGCGTTTGGCCAGGGCACCAAAGTGGACATCAAGACCACTACCCCAGCA CCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCG TCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTG ACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTC CTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCT GCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGG AGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTG CGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAA CCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGG ACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAAT CCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCCTA TAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACGACGGAC TGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTTCACATG CAGGCCCTGCCGCCTCGG
139110		
139110- aa ScFv domain	50	QVQLVQSGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVSYISS SGNTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARSTMVREDY WGQGTLVTVSSASGGGGSGGRASGGGGSDIVLTQSPLSLPVTLGQPASISCKS SESLVHNSGKTYLNWFHQRPGQSPRRLIYEVSNRDSGVPDRFTGSGSGTDFTL KISRVEAEDVGVYYCMQGTHWPGTFGQGTKLEIK
139110- nt ScFv domain	65	CAAGTGCAACTGGTGCAAAGCGGAGGAGGATTGGTCAAACCCGGAGGAAGCCT GAGACTGTCATGCGCGGCCTCTGGATTCACCTTCTCCGATTACTACATGTCAT GGATCAGACAGGCCCCGGGGAAGGGCCTCGAATGGGTGTCCTACATCTCGTCC TCCGGGAACACCATCTACTACGCCGACAGCGTGAAGGGCCGCTTTACCATTTC CCGCGACAACGCAAAGAACTCGCTGTACCTTCAGATGAATTCCCTGCGGGCTG

		AAGATACCGCGGTGTACTATTGCGCCCGGTCCACTATGGTCCGGGAGGACTAC TGGGGACAGGGCACACTCGTGACCGTGTCCAGCGCGAGCGGGGGTGGAGGCAG CGGTGGACGCGCCTCCGGCGGCGGCGGTTCAGACATCGTGCTGACTCAGTCGC CCCTGTCGCTGCCGGTCACCCTGGGCCAACCGGCCTCAATTAGCTGCAAGTCC TCGGAGAGCCTGGTGCACAACTCAGGAAAGACTTACCTGAACTGGTTCCATCA GCGGCCTGGACAGTCCCCACGGAGGCTCATCTATGAAGTGTCCAACAGGGATT CGGGGGTGCCCGACCGCTTCACTGGCTCCGGGTCCGGCACCGACTTCACCTTG AAAATCTCCAGAGTGGAAGCCGAGGACGTGGGCGTGTACTACTGTATGCAGGG TACCCACTGGCCTGGAACCTTTGGACAAGGAACTAAGCTCGAGATTAAG
139110- aa VH	80	QVQLVQSGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVSYISS SGNTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARSTMVREDY WGQGTLVTVSS
139110- aa VL	95	DIVLTQSPLSLPVTLGQPASISCKSSESLVHNSGKTYLNWFHQRPGQSPRRLI YEVSNRDSGVPDRFTGSGSGTDFTLKISRVEAEDVGVYYCMQGTHWPGTFGQG TKLEIK
139110- aa Full CAR	110	MALPVTALLLPLALLLHAARPQVQLVQSGGGLVKPGGSLRLSCAASGFTFSDY YMSWIRQAPGKGLEWVSYISSSGNTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARSTMVREDYWGQGTLVTVSSASGGGGSGGRASGGGGSDIVL TQSPLSLPVTLGQPASISCKSSESLVHNSGKTYLNWFHQRPGQSPRRLIYEVS NRDSGVPDRFTGSGSGTDFTLKISRVEAEDVGVYYCMQGTHWPGTFGQGTKLE IKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAP LAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEE EEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKD TYDALHMQALPPR
139110- nt Full CAR	125	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCCAAGTGCAACTGGTGCAAAGCGGAGGAGGATTGGTCAAACCCG GAGGAAGCCTGAGACTGTCATGCGCGGCCTCTGGATTCACCTTCTCCGATTAC TACATGTCATGGATCAGACAGGCCCCGGGGAAGGGCCTCGAATGGGTGTCCTA CATCTCGTCCTCCGGGAACACCATCTACTACGCCGACAGCGTGAAGGGCCGCT TTACCATTTCCCGCGACAACGCAAAGAACTCGCTGTACCTTCAGATGAATTCC CTGCGGGCTGAAGATACCGCGGTGTACTATTGCGCCCGGTCCACTATGGTCCG GGAGGACTACTGGGGACAGGGCACACTCGTGACCGTGTCCAGCGCGAGCGGGG GTGGAGGCAGCGGTGGACGCGCCTCCGGCGGCGGCGGTTCAGACATCGTGCTG ACTCAGTCGCCCCTGTCGCTGCCGGTCACCCTGGGCCAACCGGCCTCAATTAG CTGCAAGTCCTCGGAGAGCCTGGTGCACAACTCAGGAAAGACTTACCTGAACT GGTTCCATCAGCGGCCTGGACAGTCCCCACGGAGGCTCATCTATGAAGTGTCC AACAGGGATTCGGGGGTGCCCGACCGCTTCACTGGCTCCGGGTCCGGCACCGA CTTCACCTTGAAAATCTCCAGAGTGGAAGCCGAGGACGTGGGCGTGTACTACT GTATGCAGGGTACCCACTGGCCTGGAACCTTTGGACAAGGAACTAAGCTCGAG ATTAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGC CTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGG CCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCT CTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTG TAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGC CTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAG GAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCC AGCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGA GAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGC GGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAA GGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAA GAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGAC

		ACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
139112		
139112- aa ScFv domain	51	QVQLVESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSGIVY SGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGGESDVWG QGTTVTVSSASGGGGSGGRASGGGGSDIRLTQSPSPLSASVGDRVTITCQASE DINKFLNWYHQTPGKAPKLLIYDASTLQTGVPSRFSGSGSGTDFTLTINSLQP EDIGTYYCQQYESLPLTFGGGTKVEIK
139112- nt ScFv domain	66	CAAGTGCAACTCGTGGAATCTGGTGGAGGACTCGTGCAACCCGGTGGAAGCCT TAGGCTGTCGTGCGCCGTCAGCGGGTTTGCTCTGAGCAACCATGGAATGTCCT GGGTCCGCCGGGCACCGGGAAAAGGGCTGGAATGGGTGTCCGGCATCGTGTAC AGCGGGTCAACCTATTACGCCGCGTCCGTGAAGGGCAGATTCACTATCTCAAG AGACAACAGCCGGAACACCCTGTACTTGCAAATGAATTCCCTGCGCCCCGAGG ACACCGCCATCTACTACTGCTCCGCCCACGGAGGAGAGTCGGACGTGTGGGGC CAGGGAACGACTGTGACTGTGTCCAGCGCATCAGGAGGGGGTGGTTCGGGCGG CCGGGCCTCGGGGGGAGGAGGTTCCGACATTCGGCTGACCCAGTCCCCGTCCC CACTGTCGGCCTCCGTCGGCGACCGCGTGACCATCACTTGTCAGGCGTCCGAG GACATTAACAAGTTCCTGAACTGGTACCACCAGACCCCTGGAAAGGCCCCCAA GCTGCTGATCTACGATGCCTCGACCCTTCAAACTGGAGTGCCTAGCCGGTTCT CCGGGTCCGGCTCCGGCACTGATTTCACTCTGACCATCAACTCATTGCAGCCG GAAGATATCGGGACCTACTATTGCCAGCAGTACGAATCCCTCCCGCTCACATT CGGCGGGGGAACCAAGGTCGAGATTAAG
139112- aa VH	81	QVQLVESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSGIVY SGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGGESDVWG QGTTVTVSS
139112- aa VL	96	DIRLTQSPSPLSASVGDRVTITCQASEDINKFLNWYHQTPGKAPKLLIYDAST LQTGVPSRFSGSGSGTDFTLTINSLQPEDIGTYYCQQYESLPLTFGGGTKVEI K
139112- aa Full CAR	111	MALPVTALLLPLALLLHAARPQVQLVESGGGLVQPGGSLRLSCAVSGFALSNH GMSWVRRAPGKGLEWVSGIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSL RPEDTAIYYCSAHGGESDVWGQGTTVTVSSASGGGGSGGRASGGGGSDIRLTQ SPSPLSASVGDRVTITCQASEDINKFLNWYHQTPGKAPKLLIYDASTLQTGVP SRFSGSGSGTDFTLTINSLQPEDIGTYYCQQYESLPLTFGGGTKVEIKTTTPA PRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGV LLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKN PQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
139112- nt Full CAR	126	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCCAAGTGCAACTCGTGGAATCTGGTGGAGGACTCGTGCAACCCG GTGGAAGCCTTAGGCTGTCGTGCGCCGTCAGCGGGTTTGCTCTGAGCAACCAT GGAATGTCCTGGGTCCGCCGGGCACCGGGAAAAGGGCTGGAATGGGTGTCCGG CATCGTGTACAGCGGGTCAACCTATTACGCCGCGTCCGTGAAGGGCAGATTCA CTATCTCAAGAGACAACAGCCGGAACACCCTGTACTTGCAAATGAATTCCCTG CGCCCCGAGGACACCGCCATCTACTACTGCTCCGCCCACGGAGGAGAGTCGGA CGTGTGGGGCCAGGGAACGACTGTGACTGTGTCCAGCGCATCAGGAGGGGGTG GTTCGGGCGGCCGGGCCTCGGGGGGAGGAGGTTCCGACATTCGGCTGACCCAG TCCCCGTCCCCACTGTCGGCCTCCGTCGGCGACCGCGTGACCATCACTTGTCA GGCGTCCGAGGACATTAACAAGTTCCTGAACTGGTACCACCAGACCCCTGGAA AGGCCCCCAAGCTGCTGATCTACGATGCCTCGACCCTTCAAACTGGAGTGCCT AGCCGGTTCTCCGGGTCCGGCTCCGGCACTGATTTCACTCTGACCATCAACTC ATTGCAGCCGGAAGATATCGGGACCTACTATTGCCAGCAGTACGAATCCCTCC CGCTCACATTCGGCGGGGGAACCAAGGTCGAGATTAAGACCACTACCCCAGCA

		CCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCG TCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTG ACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTC CTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCT GCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGG AGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTG CGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAA CCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGG ACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAAT CCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCCTA TAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACGACGGAC TGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTTCACATG CAGGCCCTGCCGCCTCGG
139113		
139113- aa ScFv domain	52	EVQLVETGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSGIVY SGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGGESDVWG QGTTVTVSSASGGGGSGGRASGGGGSETTLTQSPATLSVSPGERATLSCRASQ SVGSNLAWYQQKPGQGPRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQP EDFAVYYCQQYNDWLPVTFGQGTKVEIK
139113- nt ScFv domain	67	GAAGTGCAATTGGTGGAAACTGGAGGAGGACTTGTGCAACCTGGAGGATCATT GCGGCTCTCATGCGCTGTCTCCGGCTTCGCCCTGTCAAATCACGGGATGTCGT GGGTCAGACGGGCCCCGGGAAAGGGTCTGGAATGGGTGTCGGGGATTGTGTAC AGCGGCTCCACCTACTACGCCGCTTCGGTCAAGGGCCGCTTCACTATTTCACG GGACAACAGCCGCAACACCCTCTATCTGCAAATGAACTCTCTCCGCCCGGAGG ATACCGCCATCTACTACTGCTCCGCACACGGCGGCGAATCCGACGTGTGGGGA CAGGGAACCACTGTCACCGTGTCGTCCGCATCCGGTGGCGGAGGATCGGGTGG CCGGGCCTCCGGGGGCGGCGGCAGCGAGACTACCCTGACCCAGTCCCCTGCCA CTCTGTCCGTGAGCCCGGGAGAGAGAGCCACCCTTAGCTGCCGGGCCAGCCAG AGCGTGGGCTCCAACCTGGCCTGGTACCAGCAGAAGCCAGGACAGGGTCCCAG GCTGCTGATCTACGGAGCCTCCACTCGCGCGACCGGCATCCCCGCGAGGTTCT CCGGGTCGGGTTCCGGGACCGAGTTCACCCTGACCATCTCCTCCCTCCAACCG GAGGACTTCGCGGTGTACTACTGTCAGCAGTACAACGATTGGCTGCCCGTGAC ATTTGGACAGGGGACGAAGGTGGAAATCAAA
139113- aa VH	82	EVQLVETGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSGIVY SGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGGESDVWG QGTTVTVSS
139113- aa VL	97	ETTLTQSPATLSVSPGERATLSCRASQSVGSNLAWYQQKPGQGPRLLIYGAST RATGIPARFSGSGSGTEFTLTISSLQPEDFAVYYCQQYNDWLPVTFGQGTKVE IK
139113- aa Full CAR	112	MALPVTALLLPLALLLHAARPEVQLVETGGGLVQPGGSLRLSCAVSGFALSNH GMSWVRRAPGKGLEWVSGIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSL RPEDTAIYYCSAHGGESDVWGQGTTVTVSSASGGGGSGGRASGGGGSETTLTQ SPATLSVSPGERATLSCRASQSVGSNLAWYQQKPGQGPRLLIYGASTRATGIP ARFSGSGSGTEFTLTISSLQPEDFAVYYCQQYNDWLPVTFGQGTKVEIKTTTP APRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCG VLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCE LRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRK NPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALH MQALPPR
139113- nt Full CAR	127	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCGAAGTGCAATTGGTGGAAACTGGAGGAGGACTTGTGCAACCTG GAGGATCATTGCGGCTCTCATGCGCTGTCTCCGGCTTCGCCCTGTCAAATCAC

		GGGATGTCGTGGGTCAGACGGGCCCCGGGAAAGGGTCTGGAATGGGTGTCGGG GATTGTGTACAGCGGCTCCACCTACTACGCCGCTTCGGTCAAGGGCCGCTTCA CTATTTCACGGGACAACAGCCGCAACACCCTCTATCTGCAAATGAACTCTCTC CGCCCGGAGGATACCGCCATCTACTACTGCTCCGCACACGGCGGCGAATCCGA CGTGTGGGGACAGGGAACCACTGTCACCGTGTCGTCCGCATCCGGTGGCGGAG GATCGGGTGGCCGGGCCTCCGGGGGCGGCGGCAGCGAGACTACCCTGACCCAG TCCCCTGCCACTCTGTCCGTGAGCCCGGGAGAGAGAGCCACCCTTAGCTGCCG GGCCAGCCAGAGCGTGGGCTCCAACCTGGCCTGGTACCAGCAGAAGCCAGGAC AGGGTCCCAGGCTGCTGATCTACGGAGCCTCCACTCGCGCGACCGGCATCCCC GCGAGGTTCTCCGGGTCGGGTTCCGGGACCGAGTTCACCCTGACCATCTCCTC CCTCCAACCGGAGGACTTCGCGGTGTACTACTGTCAGCAGTACAACGATTGGC TGCCCGTGACATTTGGACAGGGGACGAAGGTGGAAATCAAAACCACTACCCCA GCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTC TTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGG GTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAA GCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAG AGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAA CTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCA GAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGC TGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAG AATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGC CTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACGACG GACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTTCAC ATGCAGGCCCTGCCGCCTCGG
139114		
139114- aa ScFv domain	53	EVQLVESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSGIVY SGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGGESDVWG QGTTVTVSSASGGGGSGGRASGGGGSEIVLTQSPGTLSLSPGERATLSCRASQ SIGSSSLAWYQQKPGQAPRLLMYGASSRASGIPDRFSGSGSGTDFTLTISRLE PEDFAVYYCQQYAGSPPFTFGQGTKVEIK
139114- nt ScFv domain	68	GAAGTGCAATTGGTGGAATCTGGTGGAGGACTTGTGCAACCTGGAGGATCACT GAGACTGTCATGCGCGGTGTCCGGTTTTGCCCTGAGCAATCATGGGATGTCGT GGGTCCGGCGCGCCCCCGGAAAGGGTCTGGAATGGGTGTCGGGTATCGTCTAC TCCGGGAGCACTTACTACGCCGCGAGCGTGAAGGGCCGCTTCACCATTTCCCG CGATAACTCCCGCAACACCCTGTACTTGCAAATGAACTCGCTCCGGCCTGAGG ACACTGCCATCTACTACTGCTCCGCACACGGAGGAGAATCCGACGTGTGGGGC CAGGGAACTACCGTGACCGTCAGCAGCGCCTCCGGCGGCGGGGGCTCAGGCGG ACGGGCTAGCGGCGGCGGTGGCTCCGAGATCGTGCTGACCCAGTCGCCTGGCA CTCTCTCGCTGAGCCCCGGGGAAAGGGCAACCCTGTCCTGTCGGGCCAGCCAG TCCATTGGATCATCCTCCCTCGCCTGGTATCAGCAGAAACCGGGACAGGCTCC GCGGCTGCTTATGTATGGGGCCAGCTCAAGAGCCTCCGGCATTCCCGACCGGT TCTCCGGGTCCGGTTCCGGCACCGATTTCACCCTGACTATCTCGAGGCTGGAG CCAGAGGACTTCGCCGTGTACTACTGCCAGCAGTACGCGGGGTCCCCGCCGTT CACGTTCGGACAGGGAACCAAGGTCGAGATCAAG
139114- aa VH	83	EVQLVESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSGIVY SGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGGESDVWG QGTTVTVSS
139114- aa VL	98	EIVLTQSPGTLSLSPGERATLSCRASQSIGSSSLAWYQQKPGQAPRLLMYGAS SRASGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYAGSPPFTFGQGTKV EIK
139114- aa	113	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAVSGFALSNH

Full CAR		GMSWVRRAPGKGLEWVSGIVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSL RPEDTAIYYCSAHGGESDVWGQGTTVTVSSASGGGGSGGRASGGGGSEIVLTQ SPGTLSLSPGERATLSCRASQSIGSSSLAWYQQKPGQAPRLLMYGASSRASGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYAGSPPFTFGQGTKVEIKTTT PAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTC GVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGC ELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRR KNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDAL HMQALPPR
139114- nt Full CAR	128	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCGAAGTGCAATTGGTGGAATCTGGTGGAGGACTTGTGCAACCTG GAGGATCACTGAGACTGTCATGCGCGGTGTCCGGTTTTGCCCTGAGCAATCAT GGGATGTCGTGGGTCCGGCGCGCCCCCGGAAAGGGTCTGGAATGGGTGTCGGG TATCGTCTACTCCGGGAGCACTTACTACGCCGCGAGCGTGAAGGGCCGCTTCA CCATTTCCCGCGATAACTCCCGCAACACCCTGTACTTGCAAATGAACTCGCTC CGGCCTGAGGACACTGCCATCTACTACTGCTCCGCACACGGAGGAGAATCCGA CGTGTGGGGCCAGGGAACTACCGTGACCGTCAGCAGCGCCTCCGGCGGCGGGG GCTCAGGCGGACGGGCTAGCGGCGGCGGTGGCTCCGAGATCGTGCTGACCCAG TCGCCTGGCACTCTCTCGCTGAGCCCCGGGGAAAGGGCAACCCTGTCCTGTCG GGCCAGCCAGTCCATTGGATCATCCTCCCTCGCCTGGTATCAGCAGAAACCGG GACAGGCTCCGCGGCTGCTTATGTATGGGGCCAGCTCAAGAGCCTCCGGCATT CCCGACCGGTTCTCCGGGTCCGGTTCCGGCACCGATTTCACCCTGACTATCTC GAGGCTGGAGCCAGAGGACTTCGCCGTGTACTACTGCCAGCAGTACGCGGGGT CCCCGCCGTTCACGTTCGGACAGGGAACCAAGGTCGAGATCAAGACCACTACC CCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTC CCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGG GTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGC GGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAA GAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTC AAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGC GAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGG GCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACG TGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGA AAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGA AGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACG ACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTT CACATGCAGGCCCTGCCGCCTCGG
149362		
149362-aa ScFv domain	129	QVQLQESGPGLVKPSETLSLTCTVSGGSISSSYYYWGWIRQPPGKGLEWIGSI YYSGSAYYNPSLKSRVTISVDTSKNQFSLRLSSVTAADTAVYYCARHWQEWPD AFDIWGQGTMVTVSSGGGGSGGGGSGGGGSETTLTQSPAFMSATPGDKVIISC KASQDIDDAMNWYQQKPGEAPLFIIQSATSPVPGIPPRFSGSGFGTDFSLTIN NIESEDAAYYFCLQHDNFPLTFGQGTKLEIK
149362-nt ScFv domain	150	CAAGTGCAGCTTCAGGAAAGCGGACCGGGCCTGGTCAAGCCATCCGAAACTCT CTCCCTGACTTGCACTGTGTCTGGCGGTTCCATCTCATCGTCGTACTACTACT GGGGCTGGATTAGGCAGCCGCCCGGAAAGGGACTGGAGTGGATCGGAAGCATC TACTATTCCGGCTCGGCGTACTACAACCCTAGCCTCAAGTCGAGAGTGACCAT CTCCGTGGATACCTCCAAGAACCAGTTTTCCCTGCGCCTGAGCTCCGTGACCG CCGCTGACACCGCCGTGTACTACTGTGCTCGGCATTGGCAGGAATGGCCCGAT GCCTTCGACATTTGGGGCCAGGGCACTATGGTCACTGTGTCATCCGGGGGTGG AGGCAGCGGGGGAGGAGGGTCCGGGGGGGGAGGTTCAGAGACAACCTTGACCC AGTCACCCGCATTCATGTCCGCCACTCCGGGAGACAAGGTCATCATCTCGTGC

		AAAGCGTCCCAGGATATCGACGATGCCATGAATTGGTACCAGCAGAAGCCTGG CGAAGCGCCGCTGTTCATTATCCAATCCGCAACCTCGCCCGTGCCTGGAATCC CACCGCGGTTCAGCGGCAGCGGTTTCGGAACCGACTTTTCCCTGACCATTAAC AACATTGAGTCCGAGGACGCCGCCTACTACTTCTGCCTGCAACACGACAACTT CCCTCTCACGTTCGGCCAGGGAACCAAGCTGGAAATCAAG
149362-aa VH	171	QVQLQESGPGLVKPSETLSLTCTVSGGSISSSYYYWGWIRQPPGKGLEWIGSI YYSGSAYYNPSLKSRVTISVDTSKNQFSLRLSSVTAADTAVYYCARHWQEWPD AFDIWGQGTMVTVSS
149362-aa VL	192	ETTLTQSPAFMSATPGDKVIISCKASQDIDDAMNWYQQKPGEAPLFIIQSATS PVPGIPPRFSGSGFGTDFSLTINNIESEDAAYYFCLQHDNFPLTFGQGTKLEI K
149362-aa Full CAR	213	MALPVTALLLPLALLLHAARPQVQLQESGPGLVKPSETLSLTCTVSGGSISSS YYYWGWIRQPPGKGLEWIGSIYYSGSAYYNPSLKSRVTISVDTSKNQFSLRLS SVTAADTAVYYCARHWQEWPDAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSET TLTQSPAFMSATPGDKVIISCKASQDIDDAMNWYQQKPGEAPLFIIQSATSPV PGIPPRFSGSGFGTDFSLTINNIESEDAAYYFCLQHDNFPLTFGQGTKLEIKT TTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAG TCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEG GCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKP RRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYD ALHMQALPPR
149362-nt Full CAR	234	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCCAAGTGCAGCTTCAGGAAAGCGGACCGGGCCTGGTCAAGCCAT CCGAAACTCTCTCCCTGACTTGCACTGTGTCTGGCGGTTCCATCTCATCGTCG TACTACTACTGGGGCTGGATTAGGCAGCCGCCCGGAAAGGGACTGGAGTGGAT CGGAAGCATCTACTATTCCGGCTCGGCGTACTACAACCCTAGCCTCAAGTCGA GAGTGACCATCTCCGTGGATACCTCCAAGAACCAGTTTTCCCTGCGCCTGAGC TCCGTGACCGCCGCTGACACCGCCGTGTACTACTGTGCTCGGCATTGGCAGGA ATGGCCCGATGCCTTCGACATTTGGGGCCAGGGCACTATGGTCACTGTGTCAT CCGGGGGTGGAGGCAGCGGGGGAGGAGGGTCCGGGGGGGGAGGTTCAGAGACA ACCTTGACCCAGTCACCCGCATTCATGTCCGCCACTCCGGGAGACAAGGTCAT CATCTCGTGCAAAGCGTCCCAGGATATCGACGATGCCATGAATTGGTACCAGC AGAAGCCTGGCGAAGCGCCGCTGTTCATTATCCAATCCGCAACCTCGCCCGTG CCTGGAATCCCACCGCGGTTCAGCGGCAGCGGTTTCGGAACCGACTTTTCCCT GACCATTAACAACATTGAGTCCGAGGACGCCGCCTACTACTTCTGCCTGCAAC ACGACAACTTCCCTCTCACGTTCGGCCAGGGAACCAAGCTGGAAATCAAGACC ACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCC TCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATA CCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGT ACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGG TCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGA CTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGC GGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAA GCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGT ACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCG CGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGAT GGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAG GCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGAC GCTCTTCACATGCAGGCCCTGCCGCCTCGG
149363		
149363-aa ScFv domain	130	VNLRESGPALVKPTQTLTLTCTFSGFSLRTSGMCVSWIRQPPGKALEWLARID WDEDKFYSTSLKTRLTISKDTSDNQVVLRMTNMDPADTATYYCARSGAGGTSA

		TAFDIWGPGTMVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTIT CRASQDIYNNLAWFQLKPGSAPRSLMYAANKSQSGVPSRFSGSASGTDFTLTI SSLQPEDFATYYCQHYYRFPYSFGQGTKLEIK
149363-nt ScFv domain	151	CAAGTCAATCTGCGCGAATCCGGCCCCGCCTTGGTCAAGCCTACCCAGACCCT CACTCTGACCTGTACTTTCTCCGGCTTCTCCCTGCGGACTTCCGGGATGTGCG TGTCCTGGATCAGACAGCCTCCGGGAAAGGCCCTGGAGTGGCTCGCTCGCATT GACTGGGATGAGGACAAGTTCTACTCCACCTCACTCAAGACCAGGCTGACCAT CAGCAAAGATACCTCTGACAACCAAGTGGTGCTCCGCATGACCAACATGGACC CAGCCGACACTGCCACTTACTACTGCGCGAGGAGCGGAGCGGGCGGAACCTCC GCCACCGCCTTCGATATTTGGGGCCCGGGTACCATGGTCACCGTGTCAAGCGG AGGAGGGGGGTCCGGGGGCGGCGGTTCCGGGGGAGGCGGATCGGACATTCAGA TGACTCAGTCACCATCGTCCCTGAGCGCTAGCGTGGGCGACAGAGTGACAATC ACTTGCCGGGCATCCCAGGACATCTATAACAACCTTGCGTGGTTCCAGCTGAA GCCTGGTTCCGCACCGCGGTCACTTATGTACGCCGCCAACAAGAGCCAGTCGG GAGTGCCGTCCCGGTTTTCCGGTTCGGCCTCGGGAACTGACTTCACCCTGACG ATCTCCAGCCTGCAACCCGAGGATTTCGCCACCTACTACTGCCAGCACTACTA CCGCTTTCCCTACTCGTTCGGACAGGGAACCAAGCTGGAAATCAAG
149363-aa VH	172	QVNLRESGPALVKPTQTLTLTCTFSGFSLRTSGMCVSWIRQPPGKALEWLARI DWDEDKFYSTSLKTRLTISKDTSDNQVVLRMTNMDPADTATYYCARSGAGGTS ATAFDIWGPGTMVTVSS
149363-aa VL	193	DIQMTQSPSSLSASVGDRVTITCRASQDIYNNLAWFQLKPGSAPRSLMYAANK SQSGVPSRFSGSASGTDFTLTISSLQPEDFATYYCQHYYRFPYSFGQGTKLEI K
149363-aa Full CAR	214	MALPVTALLLPLALLLHAARPQVNLRESGPALVKPTQTLTLTCTFSGFSLRTS GMCVSWIRQPPGKALEWLARIDWDEDKFYSTSLKTRLTISKDTSDNQVVLRMT NMDPADTATYYCARSGAGGTSATAFDIWGPGTMVTVSSGGGGSGGGGSGGGGS DIQMTQSPSSLSASVGDRVTITCRASQDIYNNLAWFQLKPGSAPRSLMYAANK SQSGVPSRFSGSASGTDFTLTISSLQPEDFATYYCQHYYRFPYSFGQGTKLEI KTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPL AGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEE EGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGG KPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDT YDALHMQALPPR
149363-nt Full CAR	235	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCCAAGTCAATCTGCGCGAATCCGGCCCCGCCTTGGTCAAGCCTA CCCAGACCCTCACTCTGACCTGTACTTTCTCCGGCTTCTCCCTGCGGACTTCC GGGATGTGCGTGTCCTGGATCAGACAGCCTCCGGGAAAGGCCCTGGAGTGGCT CGCTCGCATTGACTGGGATGAGGACAAGTTCTACTCCACCTCACTCAAGACCA GGCTGACCATCAGCAAAGATACCTCTGACAACCAAGTGGTGCTCCGCATGACC AACATGGACCCAGCCGACACTGCCACTTACTACTGCGCGAGGAGCGGAGCGGG CGGAACCTCCGCCACCGCCTTCGATATTTGGGGCCCGGGTACCATGGTCACCG TGTCAAGCGGAGGAGGGGGGTCCGGGGGCGGCGGTTCCGGGGGAGGCGGATCG GACATTCAGATGACTCAGTCACCATCGTCCCTGAGCGCTAGCGTGGGCGACAG AGTGACAATCACTTGCCGGGCATCCCAGGACATCTATAACAACCTTGCGTGGT TCCAGCTGAAGCCTGGTTCCGCACCGCGGTCACTTATGTACGCCGCCAACAAG AGCCAGTCGGGAGTGCCGTCCCGGTTTTCCGGTTCGGCCTCGGGAACTGACTT CACCCTGACGATCTCCAGCCTGCAACCCGAGGATTTCGCCACCTACTACTGCC AGCACTACTACCGCTTTCCCTACTCGTTCGGACAGGGAACCAAGCTGGAAATC AAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTC CCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCG TGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTG GCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAA

		GCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTG TGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAG GAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGC CTACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAG AGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGG AAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGA TAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAG GCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACC TATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
149364		
149364-aa ScFv domain	131	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISS SSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKTIAAVYAF DIWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSPLSLPVTPEEPASISCRS SQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTL KISRVEAEDVGVYYCMQALQTPYTFGQGTKLEIK
149364-nt ScFv domain	152	GAAGTGCAGCTTGTCGAATCCGGGGGGGGACTGGTCAAGCCGGGCGGATCACT GAGACTGTCCTGCGCCGCGAGCGGCTTCACGTTCTCCTCCTACTCCATGAACT GGGTCCGCCAAGCCCCCGGGAAGGGACTGGAATGGGTGTCCTCTATCTCCTCG TCGTCGTCCTACATCTACTACGCCGACTCCGTGAAGGGAAGATTCACCATTTC CCGCGACAACGCAAAGAACTCACTGTACTTGCAAATGAACTCACTCCGGGCCG AAGATACTGCTGTGTACTATTGCGCCAAGACTATTGCCGCCGTCTACGCTTTC GACATCTGGGGCCAGGGAACCACCGTGACTGTGTCGTCCGGTGGTGGTGGCTC GGGCGGAGGAGGAAGCGGCGGCGGGGGGTCCGAGATTGTGCTGACCCAGTCGC CACTGAGCCTCCCTGTGACCCCCGAGGAACCCGCCAGCATCAGCTGCCGGTCC AGCCAGTCCCTGCTCCACTCCAACGGATACAATTACCTCGATTGGTACCTTCA GAAGCCTGGACAAAGCCCGCAGCTGCTCATCTACTTGGGATCAAACCGCGCGT CAGGAGTGCCTGACCGGTTCTCCGGCTCGGGCAGCGGTACCGATTTCACCCTG AAAATCTCCAGGGTGGAGGCAGAGGACGTGGGAGTGTATTACTGTATGCAGGC GCTGCAGACTCCGTACACATTTGGGCAGGGCACCAAGCTGGAGATCAAG
149364-aa VH	173	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISS SSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKTIAAVYAF DIWGQGTTVTVSS
149364-aa VL	194	EIVLTQSPLSLPVTPEEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLI YLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPYTFGQG TKLEIK
149364-aa Full CAR	215	MALPVTALLLPLALLLHAARPEVQLVESGGGLVKPGGSLRLSCAASGFTFSSY SMNWVRQAPGKGLEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCAKTIAAVYAFDIWGQGTTVTVSSGGGGSGGGGSGGGGSEIVL TQSPLSLPVTPEEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGS NRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPYTFGQGTKLE IKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAP LAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEE EEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKD TYDALHMQALPPR
149364-nt Full CAR	236	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCGAAGTGCAGCTTGTCGAATCCGGGGGGGGACTGGTCAAGCCGG GCGGATCACTGAGACTGTCCTGCGCCGCGAGCGGCTTCACGTTCTCCTCCTAC TCCATGAACTGGGTCCGCCAAGCCCCCGGGAAGGGACTGGAATGGGTGTCCTC TATCTCCTCGTCGTCGTCCTACATCTACTACGCCGACTCCGTGAAGGGAAGAT TCACCATTTCCCGCGACAACGCAAAGAACTCACTGTACTTGCAAATGAACTCA CTCCGGGCCGAAGATACTGCTGTGTACTATTGCGCCAAGACTATTGCCGCCGT

		CTACGCTTTCGACATCTGGGGCCAGGGAACCACCGTGACTGTGTCGTCCGGTG GTGGTGGCTCGGGCGGAGGAGGAAGCGGCGGCGGGGGGTCCGAGATTGTGCTG ACCCAGTCGCCACTGAGCCTCCCTGTGACCCCCGAGGAACCCGCCAGCATCAG CTGCCGGTCCAGCCAGTCCCTGCTCCACTCCAACGGATACAATTACCTCGATT GGTACCTTCAGAAGCCTGGACAAAGCCCGCAGCTGCTCATCTACTTGGGATCA AACCGCGCGTCAGGAGTGCCTGACCGGTTCTCCGGCTCGGGCAGCGGTACCGA TTTCACCCTGAAAATCTCCAGGGTGGAGGCAGAGGACGTGGGAGTGTATTACT GTATGCAGGCGCTGCAGACTCCGTACACATTTGGGCAGGGCACCAAGCTGGAG ATCAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGC CTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGG CCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCT CTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTG TAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGC CTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAG GAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCC AGCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGA GAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGC GGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAA GGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAA GAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGAC ACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
149365		
149365-aa ScFv domain	132	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVSYISS SGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDLRGAFDI WGQGTMVTVSSGGGGSGGGGSGGGGSSYVLTQSPSVSAAPGYTATISCGGNNI GTKSVHWYQQKPGQAPLLVIRDDSVRPSKIPGRFSGSNSGNMATLTISGVQAG DEADFYCQVWDSDSEHVVFGGGTKLTVL
149365-nt ScFv domain	153	GAAGTCCAGCTCGTGGAGTCCGGCGGAGGCCTTGTGAAGCCTGGAGGTTCGCT GAGACTGTCCTGCGCCGCCTCCGGCTTCACCTTCTCCGACTACTACATGTCCT GGATCAGACAGGCCCCGGGAAAGGGCCTGGAATGGGTGTCCTACATCTCGTCA TCGGGCAGCACTATCTACTACGCGGACTCAGTGAAGGGGCGGTTCACCATTTC CCGGGATAACGCGAAGAACTCGCTGTATCTGCAAATGAACTCACTGAGGGCCG AGGACACCGCCGTGTACTACTGCGCCCGCGATCTCCGCGGGGCATTTGACATC TGGGGACAGGGAACCATGGTCACAGTGTCCAGCGGAGGGGGAGGATCGGGTGG CGGAGGTTCCGGGGGTGGAGGCTCCTCCTACGTGCTGACTCAGAGCCCAAGCG TCAGCGCTGCGCCCGGTTACACGGCAACCATCTCCTGTGGCGGAAACAACATT GGGACCAAGTCTGTGCACTGGTATCAGCAGAAGCCGGGCCAAGCTCCCCTGTT GGTGATCCGCGATGACTCCGTGCGGCCTAGCAAAATTCCGGGACGGTTCTCCG GCTCCAACAGCGGCAATATGGCCACTCTCACCATCTCGGGAGTGCAGGCCGGA GATGAAGCCGACTTCTACTGCCAAGTCTGGGACTCAGACTCCGAGCATGTGGT GTTCGGGGGCGGAACCAAGCTGACTGTGCTC
149365-aa VH	174	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVSYISS SGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDLRGAFDI WGQGTMVTVSS
149365-aa VL	195	SYVLTQSPSVSAAPGYTATISCGGNNIGTKSVHWYQQKPGQAPLLVIRDDSVR PSKIPGRFSGSNSGNMATLTISGVQAGDEADFYCQVWDSDSEHVVFGGGTKLT VL
149365-aa Full CAR	216	MALPVTALLLPLALLLHAARPEVQLVESGGGLVKPGGSLRLSCAASGFTFSDY YMSWIRQAPGKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARDLRGAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSSYVLTQ SPSVSAAPGYTATISCGGNNIGTKSVHWYQQKPGQAPLLVIRDDSVRPSKIPG RFSGSNSGNMATLTISGVQAGDEADFYCQVWDSDSEHVVFGGGTKLTVLTTTP

		APRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCG VLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCE LRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRK NPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALH MQALPPR
149365-nt Full CAR	237	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCGAAGTCCAGCTCGTGGAGTCCGGCGGAGGCCTTGTGAAGCCTG GAGGTTCGCTGAGACTGTCCTGCGCCGCCTCCGGCTTCACCTTCTCCGACTAC TACATGTCCTGGATCAGACAGGCCCCGGGAAAGGGCCTGGAATGGGTGTCCTA CATCTCGTCATCGGGCAGCACTATCTACTACGCGGACTCAGTGAAGGGGCGGT TCACCATTTCCCGGGATAACGCGAAGAACTCGCTGTATCTGCAAATGAACTCA CTGAGGGCCGAGGACACCGCCGTGTACTACTGCGCCCGCGATCTCCGCGGGGC ATTTGACATCTGGGGACAGGGAACCATGGTCACAGTGTCCAGCGGAGGGGGAG GATCGGGTGGCGGAGGTTCCGGGGGTGGAGGCTCCTCCTACGTGCTGACTCAG AGCCCAAGCGTCAGCGCTGCGCCCGGTTACACGGCAACCATCTCCTGTGGCGG AAACAACATTGGGACCAAGTCTGTGCACTGGTATCAGCAGAAGCCGGGCCAAG CTCCCCTGTTGGTGATCCGCGATGACTCCGTGCGGCCTAGCAAAATTCCGGGA CGGTTCTCCGGCTCCAACAGCGGCAATATGGCCACTCTCACCATCTCGGGAGT GCAGGCCGGAGATGAAGCCGACTTCTACTGCCAAGTCTGGGACTCAGACTCCG AGCATGTGGTGTTCGGGGGCGGAACCAAGCTGACTGTGCTCACCACTACCCCA GCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTC TTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGG GTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAA GCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAG AGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAA CTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCA GAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGC TGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAG AATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGC CTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACGACG GACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTTCAC ATGCAGGCCCTGCCGCCTCGG
149366		
149366-aa ScFv domain	133	QVQLVQSGAEVKKPGASVKVSCKPSGYTVTSHYIHWVRRAPGQGLEWMGMINP SGGVTAYSQTLQGRVTMTSDTSSSTVYMELSSLRSEDTAMYYCAREGSGSGWY FDFWGRGTLVTVSSGGGGSGGGGSGGGGSSYVLTQPPSVSVSPGQTASITCSG DGLSKKYVSWYQQKAGQSPVVLISRDKERPSGIPDRFSGSNSADTATLTISGT QAMDEADYYCQAWDDTTVVFGGGTKLTVL
149366-nt ScFv domain	154	CAAGTGCAGCTGGTGCAGAGCGGGGCCGAAGTCAAGAAGCCGGGAGCCTCCGT GAAAGTGTCCTGCAAGCCTTCGGGATACACCGTGACCTCCCACTACATTCATT GGGTCCGCCGCGCCCCCGGCCAAGGACTCGAGTGGATGGGCATGATCAACCCT AGCGGCGGAGTGACCGCGTACAGCCAGACGCTGCAGGGACGCGTGACTATGAC CTCGGATACCTCCTCCTCCACCGTCTATATGGAACTGTCCAGCCTGCGGTCCG AGGATACCGCCATGTACTACTGCGCCCGGGAAGGATCAGGCTCCGGGTGGTAT TTCGACTTCTGGGGAAGAGGCACCCTCGTGACTGTGTCATCTGGGGGAGGGGG TTCCGGTGGTGGCGGATCGGGAGGAGGCGGTTCATCCTACGTGCTGACCCAGC CACCCTCCGTGTCCGTGAGCCCCGGCCAGACTGCATCGATTACATGTAGCGGC GACGGCCTCTCCAAGAAATACGTGTCGTGGTACCAGCAGAAGGCCGGACAGAG CCCGGTGGTGCTGATCTCAAGAGATAAGGAGCGGCCTAGCGGAATCCCGGACA GGTTCTCGGGTTCCAACTCCGCGGACACTGCTACTCTGACCATCTCGGGGACC CAGGCTATGGACGAAGCCGATTACTACTGCCAAGCCTGGGACGACACTACTGT

		CGTGTTTGGAGGGGGCACCAAGTTGACCGTCCTT
149366-aa VH	175	QVQLVQSGAEVKKPGASVKVSCKPSGYTVTSHYIHWVRRAPGQGLEWMGMINP SGGVTAYSQTLQGRVTMTSDTSSSTVYMELSSLRSEDTAMYYCAREGSGSGWY FDFWGRGTLVTVSS
149366-aa VL	196	SYVLTQPPSVSVSPGQTASITCSGDGLSKKYVSWYQQKAGQSPVVLISRDKER PSGIPDRFSGSNSADTATLTISGTQAMDEADYYCQAWDDTTVVFGGGTKLTVL
149366-aa Full CAR	217	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKPSGYTVTSH YIHWVRRAPGQGLEWMGMINPSGGVTAYSQTLQGRVTMTSDTSSSTVYMELSS LRSEDTAMYYCAREGSGSGWYFDFWGRGTLVTVSSGGGGSGGGGSGGGGSSYV LTQPPSVSVSPGQTASITCSGDGLSKKYVSWYQQKAGQSPVVLISRDKERPSG IPDRFSGSNSADTATLTISGTQAMDEADYYCQAWDDTTVVFGGGTKLTVLTTT PAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTC GVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGC ELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRR KNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDAL HMQALPPR
149366-nt Full CAR	238	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCCAAGTGCAGCTGGTGCAGAGCGGGGCCGAAGTCAAGAAGCCGG GAGCCTCCGTGAAAGTGTCCTGCAAGCCTTCGGGATACACCGTGACCTCCCAC TACATTCATTGGGTCCGCCGCGCCCCCGGCCAAGGACTCGAGTGGATGGGCAT GATCAACCCTAGCGGCGGAGTGACCGCGTACAGCCAGACGCTGCAGGGACGCG TGACTATGACCTCGGATACCTCCTCCTCCACCGTCTATATGGAACTGTCCAGC CTGCGGTCCGAGGATACCGCCATGTACTACTGCGCCCGGGAAGGATCAGGCTC CGGGTGGTATTTCGACTTCTGGGGAAGAGGCACCCTCGTGACTGTGTCATCTG GGGGAGGGGGTTCCGGTGGTGGCGGATCGGGAGGAGGCGGTTCATCCTACGTG CTGACCCAGCCACCCTCCGTGTCCGTGAGCCCCGGCCAGACTGCATCGATTAC ATGTAGCGGCGACGGCCTCTCCAAGAAATACGTGTCGTGGTACCAGCAGAAGG CCGGACAGAGCCCGGTGGTGCTGATCTCAAGAGATAAGGAGCGGCCTAGCGGA ATCCCGGACAGGTTCTCGGGTTCCAACTCCGCGGACACTGCTACTCTGACCAT CTCGGGGACCCAGGCTATGGACGAAGCCGATTACTACTGCCAAGCCTGGGACG ACACTACTGTCGTGTTTGGAGGGGGCACCAAGTTGACCGTCCTTACCACTACC CCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTC CCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGG GTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGC GGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAA GAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTC AAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGC GAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGG GCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACG TGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGA AAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGA AGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACG ACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTT CACATGCAGGCCCTGCCGCCTCGG
149367		
149367-aa ScFv domain	134	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQHPGKGLEWIGYI YYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARAGIAARL RGAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSDIVMTQSPSSVSASVGDRVII TCRASQGIRNWLAWYQQKPGKAPNLLIYAASNLQSGVPSRFSGSGSGADFTLT ISSLQPEDVATYYCQKYNSAPFTFGPGTKVDIK
149367-nt ScFv domain	155	CAAGTGCAGCTTCAGGAGAGCGGCCCGGGACTCGTGAAGCCGTCCCAGACCCT GTCCCTGACTTGCACCGTGTCGGGAGGAAGCATCTCGAGCGGAGGCTACTATT

		GGTCGTGGATTCGGCAGCACCCTGGAAAGGGCCTGGAATGGATCGGCTACATC TACTACTCCGGCTCGACCTACTACAACCCATCGCTGAAGTCCAGAGTGACAAT CTCAGTGGACACGTCCAAGAATCAGTTCAGCCTGAAGCTCTCTTCCGTGACTG CGGCCGACACCGCCGTGTACTACTGCGCACGCGCTGGAATTGCCGCCCGGCTG AGGGGTGCCTTCGACATTTGGGGACAGGGCACCATGGTCACCGTGTCCTCCGG CGGCGGAGGTTCCGGGGGTGGAGGCTCAGGAGGAGGGGGGTCCGACATCGTCA TGACTCAGTCGCCCTCAAGCGTCAGCGCGTCCGTCGGGGACAGAGTGATCATC ACCTGTCGGGCGTCCCAGGGAATTCGCAACTGGCTGGCCTGGTATCAGCAGAA GCCCGGAAAGGCCCCCAACCTGTTGATCTACGCCGCCTCAAACCTCCAATCCG GGGTGCCGAGCCGCTTCAGCGGCTCCGGTTCGGGTGCCGATTTCACTCTGACC ATCTCCTCCCTGCAACCTGAAGATGTGGCTACCTACTACTGCCAAAAGTACAA CTCCGCACCTTTTACTTTCGGACCGGGGACCAAAGTGGACATTAAG
149367-aa VH	176	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQHPGKGLEWIGYI YYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARAGIAARL RGAFDIWGQGTMVTVSS
149367-aa VL	197	DIVMTQSPSSVSASVGDRVIITCRASQGIRNWLAWYQQKPGKAPNLLIYAASN LQSGVPSRFSGSGSGADFTLTISSLQPEDVATYYCQKYNSAPFTFGPGTKVDI K
149367-aa Full CAR	218	MALPVTALLLPLALLLHAARPQVQLQESGPGLVKPSQTLSLTCTVSGGSISSG GYYWSWIRQHPGKGLEWIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLS SVTAADTAVYYCARAGIAARLRGAFDIWGQGTMVTVSSGGGGSGGGGSGGGGS DIVMTQSPSSVSASVGDRVIITCRASQGIRNWLAWYQQKPGKAPNLLIYAASN LQSGVPSRFSGSGSGADFTLTISSLQPEDVATYYCQKYNSAPFTFGPGTKVDI KTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPL AGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEE EGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGG KPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDT YDALHMQALPPR
149367-nt Full CAR	239	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCCAAGTGCAGCTTCAGGAGAGCGGCCCGGGACTCGTGAAGCCGT CCCAGACCCTGTCCCTGACTTGCACCGTGTCGGGAGGAAGCATCTCGAGCGGA GGCTACTATTGGTCGTGGATTCGGCAGCACCCTGGAAAGGGCCTGGAATGGAT CGGCTACATCTACTACTCCGGCTCGACCTACTACAACCCATCGCTGAAGTCCA GAGTGACAATCTCAGTGGACACGTCCAAGAATCAGTTCAGCCTGAAGCTCTCT TCCGTGACTGCGGCCGACACCGCCGTGTACTACTGCGCACGCGCTGGAATTGC CGCCCGGCTGAGGGGTGCCTTCGACATTTGGGGACAGGGCACCATGGTCACCG TGTCCTCCGGCGGCGGAGGTTCCGGGGGTGGAGGCTCAGGAGGAGGGGGGTCC GACATCGTCATGACTCAGTCGCCCTCAAGCGTCAGCGCGTCCGTCGGGGACAG AGTGATCATCACCTGTCGGGCGTCCCAGGGAATTCGCAACTGGCTGGCCTGGT ATCAGCAGAAGCCCGGAAAGGCCCCCAACCTGTTGATCTACGCCGCCTCAAAC CTCCAATCCGGGGTGCCGAGCCGCTTCAGCGGCTCCGGTTCGGGTGCCGATTT CACTCTGACCATCTCCTCCCTGCAACCTGAAGATGTGGCTACCTACTACTGCC AAAAGTACAACTCCGCACCTTTTACTTTCGGACCGGGGACCAAAGTGGACATT AAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTC CCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCG TGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTG GCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAA GCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTG TGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAG GAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGC CTACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAG AGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGG

		AAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGA TAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAG GCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACC TATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
149368		
149368-aa ScFv domain	135	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIP IFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARRGGYQLLR WDVGLLRSAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSSYVLTQPPSVSVAPG QTARITCGGNNIGSKSVHWYQQKPGQAPVLVLYGKNNRPSGVPDRFSGSRSGT TASLTITGAQAEDEADYYCSSRDSSGDHLRVFGTGTKVTVL
149368-nt ScFv domain	156	CAAGTGCAGCTGGTCCAGTCGGGCGCCGAGGTCAAGAAGCCCGGGAGCTCTGT GAAAGTGTCCTGCAAGGCCTCCGGGGGCACCTTTAGCTCCTACGCCATCTCCT GGGTCCGCCAAGCACCGGGTCAAGGCCTGGAGTGGATGGGGGGAATTATCCCT ATCTTCGGCACTGCCAACTACGCCCAGAAGTTCCAGGGACGCGTGACCATTAC CGCGGACGAATCCACCTCCACCGCTTATATGGAGCTGTCCAGCTTGCGCTCGG AAGATACCGCCGTGTACTACTGCGCCCGGAGGGGTGGATACCAGCTGCTGAGA TGGGACGTGGGCCTCCTGCGGTCGGCGTTCGACATCTGGGGCCAGGGCACTAT GGTCACTGTGTCCAGCGGAGGAGGCGGATCGGGAGGCGGCGGATCAGGGGGAG GCGGTTCCAGCTACGTGCTTACTCAACCCCCTTCGGTGTCCGTGGCCCCGGGA CAGACCGCCAGAATCACTTGCGGAGGAAACAACATTGGGTCCAAGAGCGTGCA TTGGTACCAGCAGAAGCCAGGACAGGCCCCTGTGCTGGTGCTCTACGGGAAGA ACAATCGGCCCAGCGGAGTGCCGGACAGGTTCTCGGGTTCACGCTCCGGTACA ACCGCTTCACTGACTATCACCGGGGCCCAGGCAGAGGATGAAGCGGACTACTA CTGTTCCTCCCGGGATTCATCCGGCGACCACCTCCGGGTGTTCGGAACCGGAA CGAAGGTCACCGTGCTG
149368-aa VH	177	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIP IFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARRGGYQLLR WDVGLLRSAFDIWGQGTMVTVSS
149368-aa VL	198	SYVLTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVLYGKNNR PSGVPDRFSGSRSGTTASLTITGAQAEDEADYYCSSRDSSGDHLRVFGTGTKV TVL
149368-aa Full CAR	219	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGSSVKVSCKASGGTFSSY AISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSS LRSEDTAVYYCARRGGYQLLRWDVGLLRSAFDIWGQGTMVTVSSGGGGSGGGG SGGGGSSYVLTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVL YGKNNRPSGVPDRFSGSRSGTTASLTITGAQAEDEADYYCSSRDSSGDHLRVF GTGTKVTVLTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFAC DIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRR GRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQG LSTATKDTYDALHMQALPPR
149368-nt Full CAR	240	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCCAAGTGCAGCTGGTCCAGTCGGGCGCCGAGGTCAAGAAGCCCG GGAGCTCTGTGAAAGTGTCCTGCAAGGCCTCCGGGGGCACCTTTAGCTCCTAC GCCATCTCCTGGGTCCGCCAAGCACCGGGTCAAGGCCTGGAGTGGATGGGGGG AATTATCCCTATCTTCGGCACTGCCAACTACGCCCAGAAGTTCCAGGGACGCG TGACCATTACCGCGGACGAATCCACCTCCACCGCTTATATGGAGCTGTCCAGC TTGCGCTCGGAAGATACCGCCGTGTACTACTGCGCCCGGAGGGGTGGATACCA GCTGCTGAGATGGGACGTGGGCCTCCTGCGGTCGGCGTTCGACATCTGGGGCC AGGGCACTATGGTCACTGTGTCCAGCGGAGGAGGCGGATCGGGAGGCGGCGGA TCAGGGGGAGGCGGTTCCAGCTACGTGCTTACTCAACCCCCTTCGGTGTCCGT GGCCCCGGGACAGACCGCCAGAATCACTTGCGGAGGAAACAACATTGGGTCCA

		AGAGCGTGCATTGGTACCAGCAGAAGCCAGGACAGGCCCCTGTGCTGGTGCTC TACGGGAAGAACAATCGGCCCAGCGGAGTGCCGGACAGGTTCTCGGGTTCACG CTCCGGTACAACCGCTTCACTGACTATCACCGGGGCCCAGGCAGAGGATGAAG CGGACTACTACTGTTCCTCCCGGGATTCATCCGGCGACCACCTCCGGGTGTTC GGAACCGGAACGAAGGTCACCGTGCTGACCACTACCCCAGCACCGAGGCCACC CACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCAT GTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGC GATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTC ACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCT TTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGT TCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAATT CAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAGCTCTACA ACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGGACAAGCGGAGA GGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAATCCCCAAGAGGG CCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCCTATAGCGAGATTG GTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGA CTCAGCACCGCCACCAAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCC GCCTCGG
149369		
149369-aa ScFv domain	136	EVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEWLGRT YYRSKWYSFYAISLKSRIIINPDTSKNQFSLQLKSVTPEDTAVYYCARSSPEG LFLYWFDPWGQGTLVTVSSGGDGSGGGGSGGGGSSSELTQDPAVSVALGQTIR ITCQGDSLGNYYATWYQQKPGQAPVLVIYGTNNRPSGIPDRFSASSSGNTASL TITGAQAEDEADYYCNSRDSSGHHLLFGTGTKVTVL
149369-nt ScFv domain	157	GAAGTGCAGCTCCAACAGTCAGGACCGGGGCTCGTGAAGCCATCCCAGACCCT GTCCCTGACTTGTGCCATCTCGGGAGATAGCGTGTCATCGAACTCCGCCGCCT GGAACTGGATTCGGCAGAGCCCGTCCCGCGGACTGGAGTGGCTTGGAAGGACC TACTACCGGTCCAAGTGGTACTCTTTCTACGCGATCTCGCTGAAGTCCCGCAT TATCATTAACCCTGATACCTCCAAGAATCAGTTCTCCCTCCAACTGAAATCCG TCACCCCCGAGGACACAGCAGTGTATTACTGCGCACGGAGCAGCCCCGAAGGA CTGTTCCTGTATTGGTTTGACCCCTGGGGCCAGGGGACTCTTGTGACCGTGTC GAGCGGCGGAGATGGGTCCGGTGGCGGTGGTTCGGGGGGCGGCGGATCATCAT CCGAACTGACCCAGGACCCGGCTGTGTCCGTGGCGCTGGGACAAACCATCCGC ATTACGTGCCAGGGAGACTCCCTGGGCAACTACTACGCCACTTGGTACCAGCA GAAGCCGGGCCAAGCCCCTGTGTTGGTCATCTACGGGACCAACAACAGACCTT CCGGCATCCCCGACCGGTTCAGCGCTTCGTCCTCCGGCAACACTGCCAGCCTG ACCATCACTGGAGCGCAGGCCGAAGATGAGGCCGACTACTACTGCAACAGCAG AGACTCCTCGGGTCATCACCTCTTGTTCGGAACTGGAACCAAGGTCACCGTGC TG
149369-aa VH	178	EVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEWLGRT YYRSKWYSFYAISLKSRIIINPDTSKNQFSLQLKSVTPEDTAVYYCARSSPEG LFLYWFDPWGQGTLVTVSS
149369-aa VL	199	SSELTQDPAVSVALGQTIRITCQGDSLGNYYATWYQQKPGQAPVLVIYGTNNR PSGIPDRFSASSSGNTASLTITGAQAEDEADYYCNSRDSSGHHLLFGTGTKVT VL
149369-aa Full CAR	220	MALPVTALLLPLALLLHAARPEVQLQQSGPGLVKPSQTLSLTCAISGDSVSSN SAAWNWIRQSPSRGLEWLGRTYYRSKWYSFYAISLKSRIIINPDTSKNQFSLQ LKSVTPEDTAVYYCARSSPEGLFLYWFDPWGQGTLVTVSSGGDGSGGGGSGGG GSSSELTQDPAVSVALGQTIRITCQGDSLGNYYATWYQQKPGQAPVLVIYGTN NRPSGIPDRFSASSSGNTASLTITGAQAEDEADYYCNSRDSSGHHLLFGTGTK VTVLTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIW APLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFP

		EEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPE MGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTAT KDTYDALHMQALPPR
149369-nt Full CAR	241	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCGAAGTGCAGCTCCAACAGTCAGGACCGGGGCTCGTGAAGCCAT CCCAGACCCTGTCCCTGACTTGTGCCATCTCGGGAGATAGCGTGTCATCGAAC TCCGCCGCCTGGAACTGGATTCGGCAGAGCCCGTCCCGCGGACTGGAGTGGCT TGGAAGGACCTACTACCGGTCCAAGTGGTACTCTTTCTACGCGATCTCGCTGA AGTCCCGCATTATCATTAACCCTGATACCTCCAAGAATCAGTTCTCCCTCCAA CTGAAATCCGTCACCCCCGAGGACACAGCAGTGTATTACTGCGCACGGAGCAG CCCCGAAGGACTGTTCCTGTATTGGTTTGACCCCTGGGGCCAGGGGACTCTTG TGACCGTGTCGAGCGGCGGAGATGGGTCCGGTGGCGGTGGTTCGGGGGGCGGC GGATCATCATCCGAACTGACCCAGGACCCGGCTGTGTCCGTGGCGCTGGGACA AACCATCCGCATTACGTGCCAGGGAGACTCCCTGGGCAACTACTACGCCACTT GGTACCAGCAGAAGCCGGGCCAAGCCCCTGTGTTGGTCATCTACGGGACCAAC AACAGACCTTCCGGCATCCCCGACCGGTTCAGCGCTTCGTCCTCCGGCAACAC TGCCAGCCTGACCATCACTGGAGCGCAGGCCGAAGATGAGGCCGACTACTACT GCAACAGCAGAGACTCCTCGGGTCATCACCTCTTGTTCGGAACTGGAACCAAG GTCACCGTGCTGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTAC CATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTG GTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGG GCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCT TTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCA TGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCA GAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGA TGCTCCAGCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTG GTCGGAGAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAA ATGGGCGGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCT CCAAAAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAAC GCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACC AAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1978-A4		
BCMA_EBB-C1978-A4 - aa ScFv domain	137	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISG SGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKVEGSGSLD YWGQGTLVTVSSGGGGSGGGGSGGGGSEIVMTQSPGTLSLSPGERATLSCRAS QSVSSAYLAWYQQKPGQPPRLLISGASTRATGIPDRFGGSGSGTDFTLTISRL EPEDFAVYYCQHYGSSFNGSSLFTFGQGTRLEIK
BCMA_EBB-C1978-A4 - nt ScFv domain	158	GAAGTGCAGCTCGTGGAGTCAGGAGGCGGCCTGGTCCAGCCGGGAGGGTCCCT TAGACTGTCATGCGCCGCAAGCGGATTCACTTTCTCCTCCTATGCCATGAGCT GGGTCCGCCAAGCCCCCGGAAAGGGACTGGAATGGGTGTCCGCCATCTCGGGG TCTGGAGGCTCAACTTACTACGCTGACTCCGTGAAGGGACGGTTCACCATTAG CCGCGACAACTCCAAGAACACCCTCTACCTCCAAATGAACTCCCTGCGGGCCG AGGATACCGCCGTCTACTACTGCGCCAAAGTGGAAGGTTCAGGATCGCTGGAC TACTGGGGACAGGGTACTCTCGTGACCGTGTCATCGGGCGGAGGAGGTTCCGG CGGTGGCGGCTCCGGCGGCGGAGGGTCGGAGATCGTGATGACCCAGAGCCCTG GTACTCTGAGCCTTTCGCCGGGAGAAAGGGCCACCCTGTCCTGCCGCGCTTCC CAATCCGTGTCCTCCGCGTACTTGGCGTGGTACCAGCAGAAGCCGGGACAGCC CCCTCGGCTGCTGATCAGCGGGGCCAGCACCCGGGCAACCGGAATCCCAGACA GATTCGGGGGTTCCGGCAGCGGCACAGATTTCACCCTGACTATTTCGAGGTTG GAGCCCGAGGACTTTGCGGTGTATTACTGTCAGCACTACGGGTCGTCCTTTAA TGGCTCCAGCCTGTTCACGTTCGGACAGGGGACCCGCCTGGAAATCAAG
BCMA_EBB-	179	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISG

C1978-A4 - aa VH		SGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKVEGSGSLD YWGQGTLVTVSS
BCMA_EBB-C1978-A4 - aa VL	200	EIVMTQSPGTLSLSPGERATLSCRASQSVSSAYLAWYQQKPGQPPRLLISGAS TRATGIPDRFGGSGSGTDFTLTISRLEPEDFAVYYCQHYGSSFNGSSLFTFGQ GTRLEIK
BCMA_EBB-C1978-A4 - aa Full CART	221	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASGFTFSSY AMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNS LRAEDTAVYYCAKVEGSGSLDYWGQGTLVTVSSGGGGSGGGGSGGGGSEIVMT QSPGTLSLSPGERATLSCRASQSVSSAYLAWYQQKPGQPPRLLISGASTRATG IPDRFGGSGSGTDFTLTISRLEPEDFAVYYCQHYGSSFNGSSLFTFGQGTRLE IKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAP LAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEE EEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKD TYDALHMQALPPR
BCMA_EBB-C1978-A4 - nt Full CART	242	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCGAAGTGCAGCTCGTGGAGTCAGGAGGCGGCCTGGTCCAGCCGG GAGGGTCCCTTAGACTGTCATGCGCCGCAAGCGGATTCACTTTCTCCTCCTAT GCCATGAGCTGGGTCCGCCAAGCCCCCGGAAAGGGACTGGAATGGGTGTCCGC CATCTCGGGGTCTGGAGGCTCAACTTACTACGCTGACTCCGTGAAGGGACGGT TCACCATTAGCCGCGACAACTCCAAGAACACCCTCTACCTCCAAATGAACTCC CTGCGGGCCGAGGATACCGCCGTCTACTACTGCGCCAAAGTGGAAGGTTCAGG ATCGCTGGACTACTGGGGACAGGGTACTCTCGTGACCGTGTCATCGGGCGGAG GAGGTTCCGGCGGTGGCGGCTCCGGCGGCGGAGGGTCGGAGATCGTGATGACC CAGAGCCCTGGTACTCTGAGCCTTTCGCCGGGAGAAAGGGCCACCCTGTCCTG CCGCGCTTCCCAATCCGTGTCCTCCGCGTACTTGGCGTGGTACCAGCAGAAGC CGGGACAGCCCCCTCGGCTGCTGATCAGCGGGGCCAGCACCCGGGCAACCGGA ATCCCAGACAGATTCGGGGGTTCCGGCAGCGGCACAGATTTCACCCTGACTAT TTCGAGGTTGGAGCCCGAGGACTTTGCGGTGTATTACTGTCAGCACTACGGGT CGTCCTTTAATGGCTCCAGCCTGTTCACGTTCGGACAGGGGACCCGCCTGGAA ATCAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGC CTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGG CCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCT CTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTG TAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGC CTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAG GAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCC AGCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGA GAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGC GGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAA GGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAA GAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGAC ACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1978-G1		
BCMA_EBB-C1978-G1 - aa ScFv domain	138	EVQLVETGGGLVQPGGSLRLSCAASGITFSRYPMSWVRQAPGKGLEW VSGISDSGVSTYYADSAKGRFTISRDNSKNTLFLQMSSLRDEDTAVYY CVTRAGSEASDIWGQGTMVTVSSGGGGSGGGGSGGGGSEIVLTQSPAT LSLSPGERATLSCRASQSVSNSLAWYQQKPGQAPRLLIYDASSRATGIP DRFSGSGSGTDFTLTISRLEPEDFAIYYCQQFGTSSGLTFGGGTKLEIK
BCMA_EBB-	159	GAAGTGCAACTGGTGGAAACCGGTGGCGGCCTGGTGCAGCCTGGAGGATCATT

C1978-G1 - nt ScFv domain		GAGGCTGTCATGCGCGGCCAGCGGTATTACCTTCTCCCGGTACCCCATGTCCT GGGTCAGACAGGCCCCGGGGAAAGGGCTTGAATGGGTGTCCGGGATCTCGGAC TCCGGTGTCAGCACTTACTACGCCGACTCCGCCAAGGGACGCTTCACCATTTC CCGGGACAACTCGAAGAACACCCTGTTCCTCCAAATGAGCTCCCTCCGGGACG AGGATACTGCAGTGTACTACTGCGTGACCCGCGCCGGGTCCGAGGCGTCTGAC ATTTGGGGACAGGGCACTATGGTCACCGTGTCGTCCGGCGGAGGGGGCTCGGG AGGCGGTGGCAGCGGAGGAGGAGGGTCCGAGATCGTGCTGACCCAATCCCCGG CCACCCTCTCGCTGAGCCCTGGAGAAAGGGCAACCTTGTCCTGTCGCGCGAGC CAGTCCGTGAGCAACTCCCTGGCCTGGTACCAGCAGAAGCCCGGACAGGCTCC GAGACTTCTGATCTACGACGCTTCGAGCCGGGCCACTGGAATCCCCGACCGCT TTTCGGGGTCCGGCTCAGGAACCGATTTCACCCTGACAATCTCACGGCTGGAG CCAGAGGATTTCGCCATCTATTACTGCCAGCAGTTCGGTACTTCCTCCGGCCT GACTTTCGGAGGCGGCACGAAGCTCGAAATCAAG
BCMA_EBB-C1978-G1 - aa VH	180	EVQLVETGGGLVQPGGSLRLSCAASGITFSRYPMSWVRQAPGKGLEWVSGISD SGVSTYYADSAKGRFTISRDNSKNTLFLQMSSLRDEDTAVYYCVTRAGSEASD IWGQGTMVTVSS
BCMA_EBB-C1978-G1 - aa VL	201	EIVLTQSPATLSLSPGERATLSCRASQSVSNSLAWYQQKPGQAPRLLIYDASS RATGIPDRFSGSGSGTDFTLTISRLEPEDFAIYYCQQFGTSSGLTFGGGTKLE IK
BCMA_EBB-C1978-G1 - aa Full CART	222	MALPVTALLLPLALLLHAARPEVQLVETGGGLVQPGGSLRLSCAASGI TFSRYPMSWVRQAPGKGLEWVSGISDSGVSTYYADSAKGRFTISRDNS KNTLFLQMSSLRDEDTAVYYCVTRAGSEASDIWGQGTMVTVSSGGGG SGGGGSGGGGSEIVLTQSPATLSLSPGERATLSCRASQSVSNSLAWYQQ KPGQAPRLLIYDASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAIYYCQ QFGTSSGLTFGGGTKLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAG GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFK QPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQN QLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQK DKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALP PR
BCMA_EBB-C1978-G1 - nt Full CART	243	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCGAAGTGCAACTGGTGGAAACCGGTGGCGGCCTGGTGCAGCCTG GAGGATCATTGAGGCTGTCATGCGCGGCCAGCGGTATTACCTTCTCCCGGTAC CCCATGTCCTGGGTCAGACAGGCCCCGGGGAAAGGGCTTGAATGGGTGTCCGG GATCTCGGACTCCGGTGTCAGCACTTACTACGCCGACTCCGCCAAGGGACGCT TCACCATTTCCCGGGACAACTCGAAGAACACCCTGTTCCTCCAAATGAGCTCC CTCCGGGACGAGGATACTGCAGTGTACTACTGCGTGACCCGCGCCGGGTCCGA GGCGTCTGACATTTGGGGACAGGGCACTATGGTCACCGTGTCGTCCGGCGGAG GGGGCTCGGGAGGCGGTGGCAGCGGAGGAGGAGGGTCCGAGATCGTGCTGACC CAATCCCCGGCCACCCTCTCGCTGAGCCCTGGAGAAAGGGCAACCTTGTCCTG TCGCGCGAGCCAGTCCGTGAGCAACTCCCTGGCCTGGTACCAGCAGAAGCCCG GACAGGCTCCGAGACTTCTGATCTACGACGCTTCGAGCCGGGCCACTGGAATC CCCGACCGCTTTTCGGGGTCCGGCTCAGGAACCGATTTCACCCTGACAATCTC ACGGCTGGAGCCAGAGGATTTCGCCATCTATTACTGCCAGCAGTTCGGTACTT CCTCCGGCCTGACTTTCGGAGGCGGCACGAAGCTCGAAATCAAGACCACTACC CCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTC CCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGG GTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGC GGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAA

		GAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTC AAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGC GAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGG GCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACG TGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGA AAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGA AGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACG ACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTT CACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1979-C1		
BCMA_EBB-C1979-C1 - aa ScFv domain	139	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISG SGGSTYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCARATYKRELR YYYGMDVWGQGTMVTVSSGGGGSGGGGSGGGGSEIVMTQSPGTVSLSPGERAT LSCRASQSVSSSFLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFT LTISRLEPEDSAVYYCQQYHSSPSWTFGQGTRLEIK
BCMA_EBB-C1979-C1 - nt ScFv domain	160	CAAGTGCAGCTCGTGGAATCGGGTGGCGGACTGGTGCAGCCGGGGGGCTCACT TAGACTGTCCTGCGCGGCCAGCGGATTCACTTTCTCCTCCTACGCCATGTCCT GGGTCAGACAGGCCCCTGGAAAGGGCCTGGAATGGGTGTCCGCAATCAGCGGC AGCGGCGGCTCGACCTATTACGCGGATTCAGTGAAGGGCAGATTCACCATTTC CCGGGACAACGCCAAGAACTCCTTGTACCTTCAAATGAACTCCCTCCGCGCGG AAGATACCGCAATCTACTACTGCGCTCGGGCCACTTACAAGAGGGAACTGCGC TACTACTACGGGATGGACGTCTGGGGCCAGGGAACCATGGTCACCGTGTCCAG CGGAGGAGGAGGATCGGGAGGAGGCGGTAGCGGGGGTGGAGGGTCGGAGATCG TGATGACCCAGTCCCCCGGCACTGTGTCGCTGTCCCCCGGCGAACGGGCCACC CTGTCATGTCGGGCCAGCCAGTCAGTGTCGTCAAGCTTCCTCGCCTGGTACCA GCAGAAACCGGGACAAGCTCCCCGCCTGCTGATCTACGGAGCCAGCAGCCGGG CCACCGGTATTCCTGACCGGTTCTCCGGTTCGGGGTCCGGGACCGACTTTACT CTGACTATCTCTCGCCTCGAGCCAGAGGACTCCGCCGTGTATTACTGCCAGCA GTACCACTCCTCCCCGTCCTGGACGTTCGGACAGGGCACAAGGCTGGAGATTA AG
BCMA_EBB-C1979-C1 - aa VH	181	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISG SGGSTYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCARATYKRELR YYYGMDVWGQGTMVTVSS
BCMA_EBB-C1979-C1 - aa VL	202	EIVMTQSPGTVSLSPGERATLSCRASQSVSSSFLAWYQQKPGQAPRLLIYGAS SRATGIPDRFSGSGSGTDFTLTISRLEPEDSAVYYCQQYHSSPSWTFGQGTRL EIK
BCMA_EBB-C1979-C1 - aa Full CART	223	MALPVTALLLPLALLLHAARPQVQLVESGGGLVQPGGSLRLSCAASGFTFSSY AMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAIYYCARATYKRELRYYYGMDVWGQGTMVTVSSGGGGSGGGGSGGGG SEIVMTQSPGTVSLSPGERATLSCRASQSVSSSFLAWYQQKPGQAPRLLIYGA SSRATGIPDRFSGSGSGTDFTLTISRLEPEDSAVYYCQQYHSSPSWTFGQGTR LEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIW APLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFP EEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPE MGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTAT KDTYDALHMQALPPR
BCMA_EBB-C1979-C1 - nt Full CART	244	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCCAAGTGCAGCTCGTGGAATCGGGTGGCGGACTGGTGCAGCCGG GGGGCTCACTTAGACTGTCCTGCGCGGCCAGCGGATTCACTTTCTCCTCCTAC

		GCCATGTCCTGGGTCAGACAGGCCCCTGGAAAGGGCCTGGAATGGGTGTCCGC AATCAGCGGCAGCGGCGGCTCGACCTATTACGCGGATTCAGTGAAGGGCAGAT TCACCATTTCCCGGGACAACGCCAAGAACTCCTTGTACCTTCAAATGAACTCC CTCCGCGCGGAAGATACCGCAATCTACTACTGCGCTCGGGCCACTTACAAGAG GGAACTGCGCTACTACTACGGGATGGACGTCTGGGGCCAGGGAACCATGGTCA CCGTGTCCAGCGGAGGAGGAGGATCGGGAGGAGGCGGTAGCGGGGGTGGAGGG TCGGAGATCGTGATGACCCAGTCCCCCGGCACTGTGTCGCTGTCCCCCGGCGA ACGGGCCACCCTGTCATGTCGGGCCAGCCAGTCAGTGTCGTCAAGCTTCCTCG CCTGGTACCAGCAGAAACCGGGACAAGCTCCCCGCCTGCTGATCTACGGAGCC AGCAGCCGGGCCACCGGTATTCCTGACCGGTTCTCCGGTTCGGGGTCCGGGAC CGACTTTACTCTGACTATCTCTCGCCTCGAGCCAGAGGACTCCGCCGTGTATT ACTGCCAGCAGTACCACTCCTCCCCGTCCTGGACGTTCGGACAGGGCACAAGG CTGGAGATTAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTAC CATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTG GTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGG GCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCT TTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCA TGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCA GAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGA TGCTCCAGCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTG GTCGGAGAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAA ATGGGCGGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCT CCAAAAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAAC GCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACC AAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1978-C7		
BCMA_EBB-C1978-C7 - aa ScFv domain	140	EVQLVETGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISG SGGSTYYADSVKGRFTISRDNSKNTLYLQMNTLKAEDTAVYYCARATYKRELR YYYGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSPSTLSLSPGESAT LSCRASQSVSTTFLAWYQQKPGQAPRLLIYGSSNRATGIPDRFSGSGSGTDFT LTIRRLEPEDFAVYYCQQYHSSPSWTFGQGTKVEIK
BCMA_EBB-C1978-C7 - nt ScFv domain	161	GAGGTGCAGCTTGTGGAAACCGGTGGCGGACTGGTGCAGCCCGGAGGAAGCCT CAGGCTGTCCTGCGCCGCGTCCGGCTTCACCTTCTCCTCGTACGCCATGTCCT GGGTCCGCCAGGCCCCCGGAAAGGGCCTGGAATGGGTGTCCGCCATCTCTGGA AGCGGAGGTTCCACGTACTACGCGGACAGCGTCAAGGGAAGGTTCACAATCTC CCGCGATAATTCGAAGAACACTCTGTACCTTCAAATGAACACCCTGAAGGCCG AGGACACTGCTGTGTACTACTGCGCACGGGCCACCTACAAGAGAGAGCTCCGG TACTACTACGGAATGGACGTCTGGGGCCAGGGAACTACTGTGACCGTGTCCTC GGGAGGGGGTGGCTCCGGGGGGGGCGGCTCCGGCGGAGGCGGTTCCGAGATTG TGCTGACCCAGTCACCTTCAACTCTGTCGCTGTCCCCGGGAGAGAGCGCTACT CTGAGCTGCCGGGCCAGCCAGTCCGTGTCCACCACCTTCCTCGCCTGGTATCA GCAGAAGCCGGGGCAGGCACCACGGCTCTTGATCTACGGGTCAAGCAACAGAG CGACCGGAATTCCTGACCGCTTCTCGGGGAGCGGTTCAGGCACCGACTTCACC CTGACTATCCGGCGCCTGGAACCCGAAGATTTCGCCGTGTATTACTGTCAACA GTACCACTCCTCGCCGTCCTGGACCTTTGGCCAAGGAACCAAAGTGGAAATCA AG
BCMA_EBB-C1978-C7 - aa VH	182	EVQLVETGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISG SGGSTYYADSVKGRFTISRDNSKNTLYLQMNTLKAEDTAVYYCARATYKRELR YYYGMDVWGQGTTVTVSS
BCMA_EBB-C1978-C7 -	203	EIVLTQSPSTLSLSPGESATLSCRASQSVSTTFLAWYQQKPGQAPRLLIYGSS

aa VL		NRATGIPDRFSGSGSGTDFTLTIRRLEPEDFAVYYCQQYHSSPSWTFGQGTKV EIK
BCMA_EBB-C1978-C7 - aa Full CART	224	MALPVTALLLPLALLLHAARPEVQLVETGGGLVQPGGSLRLSCAASGFTFSSY AMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNT LKAEDTAVYYCARATYKRELRYYYGMDVWGQGTTVTVSSGGGGSGGGGSGGGG SEIVLTQSPSTLSLSPGESATLSCRASQSVSTTFLAWYQQKPGQAPRLLIYGS SNRATGIPDRFSGSGSGTDFTLTIRRLEPEDFAVYYCQQYHSSPSWTFGQGTK VEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIW APLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFP EEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPE MGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTAT KDTYDALHMQALPPR
BCMA_EBB-C1978-C7 - nt Full CART	245	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCGAGGTGCAGCTTGTGGAAACCGGTGGCGGACTGGTGCAGCCCG GAGGAAGCCTCAGGCTGTCCTGCGCCGCGTCCGGCTTCACCTTCTCCTCGTAC GCCATGTCCTGGGTCCGCCAGGCCCCCGGAAAGGGCCTGGAATGGGTGTCCGC CATCTCTGGAAGCGGAGGTTCCACGTACTACGCGGACAGCGTCAAGGGAAGGT TCACAATCTCCCGCGATAATTCGAAGAACACTCTGTACCTTCAAATGAACACC CTGAAGGCCGAGGACACTGCTGTGTACTACTGCGCACGGGCCACCTACAAGAG AGAGCTCCGGTACTACTACGGAATGGACGTCTGGGGCCAGGGAACTACTGTGA CCGTGTCCTCGGGAGGGGGTGGCTCCGGGGGGGGCGGCTCCGGCGGAGGCGGT TCCGAGATTGTGCTGACCCAGTCACCTTCAACTCTGTCGCTGTCCCCGGGAGA GAGCGCTACTCTGAGCTGCCGGGCCAGCCAGTCCGTGTCCACCACCTTCCTCG CCTGGTATCAGCAGAAGCCGGGGCAGGCACCACGGCTCTTGATCTACGGGTCA AGCAACAGAGCGACCGGAATTCCTGACCGCTTCTCGGGGAGCGGTTCAGGCAC CGACTTCACCCTGACTATCCGGCGCCTGGAACCCGAAGATTTCGCCGTGTATT ACTGTCAACAGTACCACTCCTCGCCGTCCTGGACCTTTGGCCAAGGAACCAAA GTGGAAATCAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTAC CATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTG GTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGG GCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCT TTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCA TGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCA GAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGA TGCTCCAGCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTG GTCGGAGAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAA ATGGGCGGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCT CCAAAAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAAC GCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACC AAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1978-D10		
BCMA_EBB-C1978-D10 - aa ScFv domain	141	EVQLVETGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISW NSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCARVGKAVPDV WGQGTTVTVSSGGGGSGGGGSGGGGSDIVMTQTPSSLSASVGDRVTITCRASQ SISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQP EDFATYYCQQSYSTPYSFGQGTRLEIK
BCMA_EBB-C1978-D10-nt ScFv domain	162	GAAGTGCAGCTCGTGGAAACTGGAGGTGGACTCGTGCAGCCTGGACGGTCGCT GCGGCTGAGCTGCGCTGCATCCGGCTTCACCTTCGACGATTATGCCATGCACT GGGTCAGACAGGCGCCAGGGAAGGGACTTGAGTGGGTGTCCGGTATCAGCTGG AATAGCGGCTCAATCGGATACGCGGACTCCGTGAAGGGAAGGTTCACCATTTC CCGCGACAACGCCAAGAACTCCCTGTACTTGCAAATGAACAGCCTCCGGGATG

		AGGACACTGCCGTGTACTACTGCGCCCGCGTCGGAAAAGCTGTGCCCGACGTC TGGGGCCAGGGAACCACTGTGACCGTGTCCAGCGGCGGGGGTGGATCGGGCGG TGGAGGGTCCGGTGGAGGGGGCTCAGATATTGTGATGACCCAGACCCCCTCGT CCCTGTCCGCCTCGGTCGGCGACCGCGTGACTATCACATGTAGAGCCTCGCAG AGCATCTCCAGCTACCTGAACTGGTATCAGCAGAAGCCGGGGAAGGCCCCGAA GCTCCTGATCTACGCGGCATCATCACTGCAATCGGGAGTGCCGAGCCGGTTTT CCGGGTCCGGCTCCGGCACCGACTTCACGCTGACCATTTCTTCCCTGCAACCC GAGGACTTCGCCACTTACTACTGCCAGCAGTCCTACTCCACCCCTTACTCCTT CGGCCAAGGAACCAGGCTGGAAATCAAG
BCMA_EBB-C1978-D10 - aa VH	183	EVQLVETGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISW NSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCARVGKAVPDV WGQGTTVTVSS
BCMA_EBB-C1978-D10-aa VL	204	DIVMTQTPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASS LQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPYSFGQGTRLEI K
BCMA_EBB-C1978-D10 - aa Full CART	225	MALPVTALLLPLALLLHAARPEVQLVETGGGLVQPGRSLRLSCAASGFTFDDY AMHWVRQAPGKGLEWVSGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNS LRDEDTAVYYCARVGKAVPDVWGQGTTVTVSSGGGGSGGGGSGGGGSDIVMTQ TPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVP SRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPYSFGQGTRLEIKTTTPA PRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGV LLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKN PQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
BCMA_EBB-C1978-D10 - nt Full CART	246	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCGAAGTGCAGCTCGTGGAAACTGGAGGTGGACTCGTGCAGCCTG GACGGTCGCTGCGGCTGAGCTGCGCTGCATCCGGCTTCACCTTCGACGATTAT GCCATGCACTGGGTCAGACAGGCGCCAGGGAAGGGACTTGAGTGGGTGTCCGG TATCAGCTGGAATAGCGGCTCAATCGGATACGCGGACTCCGTGAAGGGAAGGT TCACCATTTCCCGCGACAACGCCAAGAACTCCCTGTACTTGCAAATGAACAGC CTCCGGGATGAGGACACTGCCGTGTACTACTGCGCCCGCGTCGGAAAAGCTGT GCCCGACGTCTGGGGCCAGGGAACCACTGTGACCGTGTCCAGCGGCGGGGGTG GATCGGGCGGTGGAGGGTCCGGTGGAGGGGGCTCAGATATTGTGATGACCCAG ACCCCCTCGTCCCTGTCCGCCTCGGTCGGCGACCGCGTGACTATCACATGTAG AGCCTCGCAGAGCATCTCCAGCTACCTGAACTGGTATCAGCAGAAGCCGGGGA AGGCCCCGAAGCTCCTGATCTACGCGGCATCATCACTGCAATCGGGAGTGCCG AGCCGGTTTTCCGGGTCCGGCTCCGGCACCGACTTCACGCTGACCATTTCTTC CCTGCAACCCGAGGACTTCGCCACTTACTACTGCCAGCAGTCCTACTCCACCC CTTACTCCTTCGGCCAAGGAACCAGGCTGGAAATCAAGACCACTACCCCAGCA CCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCG TCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTG ACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTC CTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCT GCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGG AGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTG CGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAA CCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGG ACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAAT CCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCCTA

		TAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACGACGGAC TGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTTCACATG CAGGCCCTGCCGCCTCGG
BCMA_EBB-C1979-C12		
BCMA_EBB-C1979-C12-aa ScFv domain	142	EVQLVESGGGLVQPGRSLRLSCTASGFTFDDYAMHWVRQRPGKGLEWVASINW KGNSLAYGDSVKGRFAISRDNAKNTVFLQMNSLRTEDTAVYYCASHQGVAYYN YAMDVWGRGTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSLSPGERATLS CRATQSIGSSFLAWYQQRPGQAPRLLIYGASQRATGIPDRFSGRGSGTDFTLT ISRVEPEDSAVYYCQHYESSPSWTFGQGTKVEIK
BCMA_EBB-C1979-C12 - nt ScFv domain	163	GAAGTGCAGCTCGTGGAGAGCGGGGGAGGATTGGTGCAGCCCGGAAGGTCCCT GCGGCTCTCCTGCACTGCGTCTGGCTTCACCTTCGACGACTACGCGATGCACT GGGTCAGACAGCGCCCGGGAAAGGGCCTGGAATGGGTCGCCTCAATCAACTGG AAGGGAAACTCCCTGGCCTATGGCGACAGCGTGAAGGGCCGCTTCGCCATTTC GCGCGACAACGCCAAGAACACCGTGTTTCTGCAAATGAATTCCCTGCGGACCG AGGATACCGCTGTGTACTACTGCGCCAGCCACCAGGGCGTGGCATACTATAAC TACGCCATGGACGTGTGGGGAAGAGGGACGCTCGTCACCGTGTCCTCCGGGGG CGGTGGATCGGGTGGAGGAGGAAGCGGTGGCGGGGGCAGCGAAATCGTGCTGA CTCAGAGCCCGGGAACTCTTTCACTGTCCCCGGGAGAACGGGCCACTCTCTCG TGCCGGGCCACCCAGTCCATCGGCTCCTCCTTCCTTGCCTGGTACCAGCAGAG GCCAGGACAGGCGCCCCGCCTGCTGATCTACGGTGCTTCCCAACGCGCCACTG GCATTCCTGACCGGTTCAGCGGCAGAGGGTCGGGAACCGATTTCACACTGACC ATTTCCCGGGTGGAGCCCGAAGATTCGGCAGTCTACTACTGTCAGCATTACGA GTCCTCCCCTTCATGGACCTTCGGTCAAGGGACCAAAGTGGAGATCAAG
BCMA_EBB-C1979-C12 - aa VH	184	EVQLVESGGGLVQPGRSLRLSCTASGFTFDDYAMHWVRQRPGKGLEWVASINW KGNSLAYGDSVKGRFAISRDNAKNTVFLQMNSLRTEDTAVYYCASHQGVAYYN YAMDVWGRGTLVTVSS
BCMA_EBB-C1979-C12 - aa VL	205	EIVLTQSPGTLSLSPGERATLSCRATQSIGSSFLAWYQQRPGQAPRLLIYGAS QRATGIPDRFSGRGSGTDFTLTISRVEPEDSAVYYCQHYESSPSWTFGQGTKV EIK
BCMA_EBB-C1979-C12 - aa Full CART	226	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGRSLRLSCTASGFTFDDY AMHWVRQRPGKGLEWVASINWKGNSLAYGDSVKGRFAISRDNAKNTVFLQMNS LRTEDTAVYYCASHQGVAYYNYAMDVWGRGTLVTVSSGGGGSGGGGSGGGGSE IVLTQSPGTLSLSPGERATLSCRATQSIGSSFLAWYQQRPGQAPRLLIYGASQ RATGIPDRFSGRGSGTDFTLTISRVEPEDSAVYYCQHYESSPSWTFGQGTKVE IKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAP LAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEE EEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKD TYDALHMQALPPR
BCMA_EBB-C1979-C12 - nt Full CART	247	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCGAAGTGCAGCTCGTGGAGAGCGGGGGAGGATTGGTGCAGCCCG GAAGGTCCCTGCGGCTCTCCTGCACTGCGTCTGGCTTCACCTTCGACGACTAC GCGATGCACTGGGTCAGACAGCGCCCGGGAAAGGGCCTGGAATGGGTCGCCTC AATCAACTGGAAGGGAAACTCCCTGGCCTATGGCGACAGCGTGAAGGGCCGCT TCGCCATTTCGCGCGACAACGCCAAGAACACCGTGTTTCTGCAAATGAATTCC CTGCGGACCGAGGATACCGCTGTGTACTACTGCGCCAGCCACCAGGGCGTGGC ATACTATAACTACGCCATGGACGTGTGGGGAAGAGGGACGCTCGTCACCGTGT CCTCCGGGGGCGGTGGATCGGGTGGAGGAGGAAGCGGTGGCGGGGGCAGCGAA ATCGTGCTGACTCAGAGCCCGGGAACTCTTTCACTGTCCCCGGGAGAACGGGC CACTCTCTCGTGCCGGGCCACCCAGTCCATCGGCTCCTCCTTCCTTGCCTGGT

		ACCAGCAGAGGCCAGGACAGGCGCCCCGCCTGCTGATCTACGGTGCTTCCCAA CGCGCCACTGGCATTCCTGACCGGTTCAGCGGCAGAGGGTCGGGAACCGATTT CACACTGACCATTTCCCGGGTGGAGCCCGAAGATTCGGCAGTCTACTACTGTC AGCATTACGAGTCCTCCCCTTCATGGACCTTCGGTCAAGGGACCAAAGTGGAG ATCAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGC CTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGG CCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCT CTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTG TAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGC CTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAG GAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCC AGCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGA GAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGC GGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAA GGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAA GAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGAC ACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1980-G4		
BCMA_EBB-C1980-G4- aa ScFv domain	143	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEW VSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYY CAKVVRDGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSPA TLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATG IPDRFSGNGSGTDFTLTISRLEPEDFAVYYCQQYGSPPRFTFGPGTKVDI K
BCMA_EBB-C1980-G4- nt ScFv domain	164	GAGGTGCAGTTGGTCGAAAGCGGGGGCGGGCTTGTGCAGCCTGGCGGATCACT GCGGCTGTCCTGCGCGGCATCAGGCTTCACGTTTTCTTCCTACGCCATGTCCT GGGTGCGCCAGGCCCCTGGAAAGGGACTGGAATGGGTGTCCGCGATTTCGGGG TCCGGCGGGAGCACCTACTACGCCGATTCCGTGAAGGGCCGCTTCACTATCTC GCGGGACAACTCCAAGAACACCCTCTACCTCCAAATGAATAGCCTGCGGGCCG AGGATACCGCCGTCTACTATTGCGCTAAGGTCGTGCGCGACGGAATGGACGTG TGGGGACAGGGTACCACCGTGACAGTGTCCTCGGGGGGAGGCGGTAGCGGCGG AGGAGGAAGCGGTGGTGGAGGTTCCGAGATTGTGCTGACTCAATCACCCGCGA CCCTGAGCCTGTCCCCCGGCGAAAGGGCCACTCTGTCCTGTCGGGCCAGCCAA TCAGTCTCCTCCTCGTACCTGGCCTGGTACCAGCAGAAGCCAGGACAGGCTCC GAGACTCCTTATCTATGGCGCATCCTCCCGCGCCACCGGAATCCCGGATAGGT TCTCGGGAAACGGATCGGGGACCGACTTCACTCTCACCATCTCCCGGCTGGAA CCGGAGGACTTCGCCGTGTACTACTGCCAGCAGTACGGCAGCCCGCCTAGATT CACTTTCGGCCCCGGCACCAAAGTGGACATCAAG
BCMA_EBB-C1980-G4- aa VH	185	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISG SGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKVVRDGMDV WGQGTTVTVSS
BCMA_EBB-C1980-G4- aa VL	206	EIVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGAS SRATGIPDRFSGNGSGTDFTLTISRLEPEDFAVYYCQQYGSPPRFTFGPGTKV DIK
BCMA_EBB-C1980-G4- aa Full CART	227	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASGF TFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNS KNTLYLQMNSLRAEDTAVYYCAKVVRDGMDVWGQGTTVTVSSGGG GSGGGGSGGGGSEIVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWY QQKPGQAPRLLIYGASSRATGIPDRFSGNGSGTDFTLTISRLEPEDFAVY YCQQYGSPPRFTFGPGTKVDIKTTTPAPRPPTPAPTIASQPLSLRPEACRP AAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLL YIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYK

		QGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYN ELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
BCMA_EBB-C1980-G4- nt Full CART	248	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCGAGGTGCAGTTGGTCGAAAGCGGGGGCGGGCTTGTGCAGCCTG GCGGATCACTGCGGCTGTCCTGCGCGGCATCAGGCTTCACGTTTTCTTCCTAC GCCATGTCCTGGGTGCGCCAGGCCCCTGGAAAGGGACTGGAATGGGTGTCCGC GATTTCGGGGTCCGGCGGGAGCACCTACTACGCCGATTCCGTGAAGGGCCGCT TCACTATCTCGCGGGACAACTCCAAGAACACCCTCTACCTCCAAATGAATAGC CTGCGGGCCGAGGATACCGCCGTCTACTATTGCGCTAAGGTCGTGCGCGACGG AATGGACGTGTGGGGACAGGGTACCACCGTGACAGTGTCCTCGGGGGGAGGCG GTAGCGGCGGAGGAGGAAGCGGTGGTGGAGGTTCCGAGATTGTGCTGACTCAA TCACCCGCGACCCTGAGCCTGTCCCCCGGCGAAAGGGCCACTCTGTCCTGTCG GGCCAGCCAATCAGTCTCCTCCTCGTACCTGGCCTGGTACCAGCAGAAGCCAG GACAGGCTCCGAGACTCCTTATCTATGGCGCATCCTCCCGCGCCACCGGAATC CCGGATAGGTTCTCGGGAAACGGATCGGGGACCGACTTCACTCTCACCATCTC CCGGCTGGAACCGGAGGACTTCGCCGTGTACTACTGCCAGCAGTACGGCAGCC CGCCTAGATTCACTTTCGGCCCCGGCACCAAAGTGGACATCAAGACCACTACC CCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTC CCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGG GTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGC GGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAA GAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTC AAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGC GAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGG GCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACG TGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGA AAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGA AGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACG ACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTT CACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1980-D2		
BCMA_EBB-C1980-D2- aa ScFv domain	144	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISG SGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIPQTGTFD YWGQGTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSLSPGERATLSCRAS QSVSSSYLAWYQQRPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRL EPEDFAVYYCQHYGSSPSWTFGQGTRLEIK
BCMA_EBB-C1980-D2- nt ScFv domain	165	GAAGTGCAGCTGCTGGAGTCCGGCGGTGGATTGGTGCAACCGGGGGGATCGCT CAGACTGTCCTGTGCGGCGTCAGGCTTCACCTTCTCGAGCTACGCCATGTCAT GGGTCAGACAGGCCCCTGGAAAGGGTCTGGAATGGGTGTCCGCCATTTCCGGG AGCGGGGGATCTACATACTACGCCGATAGCGTGAAGGGCCGCTTCACCATTTC CCGGGACAACTCCAAGAACACTCTCTATCTGCAAATGAACTCCCTCCGCGCTG AGGACACTGCCGTGTACTACTGCGCCAAAATCCCTCAGACCGGCACCTTCGAC TACTGGGGACAGGGGACTCTGGTCACCGTCAGCAGCGGTGGCGGAGGTTCGGG GGGAGGAGGAAGCGGCGGCGGAGGGTCCGAGATTGTGCTGACCCAGTCACCCG GCACTTTGTCCCTGTCGCCTGGAGAAAGGGCCACCCTTTCCTGCCGGGCATCC CAATCCGTGTCCTCCTCGTACCTGGCCTGGTACCAGCAGAGGCCCGGACAGGC CCCACGGCTTCTGATCTACGGAGCAAGCAGCCGCGCGACCGGTATCCCGGACC GGTTTTCGGGCTCGGGCTCAGGAACTGACTTCACCCTCACCATCTCCCGCCTG GAACCCGAAGATTTCGCTGTGTATTACTGCCAGCACTACGGCAGCTCCCCGTC CTGGACGTTCGGCCAGGGAACTCGGCTGGAGATCAAG
BCMA_EBB-	186	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISG

C1980-D2- aa VH		SGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIPQTGTFD YWGQGTLVTVSS
BCMA_EBB-C1980-D2- aa VL	207	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQRPGQAPRLLIYGAS SRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQHYGSSPSWTFGQGTRL EIK
BCMA_EBB-C1980-D2- aa Full CART	228	MALPVTALLLPLALLLHAARPEVQLLESGGGLVQPGGSLRLSCAASGFTFSSY AMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNS LRAEDTAVYYCAKIPQTGTFDYWGQGTLVTVSSGGGGSGGGGSGGGGSEIVLT QSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQRPGQAPRLLIYGASSRATG IPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQHYGSSPSWTFGQGTRLEIKTT TPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGT CGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGG CELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPR RKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDA LHMQALPPR
BCMA_EBB-C1980-D2- nt Full CART	249	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCGAAGTGCAGCTGCTGGAGTCCGGCGGTGGATTGGTGCAACCGG GGGGATCGCTCAGACTGTCCTGTGCGGCGTCAGGCTTCACCTTCTCGAGCTAC GCCATGTCATGGGTCAGACAGGCCCCTGGAAAGGGTCTGGAATGGGTGTCCGC CATTTCCGGGAGCGGGGGATCTACATACTACGCCGATAGCGTGAAGGGCCGCT TCACCATTTCCCGGGACAACTCCAAGAACACTCTCTATCTGCAAATGAACTCC CTCCGCGCTGAGGACACTGCCGTGTACTACTGCGCCAAAATCCCTCAGACCGG CACCTTCGACTACTGGGGACAGGGGACTCTGGTCACCGTCAGCAGCGGTGGCG GAGGTTCGGGGGGAGGAGGAAGCGGCGGCGGAGGGTCCGAGATTGTGCTGACC CAGTCACCCGGCACTTTGTCCCTGTCGCCTGGAGAAAGGGCCACCCTTTCCTG CCGGGCATCCCAATCCGTGTCCTCCTCGTACCTGGCCTGGTACCAGCAGAGGC CCGGACAGGCCCCACGGCTTCTGATCTACGGAGCAAGCAGCCGCGCGACCGGT ATCCCGGACCGGTTTTCGGGCTCGGGCTCAGGAACTGACTTCACCCTCACCAT CTCCCGCCTGGAACCCGAAGATTTCGCTGTGTATTACTGCCAGCACTACGGCA GCTCCCCGTCCTGGACGTTCGGCCAGGGAACTCGGCTGGAGATCAAGACCACT ACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCT GTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCC GGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACT TGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCG GAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTA CTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGC TGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCA GGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACG ACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGC AGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGC AGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCC ACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCT CTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1978-A10		
BCMA_EBB-C1978-A10- aa ScFv domain	145	EVQLVETGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEW VSAISGSGGSTYYADSVKGRFTMSRENDKNSVFLQMNSLRVEDTGVY YCARANYKRELRYYYGMDVWGQGTMVTVSSGGGGSGGGGSGGGGS EIVMTQSPGTLSLSPGESATLSCRASQRVASNYLAWYQHKPGQAPSLLI SGASSRATGVPDRFSGSGSGTDFTLAISRLEPEDSAVYYCQHYDSSPSW TFGQGTKVEIK
BCMA_EBB-C1978-A10-	166	GAAGTGCAACTGGTGGAAACCGGTGGAGGACTCGTGCAGCCTGGCGGCAGCCT CCGGCTGAGCTGCGCCGCTTCGGGATTCACCTTTTCCTCCTACGCGATGTCTT

nt ScFv domain		GGGTCAGACAGGCCCCCGGAAAGGGGCTGGAATGGGTGTCAGCCATCTCCGGC TCCGGCGGATCAACGTACTACGCCGACTCCGTGAAAGGCCGGTTCACCATGTC GCGCGAGAATGACAAGAACTCCGTGTTCCTGCAAATGAACTCCCTGAGGGTGG AGGACACCGGAGTGTACTATTGTGCGCGCGCCAACTACAAGAGAGAGCTGCGG TACTACTACGGAATGGACGTCTGGGGACAGGGAACTATGGTGACCGTGTCATC CGGTGGAGGGGGAAGCGGCGGTGGAGGCAGCGGGGGCGGGGGTTCAGAAATTG TCATGACCCAGTCCCCGGGAACTCTTTCCCTCTCCCCCGGGGAATCCGCGACT TTGTCCTGCCGGGCCAGCCAGCGCGTGGCCTCGAACTACCTCGCATGGTACCA GCATAAGCCAGGCCAAGCCCCTTCCCTGCTGATTTCCGGGGCTAGCAGCCGCG CCACTGGCGTGCCGGATAGGTTCTCGGGAAGCGGCTCGGGTACCGATTTCACC CTGGCAATCTCGCGGCTGGAACCGGAGGATTCGGCCGTGTACTACTGCCAGCA CTATGACTCATCCCCCTCCTGGACATTCGGACAGGGCACCAAGGTCGAGATCA AG
BCMA_EBB-C1978-A10-aa VH	187	EVQLVETGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISG SGGSTYYADSVKGRFTMSRENDKNSVFLQMNSLRVEDTGVYYCARANYKRELR YYYGMDVWGQGTMVTVSS
BCMA_EBB-C1978-A10-aa VL	208	EIVMTQSPGTLSLSPGESATLSCRASQRVASNYLAWYQHKPGQAPSLLISGAS SRATGVPDRFSGSGSGTDFTLAISRLEPEDSAVYYCQHYDSSPSWTFGQGTKV EIK
BCMA_EBB-C1978-A10-aa Full CART	229	MALPVTALLLPLALLLHAARPEVQLVETGGGLVQPGGSLRLSCAASGF TFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTMSREN DKNSVFLQMNSLRVEDTGVYYCARANYKRELRYYYGMDVWGQGTM VTVSSGGGGSGGGGSGGGGSEIVMTQSPGTLSLSPGESATLSCRASQR VASNYLAWYQHKPGQAPSLLISGASSRATGVPDRFSGSGSGTDFTLAIS RLEPEDSAVYYCQHYDSSPSWTFGQGTKVEIKTTTPAPRPPTPAPTIAS QPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVIT LYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVK FSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKP RRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLST ATKDTYDALHMQALPPR
BCMA_EBB-C1978-A10-nt Full CART	250	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCGAAGTGCAACTGGTGGAAACCGGTGGAGGACTCGTGCAGCCTG GCGGCAGCCTCCGGCTGAGCTGCGCCGCTTCGGGATTCACCTTTTCCTCCTAC GCGATGTCTTGGGTCAGACAGGCCCCCGGAAAGGGGCTGGAATGGGTGTCAGC CATCTCCGGCTCCGGCGGATCAACGTACTACGCCGACTCCGTGAAAGGCCGGT TCACCATGTCGCGCGAGAATGACAAGAACTCCGTGTTCCTGCAAATGAACTCC CTGAGGGTGGAGGACACCGGAGTGTACTATTGTGCGCGCGCCAACTACAAGAG AGAGCTGCGGTACTACTACGGAATGGACGTCTGGGGACAGGGAACTATGGTGA CCGTGTCATCCGGTGGAGGGGGAAGCGGCGGTGGAGGCAGCGGGGGCGGGGGT TCAGAAATTGTCATGACCCAGTCCCCGGGAACTCTTTCCCTCTCCCCCGGGGA ATCCGCGACTTTGTCCTGCCGGGCCAGCCAGCGCGTGGCCTCGAACTACCTCG CATGGTACCAGCATAAGCCAGGCCAAGCCCCTTCCCTGCTGATTTCCGGGGCT AGCAGCCGCGCCACTGGCGTGCCGGATAGGTTCTCGGGAAGCGGCTCGGGTAC CGATTTCACCCTGGCAATCTCGCGGCTGGAACCGGAGGATTCGGCCGTGTACT ACTGCCAGCACTATGACTCATCCCCCTCCTGGACATTCGGACAGGGCACCAAG GTCGAGATCAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTAC CATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTG GTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGG GCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCT TTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCA

		TGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCA GAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGA TGCTCCAGCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTG GTCGGAGAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAA ATGGGCGGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCT CCAAAAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAAC GCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACC AAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1978-D4		
BCMA_EBB-C1978-D4- aa ScFv domain	146	EVQLLETGGGLVQPGGSLRLSCAASGFSFSSYAMSWVRQAPGKGLEWVSAISG SGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKALVGATGA FDIWGQGTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSLSPGERATLSCR ASQSLSSNFLAWYQQKPGQAPGLLIYGASNWATGTPDRFSGSGSGTDFTLTIT RLEPEDFAVYYCQYYGTSPMYTFGQGTKVEIK
BCMA_EBB-C1978-D4- nt ScFv domain	167	GAAGTGCAGCTGCTCGAAACCGGTGGAGGGCTGGTGCAGCCAGGGGGCTCCCT GAGGCTTTCATGCGCCGCTAGCGGATTCTCCTTCTCCTCTTACGCCATGTCGT GGGTCCGCCAAGCCCCTGGAAAAGGCCTGGAATGGGTGTCCGCGATTTCCGGG AGCGGAGGTTCGACCTATTACGCCGACTCCGTGAAGGGCCGCTTTACCATCTC CCGGGATAACTCCAAGAACACTCTGTACCTCCAAATGAACTCGCTGAGAGCCG AGGACACCGCCGTGTATTACTGCGCGAAGGCGCTGGTCGGCGCGACTGGGGCA TTCGACATCTGGGGACAGGGAACTCTTGTGACCGTGTCGAGCGGAGGCGGCGG CTCCGGCGGAGGAGGGAGCGGGGGCGGTGGTTCCGAAATCGTGTTGACTCAGT CCCCGGGAACCCTGAGCTTGTCACCCGGGGAGCGGGCCACTCTCTCCTGTCGC GCCTCCCAATCGCTCTCATCCAATTTCCTGGCCTGGTACCAGCAGAAGCCCGG ACAGGCCCCGGGCCTGCTCATCTACGGCGCTTCAAACTGGGCAACGGGAACCC CTGATCGGTTCAGCGGAAGCGGATCGGGTACTGACTTTACCCTGACCATCACC AGACTGGAACCGGAGGACTTCGCCGTGTACTACTGCCAGTACTACGGCACCTC CCCCATGTACACATTCGGACAGGGTACCAAGGTCGAGATTAAG
BCMA_EBB-C1978-D4- aa VH	188	EVQLLETGGGLVQPGGSLRLSCAASGFSFSSYAMSWVRQAPGKGLEWVSAISG SGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKALVGATGA FDIWGQGTLVTVSS
BCMA_EBB-C1978-D4- aa VL	209	EIVLTQSPGTLSLSPGERATLSCRASQSLSSNFLAWYQQKPGQAPGLLIYGAS NWATGTPDRFSGSGSGTDFTLTITRLEPEDFAVYYCQYYGTSPMYTFGQGTKV EIK
BCMA_EBB-C1978-D4- aa Full CART	230	MALPVTALLLPLALLLHAARPEVQLLETGGGLVQPGGSLRLSCAASGFSFSSY AMSWVRQAPGKGLEWVSAISGSGGGSTYYADSVKGRFTISRDNSKNTLYLQMNS LRAEDTAVYYCAKALVGATGAFDIWGQGTLVTVSSGGGGSGGGGSGGGGSEIV LTQSPGTLSLSPGERATLSCRASQSLSSNFLAWYQQKPGQAPGLLIYGASNWA TGTPDRFSGSGSGTDFTLTITRLEPEDFAVYYCQYYGTSPMYTFGQGTKVEIK TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLA GTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEE GGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGK PRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTY DALHMQALPPR
BCMA_EBB-C1978-D4- nt Full CART	251	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCGAAGTGCAGCTGCTCGAAACCGGTGGAGGGCTGGTGCAGCCAG GGGGCTCCCTGAGGCTTTCATGCGCCGCTAGCGGATTCTCCTTCTCCTCTTAC GCCATGTCGTGGGTCCGCCAAGCCCCTGGAAAAGGCCTGGAATGGGTGTCCGC GATTTCCGGGAGCGGAGGTTCGACCTATTACGCCGACTCCGTGAAGGGCCGCT TTACCATCTCCCGGGATAACTCCAAGAACACTCTGTACCTCCAAATGAACTCG

		CTGAGAGCCGAGGACACCGCCGTGTATTACTGCGCGAAGGCGCTGGTCGGCGC GACTGGGGCATTCGACATCTGGGGACAGGGAACTCTTGTGACCGTGTCGAGCG GAGGCGGCGGCTCCGGCGGAGGAGGGAGCGGGGGCGGTGGTTCCGAAATCGTG TTGACTCAGTCCCCGGGAACCCTGAGCTTGTCACCCGGGGAGCGGGCCACTCT CTCCTGTCGCGCCTCCCAATCGCTCTCATCCAATTTCCTGGCCTGGTACCAGC AGAAGCCCGGACAGGCCCCGGGCCTGCTCATCTACGGCGCTTCAAACTGGGCA ACGGGAACCCCTGATCGGTTCAGCGGAAGCGGATCGGGTACTGACTTTACCCT GACCATCACCAGACTGGAACCGGAGGACTTCGCCGTGTACTACTGCCAGTACT ACGGCACCTCCCCCATGTACACATTCGGACAGGGTACCAAGGTCGAGATTAAG ACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCA GCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGC ATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCT GGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCG CGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGC AGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAA GGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTA CAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGG AGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAG CCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAA GATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCA AAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTAT GACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1980-A2		
BCMA_EBB-C1980-A2- aa ScFv domain	147	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISG SGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVLWFGEGFDP WGQGTLVTVSSGGGGSGGGGSGGGGSDIVLTQSPLSLPVTPGEPASISCRSSQ SLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCMQALQTPLTFGGGTKVDIK
BCMA_EBB-C1980-A2- nt ScFv domain	168	GAAGTGCAGCTGCTTGAGAGCGGTGGAGGTCTGGTGCAGCCCGGGGGATCACT GCGCCTGTCCTGTGCCGCGTCCGGTTTCACTTTCTCCTCGTACGCCATGTCGT GGGTCAGACAGGCACCGGGAAAGGGACTGGAATGGGTGTCAGCCATTTCGGGT TCGGGGGGCAGCACCTACTACGCTGACTCCGTGAAGGGCCGGTTCACCATTTC CCGCGACAACTCCAAGAACACCTTGTACCTCCAAATGAACTCCCTGCGGGCCG AAGATACCGCCGTGTATTACTGCGTGCTGTGGTTCGGAGAGGGATTCGACCCG TGGGGACAAGGAACACTCGTGACTGTGTCATCCGGCGGAGGCGGCAGCGGTGG CGGCGGTTCCGGCGGCGGCGGATCTGACATCGTGTTGACCCAGTCCCCTCTGA GCCTGCCGGTCACTCCTGGCGAACCAGCCAGCATCTCCTGCCGGTCGAGCCAG TCCCTCCTGCACTCCAATGGGTACAACTACCTCGATTGGTATCTGCAAAAGCC GGGCCAGAGCCCCCAGCTGCTGATCTACCTTGGGTCAAACCGCGCTTCCGGGG TGCCTGATAGATTCTCCGGGTCCGGGAGCGGAACCGACTTTACCCTGAAAATC TCGAGGGTGGAGGCCGAGGACGTCGGAGTGTACTACTGCATGCAGGCGCTCCA GACTCCCCTGACCTTCGGAGGAGGAACGAAGGTCGACATCAAGA
BCMA_EBB-C1980-A2- aa VH	189	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISG SGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVLWFGEGFDP WGQGTLVTVSS
BCMA_EBB-C1980-A2- aa VL	210	DIVLTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLI YLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPLTFGGG TKVDIK
BCMA_EBB-C1980-A2- aa Full CART	231	MALPVTALLLPLALLLHAARPEVQLLESGGGLVQPGGSLRLSCAASGFTFSSY AMSWVRQAPGKGLEWVSAISGSGGGSTYYADSVKGRFTISRDNSKNTLYLQMNS LRAEDTAVYYCVLWFGEGFDPWGQGTLVTVSSGGGGSGGGGSGGGGSDIVLTQ SPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNR

		ASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPLTFGGGTKVDIK TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLA GTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEE GGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGK PRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTY DALHMQALPPR
BCMA_EBB-C1980-A2- nt Full CART	252	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCGAAGTGCAGCTGCTTGAGAGCGGTGGAGGTCTGGTGCAGCCCG GGGGATCACTGCGCCTGTCCTGTGCCGCGTCCGGTTTCACTTTCTCCTCGTAC GCCATGTCGTGGGTCAGACAGGCACCGGGAAAGGGACTGGAATGGGTGTCAGC CATTTCGGGTTCGGGGGGCAGCACCTACTACGCTGACTCCGTGAAGGGCCGGT TCACCATTTCCCGCGACAACTCCAAGAACACCTTGTACCTCCAAATGAACTCC CTGCGGGCCGAAGATACCGCCGTGTATTACTGCGTGCTGTGGTTCGGAGAGGG ATTCGACCCGTGGGGACAAGGAACACTCGTGACTGTGTCATCCGGCGGAGGCG GCAGCGGTGGCGGCGGTTCCGGCGGCGGCGGATCTGACATCGTGTTGACCCAG TCCCCTCTGAGCCTGCCGGTCACTCCTGGCGAACCAGCCAGCATCTCCTGCCG GTCGAGCCAGTCCCTCCTGCACTCCAATGGGTACAACTACCTCGATTGGTATC TGCAAAAGCCGGGCCAGAGCCCCCAGCTGCTGATCTACCTTGGGTCAAACCGC GCTTCCGGGGTGCCTGATAGATTCTCCGGGTCCGGGAGCGGAACCGACTTTAC CCTGAAAATCTCGAGGGTGGAGGCCGAGGACGTCGGAGTGTACTACTGCATGC AGGCGCTCCAGACTCCCCTGACCTTCGGAGGAGGAACGAAGGTCGACATCAAG ACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCA GCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGC ATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCT GGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCG CGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGC AGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAA GGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTA CAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGG AGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAG CCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAA GATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCA AAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTAT GACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1981-C3		
BCMA_EBB-C1981-C3- aa ScFv domain	148	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISG SGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKVGYDSSGY YRDYYGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSLSPGER ATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGTSSRATGISDRFSGSGSGTD FTLTISRLEPEDFAVYYCQHYGNSPPKFTFGPGTKLEIK
BCMA_EBB-C1981-C3- nt ScFv domain	169	CAAGTGCAGCTCGTGGAGTCAGGCGGAGGACTGGTGCAGCCCGGGGGCTCCCT GAGACTTTCCTGCGCGGCATCGGGTTTTACCTTCTCCTCCTATGCTATGTCCT GGGTGCGCCAGGCCCCGGGAAAGGGACTGGAATGGGTGTCCGCAATCAGCGGT AGCGGGGGCTCAACATACTACGCCGACTCCGTCAAGGGTCGCTTCACTATTTC CCGGGACAACTCCAAGAATACCCTGTACCTCCAAATGAACAGCCTCAGGGCCG AGGATACTGCCGTGTACTACTGCGCCAAAGTCGGATACGATAGCTCCGGTTAC TACCGGGACTACTACGGAATGGACGTGTGGGGACAGGGCACCACCGTGACCGT GTCAAGCGGCGGAGGCGGTTCAGGAGGGGGAGGCTCCGGCGGTGGAGGGTCCG

		AAATCGTCCTGACTCAGTCGCCTGGCACTCTGTCGTTGTCCCCGGGGGAGCGC GCTACCCTGTCGTGTCGGGCGTCGCAGTCCGTGTCGAGCTCCTACCTCGCGTG GTACCAGCAGAAGCCCGGACAGGCCCCTAGACTTCTGATCTACGGCACTTCTT CACGCGCCACCGGGATCAGCGACAGGTTCAGCGGCTCCGGCTCCGGGACCGAC TTCACCCTGACCATTAGCCGGCTGGAGCCTGAAGATTTCGCCGTGTATTACTG CCAACACTACGGAAACTCGCCGCCAAAGTTCACGTTCGGACCCGGAACCAAGC TGGAAATCAAG
BCMA_EBB-C1981-C3- aa VH	190	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISG SGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKVGYDSSGY YRDYYGMDVWGQGTTVTVSS
BCMA_EBB-C1981-C3- aa VL	211	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGTS SRATGISDRFSGSGSGTDFTLTISRLEPEDFAVYYCQHYGNSPPKFTFGPGTK LEIK
BCMA_EBB-C1981-C3- aa Full CART	232	MALPVTALLLPLALLLHAARPQVQLVESGGGLVQPGGSLRLSCAASGFTFSSY AMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNS LRAEDTAVYYCAKVGYDSSGYYRDYYGMDVWGQGTTVTVSSGGGGSGGGGSGG GGSEIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIY GTSSRATGISDRFSGSGSGTDFTLTISRLEPEDFAVYYCQHYGNSPPKFTFGP GTKLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDI YIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSC RFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGR DPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLS TATKDTYDALHMQALPPR
BCMA_EBB-C1981-C3- nt Full CART	253	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCCAAGTGCAGCTCGTGGAGTCAGGCGGAGGACTGGTGCAGCCCG GGGGCTCCCTGAGACTTTCCTGCGCGGCATCGGGTTTTACCTTCTCCTCCTAT GCTATGTCCTGGGTGCGCCAGGCCCCGGGAAAGGGACTGGAATGGGTGTCCGC AATCAGCGGTAGCGGGGGCTCAACATACTACGCCGACTCCGTCAAGGGTCGCT TCACTATTTCCCGGGACAACTCCAAGAATACCCTGTACCTCCAAATGAACAGC CTCAGGGCCGAGGATACTGCCGTGTACTACTGCGCCAAAGTCGGATACGATAG CTCCGGTTACTACCGGGACTACTACGGAATGGACGTGTGGGGACAGGGCACCA CCGTGACCGTGTCAAGCGGCGGAGGCGGTTCAGGAGGGGGAGGCTCCGGCGGT GGAGGGTCCGAAATCGTCCTGACTCAGTCGCCTGGCACTCTGTCGTTGTCCCC GGGGGAGCGCGCTACCCTGTCGTGTCGGGCGTCGCAGTCCGTGTCGAGCTCCT ACCTCGCGTGGTACCAGCAGAAGCCCGGACAGGCCCCTAGACTTCTGATCTAC GGCACTTCTTCACGCGCCACCGGGATCAGCGACAGGTTCAGCGGCTCCGGCTC CGGGACCGACTTCACCCTGACCATTAGCCGGCTGGAGCCTGAAGATTTCGCCG TGTATTACTGCCAACACTACGGAAACTCGCCGCCAAAGTTCACGTTCGGACCC GGAACCAAGCTGGAAATCAAGACCACTACCCCAGCACCGAGGCCACCCACCCC GGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGAC CCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATC TACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGT GATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGC AACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGC CGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCG CAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAAC TCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGG GACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTA CAACGAGCTCCAAAAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGA

		AAGGGGAACGCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGC ACCGCCACCAAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCG G
BCMA_EBB-C1978-G4		
BCMA_EBB-C1978-G4- aa ScFv domain	149	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISG SGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKMGWSSGYL GAFDIWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSLSPGERATLS CRASQSVASSFLAWYQQKPGQAPRLLIYGASGRATGIPDRFSGSGSGTDFTLT ISRLEPEDFAVYYCQHYGGSPRLTFGGGTKVDIK
BCMA_EBB-C1978-G4- nt ScFv domain	170	GAAGTCCAACTGGTGGAGTCCGGGGGAGGGCTCGTGCAGCCCGGAGGCAGCCT TCGGCTGTCGTGCGCCGCCTCCGGGTTCACGTTCTCATCCTACGCGATGTCGT GGGTCAGACAGGCACCAGGAAAGGGACTGGAATGGGTGTCCGCCATTAGCGGC TCCGGCGGTAGCACCTACTATGCCGACTCAGTGAAGGGAAGGTTCACTATCTC CCGCGACAACAGCAAGAACACCCTGTACCTCCAAATGAACTCTCTGCGGGCCG AGGATACCGCGGTGTACTATTGCGCCAAGATGGGTTGGTCCAGCGGATACTTG GGAGCCTTCGACATTTGGGGACAGGGCACTACTGTGACCGTGTCCTCCGGGGG TGGCGGATCGGGAGGCGGCGGCTCGGGTGGAGGGGGTTCCGAAATCGTGTTGA CCCAGTCACCGGGAACCCTCTCGCTGTCCCCGGGAGAACGGGCTACACTGTCA TGTAGAGCGTCCCAGTCCGTGGCTTCCTCGTTCCTGGCCTGGTACCAGCAGAA GCCGGGACAGGCACCCCGCCTGCTCATCTACGGAGCCAGCGGCCGGGCGACCG GCATCCCTGACCGCTTCTCCGGTTCCGGCTCGGGCACCGACTTTACTCTGACC ATTAGCAGGCTTGAGCCCGAGGATTTTGCCGTGTACTACTGCCAACACTACGG GGGGAGCCCTCGCCTGACCTTCGGAGGCGGAACTAAGGTCGATATCAAAA
BCMA_EBB-C1978-G4- aa VH	191	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISG SGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKMGWSSGYL GAFDIWGQGTTVTVSS
BCMA_EBB-C1978-G4- aa VL	212	EIVLTQSPGTLSLSPGERATLSCRASQSVASSFLAWYQQKPGQAPRLLIYGAS GRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQHYGGSPRLTFGGGTKV DIK
BCMA_EBB-C1978-G4- aa Full CART	233	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASGFTFSSY AMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNS LRAEDTAVYYCAKMGWSSGYLGAFDIWGQGTTVTVSSGGGGSGGGGSGGGGSE IVLTQSPGTLSLSPGERATLSCRASQSVASSFLAWYQQKPGQAPRLLIYGASG RATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQHYGGSPRLTFGGGTKVD IKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAP LAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEE EEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKD TYDALHMQALPPR
BCMA_EBB-C1978-G4- nt Full CART	254	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGC CGCTCGGCCCGAAGTCCAACTGGTGGAGTCCGGGGGAGGGCTCGTGCAGCCCG GAGGCAGCCTTCGGCTGTCGTGCGCCGCCTCCGGGTTCACGTTCTCATCCTAC GCGATGTCGTGGGTCAGACAGGCACCAGGAAAGGGACTGGAATGGGTGTCCGC CATTAGCGGCTCCGGCGGTAGCACCTACTATGCCGACTCAGTGAAGGGAAGGT TCACTATCTCCCGCGACAACAGCAAGAACACCCTGTACCTCCAAATGAACTCT CTGCGGGCCGAGGATACCGCGGTGTACTATTGCGCCAAGATGGGTTGGTCCAG CGGATACTTGGGAGCCTTCGACATTTGGGGACAGGGCACTACTGTGACCGTGT CCTCCGGGGGTGGCGGATCGGGAGGCGGCGGCTCGGGTGGAGGGGGTTCCGAA ATCGTGTTGACCCAGTCACCGGGAACCCTCTCGCTGTCCCCGGGAGAACGGGC TACACTGTCATGTAGAGCGTCCCAGTCCGTGGCTTCCTCGTTCCTGGCCTGGT ACCAGCAGAAGCCGGGACAGGCACCCCGCCTGCTCATCTACGGAGCCAGCGGC CGGGCGACCGGCATCCCTGACCGCTTCTCCGGTTCCGGCTCGGGCACCGACTT

		TACTCTGACCATTAGCAGGCTTGAGCCCGAGGATTTTGCCGTGTACTACTGCC AACACTACGGGGGGAGCCCTCGCCTGACCTTCGGAGGCGGAACTAAGGTCGAT ATCAAAACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGC CTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGG CCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCT CTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTG TAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGC CTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAG GAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCC AGCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGA GAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGC GGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAA GGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAA GAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGAC ACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG

In embodiments, additional exemplary BCMA CAR constructs are generated using the VH and VL sequences from PCT Publication WO2012/0163805 (the contents of which are hereby incorporated by reference in its entirety), e.g., based upon the results from the pBCMA3 and pBCMA4 CARs described in Examples 2 and 3. A schematic of the exemplary BCMA constructs (BCMA-3NP and BCMA-4NP) is shown in Figure 10A. The two constructs differ in the orientation of the VH and VL chains (Fig. 10B). Exemplary BCMA CAR constructs and their corresponding DNA ID are shown below in Table 3.

Table 3. Tool CAR construct IDs

Nickname	Novartis ID	DNA2.0 ID
BCMA-3NP		126022
BCMA-4NP		126021

In embodiments, additional exemplary BCMA CAR constructs can also be generated using the VH and VL sequences found in Table 16. The amino acid sequences of exemplary scFv domains comprising the VH and VL domains and a linker sequence, and full-length CARs are also found in Table 16.

Table 16. Additional exemplary BCMA CAR sequences

Name	Sequence	SEQ ID NO:

A7D12.2 VH	QIQLVQSGPDLKKPGETVKLSCKASGYTFTNFGMNWVKQAPGKGFKWMAWINTYTGESYFA DDFKGRFAFSVETSATTAYLQINNLKTEDTATYFCARGEIYYGYDGGFAYWGQGTLVTVSA	255
A7D12.2 VL	DVVMTQSHRFMSTSVGDRVSITCRASQDVNTAVSWYQQKPGQSPKLLIFSASYRYTGVPDR FTGSGSGADFTLTISSVQAEDLAVYYCQQHYSTPWTFGGGTKLDIK	259
A7D12.2 scFv domain	QIQLVQSGPDLKKPGETVKLSCKASGYTFTNFGMNWVKQAPGKGFKWMAWINTYTGESYFA DDFKGRFAFSVETSATTAYLQINNLKTEDTATYFCARGEIYYGYDGGFAYWGQGTLVTVSA GGGGSGGGGSGGGGSDVVMTQSHRFMSTSVGDRVSITCRASQDVNTAVSWYQQKPGQSPKL LIFSASYRYTGVPDRFTGSGSGADFTLTISSVQAEDLAVYYCQQHYSTPWTFGGGTKLDIK	263
A7D12.2 Full CART	QIQLVQSGPDLKKPGETVKLSCKASGYTFTNFGMNWVKQAPGKGFKWMAWINTYTGESYFA DDFKGRFAFSVETSATTAYLQINNLKTEDTATYFCARGEIYYGYDGGFAYWGQGTLVTVSA GGGGSGGGGSGGGGSDVVMTQSHRFMSTSVGDRVSITCRASQDVNTAVSWYQQKPGQSPKL LIFSASYRYTGVPDRFTGSGSGADFTLTISSVQAEDLAVYYCQQHYSTPWTFGGGTKLDIK TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAP AYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYS EIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	267
C11D5.3 VH	QIQLVQSGPELKKPGETVKISCKASGYTFTDYSINWVKRAPGKGLKWMGWINTETREPAYA YDFRGRFAFSLETSASTAYLQINNLKYEDTATYFCALDYSYAMDYWGQGTSVTVSS	256
C11D5.3 VL	DIVLTQSPASLAMSLGKRATISCRASESVSVIGAHLIHWYQQKPGQPPKLLIYLASNLETG VPARFSGSGSGTDFTLTIDPVEEDDVAIYSCLQSRIFPRTFGGGTKLEIK	260
C11D5.3 scFv domain	QIQLVQSGPELKKPGETVKISCKASGYTFTDYSINWVKRAPGKGLKWMGWINTETREPAYA YDFRGRFAFSLETSASTAYLQINNLKYEDTATYFCALDYSYAMDYWGQGTSVTVSSGGGGS GGGGSGGGGSQIQLVQSGPELKKPGETVKISCKASGYTFTDYSINWVKRAPGKGLKWMGWI NTETREPAYAYDFRGRFAFSLETSASTAYLQINNLKYEDTATYFCALDYSYAMDYWGQGTS VTVSS	264
C11D5.3 Full CART	QIQLVQSGPELKKPGETVKISCKASGYTFTDYSINWVKRAPGKGLKWMGWINTETREPAYA YDFRGRFAFSLETSASTAYLQINNLKYEDTATYFCALDYSYAMDYWGQGTSVTVSSGGGGS GGGGSGGGGSQIQLVQSGPELKKPGETVKISCKASGYTFTDYSINWVKRAPGKGLKWMGWI NTETREPAYAYDFRGRFAFSLETSASTAYLQINNLKYEDTATYFCALDYSYAMDYWGQGTS VTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTC GVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSR SADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	268
C12A3.2 VH	QIQLVQSGPELKKPGETVKISCKASGYTFRHYSMNWVKQAPGKGLKWMGRINTESGVPIYA DDFKGRFAFSVETSASTAYLVINNLKDEDTASYFCSNDYLYSLDFWGQGTALTVSS	257
C12A3.2 VL	DIVLTQSPPSLAMSLGKRATISCRASESVTILGSHLIYWYQQKPGQPPTLLIQLASNVQTG VPARFSGSGSRTDFTLTIDPVEEDDVAVYYCLQSRTIPRTFGGGTKLEIK	261
C12A3.2 scFv domain	QIQLVQSGPELKKPGETVKISCKASGYTFRHYSMNWVKQAPGKGLKWMGRINTESGVPIYA DDFKGRFAFSVETSASTAYLVINNLKDEDTASYFCSNDYLYSLDFWGQGTALTVSSGGGGS GGGGSGGGGSDIVLTQSPPSLAMSLGKRATISCRASESVTILGSHLIYWYQQKPGQPPTLL IQLASNVQTGVPARFSGSGSRTDFTLTIDPVEEDDVAVYYCLQSRTIPRTFGGGTKLEIK	265
C12A3.2 Full CART	QIQLVQSGPELKKPGETVKISCKASGYTFRHYSMNWVKQAPGKGLKWMGRINTESGVPIYA DDFKGRFAFSVETSASTAYLVINNLKDEDTASYFCSNDYLYSLDFWGQGTALTVSSGGGGS GGGGSGGGGSDIVLTQSPPSLAMSLGKRATISCRASESVTILGSHLIYWYQQKPGQPPTLL IQLASNVQTGVPARFSGSGSRTDFTLTIDPVEEDDVAVYYCLQSRTIPRTFGGGTKLEIKT TTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLS LVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPA YKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE	269

	IGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	
C13F12.1 VH	QIQLVQSGPELKKPGETVKISCKASGYTFTHYSMNWVKQAPGKGLKWMGRINTETGEPLYA DDFKGRFAFSLETSASTAYLVINNLKNEDTATFFCSNDYLYSCDYWGQGTTLTVSS	258
C13F12.1 VL	DIVLTQSPPSLAMSLGKRATISCRASESVTILGSHLIYWYQQKPGQPPTLLIQLASNVQTG VPARFSGSGSRTDFTLTIDPVEEDDVAVYYCLQSRTIPRTFGGGTKLEIK	262
C13F12.1 scFv domain	QIQLVQSGPELKKPGETVKISCKASGYTFTHYSMNWVKQAPGKGLKWMGRINTETGEPLYA DDFKGRFAFSLETSASTAYLVINNLKNEDTATFFCSNDYLYSCDYWGQGTTLTVSSGGGGS GGGGSGGGGSDIVLTQSPPSLAMSLGKRATISCRASESVTILGSHLIYWYQQKPGQPPTLL IQLASNVQTGVPARFSGSGSRTDFTLTIDPVEEDDVAVYYCLQSRTIPRTFGGGTKLEIK	266
C13F12.1 Full CART	QIQLVQSGPELKKPGETVKISCKASGYTFTHYSMNWVKQAPGKGLKWMGRINTETGEPLYA DDFKGRFAFSLETSASTAYLVINNLKNEDTATFFCSNDYLYSCDYWGQGTTLTVSSGGGGS GGGGSGGGGSDIVLTQSPPSLAMSLGKRATISCRASESVTILGSHLIYWYQQKPGQPPTLL IQLASNVQTGVPARFSGSGSRTDFTLTIDPVEEDDVAVYYCLQSRTIPRTFGGGTKLEIKT TTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLS LVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPA YKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE IGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	270

In embodiments, the nucleic acid sequence of an exemplary humanized anti-BCMA scFv in which VH precedes the VL (H2L, e.g., pBCMA 2 and pBCMA 4) is as follows:

CAGGTGCAGCTGGTCCAGAGCGGCGCCGAAGTGAAGAAGCCCGGCAGCTCCGTGAAAGTGAGCTGCAAG
GCCAGCGGCGGCACCTTCAGCAACTACTGGATGCACTGGGTGAGGCAGGCCCCCGGACAGGGCCTGGAG
TGGATGGGCGCCACCTACAGGGGCCACAGCGACACCTACTACAACCAGAAGTTCAAGGGCCGGGTGACC
ATCACCGCCGACAAGAGCACCAGCACCGCCTACATGGAACTGAGCAGCCTCAGGAGCGAGGACACCGCT
GTGTATTACTGCGCCAGGGGCGCCATCTACAACGGCTACGACGTGCTGGACAACTGGGGCCAGGGCACA
CTAGTGACCGTGTCCAGCGGTGGAGGAGGTAGCGGAGGAGGCGGGAGCGGTGGAGGTGGCTCTGGAGGT
GGCGGAAGCGACATCCAGATGACCCAGAGCCCTAGCTCACTGAGCGCCAGCGTGGGCGACAGGGTGACC
ATTACCTGCTCCGCCAGCCAGGACATCAGCAACTACCTGAACTGGTACCAGCAGAAGCCCGGCAAGGCC
CCCAAGCTGCTGATCTACTACACCTCCAACCTGCACTCCGGCGTGCCCAGCAGGTTCAGCGGAAGCGGC
AGCGGCACCGATTTCACCCTGACCATCTCCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAG
CAGTACAGGAAGCTCCCCTGGACTTTCGGCCAGGGCACCAAACTGGAGATCAAGCGT
(SEQ ID NO: 272)

The corresponding amino acid sequence for the exemplary humanized anti-BCMA scFv in which Vh precedes the VL (H2L, e.g., pBCMA 2 and pBCMA 4) is as follows:

Q V Q L V Q S G A E V K K P G S S V K V S C K A S G G T F S N Y W M H W V R
Q A P G Q G L E W M G A T Y R G H S D T Y Y N Q K F K G R V T I T A D K S T
S T A Y M E L S S L R S E D T A V Y Y C A R G A I Y N G Y D V L D N W G Q G
T L V T V S S G G G G S G G G G S G G G G S G G G G S D I Q M T Q S P S S L
S A S V G D R V T I T C S A S Q D I S N Y L N W Y Q Q K P G K A P K L L I Y
Y T S N L H S G V P S R F S G S G S G T D F T L T I S S L Q P E D F A T Y Y
C Q Q Y R K L P W T F G Q G T K L E I K R (SEQ ID NO: 271)

In embodiments, the nucleic acid sequence of an exemplary humanized anti-BCMA scFv in which VL precedes the VH (L2H, e.g., pBCMA1 and pBCMA3) is as follows:

GACATCCAGATGACCCAGAGCCCTAGCTCACTGAGCGCCAGCGTGGGCGACAGGGTGACCATTACCTGC
TCCGCCAGCCAGGACATCAGCAACTACCTGAACTGGTACCAGCAGAAGCCCGGCAAGGCCCCCAAGCTG
CTGATCTACTACACCTCCAACCTGCACTCCGGCGTGCCCAGCAGGTTCAGCGGAAGCGGCAGCGGCACC
GATTTCACCCTGACCATCTCCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGTACAGG
AAGCTCCCCTGGACTTTCGGCCAGGGCACCAAACTGGAGATCAAGCGTGGTGGAGGAGGTAGCGGAGGA
GGCGGGAGCGGTGGAGGTGGCTCTGGAGGTGGCGGAAGCCAGGTGCAGCTGGTCCAGAGCGGCGCCGAA
GTGAAGAAGCCCGGCAGCTCCGTGAAAGTGAGCTGCAAGGCCAGCGGCGGCACCTTCAGCAACTACTGG
ATGCACTGGGTGAGGCAGGCCCCCGGACAGGGCCTGGAGTGGATGGGCGCCACCTACAGGGGCCACAGC
GACACCTACTACAACCAGAAGTTCAAGGGCCGGGTGACCATCACCGCCGACAAGAGCACCAGCACCGCC
TACATGGAACTGAGCAGCCTCAGGAGCGAGGACACCGCTGTGTATTACTGCGCCAGGGGCGCCATCTAC
AACGGCTACGACGTGCTGGACAACTGGGGCCAGGGCACACTAGTGACCGTGTCCAGC
(SEQ ID NO: 274)

The corresponding amino acid sequence of the exemplary humanized anti-BCMA scFv in which VL precedes the VH (L2H, e.g., pBCMA1 and pBCMA3) is as follows:

DIQMTQSPSS LSASVGDRVT ITCSASQDIS NYLNWYQQKP GKAPKLLIYY TSNLHSGVPSRFSGSGSGTD FTLTISSLQP EDFATYYCQQ YRKLPWTFGQ GTKLEIKRGG GGSGGGGSGGGGSGGGGSQV QLVQSGAEVK KPGSSVKVSC KASGGTFSNY WMHWVRQAPG QGLEWMGATYRGHSDTYYNQ KFKGRVTITA DKSTSTAYME LSSLRSEDTA VYYCARGAIYNGYDVLDNWGQGTLVTVSS (SEQ ID NO: 273)

The CAR scFv fragments can be cloned into lentiviral vectors to create a full length CAR construct in a single coding frame, and using the EF1 alpha promoter for expression (SEQ ID NO: 11).

The CAR construct can include a Gly/Ser linker having one or more of the following sequences: GGGGS (SEQ ID NO:25); encompassing 1-6 "Gly Gly Gly Gly Ser" repeating units, e.g., GGGGSGGGGS GGGGSGGGGS GGGGSGGGGS (SEQ ID NO:26); GGGGSGGGGS GGGGSGGGGS (SEQ ID NO:27); GGGGSGGGGS GGGGS (SEQ ID NO:28); GGGS (SEQ ID NO:29); or encompassing 1-10 "Gly Gly Gly Ser" repeating units, e.g., GGGSGGGSGG GSGGGSGGGS GGGSGGGSGG GSGGGSGGGS (SEQ ID NO:38). In embodiments, the CAR construct include a poly A sequence, e.g., a sequence encompassing 50-5000 or 100-5000 adenines (e.g., SEQ ID NO:30, SEQ ID NO:33, SEQ ID NO:34 or SEQ ID NO:35), or a sequence encompassing 50-5000 thymines (e.g., SEQ ID NO:31, SEQ ID NO:32). Alternatively, the CAR construct can include, for example, a linker including the sequence GSTSGSGKPGSGEGSTKG (SEQ ID NO: 1108)

Bispecific CARs

In an embodiment a multispecific antibody molecule is a bispecific antibody molecule. A bispecific antibody has specificity for no more than two antigens. A bispecific antibody molecule is characterized by a first immunoglobulin variable domain sequence which has binding specificity for a first epitope and a second immunoglobulin variable domain sequence that has binding specificity for a second epitope. In an embodiment the first and second epitopes are on the same antigen, e.g., the same protein (or subunit of a multimeric protein). In an embodiment the first and second epitopes overlap. In an embodiment the first and second epitopes do not overlap. In an embodiment the first and second epitopes are on different antigens, e.g., different proteins (or different subunits of a multimeric protein). In an embodiment a bispecific antibody molecule comprises a heavy chain variable domain sequence and a light chain variable domain sequence which have binding specificity for a first epitope and a heavy chain variable domain sequence and a light chain variable domain sequence which have binding specificity for a second epitope. In an embodiment a bispecific antibody molecule comprises a half antibody having binding specificity for a first epitope and a half antibody having binding specificity for a second epitope. In an embodiment a bispecific antibody molecule comprises a half antibody, or fragment thereof, having binding specificity for a first epitope and a half antibody, or fragment thereof, having binding specificity for a second epitope. In an embodiment a bispecific antibody molecule comprises a scFv, or fragment thereof, have binding specificity for a first epitope and a scFv, or fragment thereof, have binding specificity for a second epitope.

In certain embodiments, the antibody molecule is a multi-specific (*e.g.*, a bispecific or a trispecific) antibody molecule. Protocols for generating bispecific or heterodimeric antibody molecules are known in the art; including but not limited to, for example, the "knob in a hole" approach described in, *e.g.*, US 5731168; the electrostatic steering Fc pairing as described in, *e.g.*, WO 09/089004, WO 06/106905 and WO 2010/129304; Strand Exchange Engineered Domains (SEED) heterodimer formation as described in, *e.g.*, WO 07/110205; Fab arm exchange as described in, *e.g.*, WO 08/119353, WO 2011/131746, and WO 2013/060867; double antibody conjugate, *e.g.*, by antibody cross-linking to generate a bi-specific structure

using a heterobifunctional reagent having an amine-reactive group and a sulfhydryl reactive group as described in, *e.g.*, US 4433059; bispecific antibody determinants generated by recombining half antibodies (heavy-light chain pairs or Fabs) from different antibodies through cycle of reduction and oxidation of disulfide bonds between the two heavy chains, as described in, *e.g.*, US 4444878; trifunctional antibodies, *e.g.*, three Fab' fragments cross-linked through sulfhdryl reactive groups, as described in, *e.g.*, US5273743; biosynthetic binding proteins, *e.g.*, pair of scFvs cross-linked through C-terminal tails preferably through disulfide or amine-reactive chemical cross-linking, as described in, *e.g.*, US5534254; bifunctional antibodies, *e.g.*, Fab fragments with different binding specificities dimerized through leucine zippers (*e.g.*, c-fos and c-jun) that have replaced the constant domain, as described in, *e.g.*, US5582996; bispecific and oligospecific mono-and oligovalent receptors, *e.g.*, VH-CH1 regions of two antibodies (two Fab fragments) linked through a polypeptide spacer between the CH1 region of one antibody and the VH region of the other antibody typically with associated light chains, as described in, *e.g.*, US5591828; bispecific DNA-antibody conjugates, *e.g.*, crosslinking of antibodies or Fab fragments through a double stranded piece of DNA, as described in, *e.g.*, US5635602; bispecific fusion proteins, *e.g.*, an expression construct containing two scFvs with a hydrophilic helical peptide linker between them and a full constant region, as described in, *e.g.*, US5637481; multivalent and multispecific binding proteins, *e.g.*, dimer of polypeptides having first domain with binding region of Ig heavy chain variable region, and second domain with binding region of Ig light chain variable region, generally termed diabodies (higher order structures are also encompassed creating for bispecifc, trispecific, or tetraspecific molecules, as described in, *e.g.*, US5837242; minibody constructs with linked VL and VH chains further connected with peptide spacers to an antibody hinge region and CH3 region, which can be dimerized to form bispecific/multivalent molecules, as described in, *e.g.*, US5837821; VH and VL domains linked with a short peptide linker (*e.g.*, 5 or 10 amino acids) or no linker at all in either orientation, which can form dimers to form bispecific diabodies; trimers and tetramers, as described in, *e.g.*, US5844094; String of VH domains (or VL domains in family members) connected by peptide linkages with crosslinkable groups at the C-terminus futher associated with VL domains to form a series of FVs (or scFvs), as described in, *e.g.*, US5864019; and single chain binding polypeptides with both a VH and a VL domain linked through a peptide linker are combined into multivalent structures through non-covalent or chemical crosslinking to form, *e.g.*, homobivalent, heterobivalent, trivalent, and tetravalent structures using both scFV

or diabody type format, as described in, *e.g.*, US5869620. Additional exemplary multispecific and bispecific molecules and methods of making the same are found, for example, in US5910573, US5932448, US5959083, US5989830, US6005079, US6239259, US6294353, US6333396, US6476198, US6511663, US6670453, US6743896, US6809185, US6833441, US7129330, US7183076, US7521056, US7527787, US7534866, US7612181, US2002004587A1, US2002076406A1, US2002103345A1, US2003207346A1, US2003211078A1, US2004219643A1, US2004220388A1, US2004242847A1, US2005003403A1, US2005004352A1, US2005069552A1, US2005079170A1, US2005100543A1, US2005136049A1, US2005136051A1, US2005163782A1, US2005266425A1, US2006083747A1, US2006120960A1, US2006204493A1, US2006263367A1, US2007004909A1, US2007087381A1, US2007128150A1, US2007141049A1, US2007154901A1, US2007274985A1, US2008050370A1, US2008069820A1, US2008152645A1, US2008171855A1, US2008241884A1, US2008254512A1, US2008260738A1, US2009130106A1, US2009148905A1, US2009155275A1, US2009162359A1, US2009162360A1, US2009175851A1, US2009175867A1, US2009232811A1, US2009234105A1, US2009263392A1, US2009274649A1, EP346087A2, WO0006605A2, WO02072635A2, WO04081051A1, WO06020258A2, WO2007044887A2, WO2007095338A2, WO2007137760A2, WO2008119353A1, WO2009021754A2, WO2009068630A1, WO9103493A1, WO9323537A1, WO9409131A1, WO9412625A2, WO9509917A1, WO9637621A2, WO9964460A1. The contents of the above-referenced applications are incorporated herein by reference in their entireties.

Within each antibody or antibody fragment (e.g., scFv) of a bispecific antibody molecule, the VH can be upstream or downstream of the VL. In some embodiments, the upstream antibody or antibody fragment (e.g., scFv) is arranged with its VH (VH_1) upstream of its VL (VL_1) and the downstream antibody or antibody fragment (e.g., scFv) is arranged with its VL (VL_2) upstream of its VH (VH_2), such that the overall bispecific antibody molecule has the arrangement VH_1-VL_1-VL_2-VH_2. In other embodiments, the upstream antibody or antibody fragment (e.g., scFv) is arranged with its VL (VL_1) upstream of its VH (VH_1) and the downstream antibody or antibody fragment (e.g., scFv) is arranged with its VH (VH_2) upstream of its VL (VL_2), such that the overall bispecific antibody molecule has the arrangement VL_1-

VH_1-VH_2-VL_2. Optionally, a linker is disposed between the two antibodies or antibody fragments (e.g., scFvs), e.g., between VL_1 and VL_2 if the construct is arranged as VH_1-VL_1-VL_2-VH_2, or between VH_1 and VH_2 if the construct is arranged as VL_1-VH_1-VH_2-VL_2. The linker may be a linker as described herein, e.g., a (Gly_4-Ser)n linker, wherein n is 1, 2, 3, 4, 5, or 6, preferably 4 (SEQ ID NO: 26). In general, the linker between the two scFvs should be long enough to avoid mispairing between the domains of the two scFvs. Optionally, a linker is disposed between the VL and VH of the first scFv. Optionally, a linker is disposed between the VL and VH of the second scFv. In constructs that have multiple linkers, any two or more of the linkers can be the same or different. Accordingly, in some embodiments, a bispecific CAR comprises VLs, VHs, and optionally one or more linkers in an arrangement as described herein.

In one aspect, the bispecific antibody molecule is characterized by a first immunoglobulin variable domain sequence, e.g., a scFv, which has binding specificity for BCMA, e.g., comprises a scFv as described herein, e.g., as described in Table 1 or Table 16, or comprises the light chain CDRs and/or heavy chain CDRs from a BCMA scFv described herein, and a second immunoglobulin variable domain sequence that has binding specificity for a second epitope on a different antigen. In some aspects the second immunoglobulin variable domain sequence has binding specificity for an antigen expressed on AML cells, e.g., an antigen other than BCMA. For example, the second immunoglobulin variable domain sequence has binding specificity for CD123. As another example, the second immunoglobulin variable domain sequence has binding specificity for CLL-1. As another example, the second immunoglobulin variable domain sequence has binding specificity for CD34. As another example, the second immunoglobulin variable domain sequence has binding specificity for FLT3. For example, the second immunoglobulin variable domain sequence has binding specificity for folate receptor beta. In some aspects, the second immunoglobulin variable domain sequence has binding specificity for an antigen expressed on B-cells, for example, CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a.

Chimeric TCR

In one aspect, the anti-BCMA antibodies and antibody fragments of the present invention (for example, those disclosed in Tables 1 and 16) can be grafted to one or more constant domain of a T cell receptor ("TCR") chain, for example, a TCR alpha or TCR beta chain, to create an chimeric TCR that binds specificity to BCMA. Without being bound by

theory, it is believed that chimeric TCRs will signal through the TCR complex upon antigen binding. For example, a BCMA scFv as disclosed herein, can be grafted to the constant domain, e.g., at least a portion of the extracellular constant domain, the transmembrane domain and the cytoplasmic domain, of a TCR chain, for example, the TCR alpha chain and/or the TCR beta chain. As another example, a BCMA antibody fragment, for example a VL domain as described herein, can be grafted to the constant domain of a TCR alpha chain, and a BCMA antibody fragment, for example a VH domain as described herein, can be grafted to the constant domain of a TCR beta chain (or alternatively, a VL domain may be grafted to the constant domain of the TCR beta chain and a VH domain may be grafted to a TCR alpha chain). As another example, the CDRs of an anti-BCMA antibody or antibody fragment, e.g., the CDRs of an anti-BCMA antibody or antibody fragment as described in Tables 20, 21, 22, 23, 24, or 25 may be grafted into a TCR alpha and/or beta chain to create a chimeric TCR that binds specifically to BCMA. For example, the LCDRs disclosed herein may be grafted into the variable domain of a TCR alpha chain and the HCDRs disclosed herein may be grafted to the variable domain of a TCR beta chain, or vice versa. Such chimeric TCRs may be produced by methods known in the art (For example, Willemsen RA et al, Gene Therapy 2000; 7: 1369–1377; Zhang T et al, Cancer Gene Ther 2004; 11: 487–496; Aggen et al, Gene Ther. 2012 Apr;19(4):365-74).

Transmembrane domain

With respect to the transmembrane domain, in various embodiments, a CAR can be designed to comprise a transmembrane domain that is attached to the extracellular domain of the CAR. A transmembrane domain can include one or more additional amino acids adjacent to the transmembrane region, e.g., one or more amino acid associated with the extracellular region of the protein from which the transmembrane was derived (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 up to 15 amino acids of the extracellular region) and/or one or more additional amino acids associated with the intracellular region of the protein from which the transmembrane protein is derived (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 up to 15 amino acids of the intracellular region). In one aspect, the transmembrane domain is one that is associated with one of the otherdomains of the CAR is used. In some instances, the transmembrane domain can be selected or modified by amino acid substitution to avoid binding of such domains to the transmembrane domains of the

same or different surface membrane proteins, e.g., to minimize interactions with other members of the receptor complex. In one aspect, the transmembrane domain is capable of homodimerization with another CAR on the CAR-expressing cell, e.g., CART cell, surface. In a different aspect the amino acid sequence of the transmembrane domain may be modified or substituted so as to minimize interactions with the binding domains of the native binding partner present in the same CAR-expressing cell, e.g., CART.

The transmembrane domain may be derived either from a natural or from a recombinant source. Where the source is natural, the domain may be derived from any membrane-bound or transmembrane protein. In one aspect the transmembrane domain is capable of signaling to the intracellular domain(s) whenever the CAR has bound to a target. A transmembrane domain of particular use in this invention may include at least the transmembrane region(s) of e.g., the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8 (e.g., CD8 alpha, CD8 beta), CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154. In some embodiments, a transmembrane domain may include at least the transmembrane region(s) of a costimulatory molecule, e.g., MHC class I molecule, TNF receptor proteins, Immunoglobulin-like proteins, cytokine receptors, integrins, signaling lymphocytic activation molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, and a ligand that specifically binds with CD83.

In some instances, the transmembrane domain can be attached to the extracellular region of the CAR, e.g., the antigen binding domain of the CAR, via a hinge, e.g., a hinge from

a human protein. For example, in one embodiment, the hinge can be a human Ig (immunoglobulin) hinge, e.g., an IgG4 hinge, or a CD8a hinge. In one embodiment, the hinge or spacer comprises (e.g., consists of) the amino acid sequence of SEQ ID NO:2. In one aspect, the transmembrane domain comprises (e.g., consists of) a transmembrane domain of SEQ ID NO: 6.

In one aspect, the hinge or spacer comprises an IgG4 hinge. For example, in one embodiment, the hinge or spacer comprises a hinge of the amino acid sequence ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKM (SEQ ID NO:3). In some embodiments, the hinge or spacer comprises a hinge encoded by a nucleotide sequence of GAGAGCAAGTACGGCCCTCCCTGCCCCCCTTGCCCTGCCCCCGAGTTCCTGGGCGG ACCCAGCGTGTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCCGGA CCCCCGAGGTGACCTGTGTGGTGGTGGACGTGTCCCAGGAGGACCCCGAGGTCCA GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCCCGG GAGGAGCAGTTCAATAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCA GGACTGGCTGAACGGCAAGGAATACAAGTGTAAGGTGTCCAACAAGGGCCTGCCC AGCAGCATCGAGAAAACCATCAGCAAGGCCAAGGGCCAGCCTCGGGAGCCCCAGG TGTACACCCTGCCCCCTAGCCAAGAGGAGATGACCAAGAACCAGGTGTCCCTGAC CTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAAC GGCCAGCCCGAGAACAACTACAAGACCACCCCCCCTGTGCTGGACAGCGACGGCA GCTTCTTCCTGTACAGCCGGCTGACCGTGGACAAGAGCCGGTGGCAGGAGGGCAA CGTCTTTAGCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGA GCCTGAGCCTGTCCCTGGGCAAGATG (SEQ ID NO:14).

In one aspect, the hinge or spacer comprises an IgD hinge. For example, in one embodiment, the hinge or spacer comprises a hinge of the amino acid sequence RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGRGGEEKKKEKEKEEQEERET KTPECPSHTQPLGVYLLTPAVQDLWLRDKATFTCFVVGSDLKDAHLTWEVAGKVPTG GVEEGLLERHSNGSQSQHSRLTLPRSLWNAGTSVTCTLNHPSLPPQRLMALREPAAQA

PVKLSLNLLASSDPPEAASWLLCEVSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPG STTFWAWSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVSYVTDH (SEQ ID NO:4). In some embodiments, the hinge or spacer comprises a hinge encoded by a nucleotide sequence of AGGTGGCCCGAAAGTCCCAAGGCCCAGGCATCTAGTGTTCCTACTGCACAGCCCCA GGCAGAAGGCAGCCTAGCCAAAGCTACTACTGCACCTGCCACTACGCGCAATACT GGCCGTGGCGGGGAGGAGAAGAAAAAGGAGAAAGAGAAAGAAGAACAGGAAGA GAGGGAGACCAAGACCCCTGAATGTCCATCCCATACCCAGCCGCTGGGCGTCTATC TCTTGACTCCCGCAGTACAGGACTTGTGGCTTAGAGATAAGGCCACCTTTACATGT TTCGTCGTGGGCTCTGACCTGAAGGATGCCCATTTGACTTGGGAGGTTGCCGGAAA GGTACCCACAGGGGGGGTTGAGGAAGGGTTGCTGGAGCGCCATTCCAATGGCTCT CAGAGCCAGCACTCAAGACTCACCCTTCCGAGATCCCTGTGGAACGCCGGGACCTC TGTCACATGTACTCTAAATCATCCTAGCCTGCCCCCACAGCGTCTGATGGCCCTTAG AGAGCCAGCCGCCCAGGCACCAGTTAAGCTTAGCCTGAATCTGCTCGCCAGTAGTG ATCCCCCAGAGGCCGCCAGCTGGCTCTTATGCGAAGTGTCCGGCTTTAGCCCGCCC AACATCTTGCTCATGTGGCTGGAGGACCAGCGAGAAGTGAACACCAGCGGCTTCG CTCCAGCCCGGCCCCCACCCCAGCCGGGTTCTACCACATTCTGGGCCTGGAGTGTC TTAAGGGTCCCAGCACCACCTAGCCCCCAGCCAGCCACATACACCTGTGTTGTGTC CCATGAAGATAGCAGGACCCTGCTAAATGCTTCTAGGAGTCTGGAGGTTTCCTACG TGACTGACCATT (SEQ ID NO:15).

In one aspect, the transmembrane domain may be recombinant, in which case it will comprise predominantly hydrophobic residues such as leucine and valine. In one aspect a triplet of phenylalanine, tryptophan and valine can be found at each end of a recombinant transmembrane domain.

Optionally, a short oligo- or polypeptide linker, between 2 and 10 amino acids in length may form the linkage between the transmembrane domain and the cytoplasmic region of the CAR. A glycine-serine doublet provides a particularly suitable linker. For example, in one aspect, the linker comprises the amino acid sequence of GGGGSGGGGS (SEQ ID NO:5). In some embodiments, the linker is encoded by a nucleotide sequence of GGTGGCGGAGGTTCTGGAGGTGGAGGTTCC (SEQ ID NO:16).

In one aspect, the hinge or spacer comprises a KIR2DS2 hinge.

Cytoplasmic domain

The cytoplasmic domain or region of a CAR of the present invention includes an intracellular signaling domain. An intracellular signaling domain is generally responsible for activation of at least one of the normal effector functions of the immune cell in which the CAR has been introduced.

Examples of intracellular signaling domains for use in the CAR of the invention include the cytoplasmic sequences of the T cell receptor (TCR) and co-receptors that act in concert to initiate signal transduction following antigen receptor engagement, as well as any derivative or variant of these sequences and any recombinant sequence that has the same functional capability.

It is known that signals generated through the TCR alone are insufficient for full activation of the T cell and that a secondary and/or costimulatory signal is also required. Thus, T cell activation can be said to be mediated by two distinct classes of cytoplasmic signaling sequences: those that initiate antigen-dependent primary activation through the TCR (primary intracellular signaling domains) and those that act in an antigen-independent manner to provide a secondary or costimulatory signal (secondary cytoplasmic domain, e.g., a costimulatory domain).

A primary signaling domain regulates primary activation of the TCR complex either in a stimulatory way, or in an inhibitory way. Primary intracellular signaling domains that act in a stimulatory manner may contain signaling motifs which are known as immunoreceptor tyrosine-based activation motifs or ITAMs.

Examples of ITAM containing primary intracellular signaling domains that are of particular use in the invention include those of TCR zeta, FcR gamma, FcR beta, CD3 gamma, CD3 delta , CD3 epsilon, CD5, CD22, CD79a, CD79b, CD278 (also known as "ICOS"), FcεRI, DAP10, DAP12, and CD66d. In one embodiment, a CAR of the invention comprises an intracellular signaling domain, e.g., a primary signaling domain of CD3-zeta.

In one embodiment, a primary signaling domain comprises a modified ITAM domain, e.g., a mutated ITAM domain which has altered (e.g., increased or decreased) activity as compared to the native ITAM domain. In one embodiment, a primary signaling domain comprises a modified ITAM-containing primary intracellular signaling domain, e.g., an

optimized and/or truncated ITAM-containing primary intracellular signaling domain. In an embodiment, a primary signaling domain comprises one, two, three, four or more ITAM motifs.

Further examples of molecules containing a primary intracellular signaling domain that are of particular use in the invention include those of DAP10, DAP12, and CD32.

The intracellular signalling domain of the CAR can comprise the primary signalling domain, e.g., CD3-zeta signaling domain, by itself or it can be combined with any other desired intracellular signaling domain(s) useful in the context of a CAR of the invention. For example, the intracellular signaling domain of the CAR can comprise a primary signalling domain, e.g., CD3 zeta chain portion, and a costimulatory signaling domain. The costimulatory signaling domain refers to a portion of the CAR comprising the intracellular domain of a costimulatory molecule. A costimulatory molecule is a cell surface molecule other than an antigen receptor or its ligands that is required for an efficient response of lymphocytes to an antigen. Examples of such molecules include MHC class I molecule, TNF receptor proteins, Immunoglobulin-like proteins, cytokine receptors, integrins, signaling lymphocytic activation molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, and a ligand that specifically binds with CD83, and the like. For example, CD27 costimulation has been demonstrated to enhance expansion, effector function, and survival of human CART cells in vitro and augments human T cell persistence and antitumor activity in vivo (Song et al. Blood. 2012; 119(3):696-706). The intracellular signaling sequences within the cytoplasmic portion of the CAR of the invention may be linked to each other in a random or specified order. Optionally, a short oligo-

or polypeptide linker, for example, between 2 and 10 amino acids (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids) in length may form the linkage between intracellular signaling sequence. In one embodiment, a glycine-serine doublet can be used as a suitable linker. In one embodiment, a single amino acid, e.g., an alanine, a glycine, can be used as a suitable linker.

In one aspect, the intracellular signaling domain is designed to comprise two or more, e.g., 2, 3, 4, 5, or more, costimulatory signaling domains. In an embodiment, the two or more, e.g., 2, 3, 4, 5, or more, costimulatory signaling domains, are separated by a linker molecule, e.g., a linker molecule described herein. In one embodiment, the intracellular signaling domain comprises two costimulatory signaling domains. In some embodiments, the linker molecule is a glycine residue. In some embodiments, the linker is an alanine residue.

In one aspect, the intracellular signaling domain is designed to comprise the signaling domain of CD3-zeta and the signaling domain of CD28. In one aspect, the intracellular signaling domain is designed to comprise the signaling domain of CD3-zeta and the signaling domain of 4-1BB. In one aspect, the signaling domain of 4-1BB is a signaling domain of SEQ ID NO: 7. In one aspect, the signaling domain of CD3-zeta is a signaling domain of SEQ ID NO: 9 (mutant CD3zeta) or SEQ ID NO: 10 (wild type human CD3zeta).

In one aspect, the intracellular signaling domain is designed to comprise the signaling domain of CD3-zeta and the signaling domain of CD27. In one aspect, the signaling domain of CD27 comprises an amino acid sequence of QRRKYRSNKGESPVEPAEPCRYSCPREEEGSTIPIQEDYRKPEPACSP (SEQ ID NO:8). In one aspect, the signalling domain of CD27 is encoded by a nucleic acid sequence of AGGAGTAAGAGGAGCAGGCTCCTGCACAGTGACTACATGAACATGACTCCCCGCC GCCCCGGGCCCACCCGCAAGCATTACCAGCCCTATGCCCCACCACGCGACTTCGCA GCCTATCGCTCC (SEQ ID NO:19).

In one aspect, the intracellular is designed to comprise the signaling domain of CD3-zeta and the signaling domain of CD28. In one aspect, the signaling domain of CD28 comprises an amino acid sequence of SEQ ID NO: 1104. In one aspect, the signaling domain of CD28 is encoded by a nucleic acid sequence of SEQ ID NO: 1105.

In one aspect, the intracellular is designed to comprise the signaling domain of CD3-zeta and the signaling domain of ICOS. In one aspect, the signaling domain of ICOS

comprises an amino acid sequence of SEQ ID NO: 1106. In one aspect, the signaling domain of ICOS is encoded by a nucleic acid sequence of SEQ ID NO: 1107.

In one aspect, the CAR-expressing cell described herein can further comprise a second CAR, e.g., a second CAR that includes a different antigen binding domain, e.g., to the same target (BCMA) or a different target (e.g., CD19, CD20, or CS-1, or other multiple myeloma targets, e.g., kappa light chain, CD138, Lewis Y antigen, or CD38 (Garfall et al., Discovery Medicine, 2014, 17(91):37-46)). In one embodiment, the CAR-expressing cell comprises a first CAR that targets a first antigen and includes an intracellular signaling domain having a costimulatory signaling domain but not a primary signaling domain, and a second CAR that targets a second, different, antigen and includes an intracellular signaling domain having a primary signaling domain but not a costimulatory signaling domain. While not wishing to be bound by theory, placement of a costimulatory signaling domain, e.g., 4-1BB, CD28, CD27 ICOS, or OX-40, onto the first CAR, and the primary signaling domain, e.g., CD3 zeta, on the second CAR can limit the CAR activity to cells where both targets are expressed. In one embodiment, the CAR expressing cell comprises a first BCMA CAR that includes a BCMA binding domain, a transmembrane domain and a costimulatory domain and a second CAR that targets an antigen other than BCMA (e.g., an antigen expressed on leukemia or lymphoma cells, e.g., CD19, CD20, CS-1, kappa light chain, CD139, Lewis Y antigen, or CD38) and includes an antigen binding domain, a transmembrane domain and a primary signaling domain. In another embodiment, the CAR expressing cell comprises a first BCMA CAR that includes a BCMA binding domain, a transmembrane domain and a primary signaling domain and a second CAR that targets an antigen other than BCMA (e.g., an antigen expressed on leukemia or lymphoma cells, e.g., CD19, CD20, CS-1, kappa light chain, CD139, Lewis Y antigen, or CD38) and includes an antigen binding domain to the antigen, a transmembrane domain and a costimulatory signaling domain. In one embodiment, the CAR-expressing cell comprises a BCMA CAR described herein and a CAR that targets CD19 (CD19 CAR).

In one embodiment, the CAR-expressing cell comprises a BCMA CAR described herein and an inhibitory CAR. In one embodiment, the inhibitory CAR comprises an antigen binding domain that binds an antigen found on normal cells but not cancer cells, e.g., normal cells that also express mesothelin. In one embodiment, the inhibitory CAR comprises the

antigen binding domain, a transmembrane domain and an intracellular domain of an inhibitory molecule. For example, the intracellular domain of the inhibitory CAR can be an intracellular domain of PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGFR beta.

In one embodiment, when the CAR-expressing cell comprises two or more different CARs, the antigen binding domains of the different CARs can be such that the antigen binding domains do not interact with one another. For example, a cell expressing a first and second CAR can have an antigen binding domain of the first CAR, e.g., as a fragment, e.g., an scFv, that does not form an association with the antigen binding domain of the second CAR, e.g., the antigen binding domain of the second CAR is a VHH.

In some embodiments, the antigen binding domain comprises a single domain antigen binding (SDAB) molecules include molecules whose complementary determining regions are part of a single domain polypeptide. Examples include, but are not limited to, heavy chain variable domains, binding molecules naturally devoid of light chains, single domains derived from conventional 4-chain antibodies, engineered domains and single domain scaffolds other than those derived from antibodies. SDAB molecules may be any of the art, or any future single domain molecules. SDAB molecules may be derived from any species including, but not limited to mouse, human, camel, llama, lamprey, fish, shark, goat, rabbit, and bovine. This term also includes naturally occurring single domain antibody molecules from species other than Camelidae and sharks.

In one aspect, an SDAB molecule can be derived from a variable region of the immunoglobulin found in fish, such as, for example, that which is derived from the immunoglobulin isotype known as Novel Antigen Receptor (NAR) found in the serum of shark. Methods of producing single domain molecules derived from a variable region of NAR ("IgNARs") are described in WO 03/014161 and Streltsov (2005) Protein Sci. 14:2901-2909.

According to another aspect, an SDAB molecule is a naturally occurring single domain antigen binding molecule known as heavy chain devoid of light chains. Such single domain molecules are disclosed in WO 9404678 and Hamers-Casterman, C. et al. (1993) Nature

363:446-448, for example. For clarity reasons, this variable domain derived from a heavy chain molecule naturally devoid of light chain is known herein as a VHH or nanobody to distinguish it from the conventional VH of four chain immunoglobulins. Such a VHH molecule can be derived from Camelidae species, for example in camel, llama, dromedary, alpaca and guanaco. Other species besides Camelidae may produce heavy chain molecules naturally devoid of light chain; such VHHs are within the scope of the invention.

The SDAB molecules can be recombinant, CDR-grafted, humanized, camelized, de-immunized and/or in vitro generated (e.g., selected by phage display).

It has also been discovered, that cells having a plurality of chimeric membrane embedded receptors comprising an antigen binding domain that interactions between the antigen binding domain of the receptors can be undesirable, e.g., because it inhibits the ability of one or more of the antigen binding domains to bind its cognate antigen. Accordingly, disclosed herein are cells having a first and a second non-naturally occurring chimeric membrane embedded receptor comprising antigen binding domains that minimize such interactions. Also disclosed herein are nucleic acids encoding a first and a second non-naturally occurring chimeric membrane embedded receptor comprising a antigen binding domains that minimize such interactions, as well as methods of making and using such cells and nucleic acids. In an embodiment the antigen binding domain of one of said first said second non-naturally occurring chimeric membrane embedded receptor, comprises an scFv, and the other comprises a single VH domain, e.g., a camelid, shark, or lamprey single VH domain, or a single VH domain derived from a human or mouse sequence.

In some embodiments, the claimed invention comprises a first and second CAR, wherein the antigen binding domain of one of said first CAR said second CAR does not comprise a variable light domain and a variable heavy domain. In some embodiments, the antigen binding domain of one of said first CAR said second CAR is an scFv, and the other is not an scFv. In some embodiments, the antigen binding domain of one of said first CAR said second CAR comprises a single VH domain, e.g., a camelid, shark, or lamprey single VH domain, or a single VH domain derived from a human or mouse sequence. In some embodiments, the antigen binding domain of one of said first CAR said second CAR comprises a nanobody. In some embodiments, the antigen binding domain of one of said first CAR said second CAR comprises a camelid VHH domain.

In some embodiments, the antigen binding domain of one of said first CAR said second CAR comprises an scFv, and the other comprises a single VH domain, e.g., a camelid, shark, or lamprey single VH domain, or a single VH domain derived from a human or mouse sequence. In some embodiments, the antigen binding domain of one of said first CAR said second CAR comprises an scFv, and the other comprises a nanobody. In some embodiments, the antigen binding domain of one of said first CAR said second CAR comprises comprises an scFv, and the other comprises a camelid VHH domain.

In some embodiments, when present on the surface of a cell, binding of the antigen binding domain of said first CAR to its cognate antigen is not substantially reduced by the presence of said second CAR. In some embodiments, binding of the antigen binding domain of said first CAR to its cognate antigen in the presence of said second CAR is 85%, 90%, 95%, 96%, 97%, 98% or 99% of binding of the antigen binding domain of said first CAR to its cognate antigen in the absence of said second CAR.

In some embodiments, when present on the surface of a cell, the antigen binding domains of said first CAR said second CAR, associate with one another less than if both were scFv antigen binding domains. In some embodiments, the antigen binding domains of said first CAR said second CAR, associate with one another 85%, 90%, 95%, 96%, 97%, 98% or 99% less than if both were scFv antigen binding domains.

In another aspect, the CAR-expressing cell described herein can further express another agent, e.g., an agent which enhances the activity of a CAR-expressing cell. For example, in one embodiment, the agent can be an agent which inhibits an inhibitory molecule, e.g., an agent described herein. Inhibitory molecules, e.g., PD1, can, in some embodiments, decrease the ability of a CAR-expressing cell to mount an immune effector response. Examples of inhibitory molecules include PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGFR beta.In one embodiment, the agent which inhibits an inhibitory molecule comprises a first polypeptide, e.g., an inhibitory molecule, associated with a second polypeptide that provides a positive signal to the cell, e.g., an intracellular signaling domain described herein. In one embodiment, the agent comprises a first polypeptide, e.g., of an inhibitory molecule such as PD1, PD-L1, PD-L2, CTLA4, TIM3,

CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGFR beta, or a fragment of any of these (e.g., at least a portion of an extracellular domain of any of these), and a second polypeptide which is an intracellular signaling domain described herein (e.g., comprising a costimulatory domain (e.g., 41BB, CD27 ICOS, or CD28, e.g., as described herein) and/or a primary signaling domain (e.g., a CD3 zeta signaling domain described herein). In one embodiment, the agent comprises a first polypeptide of PD1 or a fragment thereof (e.g., at least a portion of an extracellular domain of PD1), and a second polypeptide of an intracellular signaling domain described herein (e.g., a CD28 signaling domain described herein and/or a CD3 zeta signaling domain described herein). In embodiments, the CAR-expressing cell described herein comprises a switch costimulatory receptor, e.g., as described in WO 2013/019615, which is incorporated herein by reference in its entirety. PD1 is an inhibitory member of the CD28 family of receptors that also includes CD28, CTLA-4, ICOS, and BTLA. PD-1 is expressed on activated B cells, T cells and myeloid cells (Agata et al. 1996 Int. Immunol 8:765-75). Two ligands for PD1, PD-L1 and PD-L2 have been shown to downregulate T cell activation upon binding to PD1 (Freeman et a. 2000 J Exp Med 192:1027-34; Latchman et al. 2001 Nat Immunol 2:261-8; Carter et al. 2002 Eur J Immunol 32:634-43). PD-L1 is abundant in human cancers (Dong et al. 2003 J Mol Med 81:281-7; Blank et al. 2005 Cancer Immunol. Immunother 54:307-314; Konishi et al. 2004 Clin Cancer Res 10:5094). Immune suppression can be reversed by inhibiting the local interaction of PD1 with PD-L1.

In one embodiment, the agent comprises the extracellular domain (ECD) of an inhibitory molecule, e.g., Programmed Death 1 (PD1), can be fused to a transmembrane domain and intracellular signaling domains such as 41BB and CD3 zeta (also referred to herein as a PD1 CAR). In one embodiment, the PD1 CAR, when used incombinations with a BCMA CAR described herein, improves the persistence of the CAR-expressing cell, e.g., T cell or NK cell. In one embodiment, the CAR is a PD1 CAR comprising the extracellular domain of PD1 indicated as underlined in SEQ ID NO: 24. In one embodiment, the PD1 CAR comprises the amino acid sequence of SEQ ID NO:24.

Malpvtalllplalllhaarppgwfldspdrpwnpptfspallvvtegdnatftcsfsntsesfvlnwyrmspsnqtdklaaf pedrsqpgqdcrfrvtqlpngrdfhmsvvrarrndsgtylcgaislapkaqikeslraelrvterraevptahpspsprpagqfqtlvttt

paprpptpaptiasqplslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqee dgcscrfpeeeeggcelrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkprrknpqeglynelqkdkma eayseigmkgerrrgkghdglyqglstatkdtydalhmqalppr (SEQ ID NO:24).

In one embodiment, the PD1 CAR comprises the amino acid sequence provided below (SEQ ID NO:22).

pgwfldspdrpwnpptfspallvvtegdnatftcsfsntsesfvlnwyrmspsnqtdklaafpedrsqpgqdcrfrvtqlp ngrdfhmsvvrarrndsgtylcgaislapkaqikeslraelrvterraevptahpspsprpagqfqtlvtttpaprpptpaptiasqplslr peacrpaaggavhtrgldfacdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeeggcelrv kfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkprrknpqeglynelqkdkmaeayseigmkgerrrgkgh dglyqglstatkdtydalhmqalppr (SEQ ID NO:22).

In one embodiment, the agent comprises a nucleic acid sequence encoding the PD1 CAR, e.g., the PD1 CAR described herein. In one embodiment, the nucleic acid sequence for the PD1 CAR is shown below, with the PD1 ECD underlined below in SEQ ID NO: 23

atggccctccctgtcactgccctgcttctccccctcgcactcctgctccacgccgctagaccacccggatggtttctggactctc cggatcgcccgtggaatcccccaaccttctcaccggcactcttggttgtgactgagggcgataatgcgaccttcacgtgctcgttctccaa cacctccgaatcattcgtgctgaactggtaccgcatgagcccgtcaaaccagaccgacaagctcgccgcgtttccggaagatcggtcgc aaccgggacaggattgtcggttccgcgtgactcaactgccgaatggcagagacttccacatgagcgtggtccgcgctaggcgaaacga ctccgggacctacctgtgcggagccatctcgctggcgcctaaggcccaaatcaaagagagcttgagggccgaactgagagtgaccga gcgcagagctgaggtgccaactgcacatccatccccatcgcctcggcctgcggggcagtttcagaccctggtcacgaccactccggcg ccgcgcccaccgactccggccccaactatcgcgagccagcccctgtcgctgaggccggaagcatgccgccctgccgccggaggtgc tgtgcatacccggggattggacttcgcatgcgacatctacatttgggctcctctcgccggaacttgtggcgtgctccttctgtccctggtcat caccctgtactgcaagcggggtcggaaaaagcttctgtacattttcaagcagcccttcatgaggcccgtgcaaaccacccaggaggagg acggttgctcctgccggttccccgaagaggaagaaggaggttgcgagctgcgcgtgaagttctcccggagcgccgacgcccccgcct ataagcagggccagaaccagctgtacaacgaactgaacctgggacggcgggaagagtacgatgtgctggacaagcggcgcggccg ggaccccgaaatgggcgggaagcctagaagaaagaaccctcaggaaggcctgtataacgagctgcagaaggacaagatggccgag gcctactccgaaattgggatgaagggagagcggcggaggggaaaggggcacgacggcctgtaccaaggactgtccaccgccacca aggacacatacgatgccctgcacatgcaggcccttcccccctcgc (SEQ ID NO: 23).

In another aspect, the present invention provides a population of CAR-expressing cells, e.g., CART cells or CAR-expressing NK cells. In some embodiments, the population of CAR-expressing cells comprises a mixture of cells expressing different CARs. For example, in one

embodiment, the population of CAR-expressing cells (e.g., CART cells or CAR-expressing NK cells) can include a first cell expressing a CAR having an anti-BCMA binding domain described herein, and a second cell expressing a CAR having a different anti- BCMA binding domain, e.g., an anti-BCMA binding domain described herein that differs from the anti-BCMA binding domain in the CAR expressed by the first cell. As another example, the population of CAR-expressing cells can include a first cell expressing a CAR that includes an anti-BCMA binding domain, e.g., as described herein, and a second cell expressing a CAR that includes an antigen binding domain to a target other than BCMA (e.g., CD19, CD20, CS-1, kappa light chain, CD139, Lewis Y antigen, or CD38). In one embodiment, the population of CAR-expressing cells includes a first cell expressing a CAR comprising an anti-BCMA binding domain, e.g., as described herein, and a second cell expressing a CAR comprising an antigen binding domain that targets CD19 (CD19 CAR). In one embodiment, the population of CAR-expressing cells includes, e.g., a first cell expressing a CAR that includes a primary intracellular signaling domain, and a second cell expressing a CAR that includes a secondary signaling domain.

In another aspect, the present invention provides a population of cells wherein at least one cell in the population expresses a CAR having an anti-BCMA domain described herein, and a second cell expressing another agent, e.g., an agent which enhances the activity of a CAR-expressing cell. For example, in one embodiment, the agent can be an agent which inhibits an inhibitory molecule. Inhibitory molecules, e.g., can, in some embodiments, decrease the ability of a CAR-expressing cell to mount an immune effector response. Examples of inhibitory molecules include PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGFR beta. In one embodiment, the agent which inhibits an inhibitory molecule comprises a first polypeptide, e.g., an inhibitory molecule, associated with a second polypeptide that provides a positive signal to the cell, e.g., an intracellular signaling domain described herein. In one embodiment, the agent comprises a first polypeptide, e.g., of an inhibitory molecule such as PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4

(VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGFR beta, or a fragment of any of these (e.g., at least a portion of an extracellular domain of any of these), and a second polypeptide which is an intracellular signaling domain described herein (e.g., comprising a costimulatory domain (e.g., 41BB, CD27, ICOS, or CD28, e.g., as described herein) and/or a primary signaling domain (e.g., a CD3 zeta signaling domain described herein). In one embodiment, the agent comprises a first polypeptide of PD1 or a fragment thereof (e.g., at least a portion of the extracellular domain of PD1), and a second polypeptide of an intracellular signaling domain described herein (e.g., a CD28 signaling domain described herein and/or a CD3 zeta signaling domain described herein).

In one aspect, the present invention provides methods comprising administering a population of CAR-expressing cells (e.g., CART cells or CAR-expressing NK cells), e.g., a mixture of cells expressing different CARs, in combination with another agent, e.g., a kinase inhibitor, such as a kinase inhibitor described herein. In another aspect, the present invention provides methods comprising administering a population of cells wherein at least one cell in the population expresses a CAR having an anti- cancer associated antigen binding domain as described herein, and a second cell expressing another agent, e.g., an agent which enhances the activity of a CAR-expressing cell, in combination with another agent, e.g., a kinase inhibitor, such as a kinase inhibitor described herein.

Natural Killer Cell Receptor (NKR) CARs

In an embodiment, the CAR molecule described herein comprises one or more components of a natural killer cell receptor (NKR), thereby forming an NKR-CAR. The NKR component can be a transmembrane domain, a hinge domain, or a cytoplasmic domain from any of the following natural killer cell receptors: killer cell immunoglobulin-like receptor (KIR), e.g., KIR2DL1, KIR2DL2/L3, KIR2DL4, KIR2DL5A, KIR2DL5B, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, DIR2DS5, KIR3DL1/S1, KIR3DL2, KIR3DL3, KIR2DP1, and KIR3DP1; natural cytotoxicity receptor (NCR), e.g., NKp30, NKp44, NKp46; signaling lymphocyte activation molecule (SLAM) family of immune cell receptors, e.g., CD48, CD229, 2B4, CD84, NTB-A, CRACC, BLAME, and CD2F-10; Fc receptor (FcR), e.g., CD16, and CD64; and Ly49 receptors, e.g., LY49A, LY49C. The NKR-CAR molecules described herein may interact with an adaptor molecule or intracellular signaling domain, e.g., DAP12.

Exemplary configurations and sequences of CAR molecules comprising NKR components are described in International Publication No. WO2014/145252, the contents of which are hereby incorporated by reference.

Strategies for Regulating Chimeric Antigen Receptors

There are many ways CAR activities can be regulated. In some embodiments, a regulatable CAR (RCAR) where the CAR activity can be controlled is desirable to optimize the safety and efficacy of a CAR therapy. For example, inducing apoptosis using, e.g., a caspase fused to a dimerization domain (see, e.g., Di et al., N Engl. J. Med. 2011 Nov. 3; 365(18):1673-1683), can be used as a safety switch in the CAR therapy of the instant invention. In another example, CAR-expressing cells can also express an inducible Caspase-9 (iCaspase-9) molecule that, upon administration of a dimerizer drug (e.g., rimiducid (also called AP1903 (Bellicum Pharmaceuticals) or AP20187 (Ariad)) leads to activation of the Caspase-9 and apoptosis of the cells. The iCaspase-9 molecule contains a chemical inducer of dimerization (CID) binding domain that mediates dimerization in the presence of a CID. This results in inducible and selective depletion of CAR-expressing cells. In some cases, the iCaspase-9 molecule is encoded by a nucleic acid molecule separate from the CAR-encoding vector(s). In some cases, the iCaspase-9 molecule is encoded by the same nucleic acid molecule as the CAR-encoding vector. The iCaspase-9 can provide a safety switch to avoid any toxicity of CAR-expressing cells. See, e.g., Song et al. Cancer Gene Ther. 2008; 15(10):667-75; Clinical Trial Id. No. NCT02107963; and Di Stasi et al. N. Engl. J. Med. 2011; 365:1673-83.

Alternative strategies for regulating the CAR therapy of the instant invention include utilizing small molecules or antibodies that deactivate or turn off CAR activity, e.g., by deleting CAR-expressing cells, e.g., by inducing antibody dependent cell-mediated cytotoxicity (ADCC). For example, CAR-expressing cells described herein may also express an antigen that is recognized by molecules capable of inducing cell death, e.g., ADCC or compliment-induced cell death. For example, CAR expressing cells described herein may also express a receptor capable of being targeted by an antibody or antibody fragment. Examples of such receptors include EpCAM, VEGFR, integrins (e.g., integrins αvβ3, α4, αI¾β3, α4β7, α5β1, αvβ3, αv), members of the TNF receptor superfamily (e.g., TRAIL-R1 , TRAIL-R2), PDGF Receptor,

interferon receptor, folate receptor, GPNMB, ICAM-1 , HLA-DR, CEA, CA-125, MUC1 , TAG-72, IL-6 receptor, 5T4, GD2, GD3, CD2, CD3, CD4, CD5, CD1 1 , CD1 1 a/LFA-1 , CD15, CD18/ITGB2, CD19, CD20, CD22, CD23/lgE Receptor, CD25, CD28, CD30, CD33, CD38, CD40, CD41 , CD44, CD51 , CD52, CD62L, CD74, CD80, CD125, CD147/basigin, CD152/CTLA-4, CD154/CD40L, CD195/CCR5, CD319/SLAMF7, and EGFR, and truncated versions thereof (e.g., versions preserving one or more extracellular epitopes but lacking one or more regions within the cytoplasmic domain). For example, CAR-expressing cells described herein may also express a truncated epidermal growth factor receptor (EGFR) which lacks signaling capacity but retains the epitope that is recognized by molecules capable of inducing ADCC, e.g., cetuximab (ERBITUX®), such that administration of cetuximab induces ADCC and subsequent depletion of the CAR-expressing cells (see, e.g., WO2011/056894, and Jonnalagadda et al., Gene Ther. 2013; 20(8)853-860). Another strategy includes expressing a highly compact marker/suicide gene that combines target epitopes from both CD32 and CD20 antigens in the CAR-expressing cells described herein, which binds rituximab, resulting in selective depletion of the CAR-expressing cells, e.g., by ADCC (see, e.g., Philip et al., Blood. 2014; 124(8)1277-1287). Other methods for depleting CAR-expressing cells described herein include administration of CAMPATH®, a monoclonal anti-CD52 antibody that selectively binds and targets mature lymphocytes, e.g., CAR-expressing cells, for destruction, e.g., by inducing ADCC. In other embodiments, CAR-expressing cells can be selectively targeted using a CAR ligand, e.g., an anti-idiotypic antibody. In some embodiments, the anti-idiotypic antibody can cause effector cell activity, e.g, ADCC or ADC activities, thereby reducing the number of CAR-expressing cells. In other embodiments, the CAR ligand, e.g., the anti-idiotypic antibody, can be coupled to an agent that induces cell killing, e.g., a toxin, thereby reducing the number of CAR-expressing cells. Alternatively, the CAR molecules themselves can be configured such that the activity can be regulated, e.g., turned on and off, as described below.

In some embodiments, a RCAR comprises a set of polypeptides, typically two in the simplest embodiments, in which the components of a standard CAR described herein, e.g., an antigen binding domain and an intracellular signaling domain, are partitioned on separate polypeptides or members. In some embodiments, the set of polypeptides include a dimerization switch that, upon the presence of a dimerization molecule, can couple the polypeptides to one

another, e.g., can couple an antigen binding domain to an intracellular signaling domain. Additional description and exemplary configurations of such regulatable CARs are provided herein and in International Publiciation No. WO 2015/090229, hereby incorporated by reference in its entirety.

In an embodiment, an RCAR comprises two polypeptides or members: 1) an intracellular signaling member comprising an intracellular signaling domain, e.g., a primary intracellular signaling domain described herein, and a first switch domain; 2) an antigen binding member comprising an antigen binding domain, e.g., that targets a tumor antigen described herein, as described herein and a second switch domain. Optionally, the RCAR comprises a transmembrane domain described herein. In an embodiment, a transmembrane domain can be disposed on the intracellular signaling member, on the antigen binding member, or on both. (Unless otherwise indicated, when members or elements of an RCAR are described herein, the order can be as provided, but other orders are included as well. In other words, in an embodiment, the order is as set out in the text, but in other embodiments, the order can be different. E.g., the order of elements on one side of a transmembrane region can be different from the example, e.g., the placement of a switch domain relative to a intracellular signaling domain can be different, e.g., reversed).

In an embodiment, the first and second switch domains can form an intracellular or an extracellular dimerization switch. In an embodiment, the dimerization switch can be a homodimerization switch, e.g., where the first and second switch domain are the same, or a heterodimerization switch, e.g., where the first and second switch domain are different from one another.

In embodiments, an RCAR can comprise a "multi switch." A multi switch can comprise heterodimerization switch domains or homodimerization switch domains. A multi switch comprises a plurality of, e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10, switch domains, independently, on a first member, e.g., an antigen binding member, and a second member, e.g., an intracellular signaling member. In an embodiment, the first member can comprise a plurality of first switch domains, e.g., FKBP-based switch domains, and the second member can comprise a plurality of second switch domains, e.g., FRB-based switch domains. In an embodiment, the first member can comprise a first and a second switch domain, e.g., a FKBP-based switch domain and a

FRB-based switch domain, and the second member can comprise a first and a second switch domain, e.g., a FKBP-based switch domain and a FRB-based switch domain.

In an embodiment, the intracellular signaling member comprises one or more intracellular signaling domains, e.g., a primary intracellular signaling domain and one or more costimulatory signaling domains.

In an embodiment, the antigen binding member may comprise one or more intracellular signaling domains, e.g., one or more costimulatory signaling domains. In an embodiment, the antigen binding member comprises a plurality, e.g., 2 or 3 costimulatory signaling domains described herein, e.g., selected from 4-1BB, CD28, CD27, ICOS, and OX40, and in embodiments, no primary intracellular signaling domain. In an embodiment, the antigen binding member comprises the following costimulatory signaling domains, from the extracellular to intracellular direction: 4-1BB-CD27; 4-1BB-CD27; CD27-4-1BB; 4-1BB-CD28; CD28-4-1BB; OX40-CD28; CD28-OX40; CD28-4-1BB; or 4-1BB-CD28. In such embodiments, the intracellular binding member comprises a CD3zeta domain. In one such embodiment the RCAR comprises (1) an antigen binding member comprising, an antigen binding domain, a transmembrane domain, and two costimulatory domains and a first switch domain; and (2) an intracellular signaling domain comprising a transmembrane domain or membrane tethering domain and at least one primary intracellular signaling domain, and a second switch domain.

An embodiment provides RCARs wherein the antigen binding member is not tethered to the surface of the CAR cell. This allows a cell having an intracellular signaling member to be conveniently paired with one or more antigen binding domains, without transforming the cell with a sequence that encodes the antigen binding member. In such embodiments, the RCAR comprises: 1) an intracellular signaling member comprising: a first switch domain, a transmembrane domain, an intracellular signaling domain, e.g., a primary intracellular signaling domain, and a first switch domain; and 2) an antigen binding member comprising: an antigen binding domain, and a second switch domain, wherein the antigen binding member does not comprise a transmembrane domain or membrane tethering domain, and, optionally, does not comprise an intracellular signaling domain. In some embodiments, the RCAR may further comprise 3) a second antigen binding member comprising: a second antigen binding

domain, e.g., a second antigen binding domain that binds a different antigen than is bound by the antigen binding domain; and a second switch domain.

Also provided herein are RCARs wherein the antigen binding member comprises bispecific activation and targeting capacity. In this embodiment, the antigen binding member can comprise a plurality, e.g., 2, 3, 4, or 5 antigen binding domains, e.g., scFvs, wherein each antigen binding domain binds to a target antigen, e.g. different antigens or the same antigen, e.g., the same or different epitopes on the same antigen. In an embodiment, the plurality of antigen binding domains are in tandem, and optionally, a linker or hinge region is disposed between each of the antigen binding domains. Suitable linkers and hinge regions are described herein.

An embodiment provides RCARs having a configuration that allows switching of proliferation. In this embodiment, the RCAR comprises: 1) an intracellular signaling member comprising: optionally, a transmembrane domain or membrane tethering domain; one or more co-stimulatory signaling domain, e.g., selected from 4-1BB, CD28, CD27, ICOS, and OX40, and a switch domain; and 2) an antigen binding member comprising: an antigen binding domain, a transmembrane domain, and a primary intracellular signaling domain, e.g., a CD3zeta domain, wherein the antigen binding member does not comprise a switch domain, or does not comprise a switch domain that dimerizes with a switch domain on the intracellular signaling member. In an embodiment, the antigen binding member does not comprise a co-stimulatory signaling domain. In an embodiment, the intracellular signaling member comprises a switch domain from a homodimerization switch. In an embodiment, the intracellular signaling member comprises a first switch domain of a heterodimerization switch and the RCAR comprises a second intracellular signaling member which comprises a second switch domain of the heterodimerization switch. In such embodiments, the second intracellular signaling member comprises the same intracellular signaling domains as the intracellular signaling member. In an embodiment, the dimerization switch is intracellular. In an embodiment, the dimerization switch is extracellular.

In any of the RCAR configurations described here, the first and second switch domains comprise a FKBP-FRB based switch as described herein.

Also provided herein are cells comprising an RCAR described herein. Any cell that is engineered to express a RCAR can be used as a RCARX cell. In an embodiment the RCARX cell is a T cell, and is referred to as a RCART cell. In an embodiment the RCARX cell is an NK cell, and is referred to as a RCARN cell.

Also provided herein are nucleic acids and vectors comprising RCAR encoding sequences. Sequence encoding various elements of an RCAR can be disposed on the same nucleic acid molecule, e.g., the same plasmid or vector, e.g., viral vector, e.g., lentiviral vector. In an embodiment, (i) sequence encoding an antigen binding member and (ii) sequence encoding an intracellular signaling member, can be present on the same nucleic acid, e.g., vector. Production of the corresponding proteins can be achieved, e.g., by the use of separate promoters, or by the use of a bicistronic transcription product (which can result in the production of two proteins by cleavage of a single translation product or by the translation of two separate protein products). In an embodiment, a sequence encoding a cleavable peptide, e.g., a P2A or F2A sequence, is disposed between (i) and (ii). In an embodiment, a sequence encoding an IRES, e.g., an EMCV or EV71 IRES, is disposed between (i) and (ii). In these embodiments, (i) and (ii) are transcribed as a single RNA. In an embodiment, a first promoter is operably linked to (i) and a second promoter is operably linked to (ii), such that (i) and (ii) are transcribed as separate mRNAs.

Alternatively, the sequence encoding various elements of an RCAR can be disposed on the different nucleic acid molecules, e.g., different plasmids or vectors, e.g., viral vector, e.g., lentiviral vector. E.g., the (i) sequence encoding an antigen binding member can be present on a first nucleic acid, e.g., a first vector, and the (ii) sequence encoding an intracellular signaling member can be present on the second nucleic acid, e.g., the second vector.

Dimerization switches

Dimerization switches can be non-covalent or covalent. In a non-covalent dimerization switch, the dimerization molecule promotes a non-covalent interaction between the switch domains. In a covalent dimerization switch, the dimerization molecule promotes a covalent interaction between the switch domains.

In an embodiment, the RCAR comprises a FKBP/FRAP, or FKBP/FRB,-based dimerization switch. FKBP12 (FKBP, or FK506 binding protein) is an abundant cytoplasmic protein that serves as the initial intracellular target for the natural product immunosuppressive drug, rapamycin. Rapamycin binds to FKBP and to the large PI3K homolog FRAP (RAFT, mTOR). FRB is a 93 amino acid portion of FRAP, that is sufficient for binding the FKBP-rapamycin complex (Chen, J., Zheng, X. F., Brown, E. J. & Schreiber, S. L. (1995) *Identification of an 11-kDa FKBP12-rapamycin-binding domain within the 289-kDa FKBP12-rapamycin-associated protein and characterization of a critical serine residue*. Proc Natl Acad Sci U S A 92: 4947-51.)

In embodiments, an FKBP/FRAP, e.g., an FKBP/FRB, based switch can use a dimerization molecule, e.g., rapamycin or a rapamycin analog.

The amino acid sequence of FKBP is as follows:

D V P D Y A S L G G P S S P K K K R K V S R G V Q V E T I S P G D G R T F P K R G Q T C V V H Y T G M L E D G K K F D S S R D R N K P F K F M L G K Q E V I R G W E E G V A Q M S V G Q R A K L T I S P D Y A Y G A T G H P G I I P P H A T L V F D V E L L K L E T S Y (SEQ ID NO: 275)

In embodiments, an FKBP switch domain can comprise a fragment of FKBP having the ability to bind with FRB, or a fragment or analog thereof, in the presence of rapamycin or a rapalog, e.g., the underlined portion of SEQ ID NO: 275, which is:

V Q V E T I S P G D G R T F P K R G Q T C V V H Y T G M L E D G K K F D S S R D R N K P F K F M L G K Q E V I R G W E E G V A Q M S V G Q R A K L T I S P D Y A Y G A T G H P G I I P P H A T L V F D V E L L K L E T S (SEQ ID NO:276)

The amino acid sequence of FRB is as follows:

ILWHEMWHEG LEEASRLYFG ERNVKGMFEV LEPLHAMMER GPQTLKETSF NQAYGRDLME AQEWCRKYMK SGNVKDLTQA WDLYYHVFRR ISK (SEQ ID NO: 277)

"FKBP/FRAP, e.g., an FKBP/FRB, based switch" as that term is used herein, refers to a dimerization switch comprising: a first switch domain, which comprises an FKBP fragment or analog thereof having the ability to bind with FRB, or a fragment or analog thereof, in the

presence of rapamycin or a rapalog, e.g., RAD001, and has at least 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99% identity with, or differs by no more than 30, 25, 20, 15, 10, 5, 4, 3, 2, or 1 amino acid residues from, the FKBP sequence of SEQ ID NO: 275 or 276; and a second switch domain, which comprises an FRB fragment or analog thereof having the ability to bind with FRB, or a fragment or analog thereof, in the presence of rapamycin or a rapalog, and has at least 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99% identity with, or differs by no more than 30, 25, 20, 15, 10, 5, 4, 3, 2, or 1 amino acid residues from, the FRB sequence of SEQ ID NO: 277. In an embodiment, a RCAR described herein comprises one switch domain comprises amino acid residues disclosed in SEQ ID NO: 275 (or SEQ ID NO: 276), and one switch domain comprises amino acid residues disclosed in SEQ ID NO: 277.

In embodiments, the FKBP/FRB dimerization switch comprises a modified FRB switch domain that exhibits altered, e.g., enhanced, complex formation between an FRB-based switch domain, e.g., the modified FRB switch domain, a FKBP-based switch domain, and the dimerization molecule, e.g., rapamycin or a rapalogue, e.g., RAD001. In an embodiment, the modified FRB switch domain comprises one or more mutations, e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10 or more, selected from mutations at amino acid position(s) L2031, E2032, S2035, R2036, F2039, G2040, T2098, W2101, D2102, Y2105, and F2108, where the wild-type amino acid is mutated to any other naturally-occurring amino acid. In an embodiment, a mutant FRB comprises a mutation at E2032, where E2032 is mutated to phenylalanine (E2032F), methionine (E2032M), arginine (E2032R), valine (E2032V), tyrosine (E2032Y), isoleucine (E2032I), e.g., SEQ ID NO: 278, or leucine (E2032L), e.g., SEQ ID NO: 279. In an embodiment, a mutant FRB comprises a mutation at T2098, where T2098 is mutated to phenylalanine (T2098F) or leucine (T2098L), e.g., SEQ ID NO: 280. In an embodiment, a mutant FRB comprises a mutation at E2032 and at T2098, where E2032 is mutated to any amino acid, and where T2098 is mutated to any amino acid, e.g., SEQ ID NO: 281. In an embodiment, a mutant FRB comprises an E2032I and a T2098L mutation, e.g., SEQ ID NO: 282. In an embodiment, a mutant FRB comprises an E2032L and a T2098L mutation, e.g., SEQ ID NO: 283.

Table 17. Exemplary mutant FRB having increased affinity for a dimerization molecule.

FRB mutant	Amino Acid Sequence	EQ ID

		NO:
E2032I mutant	ILWHEMWHEGLIEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGR DLMEAQEWCRKYMKSGNVKDLTQAWDLYYHVFRRISKTS	78
E2032L mutant	ILWHEMWHEGLLEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGR DLMEAQEWCRKYMKSGNVKDLTQAWDLYYHVFRRISKTS	79
T2098L mutant	ILWHEMWHEGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGR DLMEAQEWCRKYMKSGNVKDLLQAWDLYYHVFRRISKTS	80
E2032, T2098 mutant	ILWHEMWHEGL**X**EASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGR DLMEAQEWCRKYMKSGNVKDL**X**QAWDLYYHVFRRISKTS	81
E2032I, T2098L mutant	ILWHEMWHEGLIEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGR DLMEAQEWCRKYMKSGNVKDLLQAWDLYYHVFRRISKTS	82
E2032L, T2098L mutant	ILWHEMWHEGLLEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGR DLMEAQEWCRKYMKSGNVKDLLQAWDLYYHVFRRISKTS	83

Other suitable dimerization switches include a GyrB-GyrB based dimerization switch, a Gibberellin-based dimerization switch, a tag/binder dimerization switch, and a halo-tag/snap-tag dimerization switch. Following the guidance provided herein, such switches and relevant dimerization molecules will be apparent to one of ordinary skill.

Dimerization molecule

Association between the switch domains is promoted by the dimerization molecule. In the presence of dimerization molecule interaction or association between switch domains allows for signal transduction between a polypeptide associated with, e.g., fused to, a first switch domain, and a polypeptide associated with, e.g., fused to, a second switch domain. In the presence of non-limiting levels of dimerization molecule signal transduction is increased by 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 5, 10, 50, 100 fold, e.g., as measured in a system described herein.

Rapamycin and rapamycin analogs (sometimes referred to as rapalogues), e.g., RAD001, can be used as dimerization molecules in a FKBP/FRB-based dimerization switch described herein. In an embodiment the dimerization molecule can be selected from rapamycin (sirolimus), RAD001 (everolimus), zotarolimus, temsirolimus, AP-23573 (ridaforolimus), biolimus and AP21967. Additional rapamycin analogs suitable for use with FKBP/FRB-based dimerization switches are further described in the section entitled “Combination Therapies”, or in the subsection entitled “Combination with a Low, Immune Enhancing, Dose of an mTOR inhibitor”.

Split CAR

In some embodiments, the CAR-expressing cell uses a split CAR. The split CAR approach is described in more detail in publications WO2014/055442 and WO2014/055657, incorporated herein by reference. Briefly, a split CAR system comprises a cell expressing a first CAR having a first antigen binding domain and a costimulatory domain (e.g., 41BB), and the cell also expresses a second CAR having a second antigen binding domain and an intracellular signaling domain (e.g., CD3 zeta). When the cell encounters the first antigen, the costimulatory domain is activated, and the cell proliferates. When the cell encounters the second antigen, the intracellular signaling domain is activated and cell-killing activity begins. Thus, the CAR-expressing cell is only fully activated in the presence of both antigens. In embodiments the first antigen binding domain recognizes BCMA, e.g., comprises an antigen binding domain described herein, and the second antigen binding domain recognizes an antigen expressed on acute myeloid leukemia cells, e.g., CD123, CLL-1, CD34, FLT3, or folate receptor beta. In embodiments the first antigen binding domain recognizes BCMA, e.g., comprises an antigen binding domain described herein, and the second antigen binding domain recognizes an antigen expressed on B-cells, e.g., CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a.

Stability and Mutations

The stability of an anti-BCMA binding domain, e.g., scFv molecules (e.g., soluble scFv) can be evaluated in reference to the biophysical properties (e.g., thermal stability) of a conventional control scFv molecule or a full length antibody. In one embodiment, the humanized scFv has a thermal stability that is greater than about 0.1, about 0.25, about 0.5, about 0.75, about 1, about 1.25, about 1.5, about 1.75, about 2, about 2.5, about 3, about 3.5, about 4, about 4.5, about 5, about 5.5, about 6, about 6.5, about 7, about 7.5, about 8, about 8.5, about 9, about 9.5, about 10 degrees, about 11 degrees, about 12 degrees, about 13 degrees, about 14 degrees, or about 15 degrees Celsius than a control binding molecule (e.g. a conventional scFv molecule) in the described assays.

The improved thermal stability of the anti-BCMA binding domain, e.g., scFv is subsequently conferred to the entire CART-BCMA construct, leading to improved therapeutic properties of the CART-BCMA construct. The thermal stability of the anti-BCMA binding domain, e.g., scFv can be improved by at least about 2°C or 3°C as compared to a conventional

antibody. In one embodiment, the anti-BCMA binding domain, e.g., scFv has a 1°C improved thermal stability as compared to a conventional antibody. In another embodiment, the anti-BCMA binding domain, e.g., scFv has a 2°C improved thermal stability as compared to a conventional antibody. In another embodiment, the scFv has a 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15°C improved thermal stability as compared to a conventional antibody. Comparisons can be made, for example, between the scFv molecules disclosed herein and scFv molecules or Fab fragments of an antibody from which the scFv VH and VL were derived. Thermal stability can be measured using methods known in the art. For example, in one embodiment, Tm can be measured. Methods for measuring Tm and other methods of determining protein stability are described in more detail below.

Mutations in scFv (arising through humanization or direct mutagenesis of the soluble scFv) alter the stability of the scFv and improve the overall stability of the scFv and the CART33 construct. Stability of the human scFv can be compared against the murine scFv using measurements such as Tm, temperature denaturation and temperature aggregation.

The binding capacity of the mutant scFvs can be determined using assays described in the Examples.

In one embodiment, the anti-BCMA binding domain, e.g., scFv comprises at least one mutation arising from the humanization process such that the mutated scFv confers improved stability to the CART-BCMA construct. In another embodiment, the anti-BCMA binding domain, e.g., scFv comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 mutations arising from the humanization process such that the mutated scFv confers improved stability to the CART-BCMA construct.

Methods of Evaluating Protein Stability

The stability of an antigen binding domain may be assessed using, e.g., the methods described below. Such methods allow for the determination of multiple thermal unfolding transitions where the least stable domain either unfolds first or limits the overall stability threshold of a multidomain unit that unfolds cooperatively (e.g., a multidomain protein which exhibits a single unfolding transition). The least stable domain can be identified in a number of additional ways. Mutagenesis can be performed to probe which domain limits the overall stability. Additionally, protease resistance of a multidomain protein can be performed under conditions where the least stable domain is known to be intrinsically unfolded via DSC or other

spectroscopic methods (Fontana, *et al.*, (1997) Fold. Des., 2: R17-26; Dimasi *et al.* (2009) J. Mol. Biol. 393: 672-692). Once the least stable domain is identified, the sequence encoding this domain (or a portion thereof) may be employed as a test sequence in the methods.

a) Thermal Stability

The thermal stability of the compositions may be analyzed using a number of non-limiting biophysical or biochemical techniques known in the art. In certain embodiments, thermal stability is evaluated by analytical spectroscopy.

An exemplary analytical spectroscopy method is Differential Scanning Calorimetry (DSC). DSC employs a calorimeter which is sensitive to the heat absorbances that accompany the unfolding of most proteins or protein domains (see, e.g. Sanchez-Ruiz, et al., Biochemistry, 27: 1648-52, 1988). To determine the thermal stability of a protein, a sample of the protein is inserted into the calorimeter and the temperature is raised until the Fab or scFv unfolds. The temperature at which the protein unfolds is indicative of overall protein stability.

Another exemplary analytical spectroscopy method is Circular Dichroism (CD) spectroscopy. CD spectrometry measures the optical activity of a composition as a function of increasing temperature. Circular dichroism (CD) spectroscopy measures differences in the absorption of left-handed polarized light versus right-handed polarized light which arise due to structural asymmetry. A disordered or unfolded structure results in a CD spectrum very different from that of an ordered or folded structure. The CD spectrum reflects the sensitivity of the proteins to the denaturing effects of increasing temperature and is therefore indicative of a protein's thermal stability (see van Mierlo and Steemsma, J. Biotechnol., 79(3):281-98, 2000).

Another exemplary analytical spectroscopy method for measuring thermal stability is Fluorescence Emission Spectroscopy (see van Mierlo and Steemsma, supra). Yet another exemplary analytical spectroscopy method for measuring thermal stability is Nuclear Magnetic Resonance (NMR) spectroscopy (see, e.g. van Mierlo and Steemsma, supra).

The thermal stability of a composition can be measured biochemically. An exemplary biochemical method for assessing thermal stability is a thermal challenge assay. In a “thermal challenge assay”, a composition is subjected to a range of elevated temperatures for a set period of time. For example, in one embodiment, test scFv molecules or molecules comprising scFv molecules are subject to a range of increasing temperatures, e.g., for 1-1.5 hours. The activity

of the protein is then assayed by a relevant biochemical assay. For example, if the protein is a binding protein (e.g. an scFv or scFv-containing polypeptide) the binding activity of the binding protein may be determined by a functional or quantitative ELISA.

Such an assay may be done in a high-throughput format and those disclosed in the Examples using *E. coli* and high throughput screening. A library of anti-BCMA binding domain, e.g., scFv variants may be created using methods known in the art. Anti-BCMA binding domain, e.g., scFv expression may be induced and the anti-BCMA binding domain, e.g., scFv may be subjected to thermal challenge. The challenged test samples may be assayed for binding and those anti-BCMA binding domain, e.g., scFvs which are stable may be scaled up and further characterized.

Thermal stability is evaluated by measuring the melting temperature (Tm) of a composition using any of the above techniques (e.g. analytical spectroscopy techniques). The melting temperature is the temperature at the midpoint of a thermal transition curve wherein 50% of molecules of a composition are in a folded state (See e.g., Dimasi *et al.* (2009) J. Mol Biol. 393: 672-692). In one embodiment, Tm values for an anti-BCMA binding domain, e.g., scFv are about 40°C, 41°C, 42°C, 43°C, 44°C, 45°C, 46°C, 47°C, 48°C, 49°C, 50°C, 51°C, 52°C, 53°C, 54°C, 55°C, 56°C, 57°C, 58°C, 59°C, 60°C, 61°C, 62°C, 63°C, 64°C, 65°C, 66°C, 67°C, 68°C, 69°C, 70°C, 71°C, 72°C, 73°C, 74°C, 75°C, 76°C, 77°C, 78°C, 79°C, 80°C, 81°C, 82°C, 83°C, 84°C, 85°C, 86°C, 87°C, 88°C, 89°C, 90°C, 91°C, 92°C, 93°C, 94°C, 95°C, 96°C, 97°C, 98°C, 99°C, 100°C. In one embodiment, Tm values for an IgG is about 40°C, 41°C, 42°C, 43°C, 44°C, 45°C, 46°C, 47°C, 48°C, 49°C, 50°C, 51°C, 52°C, 53°C, 54°C, 55°C, 56°C, 57°C, 58°C, 59°C, 60°C, 61°C, 62°C, 63°C, 64°C, 65°C, 66°C, 67°C, 68°C, 69°C, 70°C, 71°C, 72°C, 73°C, 74°C, 75°C, 76°C, 77°C, 78°C, 79°C, 80°C, 81°C, 82°C, 83°C, 84°C, 85°C, 86°C, 87°C, 88°C, 89°C, 90°C, 91°C, 92°C, 93°C, 94°C, 95°C, 96°C, 97°C, 98°C, 99°C, 100°C. In one embodiment, Tm values for an multivalent antibody is about 40°C, 41°C, 42°C, 43°C, 44°C, 45°C, 46°C, 47°C, 48°C, 49°C, 50°C, 51°C, 52°C, 53°C, 54°C, 55°C, 56°C, 57°C, 58°C, 59°C, 60°C, 61°C, 62°C, 63°C, 64°C, 65°C, 66°C, 67°C, 68°C, 69°C, 70°C, 71°C, 72°C, 73°C, 74°C, 75°C, 76°C, 77°C, 78°C, 79°C, 80°C, 81°C, 82°C, 83°C, 84°C, 85°C, 86°C, 87°C, 88°C, 89°C, 90°C, 91°C, 92°C, 93°C, 94°C, 95°C, 96°C, 97°C, 98°C, 99°C, 100°C.

Thermal stability is also evaluated by measuring the specific heat or heat capacity (Cp) of a composition using an analytical calorimetric technique (e.g. DSC). The specific heat of a

composition is the energy (e.g. in kcal/mol) is required to rise by 1°C, the temperature of 1 mol of water. As large Cp is a hallmark of a denatured or inactive protein composition. The change in heat capacity (ΔCp) of a composition is measured by determining the specific heat of a composition before and after its thermal transition. Thermal stability may also be evaluated by measuring or determining other parameters of thermodynamic stability including Gibbs free energy of unfolding (ΔG), enthalpy of unfolding (ΔH), or entropy of unfolding (ΔS). One or more of the above biochemical assays (e.g. a thermal challenge assay) are used to determine the temperature (i.e. the T_C value) at which 50% of the composition retains its activity (e.g. binding activity).

In addition, mutations to the anti-BCMA binding domain, e.g., scFv alter the thermal stability of the anti-BCMA binding domain, e.g., scFv compared with the unmutated anti-BCMA binding domain, e.g., scFv. When the human or humanized anti-BCMA binding domain, e.g., scFv is incorporated into a BCMA construct, the anti-BCMA binding domain, e.g., humanized scFv confers thermal stability to the overall anti-BCMA CART construct. In one embodiment, the anti-BCMA binding domain, e.g., scFv comprises a single mutation that confers thermal stability to the anti-BCMA binding domain, e.g., scFv. In another embodiment, the anti-BCMA binding domain, e.g., scFv comprises multiple mutations that confer thermal stability to the anti-BCMA binding domain, e.g., scFv. In one embodiment, the multiple mutations in the anti-BCMA binding domain, e.g., scFv have an additive effect on thermal stability of the anti-BCMA binding domain, e.g., scFv.

b) % Aggregation

The stability of a composition can be determined by measuring its propensity to aggregate. Aggregation can be measured by a number of non-limiting biochemical or biophysical techniques. For example, the aggregation of a composition may be evaluated using chromatography, e.g. Size-Exclusion Chromatography (SEC). SEC separates molecules on the basis of size. A column is filled with semi-solid beads of a polymeric gel that will admit ions and small molecules into their interior but not large ones. When a protein composition is applied to the top of the column, the compact folded proteins (i.e. non-aggregated proteins) are distributed through a larger volume of solvent than is available to the large protein aggregates. Consequently, the large aggregates move more rapidly through the column, and in this way the mixture can be separated or fractionated into its components. Each fraction can be separately

quantified (e.g. by light scattering) as it elutes from the gel. Accordingly, the % aggregation of a composition can be determined by comparing the concentration of a fraction with the total concentration of protein applied to the gel. Stable compositions elute from the column as essentially a single fraction and appear as essentially a single peak in the elution profile or chromatogram.

c) Binding Affinity

The stability of a composition can be assessed by determining its target binding affinity. A wide variety of methods for determining binding affinity are known in the art. An exemplary method for determining binding affinity employs surface plasmon resonance. Surface plasmon resonance is an optical phenomenon that allows for the analysis of real-time biospecific interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIAcore system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, N.J.). For further descriptions, see Jonsson, U., et al. (1993) Ann. Biol. Clin. 51:19-26; Jonsson, U., i (1991) Biotechniques 11:620-627; Johnsson, B., *et al.* (1995) J. Mol. Recognit. 8:125-131; and Johnnson, B., *et al.* (1991) Anal. Biochem. 198:268-277.

In one aspect, the antigen binding domain of the CAR comprises an amino acid sequence that is homologous to an antigen binding domain amino acid sequence described herein, and the antigen binding domain retains the desired functional properties of the anti-BCMA antibody fragments described herein. In one specific aspect, the CAR composition of the invention comprises an antibody fragment. In a further aspect, that antibody fragment comprises an scFv.

In various aspects, the antigen binding domain of the CAR is engineered by modifying one or more amino acids within one or both variable regions (e.g., VH and/or VL), for example within one or more CDR regions and/or within one or more framework regions. In one specific aspect, the CAR composition of the invention comprises an antibody fragment. In a further aspect, that antibody fragment comprises a scFv.

It will be understood by one of ordinary skill in the art that the antibody or antibody fragment of the invention may further be modified such that they vary in amino acid sequence (e.g., from wild-type), but not in desired activity. For example, additional nucleotide substitutions, e.g., conservative substitutions leading to amino acid substitutions, e.g., conservative substitutions at "non-essential" amino acid residues may be made to the protein

For example, a nonessential amino acid residue in a molecule may be replaced with another amino acid residue from the same side chain family. In another embodiment, a string of amino acids can be replaced with a structurally similar string that differs in order and/or composition of side chain family members, e.g., a conservative substitution, in which an amino acid residue is replaced with an amino acid residue having a similar side chain, may be made.

Families of amino acid residues having similar side chains have been defined in the art, including basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine).

Percent identity in the context of two or more nucleic acids or polypeptide sequences, refers to two or more sequences that are the same. Two sequences are "substantially identical" if two sequences have a specified percentage of amino acid residues or nucleotides that are the same (e.g., 60% identity, optionally 70%, 71%. 72%. 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%,81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity over a specified region, or, when not specified, over the entire sequence), when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using one of the following sequence comparison algorithms or by manual alignment and visual inspection. Optionally, the identity exists over a region that is at least about 50 nucleotides (or 10 amino acids) in length, or more preferably over a region that is 100 to 500 or 1000 or more nucleotides (or 20, 50, 200 or more amino acids) in length.

For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are entered into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. Default program parameters can be used, or alternative parameters can be designated. The sequence comparison algorithm then calculates the percent sequence identities for the test sequences relative to the reference sequence, based on the program parameters. Methods of alignment of sequences for

comparison are well known in the art. Optimal alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith and Waterman, (1970) Adv. Appl. Math. 2:482c, by the homology alignment algorithm of Needleman and Wunsch, (1970) J. Mol. Biol. 48:443, by the search for similarity method of Pearson and Lipman, (1988) Proc. Nat'l. Acad. Sci. USA 85:2444, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by manual alignment and visual inspection (see, e.g., Brent et al., (2003) Current Protocols in Molecular Biology).

Two examples of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al., (1977) Nuc. Acids Res. 25:3389-3402; and Altschul et al., (1990) J. Mol. Biol. 215:403-410, respectively. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information.

The percent identity between two amino acid sequences can also be determined using the algorithm of E. Meyers and W. Miller, (1988) Comput. Appl. Biosci. 4:11-17) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch (1970) J. Mol. Biol. 48:444-453) algorithm which has been incorporated into the GAP program in the GCG software package (available at www.gcg.com), using either a Blossom 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

In one aspect, the present invention contemplates modifications of the starting antibody or fragment (e.g., scFv) amino acid sequence that generate functionally equivalent molecules. For example, the VH or VL of an anti-BCMA binding domain, e.g., scFv, comprised in the CAR can be modified to retain at least about 70%, 71%. 72%. 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%,81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity of the starting VH or VL framework region of the anti-BCMA binding domain, e.g., scFv. The present invention contemplates modifications of the entire CAR construct, e.g., modifications in one or more amino acid sequences of the various domains of the CAR construct in order to generate functionally equivalent molecules.

The CAR construct can be modified to retain at least about 70%, 71%. 72%. 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity of the starting CAR construct.

RNA Transfection

Disclosed herein are methods for producing an in vitro transcribed RNA CAR. The present invention also includes a CAR encoding RNA construct that can be directly transfected into a cell. A method for generating mRNA for use in transfection can involve in vitro transcription (IVT) of a template with specially designed primers, followed by polyA addition, to produce a construct containing 3' and 5' untranslated sequence ("UTR"), a 5' cap and/or Internal Ribosome Entry Site (IRES), the nucleic acid to be expressed, and a polyA tail, typically 50-2000 bases in length (SEQ ID NO:35). RNA so produced can efficiently transfect different kinds of cells. In one aspect, the template includes sequences for the CAR.

In one aspect the anti-BCMA CAR is encoded by a messenger RNA (mRNA). In one aspect the mRNA encoding the anti-BCMA CAR is introduced into an immune effector cell, e.g., a T cell or a NK cell, for production of a CAR-expressing cell (e.g., CART cell or CAR-expressing NK cell).

In one embodiment, the in vitro transcribed RNA CAR can be introduced to a cell as a form of transient transfection. The RNA is produced by in vitro transcription using a polymerase chain reaction (PCR)-generated template. DNA of interest from any source can be directly converted by PCR into a template for in vitro mRNA synthesis using appropriate primers and RNA polymerase. The source of the DNA can be, for example, genomic DNA, plasmid DNA, phage DNA, cDNA, synthetic DNA sequence or any other appropriate source of DNA. The desired temple for in vitro transcription is a CAR of the present invention. For example, the template for the RNA CAR comprises an extracellular region comprising a single chain variable domain of an anti-tumor antibody; a hinge region, a transmembrane domain (e.g., a transmembrane domain of CD8a); and a cytoplasmic region that includes an intracellular signaling domain, e.g., comprising the signaling domain of CD3-zeta and the signaling domain of 4-1BB.

In one embodiment, the DNA to be used for PCR contains an open reading frame. The DNA can be from a naturally occurring DNA sequence from the genome of an organism. In one embodiment, the nucleic acid can include some or all of the 5' and/or 3' untranslated regions (UTRs). The nucleic acid can include exons and introns. In one embodiment, the DNA to be used for PCR is a human nucleic acid sequence. In another embodiment, the DNA to be used for PCR is a human nucleic acid sequence including the 5' and 3' UTRs. The DNA can alternatively be an artificial DNA sequence that is not normally expressed in a naturally occurring organism. An exemplary artificial DNA sequence is one that contains portions of genes that are ligated together to form an open reading frame that encodes a fusion protein. The portions of DNA that are ligated together can be from a single organism or from more than one organism.

PCR is used to generate a template for in vitro transcription of mRNA which is used for transfection. Methods for performing PCR are well known in the art. Primers for use in PCR are designed to have regions that are substantially complementary to regions of the DNA to be used as a template for the PCR. "Substantially complementary," as used herein, refers to sequences of nucleotides where a majority or all of the bases in the primer sequence are complementary, or one or more bases are non-complementary, or mismatched. Substantially complementary sequences are able to anneal or hybridize with the intended DNA target under annealing conditions used for PCR. The primers can be designed to be substantially complementary to any portion of the DNA template. For example, the primers can be designed to amplify the portion of a nucleic acid that is normally transcribed in cells (the open reading frame), including 5' and 3' UTRs. The primers can also be designed to amplify a portion of a nucleic acid that encodes a particular domain of interest. In one embodiment, the primers are designed to amplify the coding region of a human cDNA, including all or portions of the 5' and 3' UTRs. Primers useful for PCR can be generated by synthetic methods that are well known in the art. "Forward primers" are primers that contain a region of nucleotides that are substantially complementary to nucleotides on the DNA template that are upstream of the DNA sequence that is to be amplified. "Upstream" is used herein to refer to a location 5, to the DNA sequence to be amplified relative to the coding strand. "Reverse primers" are primers that contain a region of nucleotides that are substantially complementary to a double-stranded DNA template

that are downstream of the DNA sequence that is to be amplified. "Downstream" is used herein to refer to a location 3' to the DNA sequence to be amplified relative to the coding strand.

Any DNA polymerase useful for PCR can be used in the methods disclosed herein. The reagents and polymerase are commercially available from a number of sources.

Chemical structures with the ability to promote stability and/or translation efficiency may also be used. The RNA preferably has 5' and 3' UTRs. In one embodiment, the 5' UTR is between one and 3000 nucleotides in length. The length of 5' and 3' UTR sequences to be added to the coding region can be altered by different methods, including, but not limited to, designing primers for PCR that anneal to different regions of the UTRs. Using this approach, one of ordinary skill in the art can modify the 5' and 3' UTR lengths required to achieve optimal translation efficiency following transfection of the transcribed RNA.

The 5' and 3' UTRs can be the naturally occurring, endogenous 5' and 3' UTRs for the nucleic acid of interest. Alternatively, UTR sequences that are not endogenous to the nucleic acid of interest can be added by incorporating the UTR sequences into the forward and reverse primers or by any other modifications of the template. The use of UTR sequences that are not endogenous to the nucleic acid of interest can be useful for modifying the stability and/or translation efficiency of the RNA. For example, it is known that AU-rich elements in 3' UTR sequences can decrease the stability of mRNA. Therefore, 3' UTRs can be selected or designed to increase the stability of the transcribed RNA based on properties of UTRs that are well known in the art.

In one embodiment, the 5' UTR can contain the Kozak sequence of the endogenous nucleic acid. Alternatively, when a 5' UTR that is not endogenous to the nucleic acid of interest is being added by PCR as described above, a consensus Kozak sequence can be redesigned by adding the 5' UTR sequence. Kozak sequences can increase the efficiency of translation of some RNA transcripts, but does not appear to be required for all RNAs to enable efficient translation. The requirement for Kozak sequences for many mRNAs is known in the art. In other embodiments the 5' UTR can be 5'UTR of an RNA virus whose RNA genome is stable in cells. In other embodiments various nucleotide analogues can be used in the 3' or 5' UTR to impede exonuclease degradation of the mRNA.

To enable synthesis of RNA from a DNA template without the need for gene cloning, a promoter of transcription should be attached to the DNA template upstream of the sequence to be transcribed. When a sequence that functions as a promoter for an RNA polymerase is added to the 5' end of the forward primer, the RNA polymerase promoter becomes incorporated into the PCR product upstream of the open reading frame that is to be transcribed. In one preferred embodiment, the promoter is a T7 polymerase promoter, as described elsewhere herein. Other useful promoters include, but are not limited to, T3 and SP6 RNA polymerase promoters. Consensus nucleotide sequences for T7, T3 and SP6 promoters are known in the art.

In a preferred embodiment, the mRNA has both a cap on the 5' end and a 3' poly(A) tail which determine ribosome binding, initiation of translation and stability mRNA in the cell. On a circular DNA template, for instance, plasmid DNA, RNA polymerase produces a long concatameric product which is not suitable for expression in eukaryotic cells. The transcription of plasmid DNA linearized at the end of the 3' UTR results in normal sized mRNA which is not effective in eukaryotic transfection even if it is polyadenylated after transcription.

On a linear DNA template, phage T7 RNA polymerase can extend the 3' end of the transcript beyond the last base of the template (Schenborn and Mierendorf, Nuc Acids Res., 13:6223-36 (1985); Nacheva and Berzal-Herranz, Eur. J. Biochem., 270:1485-65 (2003).

The conventional method of integration of polyA/T stretches into a DNA template is molecular cloning. However polyA/T sequence integrated into plasmid DNA can cause plasmid instability, which is why plasmid DNA templates obtained from bacterial cells are often highly contaminated with deletions and other aberrations. This makes cloning procedures not only laborious and time consuming but often not reliable. That is why a method which allows construction of DNA templates with polyA/T 3' stretch without cloning highly desirable.

The polyA/T segment of the transcriptional DNA template can be produced during PCR by using a reverse primer containing a polyT tail, such as 100T tail (SEQ ID NO: 31) (size can be 50-5000 T (SEQ ID NO: 32)), or after PCR by any other method, including, but not limited to, DNA ligation or in vitro recombination. Poly(A) tails also provide stability to RNAs and reduce their degradation. Generally, the length of a poly(A) tail positively correlates with the stability of the transcribed RNA. In one embodiment, the poly(A) tail is between 100 and 5000 adenosines (SEQ ID NO: 33).

Poly(A) tails of RNAs can be further extended following in vitro transcription with the use of a poly(A) polymerase, such as E. coli polyA polymerase (E-PAP). In one embodiment, increasing the length of a poly(A) tail from 100 nucleotides to between 300 and 400 nucleotides (SEQ ID NO: 34) results in about a two-fold increase in the translation efficiency of the RNA. Additionally, the attachment of different chemical groups to the 3' end can increase mRNA stability. Such attachment can contain modified/artificial nucleotides, aptamers and other compounds. For example, ATP analogs can be incorporated into the poly(A) tail using poly(A) polymerase. ATP analogs can further increase the stability of the RNA.

5' caps on also provide stability to RNA molecules. In a preferred embodiment, RNAs produced by the methods disclosed herein include a 5' cap. The 5' cap is provided using techniques known in the art and described herein (Cougot, et al., Trends in Biochem. Sci., 29:436-444 (2001); Stepinski, et al., RNA, 7:1468-95 (2001); Elango, et al., Biochim. Biophys. Res. Commun., 330:958-966 (2005)).

The RNAs produced by the methods disclosed herein can also contain an internal ribosome entry site (IRES) sequence. The IRES sequence may be any viral, chromosomal or artificially designed sequence which initiates cap-independent ribosome binding to mRNA and facilitates the initiation of translation. Any solutes suitable for cell electroporation, which can contain factors facilitating cellular permeability and viability such as sugars, peptides, lipids, proteins, antioxidants, and surfactants can be included.

RNA can be introduced into target cells using any of a number of different methods, for instance, commercially available methods which include, but are not limited to, electroporation (Amaxa Nucleofector-II (Amaxa Biosystems, Cologne, Germany)), (ECM 830 (BTX) (Harvard Instruments, Boston, Mass.) or the Gene Pulser II (BioRad, Denver, Colo.), Multiporator (Eppendort, Hamburg Germany), cationic liposome mediated transfection using lipofection, polymer encapsulation, peptide mediated transfection, or biolistic particle delivery systems such as “gene guns” (see, for example, Nishikawa, et al. Hum Gene Ther., 12(8):861-70 (2001).

Non-viral delivery methods

In some aspects, non-viral methods can be used to deliver a nucleic acid encoding a CAR described herein into a cell or tissue or a subject.

In some embodiments, the non-viral method includes the use of a transposon (also called a transposable element). In some embodiments, a transposon is a piece of DNA that can insert itself at a location in a genome, for example, a piece of DNA that is capable of self-replicating and inserting its copy into a genome, or a piece of DNA that can be spliced out of a longer nucleic acid and inserted into another place in a genome. For example, a transposon comprises a DNA sequence made up of inverted repeats flanking genes for transposition.

Exemplary methods of nucleic acid delivery using a transposon include a Sleeping Beauty transposon system (SBTS) and a piggyBac (PB) transposon system. See, e.g., Aronovich et al. Hum. Mol. Genet. 20.R1(2011):R14-20; Singh et al. Cancer Res. 15(2008):2961–2971; Huang et al. Mol. Ther. 16(2008):580–589; Grabundzija et al. Mol. Ther. 18(2010):1200–1209; Kebriaei et al. Blood. 122.21(2013):166; Williams. Molecular Therapy 16.9(2008):1515–16; Bell et al. Nat. Protoc. 2.12(2007):3153-65; and Ding et al. Cell. 122.3(2005):473-83, all of which are incorporated herein by reference.

The SBTS includes two components: 1) a transposon containing a transgene and 2) a source of transposase enzyme. The transposase can transpose the transposon from a carrier plasmid (or other donor DNA) to a target DNA, such as a host cell chromosome/genome. For example, the transposase binds to the carrier plasmid/donor DNA, cuts the transposon (including transgene(s)) out of the plasmid, and inserts it into the genome of the host cell. See, e.g., Aronovich et al. *supra.*

Exemplary transposons include a pT2-based transposon. See, e.g., Grabundzija et al. Nucleic Acids Res. 41.3(2013):1829-47; and Singh et al. Cancer Res. 68.8(2008): 2961–2971, all of which are incorporated herein by reference. Exemplary transposases include a Tc1/mariner-type transposase, e.g., the SB10 transposase or the SB11 transposase (a hyperactive transposase which can be expressed, e.g., from a cytomegalovirus promoter). See, e.g., Aronovich et al.; Kebriaei et al.; and Grabundzija et al., all of which are incorporated herein by reference.

Use of the SBTS permits efficient integration and expression of a transgene, e.g., a nucleic acid encoding a CAR described herein. Provided herein are methods of generating a cell, e.g., T cell or NK cell, that stably expresses a CAR described herein, e.g., using a transposon system such as SBTS.

In accordance with methods described herein, in some embodiments, one or more nucleic acids, e.g., plasmids, containing the SBTS components are delivered to a cell (e.g., T or NK cell). For example, the nucleic acid(s) are delivered by standard methods of nucleic acid (e.g., plasmid DNA) delivery, e.g., methods described herein, e.g., electroporation, transfection, or lipofection. In some embodiments, the nucleic acid contains a transposon comprising a transgene, e.g., a nucleic acid encoding a CAR described herein. In some embodiments, the nucleic acid contains a transposon comprising a transgene (e.g., a nucleic acid encoding a CAR described herein) as well as a nucleic acid sequence encoding a transposase enzyme. In other embodiments, a system with two nucleic acids is provided, e.g., a dual-plasmid system, e.g., where a first plasmid contains a transposon comprising a transgene, and a second plasmid contains a nucleic acid sequence encoding a transposase enzyme. For example, the first and the second nucleic acids are co-delivered into a host cell.

In some embodiments, cells, e.g., T or NK cells, are generated that express a CAR described herein by using a combination of gene insertion using the SBTS and genetic editing using a nuclease (e.g., Zinc finger nucleases (ZFNs), Transcription Activator-Like Effector Nucleases (TALENs), the CRISPR/Cas system, or engineered meganuclease re-engineered homing endonucleases).

In some embodiments, use of a non-viral method of delivery permits reprogramming of cells, e.g., T or NK cells, and direct infusion of the cells into a subject. Advantages of non-viral vectors include but are not limited to the ease and relatively low cost of producing sufficient amounts required to meet a patient population, stability during storage, and lack of immunogenicity.

Nucleic Acid Constructs Encoding a CAR

The present invention also provides nucleic acid molecules encoding one or more CAR constructs described herein. In one aspect, the nucleic acid molecule is provided as a messenger RNA transcript. In one aspect, the nucleic acid molecule is provided as a DNA construct.

Accordingly, in one aspect, the invention pertains to an isolated nucleic acid molecule encoding a chimeric antigen receptor (CAR), wherein the CAR comprises a anti-BCMA

binding domain (e.g., a human anti-BCMA binding domain), a transmembrane domain, and an intracellular signaling domain comprising a stimulatory domain, e.g., a costimulatory signaling domain and/or a primary signaling domain, e.g., zeta chain. In one embodiment, the anti-BCMA binding domain is an anti-BCMA binding domain described herein, e.g., an anti-BCMA binding domain which comprises a sequence selected from a group consisting of SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148 or SEQ ID NO:149, or a sequence with 95-99% identify thereof. In one embodiment, the transmembrane domain is transmembrane domain of a protein selected from the group consisting of the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 and CD154. In one embodiment, the transmembrane domain comprises a sequence of SEQ ID NO: 6, or a sequence with 95-99% identity thereof. In one embodiment, the anti-BCMA binding domain is connected to the transmembrane domain by a hinge region, e.g., a hinge described herein. In one embodiment, the hinge region comprises SEQ ID NO:2 or SEQ ID NO:3 or SEQ ID NO:4 or SEQ ID NO:5, or a sequence with 95-99% identity thereof. In one embodiment, the isolated nucleic acid molecule further comprises a sequence encoding a costimulatory domain. In one embodiment, the costimulatory domain is a functional signaling domain of a protein selected from the group consisting of MHC class I molecule, TNF receptor proteins, Immunoglobulin-like proteins, cytokine receptors, integrins, signaling lymphocytic activation molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1

(CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, and a ligand that specifically binds with CD83. In one embodiment, the costimulatory domain comprises a sequence of SEQ ID NO:7, or a sequence with 95-99% identity thereof or a CD27 costimulatory domain having a sequence of SEQ ID NO:8 (or a sequence with 95-99% identity thereof) or a CD28 costimulatory domain having a sequence of SEQ ID NO:379 (or a sequence with 95-99% identity thereof) or a ICOS costimulatory domain having a sequence of SEQ ID NO: 381 (or a sequence with 95-99% identity thereof). In one embodiment, the intracellular signaling domain comprises a functional signaling domain of 4-1BB and a functional signaling domain of CD3 zeta. In one embodiment, the intracellular signaling domain comprises the sequence of SEQ ID NO: 7 or SEQ ID NO: 8, or a sequence with 95-99% identity thereof, and the sequence of SEQ ID NO: 9 or SEQ ID NO:10, or a sequence with 95-99% identity thereof, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain.

In another aspect, the invention pertains to an isolated nucleic acid molecule encoding a CAR construct comprising a leader sequence of SEQ ID NO: 1, a scFv domain having a sequence selected from the group consisting of SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148 or SEQ ID NO:149 (or a sequence with 95-99% identify thereof), a hinge region of SEQ ID NO:2 or SEQ ID NO:3 or SEQ ID NO:4 or SEQ ID NO:5 (or a sequence with 95-99% identity thereof), a transmembrane domain having a sequence of SEQ ID NO: 6 (or a sequence with 95-99% identity thereof), a 4-1BB costimulatory domain having a sequence of SEQ ID NO:7 or a CD27 costimulatory domain having a sequence of SEQ ID NO:8 (or a sequence with 95-99% identity thereof) or a CD28 costimulatory domain having a sequence of SEQ ID

NO:1104 (or a sequence with 95-99% identity thereof) or a ICOS costimulatory domain having a sequence of SEQ ID NO: 1106 (or a sequence with 95-99% identity thereof), and a CD3 zeta stimulatory domain having a sequence of SEQ ID NO:9 or SEQ ID NO:10 (or a sequence with 95-99% identity thereof).

In another aspect, the invention pertains to an isolated polypeptide molecule encoded by the nucleic acid molecule. In one embodiment, the isolated polypeptide molecule comprises a sequence selected from the group consisting of SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148 and SEQ ID NO:149, or a sequence with 95-99% identify thereof.

In another aspect, the invention pertains to a nucleic acid molecule encoding a chimeric antigen receptor (CAR) molecule that comprises an anti-BCMA binding domain, a transmembrane domain, and an intracellular signaling domain comprising a stimulatory domain, and wherein said anti-BCMA binding domain comprises a sequence selected from the group consisting of SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148 and SEQ ID NO:149, or a sequence with 95-99% identify thereof.

In one embodiment, the encoded CAR molecule further comprises a sequence encoding a costimulatory domain. In one embodiment, the costimulatory domain is a functional signaling domain of a protein, e.g., described herein, e.g., selected from the group consisting of MHC class I molecule, TNF receptor proteins, Immunoglobulin-like proteins, cytokine receptors, integrins, signaling lymphocytic activation molecules (SLAM proteins), activating

NK cell receptors, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, and a ligand that specifically binds with CD83. In one embodiment, the costimulatory domain comprises a sequence of SEQ ID NO:7. In one embodiment, the transmembrane domain is a transmembrane domain of a protein, e.g., described herein, e.g., selected from the group consisting of the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 and CD154. In one embodiment, the transmembrane domain comprises a sequence of SEQ ID NO:6. In one embodiment, the intracellular signaling domain comprises a functional signaling domain of 4-1BB and a functional signaling domain of zeta. In one embodiment, the intracellular signaling domain comprises the sequence of SEQ ID NO: 7 and the sequence of SEQ ID NO: 9, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain. In one embodiment, the anti-BCMAbinding domain is connected to the transmembrane domain by a hinge region. In one embodiment, the hinge region comprises SEQ ID NO:2. In one embodiment, the hinge region comprises SEQ ID NO:3 or SEQ ID NO:4 or SEQ ID NO:5.

In another aspect, the invention pertains to an encoded CAR molecule comprising a leader sequence of SEQ ID NO: 1, a scFv domain having a sequence selected from the group consisting of SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO:

134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148 and SEQ ID NO:149, or a sequence with 95-99% identify thereof, a hinge region of SEQ ID NO:2 or SEQ ID NO:3 or SEQ ID NO:4 or SEQ ID NO:5, a transmembrane domain having a sequence of SEQ ID NO: 6, a 4-1BB costimulatory domain having a sequence of SEQ ID NO:7, or a CD27 costimulatory domain having a sequence of SEQ ID NO:8, or a CD28 costimulatory domain having a sequence of SEQ ID NO:1104 (or a sequence with 95-99% identity thereof) or a ICOS costimulatory domain having a sequence of SEQ ID NO: 1106 (or a sequence with 95-99% identity thereof), and a CD3 zeta stimulatory domain having a sequence of SEQ ID NO:9 or SEQ ID NO:10. In one embodiment, the encoded CAR molecule comprises a sequence selected from a group consisting of SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO: 105, SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113 , SEQ ID NO: 213, SEQ ID NO: 214, SEQ ID NO: 215, SEQ ID NO: 216, SEQ ID NO: 217, SEQ ID NO: 218, SEQ ID NO: 219, SEQ ID NO: 220, SEQ ID NO: 221, SEQ ID NO: 222, SEQ ID NO: 223, SEQ ID NO: 224, SEQ ID NO: 225, SEQ ID NO: 226, SEQ ID NO: 227, SEQ ID NO: 228, SEQ ID NO: 229, SEQ ID NO: 230, SEQ ID NO: 231, SEQ ID NO: 232, and SEQ ID NO: 233or a sequence with 95-99% identify thereof.

The nucleic acid sequences coding for the desired molecules can be obtained using recombinant methods known in the art, such as, for example by screening libraries from cells expressing the gene, by deriving the gene from a vector known to include the same, or by isolating directly from cells and tissues containing the same, using standard techniques. Alternatively, the gene of interest can be produced synthetically, rather than cloned.

The present invention also provides vectors in which a DNA of the present invention is inserted. Vectors derived from retroviruses such as the lentivirus are suitable tools to achieve long-term gene transfer since they allow long-term, stable integration of a transgene and its propagation in daughter cells. Lentiviral vectors have the added advantage over vectors derived from onco-retroviruses such as murine leukemia viruses in that they can transduce non-proliferating cells, such as hepatocytes. They also have the added advantage of low immunogenicity. A retroviral vector may also be, e.g., a gammaretroviral vector. A

gammaretroviral vector may include, e.g., a promoter, a packaging signal (ψ), a primer binding site (PBS), one or more (e.g., two) long terminal repeats (LTR), and a transgene of interest, e.g., a gene encoding a CAR. A gammaretroviral vector may lack viral structural gens such as gag, pol, and env. Exemplary gammaretroviral vectors include Murine Leukemia Virus (MLV), Spleen-Focus Forming Virus (SFFV), and Myeloproliferative Sarcoma Virus (MPSV), and vectors derived therefrom. Other gammaretroviral vectors are described, e.g., in Tobias Maetzig et al., "Gammaretroviral Vectors: Biology, Technology and Application" Viruses. 2011 Jun; 3(6): 677–713.

In another embodiment, the vector comprising the nucleic acid encoding the desired CAR of the invention is an adenoviral vector (A5/35). In another embodiment, the expression of nucleic acids encoding CARs can be accomplished using of transposons such as sleeping beauty, CRISPR, CAS9, and zinc finger nucleases. See below June et al. 2009*Nature Reviews Immunology* 9.10: 704-716, is incorporated herein by reference.

In brief summary, the expression of natural or synthetic nucleic acids encoding CARs is typically achieved by operably linking a nucleic acid encoding the CAR polypeptide or portions thereof to a promoter, and incorporating the construct into an expression vector. The vectors can be suitable for replication and integration eukaryotes. Typical cloning vectors contain transcription and translation terminators, initiation sequences, and promoters useful for regulation of the expression of the desired nucleic acid sequence.

The expression constructs of the present invention may also be used for nucleic acid immunization and gene therapy, using standard gene delivery protocols. Methods for gene delivery are known in the art. See, e.g., U.S. Pat. Nos. 5,399,346, 5,580,859, 5,589,466, incorporated by reference herein in their entireties. In another embodiment, the invention provides a gene therapy vector.

The nucleic acid can be cloned into a number of types of vectors. For example, the nucleic acid can be cloned into a vector including, but not limited to a plasmid, a phagemid, a phage derivative, an animal virus, and a cosmid. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors, and sequencing vectors.

Further, the expression vector may be provided to a cell in the form of a viral vector. Viral vector technology is well known in the art and is described, for example, in Sambrook et

al., 2012, MOLECULAR CLONING: A LABORATORY MANUAL, volumes 1 -4, Cold Spring Harbor Press, NY), and in other virology and molecular biology manuals. Viruses, which are useful as vectors include, but are not limited to, retroviruses, adenoviruses, adeno-associated viruses, herpes viruses, and lentiviruses. In general, a suitable vector contains an origin of replication functional in at least one organism, a promoter sequence, convenient restriction endonuclease sites, and one or more selectable markers, (e.g., WO 01/96584; WO 01/29058; and U.S. Pat. No. 6,326,193).

A number of viral based systems have been developed for gene transfer into mammalian cells. For example, retroviruses provide a convenient platform for gene delivery systems. A selected gene can be inserted into a vector and packaged in retroviral particles using techniques known in the art. The recombinant virus can then be isolated and delivered to cells of the subject either in vivo or ex vivo. A number of retroviral systems are known in the art. In some embodiments, adenovirus vectors are used. A number of adenovirus vectors are known in the art. In one embodiment, lentivirus vectors are used.

Additional promoter elements, e.g., enhancers, regulate the frequency of transcriptional initiation. Typically, these are located in the region 30-110 bp upstream of the start site, although a number of promoters have been shown to contain functional elements downstream of the start site as well. The spacing between promoter elements frequently is flexible, so that promoter function is preserved when elements are inverted or moved relative to one another. In the thymidine kinase (tk) promoter, the spacing between promoter elements can be increased to 50 bp apart before activity begins to decline. Depending on the promoter, it appears that individual elements can function either cooperatively or independently to activate transcription.

An example of a promoter that is capable of expressing a CAR transgene in a mammalian T cell is the EF1a promoter. The native EF1a promoter drives expression of the alpha subunit of the elongation factor-1 complex, which is responsible for the enzymatic delivery of aminoacyl tRNAs to the ribosome. The EF1a promoter has been extensively used in mammalian expression plasmids and has been shown to be effective in driving CAR expression from transgenes cloned into a lentiviral vector. See, e.g., Milone et al., Mol. Ther. 17(8): 1453–1464 (2009). In one aspect, the EF1a promoter comprises the sequence provided as SEQ ID NO:11.

Another example of a promoter is the immediate early cytomegalovirus (CMV) promoter sequence. This promoter sequence is a strong constitutive promoter sequence capable of driving high levels of expression of any polynucleotide sequence operatively linked thereto. However, other constitutive promoter sequences may also be used, including, but not limited to the simian virus 40 (SV40) early promoter, mouse mammary tumor virus (MMTV), human immunodeficiency virus (HIV) long terminal repeat (LTR) promoter, MoMuLV promoter, an avian leukemia virus promoter, an Epstein-Barr virus immediate early promoter, a Rous sarcoma virus promoter, as well as human gene promoters such as, but not limited to, the actin promoter, the myosin promoter, the elongation factor-1α promoter, the hemoglobin promoter, and the creatine kinase promoter. Further, the invention should not be limited to the use of constitutive promoters. Inducible promoters are also contemplated as part of the invention. The use of an inducible promoter provides a molecular switch capable of turning on expression of the polynucleotide sequence which it is operatively linked when such expression is desired, or turning off the expression when expression is not desired. Examples of inducible promoters include, but are not limited to a metallothionine promoter, a glucocorticoid promoter, a progesterone promoter, and a tetracycline promoter.

Another example of a promoter is the phosphoglycerate kinase (PGK) promoter. In embodiments, a truncated PGK promoter (e.g., a PGK promoter with one or more, e.g., 1, 2, 5, 10, 100, 200, 300, or 400, nucleotide deletions when compared to the wild-type PGK promoter sequence) may be desired. The nucleotide sequences of exemplary PGK promoters are provided below.

WT PGK Promoter

ACCCCTCTCTCCAGCCACTAAGCCAGTTGCTCCCTCGGCTGACGGCTGCACGCGAGGCCTCCGAACGTCTTAC
GCCTTGTGGCGCGCCCGTCCTTGTCCCGGGTGTGATGGCGGGGTGTGGGGCGGAGGGCGTGGCGGGGAAGGGC
CGGCGACGAGAGCCGCGCGGGACGACTCGTCGGCGATAACCGGTGTCGGGTAGCGCCAGCCGCGCGACGGTAA
CGAGGGACCGCGACAGGCAGACGCTCCCATGATCACTCTGCACGCCGAAGGCAAATAGTGCAGGCCGTGCGGC
GCTTGGCGTTCCTTGGAAGGGCTGAATCCCCGCCTCGTCCTTCGCAGCGGCCCCCCGGGTGTTCCCATCGCCG
CTTCTAGGCCCACTGCGACGCTTGCCTGCACTTCTTACACGCTCTGGGTCCCAGCCGCGGCGACGCAAAGGGC
CTTGGTGCGGGTCTCGTCGGCGCAGGGACGCGTTTGGGTCCCGACGGAACCTTTTCCGCGTTGGGGTTGGGGC
ACCATAAGCT

(SEQ ID NO: 1109)

Exemplary truncated PGK Promoters:

PGK100:

ACCCCTCTCTCCAGCCACTAAGCCAGTTGCTCCCTCGGCTGACGGCTGCACGCGAGGCCTCCGAACGTCTTAC
GCCTTGTGGCGCGCCCGTCCTTGTCCCGGGTGTGATGGCGGGGTG
(SEQ ID NO: 1110)

PGK200:
ACCCCTCTCTCCAGCCACTAAGCCAGTTGCTCCCTCGGCTGACGGCTGCACGCGAGGCCTCCGAACGTCTTAC
GCCTTGTGGCGCGCCCGTCCTTGTCCCGGGTGTGATGGCGGGGTGTGGGGCGGAGGGCGTGGCGGGGAAGGGC
CGGCGACGAGAGCCGCGCGGGACGACTCGTCGGCGATAACCGGTGTCGGGTAGCGCCAGCCGCGCGACGGTAA
CG
(SEQ ID NO: 1111)

PGK300:
ACCCCTCTCTCCAGCCACTAAGCCAGTTGCTCCCTCGGCTGACGGCTGCACGCGAGGCCTCCGAACGTCTTAC
GCCTTGTGGCGCGCCCGTCCTTGTCCCGGGTGTGATGGCGGGGTGTGGGGCGGAGGGCGTGGCGGGGAAGGGC
CGGCGACGAGAGCCGCGCGGGACGACTCGTCGGCGATAACCGGTGTCGGGTAGCGCCAGCCGCGCGACGGTAA
CGAGGGACCGCGACAGGCAGACGCTCCCATGATCACTCTGCACGCCGAAGGCAAATAGTGCAGGCCGTGCGGC
GCTTGGCGTTCCTTGGAAGGGCTGAATCCCCG
(SEQ ID NO: 1112)

PGK400:
ACCCCTCTCTCCAGCCACTAAGCCAGTTGCTCCCTCGGCTGACGGCTGCACGCGAGGCCTCCGAACGTCTTAC
GCCTTGTGGCGCGCCCGTCCTTGTCCCGGGTGTGATGGCGGGGTGTGGGGCGGAGGGCGTGGCGGGGAAGGGC
CGGCGACGAGAGCCGCGCGGGACGACTCGTCGGCGATAACCGGTGTCGGGTAGCGCCAGCCGCGCGACGGTAA
CGAGGGACCGCGACAGGCAGACGCTCCCATGATCACTCTGCACGCCGAAGGCAAATAGTGCAGGCCGTGCGGC
GCTTGGCGTTCCTTGGAAGGGCTGAATCCCCGCCTCGTCCTTCGCAGCGGCCCCCCGGGTGTTCCCATCGCCG
CTTCTAGGCCCACTGCGACGCTTGCCTGCACTTCTTACACGCTCTGGGTCCCAGCCG
(SEQ ID NO: 1113)

A vector may also include, e.g., a signal sequence to facilitate secretion, a polyadenylation signal and transcription terminator (e.g., from Bovine Growth Hormone (BGH) gene), an element allowing episomal replication and replication in prokaryotes (e.g. SV40 origin and ColE1 or others known in the art) and/or elements to allow selection (e.g., ampicillin resistance gene and/or zeocin marker).

In order to assess the expression of a CAR polypeptide or portions thereof, the expression vector to be introduced into a cell can also contain either a selectable marker gene or a reporter gene or both to facilitate identification and selection of expressing cells from the population of cells sought to be transfected or infected through viral vectors. In other aspects, the selectable marker may be carried on a separate piece of DNA and used in a co- transfection procedure. Both selectable markers and reporter genes may be flanked with appropriate regulatory sequences to enable expression in the host cells. Useful selectable markers include, for example, antibiotic-resistance genes, such as neo and the like.

Reporter genes are used for identifying potentially transfected cells and for evaluating the functionality of regulatory sequences. In general, a reporter gene is a gene that is not present in or expressed by the recipient organism or tissue and that encodes a polypeptide whose expression is manifested by some easily detectable property, e.g., enzymatic activity. Expression of the reporter gene is assayed at a suitable time after the DNA has been introduced into the recipient cells. Suitable reporter genes may include genes encoding luciferase, beta-galactosidase, chloramphenicol acetyl transferase, secreted alkaline phosphatase, or the green fluorescent protein gene (e.g., Ui-Tei et al., 2000 FEBS Letters 479: 79-82). Suitable expression systems are well known and may be prepared using known techniques or obtained commercially. In general, the construct with the minimal 5' flanking region showing the highest level of expression of reporter gene is identified as the promoter. Such promoter regions may be linked to a reporter gene and used to evaluate agents for the ability to modulate promoter-driven transcription.

In one embodiment, the vector can further comprise a nucleic acid encoding a second CAR. In one embodiment, the second CAR includes an antigen binding domain to a target expressed on acute myeloid leukemia cells, such as, e.g., CD123, CD34, CLL-1, folate receptor beta, or FLT3; or a target expressed on a B cell, e.g., CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a. In one embodiment, the vector comprises a nucleic acid sequence encoding a first CAR that specifically binds a first antigen and includes an intracellular signaling domain having a costimulatory signaling domain but not a primary signaling domain, and a nucleic acid encoding a second CAR that specifically binds a second, different, antigen and includes an intracellular signaling domain having a primary signaling domain but not a costimulatory signaling domain. In one embodiment, the vector comprises a nucleic acid encoding a first BCMA CAR that includes a BCMA binding domain, a transmembrane domain and a costimulatory domain and a nucleic acid encoding a second CAR that targets an antigen other than BCMA (e.g., an antigen expressed on AML cells, e.g., CD123, CD34, CLL-1, folate receptor beta, or FLT3; or an antigen expressed on a B cell, e.g., CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a) and includes an antigen binding domain, a transmembrane domain and a primary signaling domain. In another embodiment, the vector comprises a nucleic acid encoding a first BCMA CAR that includes a BCMA binding domain, a transmembrane domain and a primary signaling domain

and a nucleic acid encoding a second CAR that specifically binds an antigen other than BCMA (e.g., an antigen expressed on AML cells, e.g., CD123, CD34, CLL-1, folate receptor beta, or FLT3; or an antigen expressed on a B cell, e.g., CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a) and includes an antigen binding domain to the antigen, a transmembrane domain and a costimulatory signaling domain.

In one embodiment, the vector comprises a nucleic acid encoding a BCMA CAR described herein and a nucleic acid encoding an inhibitory CAR. In one embodiment, the inhibitory CAR comprises an antigen binding domain that binds an antigen found on normal cells but not cancer cells, e.g., normal cells that also express BCMA. In one embodiment, the inhibitory CAR comprises the antigen binding domain, a transmembrane domain and an intracellular domain of an inhibitory molecule. For example, the intracellular domain of the inhibitory CAR can be an intracellular domain of PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGFR beta.

In embodiments, the vector may comprise two or more nucleic acid sequences encoding a CAR, e.g., a BCMA CAR described herein and a second CAR, e.g., an inhibitory CAR or a CAR that specifically binds to an antigen other than BCMA (e.g., an antigen expressed on AML cells, e.g., CD123, CLL-1, CD34, FLT3, or folate receptor beta; or antigen expresson B cells, e.g., CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a). In such embodiments, the two or more nucleic acid sequences encoding the CAR are encoded by a single nucleic molecule in the same frame and as a single polypeptide chain. In this aspect, the two or more CARs, can, e.g., be separated by one or more peptide cleavage sites. (e.g., an auto-cleavage site or a substrate for an intracellular protease). Examples of peptide cleavage sites include the following, wherein the GSG residues are optional:

T2A: (GSG) E G R G S L L T C G D V E E N P G P (SEQ ID NO: 1114)

P2A: (GSG) A T N F S L L K Q A G D V E E N P G P (SEQ ID NO: 1115)

E2A: (GSG) Q C T N Y A L L K L A G D V E S N P G P (SEQ ID NO: 1116)

F2A: (GSG) V K Q T L N F D L L K L A G D V E S N P G P (SEQ ID NO: 1117)

Methods of introducing and expressing genes into a cell are known in the art. In the context of an expression vector, the vector can be readily introduced into a host cell, e.g., mammalian, bacterial, yeast, or insect cell by any method in the art. For example, the expression vector can be transferred into a host cell by physical, chemical, or biological means.

Physical methods for introducing a polynucleotide into a host cell include calcium phosphate precipitation, lipofection, particle bombardment, microinjection, electroporation, and the like. Methods for producing cells comprising vectors and/or exogenous nucleic acids are well-known in the art. See, for example, Sambrook et al., 2012, MOLECULAR CLONING: A LABORATORY MANUAL, volumes 1 -4, Cold Spring Harbor Press, NY). A preferred method for the introduction of a polynucleotide into a host cell is calcium phosphate transfection

Biological methods for introducing a polynucleotide of interest into a host cell include the use of DNA and RNA vectors. Viral vectors, and especially retroviral vectors, have become the most widely used method for inserting genes into mammalian, e.g., human cells. Other viral vectors can be derived from lentivirus, poxviruses, herpes simplex virus I, adenoviruses and adeno-associated viruses, and the like. See, for example, U.S. Pat. Nos. 5,350,674 and 5,585,362.

Chemical means for introducing a polynucleotide into a host cell include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. An exemplary colloidal system for use as a delivery vehicle in vitro and in vivo is a liposome (e.g. , an artificial membrane vesicle). Other methods of state-of-the-art targeted delivery of nucleic acids are available, such as delivery of polynucleotides with targeted nanoparticles or other suitable sub-micron sized delivery system.

In the case where a non-viral delivery system is utilized, an exemplary delivery vehicle is a liposome. The use of lipid formulations is contemplated for the introduction of the nucleic acids into a host cell (in vitro, ex vivo or in vivo). In another aspect, the nucleic acid may be associated with a lipid. The nucleic acid associated with a lipid may be encapsulated in the aqueous interior of a liposome, interspersed within the lipid bilayer of a liposome, attached to a liposome via a linking molecule that is associated with both the liposome and the

oligonucleotide, entrapped in a liposome, complexed with a liposome, dispersed in a solution containing a lipid, mixed with a lipid, combined with a lipid, contained as a suspension in a lipid, contained or complexed with a micelle, or otherwise associated with a lipid. Lipid, lipid/DNA or lipid/expression vector associated compositions are not limited to any particular structure in solution. For example, they may be present in a bilayer structure, as micelles, or with a "collapsed" structure. They may also simply be interspersed in a solution, possibly forming aggregates that are not uniform in size or shape. Lipids are fatty substances which may be naturally occurring or synthetic lipids. For example, lipids include the fatty droplets that naturally occur in the cytoplasm as well as the class of compounds which contain long-chain aliphatic hydrocarbons and their derivatives, such as fatty acids, alcohols, amines, amino alcohols, and aldehydes.

Lipids suitable for use can be obtained from commercial sources. For example, dimyristyl phosphatidylcholine ("DMPC") can be obtained from Sigma, St. Louis, MO; dicetyl phosphate ("DCP") can be obtained from K & K Laboratories (Plainview, NY); cholesterol ("Choi") can be obtained from Calbiochem-Behring; dimyristyl phosphatidylglycerol ("DMPG") and other lipids may be obtained from Avanti Polar Lipids, Inc. (Birmingham, AL.). Stock solutions of lipids in chloroform or chloroform/methanol can be stored at about -20ºC. Chloroform is used as the only solvent since it is more readily evaporated than methanol. "Liposome" is a generic term encompassing a variety of single and multilamellar lipid vehicles formed by the generation of enclosed lipid bilayers or aggregates. Liposomes can be characterized as having vesicular structures with a phospholipid bilayer membrane and an inner aqueous medium. Multilamellar liposomes have multiple lipid layers separated by aqueous medium. They form spontaneously when phospholipids are suspended in an excess of aqueous solution. The lipid components undergo self-rearrangement before the formation of closed structures and entrap water and dissolved solutes between the lipid bilayers (Ghosh et al., 1991 Glycobiology 5: 505-10). However, compositions that have different structures in solution than the normal vesicular structure are also encompassed. For example, the lipids may assume a micellar structure or merely exist as nonuniform aggregates of lipid molecules. Also contemplated are lipofectamine-nucleic acid complexes.

Regardless of the method used to introduce exogenous nucleic acids into a host cell or otherwise expose a cell to the inhibitor of the present invention, in order to confirm the

presence of the recombinant DNA sequence in the host cell, a variety of assays may be performed. Such assays include, for example, "molecular biological" assays well known to those of skill in the art, such as Southern and Northern blotting, RT-PCR and PCR; "biochemical" assays, such as detecting the presence or absence of a particular peptide, e.g., by immunological means (ELISAs and Western blots) or by assays described herein to identify agents falling within the scope of the invention.

The present invention further provides a vector comprising a CAR encoding nucleic acid molecule. In one aspect, a CAR vector can be directly transduced into a cell, *e.g.,* a T cell or NK cell. In one aspect, the vector is a cloning or expression vector, *e.g.,* a vector including, but not limited to, one or more plasmids (*e.g.*, expression plasmids, cloning vectors, minicircles, minivectors, double minute chromosomes), retroviral and lentiviral vector constructs. In one aspect, the vector is capable of expressing the CAR construct in mammalian T cells or NK cells. In one aspect, the mammalian T cell is a human T cell. In one aspect, the mammalian NK cell is a human NK cell.

Sources of cells

Prior to expansion and genetic modification, a source of cells, e.g., immune effector cells (e.g., T cells or NK cells), is obtained from a subject. The term "subject" is intended to include living organisms in which an immune response can be elicited (e.g., mammals). Examples of subjects include humans, dogs, cats, mice, rats, and transgenic species thereof. T cells can be obtained from a number of sources, including peripheral blood mononuclear cells, bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion, spleen tissue, and tumors.

In certain aspects of the present invention, any number of immune effector cell (e.g., T cell or NK cell) lines available in the art, may be used. In certain aspects of the present invention, T cells can be obtained from a unit of blood collected from a subject using any number of techniques known to the skilled artisan, such as Ficoll™ separation. In one preferred aspect, cells from the circulating blood of an individual are obtained by apheresis. The apheresis product typically contains lymphocytes, including T cells, monocytes, granulocytes, B cells, other nucleated white blood cells, red blood cells, and platelets. In one aspect, the cells

collected by apheresis may be washed to remove the plasma fraction and to place the cells in an appropriate buffer or media for subsequent processing steps. In one aspect of the invention, the cells are washed with phosphate buffered saline (PBS). In an alternative aspect, the wash solution lacks calcium and may lack magnesium or may lack many if not all divalent cations.

Initial activation steps in the absence of calcium can lead to magnified activation. As those of ordinary skill in the art would readily appreciate a washing step may be accomplished by methods known to those in the art, such as by using a semi-automated "flow-through" centrifuge (for example, the Cobe 2991 cell processor, the Baxter CytoMate, or the Haemonetics Cell Saver 5) according to the manufacturer's instructions. After washing, the cells may be resuspended in a variety of biocompatible buffers, such as, for example, Ca-free, Mg-free PBS, PlasmaLyte A, or other saline solution with or without buffer. Alternatively, the undesirable components of the apheresis sample may be removed and the cells directly resuspended in culture media.

It is recognized that the methods of the application can utilize culture media conditions comprising 5% or less, for example 2%, human AB serum, and employ known culture media conditions and compositions, for example those described in Smith *et al.*, "Ex vivo expansion of human T cells for adoptive immunotherapy using the novel Xeno-free CTS Immune Cell Serum Replacement" *Clinical & Translational Immunology* (2015) 4, e31; doi:10.1038/cti.2014.31.

In one aspect, T cells are isolated from peripheral blood lymphocytes by lysing the red blood cells and depleting the monocytes, for example, by centrifugation through a PERCOLLTM gradient or by counterflow centrifugal elutriation. A specific subpopulation of T cells, such as CD3+, CD28+, CD4+, CD8+, CD45RA+, and CD45RO+T cells, can be further isolated by positive or negative selection techniques. For example, in one aspect, T cells are isolated by incubation with anti-CD3/anti-CD28 (e.g., 3x28)-conjugated beads, such as DYNABEADS® M-450 CD3/CD28 T, for a time period sufficient for positive selection of the desired T cells. In one aspect, the time period is about 30 minutes. In a further aspect, the time period ranges from 30 minutes to 36 hours or longer and all integer values there between. In a further aspect, the time period is at least 1, 2, 3, 4, 5, or 6 hours. In yet another preferred aspect, the time period is 10 to 24 hours. In one aspect, the incubation time period is 24 hours. Longer incubation times may be used to isolate T cells in any situation where there are few T cells as

compared to other cell types, such in isolating tumor infiltrating lymphocytes (TIL) from tumor tissue or from immunocompromised individuals. Further, use of longer incubation times can increase the efficiency of capture of CD8+ T cells. Thus, by simply shortening or lengthening the time T cells are allowed to bind to the CD3/CD28 beads and/or by increasing or decreasing the ratio of beads to T cells (as described further herein), subpopulations of T cells can be preferentially selected for or against at culture initiation or at other time points during the process. Additionally, by increasing or decreasing the ratio of anti-CD3 and/or anti-CD28 antibodies on the beads or other surface, subpopulations of T cells can be preferentially selected for or against at culture initiation or at other desired time points. The skilled artisan would recognize that multiple rounds of selection can also be used in the context of this invention. In certain aspects, it may be desirable to perform the selection procedure and use the "unselected" cells in the activation and expansion process. "Unselected" cells can also be subjected to further rounds of selection.

Enrichment of a T cell population by negative selection can be accomplished with a combination of antibodies directed to surface markers unique to the negatively selected cells. One method is cell sorting and/or selection via negative magnetic immunoadherence or flow cytometry that uses a cocktail of monoclonal antibodies directed to cell surface markers present on the cells negatively selected. For example, to enrich for CD4+ cells by negative selection, a monoclonal antibody cocktail typically includes antibodies to CD14, CD20, CD11b, CD16, HLA-DR, and CD8. In certain aspects, it may be desirable to enrich for or positively select for regulatory T cells which typically express CD4+, CD25+, CD62Lhi, GITR+, and FoxP3+. Alternatively, in certain aspects, T regulatory cells are depleted by anti-C25 conjugated beads or other similar method of selection.

The methods described herein can include, e.g., selection of a specific subpopulation of immune effector cells, e.g., T cells, that are a T regulatory cell-depleted population, CD25+ depleted cells, using, e.g., a negative selection technique, e.g., described herein. Preferably, the population of T regulatory depleted cells contains less than 30%, 25%, 20%, 15%, 10%, 5%, 4%, 3%, 2%, 1% of CD25+ cells.

In one embodiment, T regulatory cells, e.g., CD25+ T cells, are removed from the population using an anti-CD25 antibody, or fragment thereof, or a CD25-binding ligand, IL-2. In one embodiment, the anti-CD25 antibody, or fragment thereof, or CD25-binding ligand is

conjugated to a substrate, e.g., a bead, or is otherwise coated on a substrate, e.g., a bead. In one embodiment, the anti-CD25 antibody, or fragment thereof, is conjugated to a substrate as described herein.

In one embodiment, the T regulatory cells, e.g., CD25+ T cells, are removed from the population using CD25 depletion reagent from Miltenyi™. In one embodiment, the ratio of cells to CD25 depletion reagent is 1e7 cells to 20 uL, or 1e7 cells to15 uL, or 1e7 cells to 10 uL, or 1e7 cells to 5 uL, or 1e7 cells to 2.5 uL, or 1e7 cells to 1.25 uL. In one embodiment, e.g., for T regulatory cells, e.g., CD25+ depletion, greater than 500 million cells/ml is used. In a further aspect, a concentration of cells of 600, 700, 800, or 900 million cells/ml is used.

In one embodiment, the population of immune effector cells to be depleted includes about 6 x 10^9 CD25+ T cells. In other aspects, the population of immune effector cells to be depleted include about 1 x 10^9 to 1x 10^{10} CD25+ T cell, and any integer value in between. In one embodiment, the resulting population T regulatory depleted cells has 2 x 10^9 T regulatory cells, e.g., CD25+ cells, or less (e.g., 1 x 10^9, 5 x 10^8, 1 x 10^8, 5 x 10^7, 1 x 10^7, or less CD25+ cells).

In one embodiment, the T regulatory cells, e.g., CD25+ cells, are removed from the population using the CliniMAC system with a depletion tubing set, such as, e.g., tubing 162-01. In one embodiment, the CliniMAC system is run on a depletion setting such as, e.g., DEPLETION2.1.

Without wishing to be bound by a particular theory, decreasing the level of negative regulators of immune cells (e.g., decreasing the number of unwanted immune cells, e.g., T_{REG} cells), in a subject prior to apheresis or during manufacturing of a CAR-expressing cell product can reduce the risk of subject relapse. For example, methods of depleting T_{REG} cells are known in the art. Methods of decreasing T_{REG} cells include, but are not limited to, cyclophosphamide, anti-GITR antibody (an anti-GITR antibody described herein), CD25-depletion, and combinations thereof.

In some embodiments, the manufacturing methods comprise reducing the number of (e.g., depleting) T_{REG} cells prior to manufacturing of the CAR-expressing cell. For example, manufacturing methods comprise contacting the sample, e.g., the apheresis sample, with an anti-GITR antibody and/or an anti-CD25 antibody (or fragment thereof, or a CD25-binding

ligand), e.g., to deplete T_{REG} cells prior to manufacturing of the CAR-expressing cell (e.g., T cell, NK cell) product.

In an embodiment, a subject is pre-treated with one or more therapies that reduce T_{REG} cells prior to collection of cells for CAR-expressing cell product manufacturing, thereby reducing the risk of subject relapse to CAR-expressing cell treatment. In an embodiment, methods of decreasing T_{REG} cells include, but are not limited to, administration to the subject of one or more of cyclophosphamide, anti-GITR antibody, CD25-depletion, or a combination thereof. Administration of one or more of cyclophosphamide, anti-GITR antibody, CD25-depletion, or a combination thereof, can occur before, during or after an infusion of the CAR-expressing cell product.

In an embodiment, a subject is pre-treated with cyclophosphamide prior to collection of cells for CAR-expressing cell product manufacturing, thereby reducing the risk of subject relapse to CAR-expressing cell treatment. In an embodiment, a subject is pre-treated with an anti-GITR antibody prior to collection of cells for CAR-expressing cell product manufacturing, thereby reducing the risk of subject relapse to CAR-expressing cell treatment.

In one embodiment, the population of cells to be removed are neither the regulatory T cells or tumor cells, but cells that otherwise negatively affect the expansion and/or function of CART cells, e.g. cells expressing CD14, CD11b, CD33, CD15, or other markers expressed by potentially immune suppressive cells. In one embodiment, such cells are envisioned to be removed concurrently with regulatory T cells and/or tumor cells, or following said depletion, or in another order.

The methods described herein can include more than one selection step, e.g., more than one depletion step. Enrichment of a T cell population by negative selection can be accomplished, e.g., with a combination of antibodies directed to surface markers unique to the negatively selected cells. One method is cell sorting and/or selection via negative magnetic immunoadherence or flow cytometry that uses a cocktail of monoclonal antibodies directed to cell surface markers present on the cells negatively selected. For example, to enrich for CD4+ cells by negative selection, a monoclonal antibody cocktail can include antibodies to CD14, CD20, CD11b, CD16, HLA-DR, and CD8.

The methods described herein can further include removing cells from the population which express a tumor antigen, e.g., a tumor antigen that does not comprise CD25, e.g., CD19, CD30, CD38, CD123, CD20, CD14 or CD11b, to thereby provide a population of T regulatory depleted, e.g., CD25+ depleted, and tumor antigen depleted cells that are suitable for expression of a CAR, e.g., a CAR described herein. In one embodiment, tumor antigen expressing cells are removed simultaneously with the T regulatory, e.g., CD25+ cells. For example, an anti-CD25 antibody, or fragment thereof, and an anti-tumor antigen antibody, or fragment thereof, can be attached to the same substrate, e.g., bead, which can be used to remove the cells or an anti-CD25 antibody, or fragment thereof, or the anti-tumor antigen antibody, or fragment thereof, can be attached to separate beads, a mixture of which can be used to remove the cells. In other embodiments, the removal of T regulatory cells, e.g., CD25+ cells, and the removal of the tumor antigen expressing cells is sequential, and can occur, e.g., in either order.

Also provided are methods that include removing cells from the population which express a check point inhibitor, e.g., a check point inhibitor described herein, e.g., one or more of PD1+ cells, LAG3+ cells, and TIM3+ cells, to thereby provide a population of T regulatory depleted, e.g., CD25+ depleted cells, and check point inhibitor depleted cells, e.g., PD1+, LAG3+ and/or TIM3+ depleted cells. Exemplary check point inhibitors include PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGFR beta. In embodiments, the checkpoint inhibitor is PD1 or PD-L1. In one embodiment, check point inhibitor expressing cells are removed simultaneously with the T regulatory, e.g., CD25+ cells. For example, an anti-CD25 antibody, or fragment thereof, and an anti-check point inhibitor antibody, or fragment thereof, can be attached to the same bead which can be used to remove the cells, or an anti-CD25 antibody, or fragment thereof, and the anti-check point inhibitor antibody, or fragment there, can be attached to separate beads, a mixture of which can be used to remove the cells. In other embodiments, the removal of T regulatory cells, e.g., CD25+ cells, and the removal of the check point inhibitor expressing cells is sequential, and can occur, e.g., in either order.

In one embodiment, a T cell population can be selected that expresses one or more of IFN-γ, TNFα, IL-17A, IL-2, IL-3, IL-4, GM-CSF, IL-10, IL-13, granzyme B, and perforin, or other appropriate molecules, e.g., other cytokines. Methods for screening for cell expression can be determined, e.g., by the methods described in PCT Publication No.: WO 2013/126712.

For isolation of a desired population of cells by positive or negative selection, the concentration of cells and surface (e.g., particles such as beads) can be varied. In certain aspects, it may be desirable to significantly decrease the volume in which beads and cells are mixed together (e.g., increase the concentration of cells), to ensure maximum contact of cells and beads. For example, in one aspect, a concentration of 2 billion cells/ml is used. In one aspect, a concentration of 1 billion cells/ml is used. In a further aspect, greater than 100 million cells/ml is used. In a further aspect, a concentration of cells of 10, 15, 20, 25, 30, 35, 40, 45, or 50 million cells/ml is used. In yet one aspect, a concentration of cells from 75, 80, 85, 90, 95, or 100 million cells/ml is used. In further aspects, concentrations of 125 or 150 million cells/ml can be used. Using high concentrations can result in increased cell yield, cell activation, and cell expansion. Further, use of high cell concentrations allows more efficient capture of cells that may weakly express target antigens of interest, such as CD28-negative T cells, or from samples where there are many tumor cells present (e.g., leukemic blood, tumor tissue, etc.). Such populations of cells may have therapeutic value and would be desirable to obtain. For example, using high concentration of cells allows more efficient selection of CD8+ T cells that normally have weaker CD28 expression.

In a related aspect, it may be desirable to use lower concentrations of cells. By significantly diluting the mixture of T cells and surface (e.g., particles such as beads), interactions between the particles and cells is minimized. This selects for cells that express high amounts of desired antigens to be bound to the particles. For example, CD4+ T cells express higher levels of CD28 and are more efficiently captured than CD8+ T cells in dilute concentrations. In one aspect, the concentration of cells used is 5 X 10e6/ml. In other aspects, the concentration used can be from about 1 X 10^5/ml to 1 X 10^6/ml, and any integer value in between.

In other aspects, the cells may be incubated on a rotator for varying lengths of time at varying speeds at either 2-10°C or at room temperature.

T cells for stimulation can also be frozen after a washing step. Wishing not to be bound by theory, the freeze and subsequent thaw step provides a more uniform product by removing granulocytes and to some extent monocytes in the cell population. After the washing step that removes plasma and platelets, the cells may be suspended in a freezing solution. While many freezing solutions and parameters are known in the art and will be useful in this context, one method involves using PBS containing 20% DMSO and 8% human serum albumin, or culture media containing 10% Dextran 40 and 5% Dextrose, 20% Human Serum Albumin and 7.5% DMSO, or 31.25% Plasmalyte-A, 31.25% Dextrose 5%, 0.45% NaCl, 10% Dextran 40 and 5% Dextrose, 20% Human Serum Albumin, and 7.5% DMSO or other suitable cell freezing media containing for example, Hespan and PlasmaLyte A, the cells then are frozen to -80°C at a rate of 1° per minute and stored in the vapor phase of a liquid nitrogen storage tank. Other methods of controlled freezing may be used as well as uncontrolled freezing immediately at -20° C or in liquid nitrogen.

In certain aspects, cryopreserved cells are thawed and washed as described herein and allowed to rest for one hour at room temperature prior to activation using the methods of the present invention.

Also contemplated in the context of the invention is the collection of blood samples or apheresis product from a subject at a time period prior to when the expanded cells as described herein might be needed. As such, the source of the cells to be expanded can be collected at any time point necessary, and desired cells, such as immune effector cells, e.g., T cells or NK cells, isolated and frozen for later use in cell therapy, e.g., T cell therapy, for any number of diseases or conditions that would benefit from cell therapy, e.g., T cell therapy, such as those described herein. In one aspect a blood sample or an apheresis is taken from a generally healthy subject. In certain aspects, a blood sample or an apheresis is taken from a generally healthy subject who is at risk of developing a disease, but who has not yet developed a disease, and the cells of interest are isolated and frozen for later use. In certain aspects, the immune effector cells (e.g., T cells or NK cells) may be expanded, frozen, and used at a later time. In certain aspects, samples are collected from a patient shortly after diagnosis of a particular disease as described herein but prior to any treatments. In a further aspect, the cells are isolated from a blood sample or an apheresis from a subject prior to any number of relevant treatment modalities, including but not limited to treatment with agents such as natalizumab, efalizumab, antiviral agents,

chemotherapy, radiation, immunosuppressive agents, such as cyclosporin, azathioprine, methotrexate, mycophenolate, and FK506, antibodies, or other immunoablative agents such as CAMPATH, anti-CD3 antibodies, cytoxan, fludarabine, cyclosporin, FK506, rapamycin, mycophenolic acid, steroids, FR901228, and irradiation.

In a further aspect of the present invention, T cells are obtained from a patient directly following treatment that leaves the subject with functional T cells. In this regard, it has been observed that following certain cancer treatments, in particular treatments with drugs that damage the immune system, shortly after treatment during the period when patients would normally be recovering from the treatment, the quality of T cells obtained may be optimal or improved for their ability to expand ex vivo. Likewise, following ex vivo manipulation using the methods described herein, these cells may be in a preferred state for enhanced engraftment and in vivo expansion. Thus, it is contemplated within the context of the present invention to collect blood cells, including T cells, dendritic cells, or other cells of the hematopoietic lineage, during this recovery phase. Further, in certain aspects, mobilization (for example, mobilization with GM-CSF) and conditioning regimens can be used to create a condition in a subject wherein repopulation, recirculation, regeneration, and/or expansion of particular cell types is favored, especially during a defined window of time following therapy. Illustrative cell types include T cells, B cells, dendritic cells, and other cells of the immune system.

In one embodiment, the immune effector cells expressing a CAR molecule, e.g., a CAR molecule described herein, are obtained from a subject that has received a low, immune enhancing dose of an mTOR inhibitor. In an embodiment, the population of immune effector cells, e.g., T cells, to be engineered to express a CAR, are harvested after a sufficient time, or after sufficient dosing of the low, immune enhancing, dose of an mTOR inhibitor, such that the level of PD1 negative immune effector cells, e.g., T cells, or the ratio of PD1 negative immune effector cells, e.g., T cells/ PD1 positive immune effector cells, e.g., T cells, in the subject or harvested from the subject has been, at least transiently, increased.

In other embodiments, population of immune effector cells, e.g., T cells, which have, or will be engineered to express a CAR, can be treated ex vivo by contact with an amount of an mTOR inhibitor that increases the number of PD1 negative immune effector cells, e.g., T cells or increases the ratio of PD1 negative immune effector cells, e.g., T cells/ PD1 positive immune effector cells, e.g., T cells.

In one embodiment, a T cell population is diaglycerol kinase (DGK)-deficient. DGK-deficient cells include cells that do not express DGK RNA or protein, or have reduced or inhibited DGK activity. DGK-deficient cells can be generated by genetic approaches, e.g., administering RNA-interfering agents, e.g., siRNA, shRNA, miRNA, to reduce or prevent DGK expression. Alternatively, DGK-deficient cells can be generated by treatment with DGK inhibitors described herein.

In one embodiment, a T cell population is Ikaros-deficient. Ikaros-deficient cells include cells that do not express Ikaros RNA or protein, or have reduced or inhibited Ikaros activity, Ikaros-deficient cells can be generated by genetic approaches, e.g., administering RNA-interfering agents, e.g., siRNA, shRNA, miRNA, to reduce or prevent Ikaros expression. Alternatively, Ikaros-deficient cells can be generated by treatment with Ikaros inhibitors, e.g., lenalidomide.

In embodiments, a T cell population is DGK-deficient and Ikaros-deficient, e.g., does not express DGK and Ikaros, or has reduced or inhibited DGK and Ikaros activity. Such DGK and Ikaros-deficient cells can be generated by any of the methods described herein.

In an embodiment, the NK cells are obtained from the subject. In another embodiment, the NK cells are an NK cell line, e.g., NK-92 cell line (Conkwest).

Allogeneic CAR

In embodiments described herein, the immune effector cell can be an allogeneic immune effector cell, e.g., T cell or NK cell. For example, the cell can be an allogeneic T cell, e.g., an allogeneic T cell lacking expression of a functional T cell receptor (TCR) and/or human leukocyte antigen (HLA), e.g., HLA class I and/or HLA class II.

A T cell lacking a functional TCR can be, e.g., engineered such that it does not express any functional TCR on its surface, engineered such that it does not express one or more subunits that comprise a functional TCR (e.g., engineered such that it does not express (or exhibits reduced expression) of TCR alpha, TCR beta, TCR gamma, TCR delta, TCR epsilon, and/or TCR zeta) or engineered such that it produces very little functional TCR on its surface. Alternatively, the T cell can express a substantially impaired TCR, e.g., by expression of mutated or truncated forms of one or more of the subunits of the TCR. The term "substantially impaired TCR" means that this TCR will not elicit an adverse immune reaction in a host.

A T cell described herein can be, e.g., engineered such that it does not express a functional HLA on its surface. For example, a T cell described herein, can be engineered such that cell surface expression HLA, e.g., HLA class 1 and/or HLA class II, is downregulated. In some aspects, downregulation of HLA may be accomplished by reducing or eliminating expression of beta-2 microglobulin (B2M).In some embodiments, the T cell can lack a functional TCR and a functional HLA, e.g., HLA class I and/or HLA class II.

Modified T cells that lack expression of a functional TCR and/or HLA can be obtained by any suitable means, including a knock out or knock down of one or more subunit of TCR or HLA. For example, the T cell can include a knock down of TCR and/or HLA using siRNA, shRNA, clustered regularly interspaced short palindromic repeats (CRISPR) transcription-activator like effector nuclease (TALEN), or zinc finger endonuclease (ZFN).

In some embodiments, the allogeneic cell can be a cell which does not expresses or expresses at low levels an inhibitory molecule, e.g. a cell engineered by any method described herein. For example, the cell can be a cell that does not express or expresses at low levels an inhibitory molecule, e.g., that can decrease the ability of a CAR-expressing cell to mount an immune effector response. Examples of inhibitory molecules include PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGFR beta. Inhibition of an inhibitory molecule, e.g., by inhibition at the DNA, RNA or protein level, can optimize a CAR-expressing cell performance. In embodiments, an inhibitory nucleic acid, e.g., an inhibitory nucleic acid, e.g., a dsRNA, e.g., an siRNA or shRNA, a clustered regularly interspaced short palindromic repeats (CRISPR), a transcription-activator like effector nuclease (TALEN), or a zinc finger endonuclease (ZFN), e.g., as described herein, can be used.

siRNA and shRNA to inhibit TCR or HLA

In some embodiments, TCR expression and/or HLA expression can be inhibited using siRNA or shRNA that targets a nucleic acid encoding a TCR, and/or HLA, and/or an inhibitory molecule described herein (e.g., PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGFR beta), in a cell, e.g., T cell.

Expression of siRNA and shRNAs in T cells can be achieved using any conventional expression system, e.g., such as a lentiviral expression system.

Exemplary shRNAs that downregulate expression of components of the TCR are described, e.g., in US Publication No.: 2012/0321667. Exemplary siRNA and shRNA that downregulate expression of HLA class I and/or HLA class II genes are described, e.g., in U.S. publication No.: US 2007/0036773.

CRISPR to inhibit TCR or HLA

"CRISPR" or "CRISPR to TCR and/or HLA" or "CRISPR to inhibit TCR and/or HLA" as used herein refers to a set of clustered regularly interspaced short palindromic repeats, or a system comprising such a set of repeats. "Cas", as used herein, refers to a CRISPR-associated protein. A "CRISPR/Cas" system refers to a system derived from CRISPR and Cas which can be used to silence or mutate a TCR and/or HLA gene, and/or an inhibitory molecule described herein (e.g., PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGFR beta).

Naturally-occurring CRISPR/Cas systems are found in approximately 40% of sequenced eubacteria genomes and 90% of sequenced archaea. Grissa *et al.* (2007) *BMC Bioinformatics* 8: 172. This system is a type of prokaryotic immune system that confers resistance to foreign genetic elements such as plasmids and phages and provides a form of acquired immunity. Barrangou *et al.* (2007) *Science* 315: 1709-1712; Marragini *et al.* (2008) *Science* 322: 1843-1845.

The CRISPR/Cas system has been modified for use in gene editing (silencing, enhancing or changing specific genes) in eukaryotes such as mice or primates. Wiedenheft *et al.* (2012) *Nature* 482: 331-8. This is accomplished by introducing into the eukaryotic cell a plasmid containing a specifically designed CRISPR and one or more appropriate Cas.

The CRISPR sequence, sometimes called a CRISPR locus, comprises alternating repeats and spacers. In a naturally-occurring CRISPR, the spacers usually comprise sequences foreign to the bacterium such as a plasmid or phage sequence; in the TCR and/or HLA CRISPR/Cas system, the spacers are derived from the TCR or HLA gene sequence.

RNA from the CRISPR locus is constitutively expressed and processed by Cas proteins into small RNAs. These comprise a spacer flanked by a repeat sequence. The RNAs guide

other Cas proteins to silence exogenous genetic elements at the RNA or DNA level. Horvath *et al.* (2010) *Science* 327: 167-170; Makarova *et al.* (2006) *Biology Direct* 1: 7. The spacers thus serve as templates for RNA molecules, analogously to siRNAs. Pennisi (2013) *Science* 341: 833-836.

As these naturally occur in many different types of bacteria, the exact arrangements of the CRISPR and structure, function and number of Cas genes and their product differ somewhat from species to species. Haft *et al.* (2005) *PLoS Comput. Biol.* 1: e60; Kunin *et al.* (2007) *Genome Biol.* 8: R61; Mojica *et al.* (2005) *J. Mol. Evol.* 60: 174-182; Bolotin *et al.* (2005) *Microbiol.* 151: 2551-2561; Pourcel et al. (2005) *Microbiol.* 151: 653-663; and Stern *et al.* (2010) *Trends. Genet.* 28: 335-340. For example, the Cse (Cas subtype, E. coli) proteins (e.g., CasA) form a functional complex, Cascade, that processes CRISPR RNA transcripts into spacer-repeat units that Cascade retains. Brouns et al. (2008) *Science* 321: 960-964. In other prokaryotes, Cas6 processes the CRISPR transcript. The CRISPR-based phage inactivation in E. coli requires Cascade and Cas3, but not Cas1 or Cas2. The Cmr (Cas RAMP module) proteins in Pyrococcus furiosus and other prokaryotes form a functional complex with small CRISPR RNAs that recognizes and cleaves complementary target RNAs. A simpler CRISPR system relies on the protein Cas9, which is a nuclease with two active cutting sites, one for each strand of the double helix. Combining Cas9 and modified CRISPR locus RNA can be used in a system for gene editing. Pennisi (2013) *Science* 341: 833-836.

The CRISPR/Cas system can thus be used to edit a TCR and/or HLA gene (adding or deleting a basepair), or introducing a premature stop which thus decreases expression of a TCR and/or HLA. The CRISPR/Cas system can alternatively be used like RNA interference, turning off TCR and/or HLA gene in a reversible fashion. In a mammalian cell, for example, the RNA can guide the Cas protein to a TCR and/or HLA promoter, sterically blocking RNA polymerases.

Artificial CRISPR/Cas systems can be generated which inhibit TCR and/or HLA, using technology known in the art, e.g., that described in U.S. Publication No.20140068797, and Cong (2013) Science 339: 819-823. Other artificial CRISPR/Cas systems that are known in the art may also be generated which inhibit TCR and/or HLA, e.g., that described in Tsai (2014) Nature Biotechnol., 32:6 569-576, U.S. Patent No.: 8,871,445; 8,865,406; 8,795,965; 8,771,945; and 8,697,359.

TALEN to inhibit TCR and/or HLA

"TALEN" or "TALEN to HLA and/or TCR" or "TALEN to inhibit HLA and/or TCR" refers to a transcription activator-like effector nuclease, an artificial nuclease which can be used to edit the HLA, and/or TCR gene, and/or an inhibitory molecule described herein (e.g., PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGFR beta).

TALENs are produced artificially by fusing a TAL effector DNA binding domain to a DNA cleavage domain. Transcription activator-like effects (TALEs) can be engineered to bind any desired DNA sequence, including a portion of the HLA or TCR gene. By combining an engineered TALE with a DNA cleavage domain, a restriction enzyme can be produced which is specific to any desired DNA sequence, including a HLA or TCR sequence. These can then be introduced into a cell, wherein they can be used for genome editing. Boch (2011) *Nature Biotech.* 29: 135-6; and Boch et al. (2009) *Science* 326: 1509-12; Moscou et al. (2009) *Science* 326: 3501.

TALEs are proteins secreted by Xanthomonas bacteria. The DNA binding domain contains a repeated, highly conserved 33-34 amino acid sequence, with the exception of the 12th and 13th amino acids. These two positions are highly variable, showing a strong correlation with specific nucleotide recognition. They can thus be engineered to bind to a desired DNA sequence.

To produce a TALEN, a TALE protein is fused to a nuclease (N), which is a wild-type or mutated FokI endonuclease. Several mutations to FokI have been made for its use in TALENs; these, for example, improve cleavage specificity or activity. Cermak et al. (2011) *Nucl. Acids Res.* 39: e82; Miller et al. (2011) *Nature Biotech.* 29: 143-8; Hockemeyer et al. (2011) *Nature Biotech.* 29: 731-734; Wood et al. (2011) *Science* 333: 307; Doyon et al. (2010) *Nature Methods* 8: 74-79; Szczepek et al. (2007) *Nature Biotech.* 25: 786-793; and Guo et al. (2010) *J. Mol. Biol.* 200: 96.

The FokI domain functions as a dimer, requiring two constructs with unique DNA binding domains for sites in the target genome with proper orientation and spacing. Both the number of amino acid residues between the TALE DNA binding domain and the FokI cleavage domain and the number of bases between the two individual TALEN binding sites appear to be

important parameters for achieving high levels of activity. Miller et al. (2011) *Nature Biotech.* 29: 143-8.

A HLA or TCR TALEN can be used inside a cell to produce a double-stranded break (DSB). A mutation can be introduced at the break site if the repair mechanisms improperly repair the break via non-homologous end joining. For example, improper repair may introduce a frame shift mutation. Alternatively, foreign DNA can be introduced into the cell along with the TALEN; depending on the sequences of the foreign DNA and chromosomal sequence, this process can be used to correct a defect in the HLA or TCR gene or introduce such a defect into a wt HLA or TCR gene, thus decreasing expression of HLA or TCR.

TALENs specific to sequences in HLA or TCR can be constructed using any method known in the art, including various schemes using modular components. Zhang et al. (2011) *Nature Biotech.* 29: 149-53; Geibler et al. (2011) *PLoS ONE* 6: e19509.

Zinc finger nuclease to inhibit HLA and/or TCR

"ZFN" or "Zinc Finger Nuclease" or "ZFN to HLA and/or TCR" or "ZFN to inhibit HLA and/or TCR" refer to a zinc finger nuclease, an artificial nuclease which can be used to edit the HLA, and/or TCR gene, and/or an inhibitory molecule described herein (e.g., PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGFR beta).

Like a TALEN, a ZFN comprises a FokI nuclease domain (or derivative thereof) fused to a DNA-binding domain. In the case of a ZFN, the DNA-binding domain comprises one or more zinc fingers. Carroll et al. (2011) *Genetics Society of America* 188: 773-782; and Kim et al. (1996) *Proc. Natl. Acad. Sci. USA* 93: 1156-1160.

A zinc finger is a small protein structural motif stabilized by one or more zinc ions. A zinc finger can comprise, for example, Cys2His2, and can recognize an approximately 3-bp sequence. Various zinc fingers of known specificity can be combined to produce multi-finger polypeptides which recognize about 6, 9, 12, 15 or 18-bp sequences. Various selection and modular assembly techniques are available to generate zinc fingers (and combinations thereof) recognizing specific sequences, including phage display, yeast one-hybrid systems, bacterial one-hybrid and two-hybrid systems, and mammalian cells.

Like a TALEN, a ZFN must dimerize to cleave DNA. Thus, a pair of ZFNs are required to target non-palindromic DNA sites. The two individual ZFNs must bind opposite strands of the DNA with their nucleases properly spaced apart. Bitinaite et al. (1998) *Proc. Natl. Acad. Sci. USA* 95: 10570-5.

Also like a TALEN, a ZFN can create a double-stranded break in the DNA, which can create a frame-shift mutation if improperly repaired, leading to a decrease in the expression and amount of HLA and/or TCR in a cell. ZFNs can also be used with homologous recombination to mutate in the HLA or TCR gene.

ZFNs specific to sequences in HLA AND/OR TCR can be constructed using any method known in the art. See, e.g., Provasi (2011) Nature Med. 18: 807-815; Torikai (2013) Blood 122: 1341-1349; Cathomen et al. (2008) *Mol. Ther.* 16: 1200-7; Guo et al. (2010) *J. Mol. Biol.* 400: 96; U.S. Patent Publication 2011/0158957; and U.S. Patent Publication 2012/0060230.

Telomerase expression

While not wishing to be bound by any particular theory, in some embodiments, a therapeutic T cell has short term persistence in a patient, due to shortened telomeres in the T cell; accordingly, transfection with a telomerase gene can lengthen the telomeres of the T cell and improve persistence of the T cell in the patient. See Carl June, "Adoptive T cell therapy for cancer in the clinic", Journal of Clinical Investigation, 117:1466-1476 (2007). Thus, in an embodiment, an immune effector cell, e.g., a T cell, ectopically expresses a telomerase subunit, e.g., the catalytic subunit of telomerase, e.g., TERT, e.g., hTERT. In some aspects, this disclosure provides a method of producing a CAR-expressing cell, comprising contacting a cell with a nucleic acid encoding a telomerase subunit, e.g., the catalytic subunit of telomerase, e.g., TERT, e.g., hTERT. The cell may be contacted with the nucleic acid before, simultaneous with, or after being contacted with a construct encoding a CAR.

In one aspect, the disclosure features a method of making a population of immune effector cells (e.g., T cells, NK cells). In an embodiment, the method comprises: providing a population of immune effector cells (e.g., T cells or NK cells), contacting the population of immune effector cells with a nucleic acid encoding a CAR; and contacting the population of

immune effector cells with a nucleic acid encoding a telomerase subunit, e.g., hTERT, under conditions that allow for CAR and telomerase expression.

In an embodiment, the nucleic acid encoding the telomerase subunit is DNA. In an embodiment, the nucleic acid encoding the telomerase subunit comprises a promoter capable of driving expression of the telomerase subunit.

In an embodiment, hTERT has the amino acid sequence of GenBank Protein ID AAC51724.1 (Meyerson et al., "hEST2, the Putative Human Telomerase Catalytic Subunit Gene, Is Up-Regulated in Tumor Cells and during Immortalization" Cell Volume 90, Issue 4, 22 August 1997, Pages 785–795) as follows:

MPRAPRCRAVRSLLRSHYREVLPLATFVRRLGPQGWRLVQRGDPAAFRALVA
QCLVCVPWDARPPPAAPSFRQVSCLKELVARVLQRLCERGAKNVLAFGFALLDGARG
GPPEAFTTSVRSYLPNTVTDALRGSGAWGLLLRRVGDDVLVHLLARCALFVLVAPSCA
YQVCGPPLYQLGAATQARPPPHASGPRRRLGCERAWNHSVREAGVPLGLPAPGARRR
GGSASRSLPLPKRPRRGAAPEPERTPVGQGSWAHPGRTRGPSDRGFCVVSPARPAEEA
TSLEGALSGTRHSHPSVGRQHHAGPPSTSRPPRPWDTPCPPVYAETKHFLYSSGDKEQL
RPSFLLSSLRPSLTGARRLVETIFLGSRPWMPGTPRRLPRLPQRYWQMRPLFLELLGNH
AQCPYGVLLKTHCPLRAAVTPAAGVCAREKPQGSVAAPEEEDTDPRRLVQLLRQHSSP
WQVYGFVRACLRRLVPPGLWGSRHNERRFLRNTKKFISLGKHAKLSLQELTWKMSVR
GCAWLRRSPGVGCVPAAEHRLREEILAKFLHWLMSVYVVELLRSFFYVTETTFQKNRL
FFYRKSVWSKLQSIGIRQHLKRVQLRELSEAEVRQHREARPALLTSRLRFIPKPDGLRPI
VNMDYVVGARTFRREKRAERLTSRVKALFSVLNYERARRPGLLGASVLGLDDIHRAW
RTFVLRVRAQDPPPELYFVKVDVTGAYDTIPQDRLTEVIASIIKPQNTYCVRRYAVVQK
AAHGHVRKAFKSHVSTLTDLQPYMRQFVAHLQETSPLRDAVVIEQSSSLNEASSGLFD
VFLRFMCHHAVRIRGKSYVQCQGIPQGSILSTLLCSLCYGDMENKLFAGIRRDGLLLRL
VDDFLLVTPHLTHAKTFLRTLVRGVPEYGCVVNLRKTVVNFPVEDEALGGTAFVQMP
AHGLFPWCGLLLDTRTLEVQSDYSSYARTSIRASLTFNRGFKAGRNMRRKLFGVLRLK
CHSLFLDLQVNSLQTVCTNIYKILLLQAYRFHACVLQLPFHQQVWKNPTFFLRVISDTA
SLCYSILKAKNAGMSLGAKGAAGPLPSEAVQWLCHQAFLLKLTRHRVTYVPLLGSLR
TAQTQLSRKLPGTTLTALEAAANPALPSDFKTILD (SEQ ID NO: 284)

In an embodiment, the hTERT has a sequence at least 80%, 85%, 90%, 95%, 96^, 97%, 98%, or 99% identical to the sequence of SEQ ID NO: 284. In an embodiment, the hTERT has a sequence of SEQ ID NO: 284. In an embodiment, the hTERT comprises a deletion (e.g., of no more than 5, 10, 15, 20, or 30 amino acids) at the N-terminus, the C-terminus, or both. In an embodiment, the hTERT comprises a transgenic amino acid sequence (e.g., of no more than 5, 10, 15, 20, or 30 amino acids) at the N-terminus, the C-terminus, or both.

In an embodiment, the hTERT is encoded by the nucleic acid sequence of GenBank Accession No. AF018167 (Meyerson et al., "hEST2, the Putative Human Telomerase Catalytic Subunit Gene, Is Up-Regulated in Tumor Cells and during Immortalization" Cell Volume 90, Issue 4, 22 August 1997, Pages 785–795):

1 caggcagcgt ggtcctgctg cgcacgtggg aagccctggc cccggccacc cccgcgatgc
61 cgcgcgctcc ccgctgccga gccgtgcgct ccctgctgcg cagccactac cgcgaggtgc
121 tgccgctggc cacgttcgtg cggcgcctgg ggccccaggg ctggcggctg gtgcagcgcg
181 gggacccggc ggctttccgc gcgctggtgg cccagtgcct ggtgtgcgtg ccctgggacg
241 cacggccgcc ccccgccgcc ccctccttcc gccaggtgtc ctgcctgaag gagctggtgg
301 cccgagtgct gcagaggctg tgcgagcgcg gcgcgaagaa cgtgctggcc ttcggcttcg
361 cgctgctgga cggggcccgc gggggccccc ccgaggcctt caccaccagc gtgcgcagct
421 acctgcccaa cacggtgacc gacgcactgc gggggagcgg ggcgtggggg ctgctgttgc
481 gccgcgtggg cgacgacgtg ctggttcacc tgctggcacg ctgcgcgctc tttgtgctgg
541 tggctcccag ctgcgcctac caggtgtgcg ggccgccgct gtaccagctc ggcgctgcca
601 ctcaggcccg gcccccgcca cacgctagtg gaccccgaag gcgtctggga tgcgaacggg
661 cctggaacca tagcgtcagg gaggccgggg tccccctggg cctgccagcc ccgggtgcga
721 ggaggcgcgg gggcagtgcc agccgaagtc tgccgttgcc caagaggccc aggcgtggcg
781 ctgcccctga gccggagcgg acgcccgttg ggcaggggtc ctgggcccac ccgggcagga
841 cgcgtggacc gagtgaccgt ggtttctgtg tggtgtcacc tgccagaccc gccgaagaag
901 ccacctcttt ggagggtgcg ctctctggca cgcgccactc ccacccatcc gtgggccgcc
961 agcaccacgc gggcccccca tccacatcgc ggccaccacg tccctgggac acgccttgtc
1021 ccccggtgta cgccgagacc aagcacttcc tctactcctc aggcgacaag gagcagctgc
1081 ggccctcctt cctactcagc tctctgaggc ccagcctgac tggcgctcgg aggctcgtgg
1141 agaccatctt tctgggttcc aggccctgga tgccagggac tccccgcagg ttgccccgcc
1201 tgccccagcg ctactggcaa atgcggcccc tgtttctgga gctgcttggg aaccacgcgc
1261 agtgccccta cggggtgctc ctcaagacgc actgcccgct gcgagctgcg gtcaccccag

1321 cagccggtgt ctgtgcccgg gagaagcccc agggctctgt ggcggccccc gaggaggagg
1381 acacagaccc ccgtcgcctg gtgcagctgc tccgccagca cagcagcccc tggcaggtgt
1441 acggcttcgt gcgggcctgc ctgcgccggc tggtgccccc aggcctctgg ggctccaggc
1501 acaacgaacg ccgcttcctc aggaacacca agaagttcat ctccctgggg aagcatgcca
1561 agctctcgct gcaggagctg acgtggaaga tgagcgtgcg gggctgcgct tggctgcgca
1621 ggagcccagg ggttggctgt gttccggccg cagagcaccg tctgcgtgag gagatcctgg
1681 ccaagttcct gcactggctg atgagtgtgt acgtcgtcga gctgctcagg tctttctttt
1741 atgtcacgga gaccacgttt caaaagaaca ggctcttttt ctaccggaag agtgtctgga
1801 gcaagttgca aagcattgga atcagacagc acttgaagag ggtgcagctg cgggagctgt
1861 cggaagcaga ggtcaggcag catcgggaag ccaggcccgc cctgctgacg tccagactcc
1921 gcttcatccc caagcctgac gggctgcggc cgattgtgaa catggactac gtcgtgggag
1981 ccagaacgtt ccgcagagaa aagagggccg agcgtctcac ctcgagggtg aaggcactgt
2041 tcagcgtgct caactacgag cgggcgcggc gccccggcct cctgggcgcc tctgtgctgg
2101 gcctggacga tatccacagg gcctggcgca ccttcgtgct gcgtgtgcgg gcccaggacc
2161 cgccgcctga gctgtacttt gtcaaggtgg atgtgacggg cgcgtacgac accatccccc
2221 aggacaggct cacggaggtc atcgccagca tcatcaaacc ccagaacacg tactgcgtgc
2281 gtcggtatgc cgtggtccag aaggccgccc atgggcacgt ccgcaaggcc ttcaagagcc
2341 acgtctctac cttgacagac ctccagccgt acatgcgaca gttcgtggct cacctgcagg
2401 agaccagccc gctgagggat gccgtcgtca tcgagcagag ctcctccctg aatgaggcca
2461 gcagtggcct cttcgacgtc ttcctacgct tcatgtgcca ccacgccgtg cgcatcaggg
2521 gcaagtccta cgtccagtgc caggggatcc cgcagggctc catcctctcc acgctgctct
2581 gcagcctgtg ctacggcgac atggagaaca agctgtttgc ggggattcgg cgggacgggc
2641 tgctcctgcg tttggtggat gatttcttgt tggtgacacc tcacctcacc cacgcgaaaa
2701 ccttcctcag gaccctggtc cgaggtgtcc ctgagtatgg ctgcgtggtg aacttgcgga
2761 agacagtggt gaacttccct gtagaagacg aggccctggg tggcacggct tttgttcaga
2821 tgccggccca cggcctattc ccctggtgcg gcctgctgct ggatacccgg accctggagg
2881 tgcagagcga ctactccagc tatgcccgga cctccatcag agccagtctc accttcaacc
2941 gcggcttcaa ggctgggagg aacatgcgtc gcaaactctt tggggtcttg cggctgaagt
3001 gtcacagcct gtttctggat ttgcaggtga acagcctcca gacggtgtgc accaacatct
3061 acaagatcct cctgctgcag gcgtacaggt ttcacgcatg tgtgctgcag ctcccatttc
3121 atcagcaagt ttggaagaac cccacatttt tcctgcgcgt catctctgac acggcctccc
3181 tctgctactc catcctgaaa gccaagaacg cagggatgtc gctgggggcc aagggcgccg

3241 ccggccctct gccctccgag gccgtgcagt ggctgtgcca ccaagcattc ctgctcaagc
3301 tgactcgaca ccgtgtcacc tacgtgccac tcctggggtc actcaggaca gcccagacgc
3361 agctgagtcg gaagctcccg gggacgacgc tgactgccct ggaggccgca gccaacccgg
3421 cactgccctc agacttcaag accatcctgg actgatggcc acccgcccac agccaggccg
3481 agagcagaca ccagcagccc tgtcacgccg ggctctacgt cccagggagg gaggggcggc
3541 ccacacccag gcccgcaccg ctgggagtct gaggcctgag tgagtgtttg gccgaggcct
3601 gcatgtccgg ctgaaggctg agtgtccggc tgaggcctga gcgagtgtcc agccaagggc
3661 tgagtgtcca gcacacctgc cgtcttcact tccccacagg ctggcgctcg gctccacccc
3721 agggccagct tttcctcacc aggagcccgg cttccactcc ccacatagga atagtccatc
3781 cccagattcg ccattgttca cccctcgccc tgccctcctt tgccttccac ccccaccatc
3841 caggtggaga ccctgagaag gaccctggga gctctgggaa tttggagtga ccaaaggtgt
3901 gccctgtaca caggcgagga ccctgcacct ggatgggggt ccctgtgggt caaattgggg
3961 ggaggtgctg tgggagtaaa atactgaata tatgagtttt tcagttttga aaaaaaaaaa
4021 aaaaaaa (SEQ ID NO: 285)

In an embodiment, the hTERT is encoded by a nucleic acid having a sequence at least 80%, 85%, 90%, 95%, 96, 97%, 98%, or 99% identical to the sequence of SEQ ID NO: 285. In an embodiment, the hTERT is encoded by a nucleic acid of SEQ ID NO: 285.

Activation and Expansion of T Cells

T cells may be activated and expanded generally using methods as described, for example, in U.S. Patents 6,352,694; 6,534,055; 6,905,680; 6,692,964; 5,858,358; 6,887,466; 6,905,681; 7,144,575; 7,067,318; 7,172,869; 7,232,566; 7,175,843; 5,883,223; 6,905,874; 6,797,514; 6,867,041; and U.S. Patent Application Publication No. 20060121005.

Generally, the T cells of the invention may be expanded by contact with a surface having attached thereto an agent that stimulates a CD3/TCR complex associated signal and a ligand that stimulates a costimulatory molecule on the surface of the T cells. In particular, T cell populations may be stimulated as described herein, such as by contact with an anti-CD3 antibody, or antigen-binding fragment thereof, or an anti-CD2 antibody immobilized on a surface, or by contact with a protein kinase C activator (e.g., bryostatin) in conjunction with a calcium ionophore. For co-stimulation of an accessory molecule on the surface of the T cells, a ligand that binds the accessory molecule is used. For example, a population of T cells can be

contacted with an anti-CD3 antibody and an anti-CD28 antibody, under conditions appropriate for stimulating proliferation of the T cells. To stimulate proliferation of either CD4+ T cells or CD8+ T cells, an anti-CD3 antibody and an anti-CD28 antibody can be used. Examples of an anti-CD28 antibody include 9.3, B-T3, XR-CD28 (Diaclone, Besançon, France) can be used as can other methods commonly known in the art (Berg et al., Transplant Proc. 30(8):3975-3977, 1998; Haanen et al., J. Exp. Med. 190(9):13191328, 1999; Garland et al., J. Immunol Meth. 227(1-2):53-63, 1999).

In certain aspects, the primary stimulatory signal and the costimulatory signal for the T cell may be provided by different protocols. For example, the agents providing each signal may be in solution or coupled to a surface. When coupled to a surface, the agents may be coupled to the same surface (i.e., in "cis" formation) or to separate surfaces (i.e., in "trans" formation). Alternatively, one agent may be coupled to a surface and the other agent in solution. In one aspect, the agent providing the costimulatory signal is bound to a cell surface and the agent providing the primary activation signal is in solution or coupled to a surface. In certain aspects, both agents can be in solution. In one aspect, the agents may be in soluble form, and then cross-linked to a surface, such as a cell expressing Fc receptors or an antibody or other binding agent which will bind to the agents. In this regard, see for example, U.S. Patent Application Publication Nos. 20040101519 and 20060034810 for artificial antigen presenting cells (aAPCs) that are contemplated for use in activating and expanding T cells in the present invention.

In one aspect, the two agents are immobilized on beads, either on the same bead, i.e., "cis," or to separate beads, i.e., "trans." By way of example, the agent providing the primary activation signal is an anti-CD3 antibody or an antigen-binding fragment thereof and the agent providing the costimulatory signal is an anti-CD28 antibody or antigen-binding fragment thereof; and both agents are co-immobilized to the same bead in equivalent molecular amounts. In one aspect, a 1:1 ratio of each antibody bound to the beads for CD4+ T cell expansion and T cell growth is used. In certain aspects of the present invention, a ratio of anti CD3:CD28 antibodies bound to the beads is used such that an increase in T cell expansion is observed as compared to the expansion observed using a ratio of 1:1. In one particular aspect an increase of from about 1 to about 3 fold is observed as compared to the expansion observed using a ratio of 1:1. In one aspect, the ratio of CD3:CD28 antibody bound to the beads ranges from 100:1 to 1:100 and all integer values there between. In one aspect of the present invention, more anti-

CD28 antibody is bound to the particles than anti-CD3 antibody, i.e., the ratio of CD3:CD28 is less than one. In certain aspects of the invention, the ratio of anti CD28 antibody to anti CD3 antibody bound to the beads is greater than 2:1. In one particular aspect, a 1:100 CD3:CD28 ratio of antibody bound to beads is used. In one aspect, a 1:75 CD3:CD28 ratio of antibody bound to beads is used. In a further aspect, a 1:50 CD3:CD28 ratio of antibody bound to beads is used. In one aspect, a 1:30 CD3:CD28 ratio of antibody bound to beads is used. In one preferred aspect, a 1:10 CD3:CD28 ratio of antibody bound to beads is used. In one aspect, a 1:3 CD3:CD28 ratio of antibody bound to the beads is used. In yet one aspect, a 3:1 CD3:CD28 ratio of antibody bound to the beads is used.

Ratios of particles to cells from 1:500 to 500:1 and any integer values in between may be used to stimulate T cells or other target cells. As those of ordinary skill in the art can readily appreciate, the ratio of particles to cells may depend on particle size relative to the target cell. For example, small sized beads could only bind a few cells, while larger beads could bind many. In certain aspects the ratio of cells to particles ranges from 1:100 to 100:1 and any integer values in-between and in further aspects the ratio comprises 1:9 to 9:1 and any integer values in between, can also be used to stimulate T cells. The ratio of anti-CD3- and anti-CD28-coupled particles to T cells that result in T cell stimulation can vary as noted above, however certain preferred values include 1:100, 1:50, 1:40, 1:30, 1:20, 1:10, 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, and 15:1 with one preferred ratio being at least 1:1 particles per T cell. In one aspect, a ratio of particles to cells of 1:1 or less is used. In one particular aspect, a preferred particle: cell ratio is 1:5. In further aspects, the ratio of particles to cells can be varied depending on the day of stimulation. For example, in one aspect, the ratio of particles to cells is from 1:1 to 10:1 on the first day and additional particles are added to the cells every day or every other day thereafter for up to 10 days, at final ratios of from 1:1 to 1:10 (based on cell counts on the day of addition). In one particular aspect, the ratio of particles to cells is 1:1 on the first day of stimulation and adjusted to 1:5 on the third and fifth days of stimulation. In one aspect, particles are added on a daily or every other day basis to a final ratio of 1:1 on the first day, and 1:5 on the third and fifth days of stimulation. In one aspect, the ratio of particles to cells is 2:1 on the first day of stimulation and adjusted to 1:10 on the third and fifth days of stimulation. In one aspect, particles are added on a daily or every other day basis to a final ratio of 1:1 on the first day, and 1:10 on the third and fifth days of

stimulation. One of skill in the art will appreciate that a variety of other ratios may be suitable for use in the present invention. In particular, ratios will vary depending on particle size and on cell size and type. In one aspect, the most typical ratios for use are in the neighborhood of 1:1, 2:1 and 3:1 on the first day.

In further aspects of the present invention, the cells, such as T cells, are combined with agent-coated beads, the beads and the cells are subsequently separated, and then the cells are cultured. In an alternative aspect, prior to culture, the agent-coated beads and cells are not separated but are cultured together. In a further aspect, the beads and cells are first concentrated by application of a force, such as a magnetic force, resulting in increased ligation of cell surface markers, thereby inducing cell stimulation.

By way of example, cell surface proteins may be ligated by allowing paramagnetic beads to which anti-CD3 and anti-CD28 are attached (3x28 beads) to contact the T cells. In one aspect the cells (for example, 10^4 to 10^9 T cells) and beads (for example, DYNABEADS® M-450 CD3/CD28 T paramagnetic beads at a ratio of 1:1) are combined in a buffer, for example PBS (without divalent cations such as, calcium and magnesium). Again, those of ordinary skill in the art can readily appreciate any cell concentration may be used. For example, the target cell may be very rare in the sample and comprise only 0.01% of the sample or the entire sample (i.e., 100%) may comprise the target cell of interest. Accordingly, any cell number is within the context of the present invention. In certain aspects, it may be desirable to significantly decrease the volume in which particles and cells are mixed together (i.e., increase the concentration of cells), to ensure maximum contact of cells and particles. For example, in one aspect, a concentration of about 10 billion cells/ml, 9 billion/ml, 8 billion/ml, 7 billion/ml, 6 billion/ml, 5 billion/ml, or 2 billion cells/ml is used. In one aspect, greater than 100 million cells/ml is used. In a further aspect, a concentration of cells of 10, 15, 20, 25, 30, 35, 40, 45, or 50 million cells/ml is used. In yet one aspect, a concentration of cells from 75, 80, 85, 90, 95, or 100 million cells/ml is used. In further aspects, concentrations of 125 or 150 million cells/ml can be used. Using high concentrations can result in increased cell yield, cell activation, and cell expansion. Further, use of high cell concentrations allows more efficient capture of cells that may weakly express target antigens of interest, such as CD28-negative T cells. Such populations of cells may have therapeutic value and would be desirable to obtain in certain

aspects. For example, using high concentration of cells allows more efficient selection of CD8+ T cells that normally have weaker CD28 expression.

In one embodiment, cells transduced with a nucleic acid encoding a CAR, e.g., a CAR described herein, are expanded, e.g., by a method described herein. In one embodiment, the cells are expanded in culture for a period of several hours (e.g., about 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 18, 21 hours) to about 14 days (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 days). In one embodiment, the cells are expanded for a period of 4 to 9 days. In one embodiment, the cells are expanded for a period of 8 days or less, e.g., 7, 6 or 5 days. In one embodiment, the cells, e.g., a BCMA CAR cell described herein, are expanded in culture for 5 days, and the resulting cells are more potent than the same cells expanded in culture for 9 days under the same culture conditions. Potency can be defined, e.g., by various T cell functions, e.g. proliferation, target cell killing, cytokine production, activation, migration, or combinations thereof. In one embodiment, the cells, e.g., a BCMA CAR cell described herein, expanded for 5 days show at least a one, two, three or four fold increase in cells doublings upon antigen stimulation as compared to the same cells expanded in culture for 9 days under the same culture conditions. In one embodiment, the cells, e.g., the cells expressing a BCMA CAR described herein, are expanded in culture for 5 days, and the resulting cells exhibit higher proinflammatory cytokine production, e.g., IFN-γ and/or GM-CSF levels, as compared to the same cells expanded in culture for 9 days under the same culture conditions. In one embodiment, the cells, e.g., a BCMA CAR cell described herein, expanded for 5 days show at least a one, two, three, four, five, ten fold or more increase in pg/ml of proinflammatory cytokine production, e.g., IFN-γ and/or GM-CSF levels, as compared to the same cells expanded in culture for 9 days under the same culture conditions.

In one aspect of the present invention, the mixture may be cultured for several hours (about 3 hours) to about 14 days or any hourly integer value in between. In one aspect, the mixture may be cultured for 21 days. In one aspect of the invention the beads and the T cells are cultured together for about eight days. In one aspect, the beads and T cells are cultured together for 2-3 days. Several cycles of stimulation may also be desired such that culture time of T cells can be 60 days or more. Conditions appropriate for T cell culture include an appropriate media (e.g., Minimal Essential Media or RPMI Media 1640 or, X-vivo 15, (Lonza)) that may contain factors necessary for proliferation and viability, including serum (e.g., fetal

bovine or human serum), interleukin-2 (IL-2), insulin, IFN-γ, IL-4, IL-7, GM-CSF, IL-10, IL-12, IL-15, TGFβ, and TNF-α or any other additives for the growth of cells known to the skilled artisan. Other additives for the growth of cells include, but are not limited to, surfactant, plasmanate, and reducing agents such as N-acetyl-cysteine and 2-mercaptoethanol. Media can include RPMI 1640, AIM-V, DMEM, MEM, α-MEM, F-12, X-Vivo 15, and X-Vivo 20, Optimizer, with added amino acids, sodium pyruvate, and vitamins, either serum-free or supplemented with an appropriate amount of serum (or plasma) or a defined set of hormones, and/or an amount of cytokine(s) sufficient for the growth and expansion of T cells. Antibiotics, e.g., penicillin and streptomycin, are included only in experimental cultures, not in cultures of cells that are to be infused into a subject. The target cells are maintained under conditions necessary to support growth, for example, an appropriate temperature (e.g., 37° C) and atmosphere (e.g., air plus 5% CO_2).

In one embodiment, the cells are expanded in an appropriate media (e.g., media described herein) that includes one or more interleukin that result in at least a 200-fold (e.g., 200-fold, 250-fold, 300-fold, 350-fold) increase in cells over a 14 day expansion period, e.g., as measured by a method described herein such as flow cytometry. In one embodiment, the cells are expanded in the presence of IL-15 and/or IL-7 (e.g., IL-15 and IL-7).

In embodiments, methods described herein, e.g., CAR-expressing cell manufacturing methods, comprise removing T regulatory cells, e.g., CD25+ T cells, from a cell population, e.g., using an anti-CD25 antibody, or fragment thereof, or a CD25-binding ligand, IL-2. Methods of removing T regulatory cells, e.g., CD25+ T cells, from a cell population are described herein. In embodiments, the methods, e.g., manufacturing methods, further comprise contacting a cell population (e.g., a cell population in which T regulatory cells, such as CD25+ T cells, have been depleted; or a cell population that has previously contacted an anti-CD25 antibody, fragment thereof, or CD25-binding ligand) with IL-15 and/or IL-7. For example, the cell population (e.g., that has previously contacted an anti-CD25 antibody, fragment thereof, or CD25-binding ligand) is expanded in the presence of IL-15 and/or IL-7.

In some embodiments a CAR-expressing cell described herein is contacted with a composition comprising a interleukin-15 (IL-15) polypeptide, a interleukin-15 receptor alpha (IL-15Ra) polypeptide, or a combination of both a IL-15 polypeptide and a IL-15Ra polypeptide e.g., hetIL-15, during the manufacturing of the CAR-expressing cell, e.g., ex vivo.

In embodiments, a CAR-expressing cell described herein is contacted with a composition comprising a IL-15 polypeptide during the manufacturing of the CAR-expressing cell, e.g., ex vivo. In embodiments, a CAR-expressing cell described herein is contacted with a composition comprising a combination of both a IL-15 polypeptide and a IL-15 Ra polypeptide during the manufacturing of the CAR-expressing cell, e.g., ex vivo. In embodiments, a CAR-expressing cell described herein is contacted with a composition comprising hetIL-15 during the manufacturing of the CAR-expressing cell, e.g., ex vivo.

In one embodiment the CAR-expressing cell described herein is contacted with a composition comprising hetIL-15 during ex vivo expansion. In an embodiment, the CAR-expressing cell described herein is contacted with a composition comprising an IL-15 polypeptide during ex vivo expansion. In an embodiment, the CAR-expressing cell described herein is contacted with a composition comprising both an IL-15 polypeptide and an IL-15Ra polypeptide during ex vivo expansion. In one embodiment the contacting results in the survival and proliferation of a lymphocyte subpopulation, e.g., CD8+ T cells.

T cells that have been exposed to varied stimulation times may exhibit different characteristics. For example, typical blood or apheresed peripheral blood mononuclear cell products have a helper T cell population (TH, CD4+) that is greater than the cytotoxic or suppressor T cell population (TC, CD8+). Ex vivo expansion of T cells by stimulating CD3 and CD28 receptors produces a population of T cells that prior to about days 8-9 consists predominately of TH cells, while after about days 8-9, the population of T cells comprises an increasingly greater population of TC cells. Accordingly, depending on the purpose of treatment, infusing a subject with a T cell population comprising predominately of TH cells may be advantageous. Similarly, if an antigen-specific subset of TC cells has been isolated it may be beneficial to expand this subset to a greater degree.

Further, in addition to CD4 and CD8 markers, other phenotypic markers vary significantly, but in large part, reproducibly during the course of the cell expansion process. Thus, such reproducibility enables the ability to tailor an activated T cell product for specific purposes.

Once a BCMA CAR is constructed, various assays can be used to evaluate the activity of the molecule, such as but not limited to, the ability to expand T cells following antigen

stimulation, sustain T cell expansion in the absence of re-stimulation, and anti-cancer activities in appropriate in vitro and animal models. Assays to evaluate the effects of a BCMA CAR are described in further detail below

Western blot analysis of CAR expression in primary T cells can be used to detect the presence of monomers and dimers. See, *e.g.*, Milone *et al.*, Molecular Therapy 17(8): 1453-1464 (2009). Very briefly, T cells (1:1 mixture of $CD4^+$ and $CD8^+$ T cells) expressing the CARs are expanded *in vitro* for more than 10 days followed by lysis and SDS-PAGE under reducing conditions. CARs containing the full length TCR-ζ cytoplasmic domain and the endogenous TCR-ζ chain are detected by western blotting using an antibody to the TCR-ζ chain. The same T cell subsets are used for SDS-PAGE analysis under non-reducing conditions to permit evaluation of covalent dimer formation.

In vitro expansion of CAR^+ T cells following antigen stimulation can be measured by flow cytometry. For example, a mixture of $CD4^+$ and $CD8^+$ T cells are stimulated with αCD3/αCD28 aAPCs followed by transduction with lentiviral vectors expressing GFP under the control of the promoters to be analyzed. Exemplary promoters include the CMV IE gene, EF-1α, ubiquitin C, or phosphoglycerokinase (PGK) promoters. GFP fluorescence is evaluated on day 6 of culture in the $CD4^+$ and/or $CD8^+$ T cell subsets by flow cytometry. See, *e.g.*, Milone *et al.*, Molecular Therapy 17(8): 1453-1464 (2009). Alternatively, a mixture of $CD4^+$ and $CD8^+$ T cells are stimulated with αCD3/αCD28 coated magnetic beads on day 0, and transduced with CAR on day 1 using a bicistronic lentiviral vector expressing CAR along with eGFP using a 2A ribosomal skipping sequence. Cultures are re-stimulated with BCMA-expressing cells, such as multiple myeloma cell lines or K562-BCMA, following washing. Exogenous IL-2 is added to the cultures every other day at 100 IU/ml. GFP^+ T cells are enumerated by flow cytometry using bead-based counting. See, *e.g.*, Milone *et al.*, Molecular Therapy 17(8): 1453-1464 (2009).

Sustained CAR^+ T cell expansion in the absence of re-stimulation can also be measured. See, *e.g.*, Milone *et al.*, Molecular Therapy 17(8): 1453-1464 (2009). Briefly, mean T cell volume (fl) is measured on day 8 of culture using a Coulter Multisizer III particle counter, a Nexcelom Cellometer Vision or Millipore Scepter, following stimulation with αCD3/αCD28 coated magnetic beads on day 0, and transduction with the indicated CAR on day 1.

Animal models can also be used to measure a CART activity. For example, xenograft model using human BCMA-specific CAR$^+$ T cells to treat a primary human multiple myeloma in immunodeficient mice can be used. See, *e.g.*, Milone *et al.*, Molecular Therapy 17(8): 1453-1464 (2009). Very briefly, after establishment of MM, mice are randomized as to treatment groups. Different numbers of BCMA CART cells can be injected into immunodeficient mice bearing MM. Animals are assessed for disease progression and tumor burden at weekly intervals. Survival curves for the groups are compared using the log-rank test. In addition, absolute peripheral blood CD4$^+$ and CD8$^+$ T cell counts 4 weeks following T cell injection in the immunodeficient mice can also be analyzed. Mice are injected with multiple myeloma cells and 3 weeks later are injected with T cells engineered to express BCMA CAR, e.g., by a bicistronic lentiviral vector that encodes the CAR linked to eGFP. T cells are normalized to 45–50% input GFP$^+$ T cells by mixing with mock-transduced cells prior to injection, and confirmed by flow cytometry. Animals are assessed for leukemia at 1-week intervals. Survival curves for the CAR$^+$ T cell groups are compared using the log-rank test.

Assessment of cell proliferation and cytokine production has been previously described, *e.g.*, at Milone *et al.*, Molecular Therapy 17(8): 1453-1464 (2009). Briefly, assessment of CAR-mediated proliferation is performed in microtiter plates by mixing washed T cells with K562 cells expressing BCMA or other BCMA-expressing myeloma cells are irradiated with gamma-radiation prior to use. Anti-CD3 (clone OKT3) and anti- CD28 (clone 9.3) monoclonal antibodies are added to cultures with KT32-BBL cells to serve as a positive control for stimulating T-cell proliferation since these signals support long-term CD8$^+$ T cell expansion *ex vivo*. T cells are enumerated in cultures using CountBright™ fluorescent beads (Invitrogen, Carlsbad, CA) and flow cytometry as described by the manufacturer. CAR$^+$ T cells are identified by GFP expression using T cells that are engineered with eGFP-2A linked CAR-expressing lentiviral vectors. For CAR+ T cells not expressing GFP, the CAR+ T cells are detected with biotinylated recombinant BCMA protein and a secondary avidin-PE conjugate. CD4+ and CD8$^+$ expression on T cells are also simultaneously detected with specific monoclonal antibodies (BD Biosciences). Cytokine measurements are performed on supernatants collected 24 hours following re-stimulation using the human TH1/TH2 cytokine cytometric bead array kit (BD Biosciences, San Diego, CA) according the manufacturer's

instructions. Fluorescence is assessed using a FACScalibur flow cytometer, and data is analyzed according to the manufacturer's instructions.

Cytotoxicity can be assessed by a standard 51Cr-release assay. See, *e.g.*, Milone *et al.*, Molecular Therapy 17(8): 1453-1464 (2009). Briefly, target cells (e.g., K562 lines expressing BCMA and primary multiple myeloma cells) are loaded with 51Cr (as NaCrO4, New England Nuclear, Boston, MA) at 37°C for 2 hours with frequent agitation, washed twice in complete RPMI and plated into microtiter plates. Effector T cells are mixed with target cells in the wells in complete RPMI at varying ratios of effector cell:target cell (E:T). Additional wells containing media only (spontaneous release, SR) or a 1% solution of triton-X 100 detergent (total release, TR) are also prepared. After 4 hours of incubation at 37°C, supernatant from each well is harvested. Released 51Cr is then measured using a gamma particle counter (Packard Instrument Co., Waltham, MA). Each condition is performed in at least triplicate, and the percentage of lysis is calculated using the formula: % Lysis = (ER– SR) / (TR – SR), where ER represents the average 51Cr released for each experimental condition.

Imaging technologies can be used to evaluate specific trafficking and proliferation of CARs in tumor-bearing animal models. Such assays have been described, for example, in Barrett *et al.*, Human Gene Therapy 22:1575-1586 (2011). Briefly, NOD/SCID/$\gamma c^{-/-}$ (NSG) mice or other immunodeficient are injected IV with multiple myeloma cells followed 7 days later with BCMA CART cells 4 hour after electroporation with the CAR constructs. The T cells are stably transfected with a lentiviral construct to express firefly luciferase, and mice are imaged for bioluminescence. Alternatively, therapeutic efficacy and specificity of a single injection of CAR^+ T cells in a multiple myeloma xenograft model can be measured as the following: NSG mice are injected with multiple myeloma cells transduced to stably express firefly luciferase, followed by a single tail-vein injection of T cells electroporated with BCMA CAR construct days later. Animals are imaged at various time points post injection. For example, photon-density heat maps of firefly luciferasepositive tumors in representative mice at day 5 (2 days before treatment) and day 8 (24 hr post CAR^+ PBLs) can be generated.

Alternatively, or in combination to the methods disclosed herein, methods and compositions for one or more of: detection and/or quantification of CAR-expressing cells (*e.g.*, *in vitro* or *in vivo* (e.g., clinical monitoring)); immune cell expansion and/or activation; and/or CAR-specific selection, that involve the use of a CAR ligand, are disclosed. In one exemplary

embodiment, the CAR ligand is an antibody that binds to the CAR molecule, e.g., binds to the extracellular antigen binding domain of CAR (e.g., an antibody that binds to the antigen binding domain, e.g., an anti-idiotypic antibody; or an antibody that binds to a constant region of the extracellular binding domain). In other embodiments, the CAR ligand is a CAR antigen molecule (e.g., a CAR antigen molecule as described herein).

In one aspect, a method for detecting and/or quantifying CAR-expressing cells is disclosed. For example, the CAR ligand can be used to detect and/or quantify CAR-expressing cells *in vitro* or *in vivo* (e.g., clinical monitoring of CAR-expressing cells in a patient, or dosing a patient). The method includes:

providing the CAR ligand (optionally, a labelled CAR ligand, e.g., a CAR ligand that includes a tag, a bead, a radioactive or fluorescent label);

acquiring the CAR-expressing cell (e.g., acquiring a sample containing CAR-expressing cells, such as a manufacturing sample or a clinical sample);

contacting the CAR-expressing cell with the CAR ligand under conditions where binding occurs, thereby detecting the level (e.g., amount) of the CAR-expressing cells present. Binding of the CAR-expressing cell with the CAR ligand can be detected using standard techniques such as FACS, ELISA and the like.

In another aspect, a method of expanding and/or activating cells (e.g., immune effector cells) is disclosed. The method includes:

providing a CAR-expressing cell (e.g., a first CAR-expressing cell or a transiently expressing CAR cell);

contacting said CAR-expressing cell with a CAR ligand, e.g., a CAR ligand as described herein), under conditions where immune cell expansion and/or proliferation occurs, thereby producing the activated and/or expanded cell population.

In certain embodiments, the CAR ligand is present on (e.g., is immobilized or attached to a substrate, e.g., a non-naturally occurring substrate). In some embodiments, the substrate is a non-cellular substrate. The non-cellular substrate can be a solid support chosen from, e.g., a plate (e.g., a microtiter plate), a membrane (e.g., a nitrocellulose membrane), a

matrix, a chip or a bead. In embodiments, the CAR ligand is present in the substrate (e.g., on the substrate surface). The CAR ligand can be immobilized, attached, or associated covalently or non-covalently (e.g., cross-linked) to the substrate. In one embodiment, the CAR ligand is attached (e.g., covalently attached) to a bead. In the aforesaid embodiments, the immune cell population can be expanded *in vitro* or *ex vivo*. The method can further include culturing the population of immune cells in the presence of the ligand of the CAR molecule, e.g., using any of the methods described herein.

In other embodiments, the method of expanding and/or activating the cells further comprises addition of a second stimulatory molecule, e.g., CD28. For example, the CAR ligand and the second stimulatory molecule can be immobilized to a substrate, e.g., one or more beads, thereby providing increased cell expansion and/or activation.

In yet another aspect, a method for selecting or enriching for a CAR expressing cell is provided. The method includes contacting the CAR expressing cell with a CAR ligand as described herein; and selecting the cell on the basis of binding of the CAR ligand.

In yet other embodiments, a method for depleting, reducing and/or killing a CAR expressing cell is provided. The method includes contacting the CAR expressing cell with a CAR ligand as described herein; and targeting the cell on the basis of binding of the CAR ligand, thereby reducing the number, and/or killing, the CAR-expressing cell. In one embodiment, the CAR ligand is coupled to a toxic agent (e.g., a toxin or a cell ablative drug). In another embodiment, the anti-idiotypic antibody can cause effector cell activity, e.g., ADCC or ADC activities.

Exemplary anti-CAR antibodies that can be used in the methods disclosed herein are described, e.g., in WO 2014/190273 and by Jena et al., "Chimeric Antigen Receptor (CAR)-Specific Monoclonal Antibody to Detect CD19-Specific T cells in Clinical Trials", PLOS March 2013 8:3 e57838, the contents of which are incorporated by reference. In one embodiment, the anti-idiotypic antibody molecule recognizes an anti-CD19 antibody molecule, e.g., an anti-CD19 scFv. For instance, the anti-idiotypic antibody molecule can compete for binding with the CD19-specific CAR mAb clone no. 136.20.1 described in Jena et al., PLOS March 2013 8:3 e57838; may have the same CDRs (e.g., one or more of, e.g., all of, VH CDR1, VH CDR2, CH CDR3, VL CDR1, VL CDR2, and VL CDR3, using the Kabat

definition, the Chothia definition, or a combination of tthe Kabat and Chothia definitions) as the CD19-specific CAR mAb clone no. 136.20.1; may have one or more (e.g., 2) variable regions as the CD19-specific CAR mAb clone no. 136.20.1, or may comprise the CD19-specific CAR mAb clone no. 136.20.1. In some embodiments, the anti-idiotypic antibody was made according to a method described in Jena et al. In another embodiment, the anti-idiotypic antibody molecule is an anti-idiotypic antibody molecule described in WO 2014/190273. In some embodiments, the anti-idiotypic antibody molecule has the same CDRs (e.g., one or more of, e.g., all of, VH CDR1, VH CDR2, CH CDR3, VL CDR1, VL CDR2, and VL CDR3) as an antibody molecule of WO 2014/190273 such as 136.20.1; may have one or more (e.g., 2) variable regions of an antibody molecule of WO 2014/190273, or may comprise an antibody molecule of WO 2014/190273 such as 136.20.1. In other embodiments, the anti-CAR antibody binds to a constant region of the extracellular binding domain of the CAR molecule, e.g., as described in WO 2014/190273. In some embodiments, the anti-CAR antibody binds to a constant region of the extracellular binding domain of the CAR molecule, e.g., a heavy chain constant region (e.g., a CH2-CH3 hinge region) or light chain constant region. For instance, in some embodiments the anti-CAR antibody competes for binding with the 2D3 monoclonal antibody described in WO 2014/190273, has the same CDRs (e.g., one or more of, e.g., all of, VH CDR1, VH CDR2, CH CDR3, VL CDR1, VL CDR2, and VL CDR3) as 2D3, or has one or more (e.g., 2) variable regions of 2D3, or comprises 2D3 as described in WO 2014/190273.

In some aspects and embodiments, the compositions and methods herein are optimized for a specific subset of T cells, e.g., as described in US Serial No. 62/031,699 filed July 31, 2014, the contents of which are incorporated herein by reference in their entirety. In some embodiments, the optimized subsets of T cells display an enhanced persistence compared to a control T cell, e.g., a T cell of a different type (e.g., $CD8^+$ or $CD4^+$) expressing the same construct.

In some embodiments, a $CD4^+$ T cell comprises a CAR described herein, which CAR comprises an intracellular signaling domain suitable for (e.g., optimized for, e.g., leading to enhanced persistence in) a $CD4^+$ T cell, e.g., an ICOS domain. In some embodiments, a $CD8^+$ T cell comprises a CAR described herein, which CAR comprises an intracellular

signaling domain suitable for (e.g., optimized for, e.g., leading to enhanced persistence of) a $CD8^+$ T cell, e.g., a 4-1BB domain, a CD28 domain, or another costimulatory domain other than an ICOS domain. In some embodiments, the CAR described herein comprises an antigen binding domain described herein, e.g., a CAR comprising an antigen binding domain that targets BCMA, e.g., a CAR of Table 1 or 16).

In an aspect, described herein is a method of treating a subject, e.g., a subject having cancer. The method includes administering to said subject, an effective amount of:

1) a $CD4^+$ T cell comprising a CAR (the CAR^{CD4+})

comprising:

an antigen binding domain, e.g., an antigen binding domain described herein, e.g., an antigen binding domain that targets BCMA, e.g., an antigen-binding domain of Table 1 or 16;

a transmembrane domain; and

an intracellular signaling domain, e.g., a first costimulatory domain, e.g., an ICOS domain; and

2) a $CD8^+$ T cell comprising a CAR (the CAR^{CD8+}) comprising:

an antigen binding domain, e.g., an antigen binding domain described herein, e.g., an antigen binding domain that targets BCMA, e.g., an antigen-binding domain of Table 1 or 16;

a transmembrane domain; and

an intracellular signaling domain, e.g., a second costimulatory domain, e.g., a 4-1BB domain, a CD28 domain, or another costimulatory domain other than an ICOS domain;

wherein the CAR^{CD4+} and the CAR^{CD8+} differ from one another.

Optionally, the method further includes administering:

3) a second CD8+ T cell comprising a CAR (the second CAR^{CD8+}) comprising:

an antigen binding domain, e.g., an antigen binding domain described herein, e.g., an antigen binding domain that specifically binds BCMA, e.g., an antigen-binding domain of Table 1 or 16;

a transmembrane domain; and

an intracellular signaling domain, wherein the second CAR^{CD8+} comprises an intracellular signaling domain, e.g., a costimulatory signaling domain, not present on the CAR^{CD8+}, and, optionally, does not comprise an ICOS signaling domain.

Other assays, including those described in the Example section herein as well as those that are known in the art can also be used to evaluate the BCMA CAR constructs of the invention.

Therapeutic Application

BCMA Associated Diseases and/or Disorders

In one aspect, the invention provides methods for treating a disease associated with BCMA expression. In one aspect, the invention provides methods for treating a disease wherein part of the tumor is negative for BCMA and part of the tumor is positive for BCMA For example, the CAR of the invention is useful for treating subjects that have undergone treatment for a disease associated with elevated expression of BCMA, wherein the subject that has undergone treatment for elevated levels of BCMA exhibits a disease associated with elevated levels of BCMA. In embodiments, the CAR of the invention is useful for treating subjects that have undergone treatment for a disease associated with expression of BCMA, wherein the subject that has undergone treatment related to expression of BCMA exhibits a disease associated with expression of BCMA.

In one embodiment, the invention provides methods for treating a disease wherein BCMA is expressed on both normal cells and cancers cells, but is expressed at lower levels on normal cells. In one embodiment, the method further comprises selecting a CAR that binds of the invention with an affinity that allows the BCMA CAR to bind and kill the cancer cells expressing BCMA but less than 30%, 25%, 20%, 15%, 10%, 5% or less of the normal cells expressing BCMA are killed, e.g., as determined by an assay described herein. For example, a killing assay such as flow cytometry based on Cr51 CTL can be used. In one embodiment, the BCMA CAR has an antigen binding domain that has a binding affinity KD of 10^{-4} M to 10^{-8} M, e.g., 10^{-5} M to 10^{-7} M, e.g., 10^{-6} M or 10^{-7} M, for the target antigen. In one embodiment, the BCMA antigen binding domain has a binding affinity that is at least five-fold, 10-fold, 20-fold, 30-fold, 50-fold, 100-fold or 1,000-fold less than a reference antibody, e.g., an antibody described herein.

In one aspect, the invention pertains to a vector comprising BCMA CAR operably linked to promoter for expression in mammalian immune effector cells, e.g., T cells or NK

cells. In one aspect, the invention provides a recombinant immune effector cell, e.g., T cell or NK cell, expressing the BCMA CAR for use in treating BCMA-expressing tumors, wherein the recombinant immune effector cell (e.g., T cell or NK cell) expressing the BCMA CAR is termed a BCMA CAR-expressing cell (e.g., BCMA CART or BCMA CAR-expressing NK cell). In one aspect, the BCMA CAR-expressing cell (e.g., BCMA CART or BCMA CAR-expressing NK cell)of the invention is capable of contacting a tumor cell with at least one BCMA CAR of the invention expressed on its surface such that the BCMA CAR-expressing cell (e.g., BCMA CART or BCMA CAR-expressing NK cell)targets the tumor cell and growth of the tumor is inhibited.

In one aspect, the invention pertains to a method of inhibiting growth of a BCMA-expressing tumor cell, comprising contacting the tumor cell with a BCMA CAR-expressing cell (e.g., BCMA CART or BCMA CAR-expressing NK cell)of the present invention such that the BCMA CAR-expressing cell (e.g., BCMA CART or BCMA CAR-expressing NK cell) is activated in response to the antigen and targets the cancer cell, wherein the growth of the tumor is inhibited.

In one aspect, the invention pertains to a method of treating cancer in a subject. The method comprises administering to the subject a BCMA CAR-expressing cell (e.g., BCMA CART or BCMA CAR-expressing NK cell)of the present invention such that the cancer is treated in the subject. An example of a cancer that is treatable by the BCMA CAR-expressing cell (e.g., BCMA CART or BCMA CAR-expressing NK cell)of the invention is a cancer associated with expression of BCMA.

The invention includes a type of cellular therapy where immune effector cells (e.g., T cells or NK cells) are genetically modified to express a chimeric antigen receptor (CAR) and the BCMA CAR-expressing cell (e.g., BCMA CART or BCMA CAR-expressing NK cell)is infused to a recipient in need thereof. The infused cell is able to kill tumor cells in the recipient. Unlike antibody therapies, CAR-modified cells, e.g., T cells or NK cells, are able to replicate in vivo resulting in long-term persistence that can lead to sustained tumor control. In various aspects, the cells (e.g., T cells or NK cells) administered to the patient, or their progeny, persist in the patient for at least four months, five months, six months, seven months, eight months, nine months, ten months, eleven months, twelve months, thirteen months, fourteen month, fifteen months, sixteen months, seventeen months, eighteen months, nineteen months, twenty

months, twenty-one months, twenty-two months, twenty-three months, two years, three years, four years, or five years after administration of the cell (e.g., T cell or NK cell) to the patient.

The invention also includes a type of cellular therapy where immune effector cells (e.g., T cells or NK cells) are modified, e.g., by in vitro transcribed RNA, to transiently express a chimeric antigen receptor (CAR) and the immune effector cell (e.g., T cell or NK cell) is infused to a recipient in need thereof. The infused cell is able to kill tumor cells in the recipient. Thus, in various aspects, the immune effector cells (e.g., T cells or NK cells) administered to the patient, is present for less than one month, e.g., three weeks, two weeks, one week, after administration of the immune effector cell (e.g., T cell or NK cell) to the patient.

Without wishing to be bound by any particular theory, the anti-tumor immunity response elicited by the CAR-modified immune effector cells (e.g., T cells or NK cells) may be an active or a passive immune response, or alternatively may be due to a direct vs indirect immune response. In one aspect, the CAR transduced immune effector cells (e.g., T cells or NK cells) exhibit specific proinflammatory cytokine secretion and potent cytolytic activity in response to human cancer cells expressing the BCMA, resist soluble BCMA inhibition, mediate bystander killing and mediate regression of an established human tumor. For example, antigen-less tumor cells within a heterogeneous field of BCMA-expressing tumor may be susceptible to indirect destruction by BCMA-redirected immune effector cells (e.g., T cells or NK cells) that has previously reacted against adjacent antigen-positive cancer cells.

In one aspect, the fully-human CAR-modified immune effector cells (e.g., T cells or NK cells) of the invention may be a type of vaccine for ex vivo immunization and/or in vivo therapy in a mammal. In one aspect, the mammal is a human.

With respect to ex vivo immunization, at least one of the following occurs in vitro prior to administering the cell into a mammal: i) expansion of the cells, ii) introducing a nucleic acid encoding a CAR to the cells or iii) cryopreservation of the cells.

Ex vivo procedures are well known in the art and are discussed more fully below. Briefly, cells are isolated from a mammal (e.g., a human) and genetically modified (i.e., transduced or transfected in vitro) with a vector expressing a CAR disclosed herein. The CAR-modified cell can be administered to a mammalian recipient to provide a therapeutic benefit. The mammalian recipient may be a human and the CAR-modified cell can be autologous with

respect to the recipient. Alternatively, the cells can be allogeneic, syngeneic or xenogeneic with respect to the recipient.

The procedure for ex vivo expansion of hematopoietic stem and progenitor cells is described in U.S. Pat. No. 5,199,942, incorporated herein by reference, can be applied to the cells of the present invention. Other suitable methods are known in the art, therefore the present invention is not limited to any particular method of ex vivo expansion of the cells. Briefly, ex vivo culture and expansion of T cells comprises: (1) collecting CD34+ hematopoietic stem and progenitor cells from a mammal from peripheral blood harvest or bone marrow explants; and (2) expanding such cells ex vivo. In addition to the cellular growth factors described in U.S. Pat. No. 5,199,942, other factors such as flt3-L, IL-1, IL-3 and c-kit ligand, can be used for culturing and expansion of the cells.

In addition to using a cell-based vaccine in terms of ex vivo immunization, the present invention also provides compositions and methods for in vivo immunization to elicit an immune response directed against an antigen in a patient.

Generally, the cells activated and expanded as described herein may be utilized in the treatment and prevention of diseases that arise in individuals who are immunocompromised. In particular, the CAR-modified immune effector cells (e.g., T cells or NK cells) of the invention are used in the treatment of diseases, disorders and conditions associated with expression of BCMA. In certain aspects, the cells of the invention are used in the treatment of patients at risk for developing diseases, disorders and conditions associated with expression of BCMA. Thus, the present invention provides methods for the treatment or prevention of diseases, disorders and conditions associated with expression of BCMA comprising administering to a subject in need thereof, a therapeutically effective amount of the CAR-modified immune effector cells (e.g., T cells or NK cells) of the invention.

In one aspect the CAR-expressing cells (e.g., CART cells or CAR-expressing NK cells) of the inventions may be used to treat a proliferative disease such as a cancer or malignancy or is a precancerous condition such as a myelodysplasia, a myelodysplastic syndrome or a preleukemia. In one aspect, the cancer is a hematolical cancer. Hematological cancer conditions are the types of cancer such as leukemia and malignant lymphoproliferative conditions that affect blood, bone marrow and the lymphatic system.In one aspect, the

hematological cancer is a leukemia or a hematological. An example of a disease or disorder associated with BCMA is multiple myeloma (also known as MM) (See Claudio et al., *Blood.* 2002, 100(6):2175-86; and Novak et al., *Blood.* 2004, 103(2):689-94). Multiple myeloma, also known as plasma cell myeloma or Kahler's disease, is a cancer characterized by an accumulation of abnormal or malignant plasma B-cells in the bone marrow. Frequently, the cancer cells invade adjacent bone, destroying skeletal structures and resulting in bone pain and fractures. Most cases of myeloma also features the production of a paraprotein (also known as M proteins or myeloma proteins), which is an abnormal immunoglobulin produced in excess by the clonal proliferation of the malignant plasma cells. Blood serum paraprotein levels of more than 30g/L is diagnostic of multiple myeloma, according to the diagnostic criteria of the International Myeloma Working Group (IMWG) (*See* Kyle et al. (2009), Leukemia. 23:3-9). Other symptoms or signs of multiple myeloma include reduced kidney function or renal failure, bone lesions, anemia, hypercalcemia, and neurological symptoms.

Criteria for distinguishing multiple myeloma from other plasma cell proliferative disorders have been established by the International Myeloma Working Group (*See* Kyle et al. (2009), Leukemia. 23:3-9). All three of the following criteria must be met:

- Clonal bone marrow plasma cells ≥10%
- Present of serum and/or urinary monoclonal protein (except in patients with true non-secretory multiple myeloma)
- Evidence of end-organ damage attributable to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcemia: serum calcium ≥11.5 mg/100 ml
    - Renal insufficienty: serum creatinine > 1.73 mmol/l
    - Anemia: normochromic, normocytic with a hemoglobin value of >2g/100 ml below the lower limit of normal, or a hemoglobin value <10g/100ml
    - Bone lesions: lytic lesions, severe osteopenia, or pathologic fractures.

Other plasma cell proliferative disorders that can be treated by the compositions and methods described herein include, but are not limited to, asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), monoclonal gammapathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia, plasmacytomas (e.g., plasma cell

dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, and POEMS syndrome (also known as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome).

Two staging systems are used in the staging of multiple myeloma: the International Staging System (ISS) (*See* Greipp et al. (2005), J. Clin. Oncol. 23 (15):3412-3420) and the Durie-Salmon Staging system (DSS) (*See* Durie et al. (1975), Cancer 36 (3): 842-854). The two staging systems are summarized in the table below:

Table 18

Stage	International Staging System		Durie-Salmon Staging System	
	Criteria	Median survival	Criteria	Median survival*
I	β_2M <3.5 mg/l and serum albumin ≥3.5 g/dL	62 months	All of the following: Hemoglobin level >10g/dL Serum calcium, normal or <12 mg/dL Bone x-ray, normal or 1 plasmacytoma only Low monoclonal protein production (IgG <5g/dL, IgA<3g/dL, Bence Jones protein <4g/dL per 24 hours	IA: 62 months IB: 22 months
II	Neither stage I or stage III	44 months	Neither stage I or stage III	IIA: 58 months IIB: 354 months
III	β_2M ≥5.5 mg/l	29 months	One or more of the following: Hemoglobin level <8.5g/dL Serum calcium, normal or >12 mg/dL Advanced osteolytic lesions High monoclonal protein production (IgG >7g/dL,	IIIA: 45 months IIIB: 24 months

			IgA>5g/dL, Bence Jones protein >12g/dL per 24 hours	

*The Durie-Salmon Staging system also includes a subclassification that designates the status of renal function. The designation of "A" or "B" is added after the stage number, wherein "A" indicates relatively normal renal function (serum creatinine value <2.0 mg/dL), and B indicates abnormal renal function (serum creatinine value >2.0 mg/dL).

Standard treatment for multiple myeloma and associated diseases includes chemotherapy, stem cell transplant (autologous or allogeneic), radiation therapy, and other drug therapies. Frequently used anti-myeloma drugs include alkylating agents (e.g., bendamustine, cyclophosphamide and melphalan), proteasome inhibitors (e.g., bortezomib), corticosteroids (e.g., dexamethasone and prednisone), and immunomodulators (e.g., thalidomide and lenalidomide or Revlimid®), or any combination thereof. Biphosphonate drugs are also frequently administered in combination with the standard anti-MM treamtents to prevent bone loss. Patients older than 65-70 years of age are unlikely candidates for stem cell transplant. In some cases, double-autologous stem cell transplants are options for patients less than 60 years of age with suboptimal response to the first transplant. The compositions and methods of the present invention may be administered in combination with any of the currently prescribed treatments for multiple myeloma.

Another example of a disease or disorder associated with BCMA is Hodgkin's lymphoma and non-Hodgkin's lymphoma (*See* Chiu et al., *Blood.* 2007, 109(2):729-39; He et al., *J Immunol.* 2004, 172(5):3268-79).

Hodgkin's lymphoma (HL), also known as Hodgkin's disease, is a cancer of the lymphatic system that originates from white blood cells, or lymphocytes. The abnormal cells that comprise the lymphoma are called Reed-Sternberg cells. In Hodgkin's lymphoma, the cancer spreads from one lymph node group to another. Hodgkin's lymphoma can be subclassified into four pathologic subtypes based upon Reed-Sternberg cell morphology and the cell composition around the Reed-Sternberg cells (as determined through lymph node biopsy): nodular sclerosing HL, mixed-cellularity subtype, lymphocyte-rich or lymphocytic predominance, lymphocyte depleted. Some Hodgkin's lymphoma can also be nodular lymphocyte predominant Hodgkin's lymphoma, or can be unspecified. Symptoms and signs of

Hodgkin's lymphoma include painless swelling in the lymph nodes in the neck, armpits, or groin, fever, night sweats, weight loss, fatigue, itching, or abdominal pain.

Non-Hodgkin's lymphoma (NHL) comprises a diverse group of blood cancers that include any kind of lymphoma other than Hodgkin's lymphoma. Subtypes of non-Hodgkin's lymphoma are classified primarily by cell morphology, chromosomal aberrations, and surface markers. NHL subtypes (or NHL-associated cancers) include B cell lymphomas such as, but not limited to, Burkitt's lymphoma, B-cell chronic lymphocytic leukemia (B-CLL), B-cell prolymphocytic leukemia (B-PLL), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL) (e.g., intravascular large B-cell lymphoma and primary mediastinal B-cell lymphoma), follicular lymphoma (e.g., follicle center lymphoma, follicular small cleaved cell), hair cell leukemia, high grade B-cell lymphoma (Burkitt's like), lymphoplasmacytic lymphoma (Waldenstrom's macroglublinemia), mantle cell lymphoma, marginal zone B-cell lymphomas (e.g., extranodal marginal zone B-cell lymphoma or mucosa-associated lymphoid tissue (MALT) lymphoma, nodal marginal zone B-cell lymphoma, and splenic marginal zone B-cell lymphoma), plasmacytoma/myeloma, precursor B-lymphoblastic leukemia/lymphoma (PB-LBL/L), primary central nervous system (CNS) lymphoma, primary intraocular lymphoma, small lymphocytic lymphoma (SLL); and T cell lymphomas, such as, but not limited to, anaplastic large cell lymphoma (ALCL), adult T-cell lymphoma/leukemia (e.g., smoldering, chronic, acute and lymphomatous), angiocentric lymphoma, angioimmunoblastic T-cell lymphoma, cutaneous T-cell lymphomas (e.g., mycosis fungoides, Sezary syndrome, etc.), extranodal natural killer/T-cell lymphoma (nasal-type), enteropathy type intestinal T-cell lymphoma, large granular lymphocyte leukemia, precursor T-lymphoblastic lymphoma/leukemia (T-LBL/L), T-cell chronic lymphocytic leukemia/prolymphocytic leukemia (T-CLL/PLL), and unspecified peripheral T-cell lymphoma. Symptoms and signs of Hodgkin's lymphoma include painless swelling in the lymph nodes in the neck, armpits, or groin, fever, night sweats, weight loss, fatigue, itching, abdominal pain, coughing, or chest pain.

The staging is the same for both Hodgkin's and non-Hodgkin's lymphoma, and refers to the extent of spread of the cancer cells within the body. In stage I, the lymphoma cells are in one lymph node group. In stage II, lymphoma cells are present in at least two lymph node groups, but both groups are on the same side of the diaphragm, or in one part of a tissue or

organ and the lymph nodes near that organ on the same side of the diaphragm. In stage III, lymphoma cells are in lymph nodes on both sides of the diaphragm, or in one part of a tissue or organ near these lymph node groups or in the spleen. In stage IV, lymphoma cells are found in several parts of at least one organ or tissue, or lymphoma cells are in an organ and in lymph nodes on the other side of the diaphragm. In addition to the Roman numeral staging designation, the stages of can also be described by letters A, B, E, and S, wherein A refers to patients without symptoms, B refers to patients with symptoms, E refers to patients in which lymphoma is found in tissues outside the lymph system, and S refers to patients in which lymphoma is found in the spleen.

Hodgkin's lymphoma is commonly treated with radiation therapy, chemotherapy, or hematopoietic stem cell transplantation. The most common therapy for non-Hodgkin's lymphoma is R-CHOP, which consists of four different chemotherapies (cyclophosphamide, doxorubicin, vincristine, and prenisolone) and rituximab (Rituxan®). Other therapies commonly used to treat NHL include other chemotherapeutic agents, radiation therapy, stem cell transplantation (autologous or allogeneic bone marrow transplantation), or biological therapy, such as immunotherapy. Other examples of biological therapeutic agents include, but are not limited to, rituximab (Rituxan®), tositumomab (Bexxar®), epratuzumab (LymphoCide®), and alemtuzumab (MabCampath®). The compositions and methods of the present invention may be administered in combination with any of the currently prescribed treatments for Hodgkin's lymphoma or non-Hodgkin's lymphoma.

BCMA expression has also been associated Waldenstrom's macroglobulinemia (WM), also known as lymphoplasmacytic lymphoma (LPL). (See Elsawa et al., *Blood*. 2006, 107(7):2882-8). Waldenstrom's macroglobulinemia was previously considered to be related to multiple myeloma, but has more recently been classified as a subtype of non-Hodgkin's lymphoma. WM is characterized by uncontrolled B-cell lymphocyte proliferation, resulting in anemia and production of excess amounts of paraprotein, or immunoglobulin M (IgM), which thickens the blood and results in hyperviscosity syndrome. Other symptoms or signs of WM include fever, night sweats, fatigue, anemia, weight loss, lymphadenopathy or splenomegaly, blurred vision, dizziness, nose bleeds, bleeding gums, unusual bruises, renal impairment or failure, amyloidosis, or peripheral neuropathy.

Standard treatment for WM consists of chemotherapy, specifically with rituximab (Rituxan®). Other chemotherapeutic drugs can be used in combination, such as chlorambucil (Leukeran®), cyclophosphamide (Neosar®), fludarabine (Fludara®), cladribine (Leustatin®), vincristine, and/or thalidomide. Corticosteriods, such as prednisone, can also be administered in combination with the chemotherapy. Plasmapheresis, or plasma exchange, is commonly used throughout treatment of the patient to alleviate some symptoms by removing the paraprotein from the blood. In some cases, stem cell transplantation is an option for some patients.

Another example of a disease or disorder associated with BCMA is brain cancer. Specifically, expression of BCMA has been associated with astrocytoma or glioblastoma (*See* Deshayes et al, *Oncogene*. 2004, 23(17):3005-12, Pelekanou et al., *PLoS One*. 2013, 8(12):e83250). Astrocytomas are tumors that arise from astrocytes, which are a type of glial cell in the brain. Glioblastoma (also known as glioblastoma multiforme or GBM) is the most malignant form of astrocytoma, and is considered the most advanced stage of brain cancer (stage IV). There are two variants of glioblastoma: giant cell glioblastoma and gliosarcoma. Other astrocytomas include juvenile pilocytic astrocytoma (JPA), fibrillary astrocytoma, pleomorphic xantroastrocytoma (PXA), desembryoplastic neuroepithelial tumor (DNET), and anaplastic astrocytoma (AA).

Symptoms or signs associated with glioblastoma or astrocytoma include increased pressure in the brain, headaches, seizures, memory loss, changes in behavior, loss in movement or sensation on one side of the body, language dysfunction, cognitive impairments, visual impairment, nausea, vomiting, and weakness in the arms or legs.

Surgical removal of the tumor (or resection) is the standard treatment for removal of as much of the glioma as possible without damaging or with minimal damage to the normal, surrounding brain. Radiation therapy and/or chemotherapy are often used after surgery to suppress and slow recurrent disease from any remaining cancer cells or satellite lesions. Radiation therapy includes whole brain radiotherapy (conventional external beam radiation), targeted three-dimensional conformal radiotherapy, and targeted radionuclides. Chemotherapeutic agents commonly used to treat glioblastoma include temozolomide, gefitinib or erlotinib, and cisplatin. Angiogenesis inhibitors, such as Bevacizumab (Avastin®), are also commonly used in combination with chemotherapy and/or radiotherapy.

Supportive treatment is also frequently used to relieve neurological symptoms and improve neurologic function, and is administered in combination any of the cancer therapies described herein. The primary supportive agents include anticonvulsants and corticosteroids. Thus, the compositions and methods of the present invention may be used in combination with any of the standard or supportive treatments to treat a glioblastoma or astrocytoma.

Non-cancer related diseases and disorders associated with BCMA expression can also be treated by the compositions and methods disclosed herein. Examples of non-cancer related diseases and disorders associated with BCMA expression include, but are not limited to: viral infections; e.g., HIV, fungal invections, e.g.,*C. neoformans*; irritable bowel disease; ulcerative colitis, and disorders related to mucosal immunity.

The CAR-modified immune effector cells (e.g., T cells or NK cells) of the present invention may be administered either alone, or as a pharmaceutical composition in combination with diluents and/or with other components such as IL-2 or other cytokines or cell populations.

The present invention provides for compositions and methods for treating cancer. In one aspect, the cancer is a hematologic cancer including but is not limited to hematolical cancer is a leukemia or a lymphoma. In one aspect, the CAR-expressing cells (e.g., CART cells or CAR-expressing NK cells)of the invention may be used to treat cancers and malignancies such as, but not limited to, e.g., acute leukemias including but not limited to, e.g., B-cell acute lymphoid leukemia ("BALL"), T-cell acute lymphoid leukemia ("TALL"), acute lymphoid leukemia (ALL); one or more chronic leukemias including but not limited to, e.g., chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL); additional hematologic cancers or hematologic conditions including, but not limited to, e.g., B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, Follicular lymphoma, Hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, and "preleukemia" which are a diverse collection of hematological conditions united by ineffective production (or dysplasia) of myeloid blood cells, and the like. Further a disease associated with BCMA expression includes, but not

limited to, e.g., atypical and/or non-classical cancers, malignancies, precancerous conditions or proliferative diseases expressing BCMA.

In embodiments, a composition described herein can be used to treat a disease including but not limited to a plasma cell proliferative disorder, e.g., asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), monoclonal gammapathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia, plasmacytomas (e.g., plasma cell dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, and POEMS syndrome (also known as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome).

In embodiments, a composition described herein can be used to treat a disease including but not limited to a cancer, e.g., a cancer described herein, e.g., a prostate cancer (e.g., castrate-resistant or therapy-resistant prostate cancer, or metastatic prostate cancer), pancreatic cancer, or lung cancer.

The present invention also provides methods for inhibiting the proliferation or reducing a BCMA-expressing cell population, the methods comprising contacting a population of cells comprising a BMCA-expressing cell with an anti-BCMA CAR-expressing cell (e.g., BCMA CART cell or BCMA CAR-expressing NK cell)of the invention that binds to the BCMA-expressing cell. In a specific aspect, the present invention provides methods for inhibiting the proliferation or reducing the population of cancer cells expressing BCMA, the methods comprising contacting the BCMA-expressing cancer cell population with an anti-BCMA CAR-expressing cell (e.g., BCMA CART cell or BCMA CAR-expressing NK cell)of the invention that binds to the BCMA-expressing cell. In one aspect, the present invention provides methods for inhibiting the proliferation or reducing the population of cancer cells expressing BCMA, the methods comprising contacting the BMCA-expressing cancer cell population with an anti-BCMA CAR-expressing cell (e.g., BCMA CART cell or BCMA CAR-expressing NK cell)of the invention that binds to the BCMA-expressing cell. In certain aspects, the anti-BCMA CAR-expressing cell (e.g., BCMA CART cell or BCMA CAR-expressing NK cell)of the invention reduces the quantity, number, amount or percentage of cells and/or cancer cells by at least 25%, at least 30%, at least 40%, at least 50%, at least 65%, at least 75%, at least 85%, at least 95%, or at least 99% in a subject with or animal model for myeloid leukemia or another cancer

associated with BCMA-expressing cells relative to a negative control. In one aspect, the subject is a human.

The present invention also provides methods for preventing, treating and/or managing a disease associated with BCMA-expressing cells (e.g., a hematologic cancer or atypical cancer expessing BCMA), the methods comprising administering to a subject in need an anti-BCMA CAR-expressing cell (e.g., BCMA CART cell or BCMA CAR-expressing NK cell)of the invention that binds to the BCMA-expressing cell. In one aspect, the subject is a human. Non-limiting examples of disorders associated with BCMA-expressing cells include viral or fungal infections, and disorders related to mucosal immunity.

The present invention also provides methods for preventing, treating and/or managing a disease associated with BCMA-expressing cells, the methods comprising administering to a subject in need an anti-BCMA CAR-expressing cell (e.g., BCMA CART cell or BCMA CAR-expressing NK cell)of the invention that binds to the BCMA-expressing cell. In one aspect, the subject is a human.

The present invention provides methods for preventing relapse of cancer associated with BCMA-expressing cells, the methods comprising administering to a subject in need thereof an anti-BCMA CAR-expressing cell (e.g., BCMA CART cell or BCMA CAR-expressing NK cell)of the invention that binds to the BCMA-expressing cell. In one aspect, the methods comprise administering to the subject in need thereof an effective amount of an anti-BCMA CAR-expressing cell (e.g., BCMA CART cell or BCMA CAR-expressing NK cell)described herein that binds to the BCMA-expressing cell in combination with an effective amount of another therapy.

Combination Therapies

A CAR-expressing cell described herein may be used in combination with other known agents and therapies. Administered “in combination”, as used herein, means that two (or more) different treatments are delivered to the subject during the course of the subject's affliction with the disorder, e.g., the two or more treatments are delivered after the subject has been diagnosed with the disorder and before the disorder has been cured or eliminated or treatment has ceased for other reasons. In some embodiments, the delivery of one treatment is still occurring when

the delivery of the second begins, so that there is overlap in terms of administration. This is sometimes referred to herein as "simultaneous" or "concurrent delivery". In other embodiments, the delivery of one treatment ends before the delivery of the other treatment begins. In some embodiments of either case, the treatment is more effective because of combined administration. For example, the second treatment is more effective, e.g., an equivalent effect is seen with less of the second treatment, or the second treatment reduces symptoms to a greater extent, than would be seen if the second treatment were administered in the absence of the first treatment, or the analogous situation is seen with the first treatment. In some embodiments, delivery is such that the reduction in a symptom, or other parameter related to the disorder is greater than what would be observed with one treatment delivered in the absence of the other. The effect of the two treatments can be partially additive, wholly additive, or greater than additive. The delivery can be such that an effect of the first treatment delivered is still detectable when the second is delivered.

A CAR-expressing cell described herein and the at least one additional therapeutic agent can be administered simultaneously, in the same or in separate compositions, or sequentially. For sequential administration, the CAR-expressing cell described herein can be administered first, and the additional agent can be administered second, or the order of administration can be reversed.

The CAR therapy and/or other therapeutic agents, procedures or modalities can be administered during periods of active disorder, or during a period of remission or less active disease. The CAR therapy can be administered before the other treatment, concurrently with the treatment, post-treatment, or during remission of the disorder.

When administered in combination, the CAR therapy and the additional agent (e.g., second or third agent), or all, can be administered in an amount or dose that is higher, lower or the same than the amount or dosage of each agent used individually, e.g., as a monotherapy. In certain embodiments, the administered amount or dosage of the CAR therapy, the additional agent (e.g., second or third agent), or all, is lower (e.g., at least 20%, at least 30%, at least 40%, or at least 50%) than the amount or dosage of each agent used individually, e.g., as a monotherapy. In other embodiments, the amount or dosage of the CAR therapy, the additional agent (e.g., second or third agent), or all, that results in a desired effect (e.g., treatment of cancer) is lower (e.g., at least 20%, at least 30%, at least 40%, or at least 50% lower) than the

amount or dosage of each agent used individually, e.g., as a monotherapy, required to achieve the same therapeutic effect.

In further aspects, a CAR-expressing cell described herein may be used in a treatment regimen in combination with surgery, chemotherapy, radiation, immunosuppressive agents, such as cyclosporin, azathioprine, methotrexate, mycophenolate, and FK506, antibodies, or other immunoablative agents such as CAMPATH, anti-CD3 antibodies or other antibody therapies, cytoxin, fludarabine, cyclosporin, FK506, rapamycin, mycophenolic acid, steroids, FR901228, cytokines, and irradiation. peptide vaccine, such as that described in Izumoto et al. 2008 J Neurosurg 108:963-971.

In certain instances, compounds of the present invention are combined with other therapeutic agents, such as other anti-cancer agents, anti-allergic agents, anti-nausea agents (or anti-emetics), pain relievers, cytoprotective agents, and combinations thereof.

In one embodiment, a first CAR-expressing cell described herein, e.g., a BCMA CAR-expressing cell described herein, may be used in combination with a second CAR-expressing cell. In one embodiment, the second CAR-expressing cell expresses a CAR comprising a different anti-BMCA binding domain, e.g., an anti-BCMA binding domain described herein that differs from the anti-BCMA binding domain in the CAR expressed by the first CAR-expressing cell. In one embodiment, the second CAR-expressing cell expresses a CAR comprising an antigen-binding domain that targets an antigen other than BCMA (e.g., CD19, CD20, CS-1, kappa light chain, CD139, Lewis Y antigen, or CD38). In one embodiment, a first CAR-expressing cell described herein, e.g., a BCMA CAR-expressing cell described herein, is used in combination with a second CAR-expressing cell comprising a CD19 CAR. In one embodiment, a BCMA CAR-expressing cell described herein is used in combination with a CD19 CAR-expressing cell to treat a BCMA-associated cancer described herein, e.g., multiple myeloma. In some embodiments, the multiple myeloma is CD19-negative, e.g., having a vast majority (e.g., at least 98%, 99%, 99.5%, 99.9%, or 99.95%) of the neoplastic plasma cells with a CD19-negative phenotype, e.g., as detected flow cytometry, RT-PCR, or both flow cytometry and RT-PCR. As shown in Example 17 herein, a CD19 CAR can be effective even against a CD19-negative multiple myeloma. While not wishing to be bound by theory, the CD19 CAR may act on a small but important CD19-positive population of neoplastic cells, by targeting a cell that expresses levels of CD19 that fall below the detection threshold of the assays

described herein, or by targeting a non-neoplastic cell that supports the neoplastic cells. In embodiments, a CD19 CAR can remove B cells, e.g., B regulatory B cells.

For example, in one embodiment, the first CAR-expressing cell described herein, e.g., a BCMA CAR-expressing cell, and the second CAR-expressing cell described herein, e.g., a CD19 CAR-expressing cell, are prepared in the same composition and are administered simultaneously. In another embodiment, the first CAR-expressing cell described herein, e.g., a BCMA CAR-expressing cell, and the second CAR-expressing cell described herein, e.g., a CD19 CAR-expressing cell, are prepared in separate compositions, and the separate compositions are administered simultaneously or sequentially. When the BCMA CAR-expressing cell and the second CAR-expressing cell are prepared in separate compositions, the BCMA CAR-expressing cell can be administered first, and the second CAR-expressing cell can be administered second, or the order of administration can be reversed.

In one embodiment, a CD19 CAR is a CD19 CAR, e.g., a humanized CD19 CAR, described in WO2014/153270, filed March 15, 2014 (which is incorporated by reference herein in its entirety) or a sequence at least 95%, e.g., 95-99%, identical thereto. In some embodiments, the CD19 CAR construct is a CAR19 construct provided in PCT publication WO2012/079000 (which is incorporated by reference herein in its entirety) or a sequence at least 95%, e.g., 95-99%, identical thereto. In one embodiment, the anti-CD19 binding domain is a scFv described in WO2012/079000, or a sequence at least 95%, e.g., 95-99%, identical thereto.

In embodiments, a first CAR-expressing cell is administered to a subject, and a second CAR-expressing cell is administered to the subject. In embodiments, the first CAR-expressing cell comprises a CAR (e.g., BCMA or CD19 CAR) comprising a CD27 costimulatory domain and a CD3zeta (mutant or wild type) primary signaling domain. In embodiments, the second CAR-expressing cell comprises a CAR (e.g., BCMA CAR) comprising a 4-1BB costimulatory domain and a CD3zeta (mutant or wild type) primary signaling domain. Without wishing to be bound by theory, in embodiments, the first CAR-expressing cell can be less toxic than the second CAR-expressing cell and be used to debulk a tumor.

In one embodiment, a CAR-expressing cell described herein can be used in combination with a chemotherapeutic agent. Exemplary chemotherapeutic agents include an anthracycline

(e.g., doxorubicin (e.g., liposomal doxorubicin)), a vinca alkaloid (e.g., vinblastine, vincristine, vindesine, vinorelbine), an alkylating agent (e.g., cyclophosphamide, decarbazine, melphalan, ifosfamide, temozolomide), an immune cell antibody (e.g., alemtuzamab, gemtuzumab, rituximab, tositumomab), an antimetabolite (including, e.g., folic acid antagonists, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors (e.g., fludarabine)), an mTOR inhibitor, a TNFR glucocorticoid induced TNFR related protein (GITR) agonist, a proteasome inhibitor (e.g., aclacinomycin A, gliotoxin or bortezomib), an immunomodulator such as thalidomide or a thalidomide derivative (e.g., lenalidomide).

General Chemotherapeutic agents considered for use in combination therapies include anastrozole (Arimidex®), bicalutamide (Casodex®), bleomycin sulfate (Blenoxane®), busulfan (Myleran®), busulfan injection (Busulfex®), capecitabine (Xeloda®), N4-pentoxycarbonyl-5-deoxy-5-fluorocytidine, carboplatin (Paraplatin®), carmustine (BiCNU®), chlorambucil (Leukeran®), cisplatin (Platinol®), cladribine (Leustatin®), cyclophosphamide (Cytoxan® or Neosar®), cytarabine, cytosine arabinoside (Cytosar-U®), cytarabine liposome injection (DepoCyt®), dacarbazine (DTIC-Dome®), dactinomycin (Actinomycin D, Cosmegan), daunorubicin hydrochloride (Cerubidine®), daunorubicin citrate liposome injection (DaunoXome®), dexamethasone, docetaxel (Taxotere®), doxorubicin hydrochloride (Adriamycin®, Rubex®), etoposide (Vepesid®), fludarabine phosphate (Fludara®), 5-fluorouracil (Adrucil®, Efudex®), flutamide (Eulexin®), tezacitibine, Gemcitabine (difluorodeoxycitidine), hydroxyurea (Hydrea®), Idarubicin (Idamycin®), ifosfamide (IFEX®), irinotecan (Camptosar®), L-asparaginase (ELSPAR®), leucovorin calcium, melphalan (Alkeran®), 6-mercaptopurine (Purinethol®), methotrexate (Folex®), mitoxantrone (Novantrone®), mylotarg, paclitaxel (Taxol®), phoenix (Yttrium90/MX-DTPA), pentostatin, polifeprosan 20 with carmustine implant (Gliadel®), tamoxifen citrate (Nolvadex®), teniposide (Vumon®), 6-thioguanine, thiotepa, tirapazamine (Tirazone®), topotecan hydrochloride for injection (Hycamptin®), vinblastine (Velban®), vincristine (Oncovin®), and vinorelbine (Navelbine®).

Anti-cancer agents of particular interest for combinations with the compounds of the present invention include: anthracyclines; alkylating agents; antimetabolites; drugs that inhibit either the calcium dependent phosphatase calcineurin or the p70S6 kinase FK506) or inhibit the p70S6 kinase; mTOR inhibitors; immunomodulators; anthracyclines; vinca alkaloids;

proteosome inhibitors; GITR agonists; protein tyrosine phosphatase inhibitors; a CDK4 kinase inhibitor; a BTK inhibitor; a MKN kinase inhibitor; a DGK kinase inhibitor; or an oncolytic virus.

Exemplary alkylating agents include, without limitation, nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes): uracil mustard (Aminouracil Mustard®, Chlorethaminacil®, Demethyldopan®, Desmethyldopan®, Haemanthamine®, Nordopan®, Uracil nitrogen mustard®, Uracillost®, Uracilmostaza®, Uramustin®, Uramustine®), chlormethine (Mustargen®), cyclophosphamide (Cytoxan®, Neosar®, Clafen®, Endoxan®, Procytox®, Revimmune™), ifosfamide (Mitoxana®), melphalan (Alkeran®), Chlorambucil (Leukeran®), pipobroman (Amedel®, Vercyte®), triethylenemelamine (Hemel®, Hexalen®, Hexastat®), triethylenethiophosphoramine, Temozolomide (Temodar®), thiotepa (Thioplex®), busulfan (Busilvex®, Myleran®), carmustine (BiCNU®), lomustine (CeeNU®), streptozocin (Zanosar®), and Dacarbazine (DTIC-Dome®). Additional exemplary alkylating agents include, without limitation, Oxaliplatin (Eloxatin®); Temozolomide (Temodar® and Temodal®); Dactinomycin (also known as actinomycin-D, Cosmegen®); Melphalan (also known as L-PAM, L-sarcolysin, and phenylalanine mustard, Alkeran®); Altretamine (also known as hexamethylmelamine (HMM), Hexalen®); Carmustine (BiCNU®); Bendamustine (Treanda®); Busulfan (Busulfex® and Myleran®); Carboplatin (Paraplatin®); Lomustine (also known as CCNU, CeeNU®); Cisplatin (also known as CDDP, Platinol® and Platinol®-AQ); Chlorambucil (Leukeran®); Cyclophosphamide (Cytoxan® and Neosar®); Dacarbazine (also known as DTIC, DIC and imidazole carboxamide, DTIC-Dome®); Altretamine (also known as hexamethylmelamine (HMM), Hexalen®); Ifosfamide (Ifex®); Prednumustine; Procarbazine (Matulane®); Mechlorethamine (also known as nitrogen mustard, mustine and mechloroethamine hydrochloride, Mustargen®); Streptozocin (Zanosar®); Thiotepa (also known as thiophosphoamide, TESPA and TSPA, Thioplex®); Cyclophosphamide (Endoxan®, Cytoxan®, Neosar®, Procytox®, Revimmune®); and Bendamustine HCl (Treanda®).

Exemplary mTOR inhibitors include, e.g., temsirolimus; ridaforolimus (formally known as deferolimus, (1*R*,2*R*,4*S*)-4-[(2*R*)-2 [(1*R*,9*S*,12*S*,15*R*,16*E*,18*R*,19*R*,21*R*, 23*S*,24*E*,26*E*,28*Z*,30*S*,32*S*,35*R*)-1,18-dihydroxy-19,30-dimethoxy-15,17,21,23, 29,35-hexamethyl-2,3,10,14,20-pentaoxo-11,36-dioxa-4-azatricyclo[30.3.1.$0^{4,9}$] hexatriaconta-

16,24,26,28-tetraen-12-yl]propyl]-2-methoxycyclohexyl dimethylphosphinate, also known as AP23573 and MK8669, and described in PCT Publication No. WO 03/064383); everolimus (Afinitor® or RAD001); rapamycin (AY22989, Sirolimus®); simapimod (CAS 164301-51-3); emsirolimus, (5-{2,4-Bis[(3*S*)-3-methylmorpholin-4-yl]pyrido[2,3-*d*]pyrimidin-7-yl}-2-methoxyphenyl)methanol (AZD8055); 2-Amino-8-[*trans*-4-(2-hydroxyethoxy)cyclohexyl]-6-(6-methoxy-3-pyridinyl)-4-methyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (PF04691502, CAS 1013101-36-4); and N^2-[1,4-dioxo-4-[[4-(4-oxo-8-phenyl-4*H*-1-benzopyran-2-yl)morpholinium-4-yl]methoxy]butyl]-L-arginylglycyl-L-α-aspartylL-serine- (SEQ ID NO: 383), inner salt (SF1126, CAS 936487-67-1), and XL765.

Exemplary immunomodulators include, e.g., afutuzumab (available from Roche®); pegfilgrastim (Neulasta®); lenalidomide (CC-5013, Revlimid®); thalidomide (Thalomid®), actimid (CC4047); and IRX-2 (mixture of human cytokines including interleukin 1, interleukin 2, and interferon γ, CAS 951209-71-5, available from IRX Therapeutics).

Exemplary anthracyclines include, e.g., doxorubicin (Adriamycin® and Rubex®); bleomycin (lenoxane®); daunorubicin (dauorubicin hydrochloride, daunomycin, and rubidomycin hydrochloride, Cerubidine®); daunorubicin liposomal (daunorubicin citrate liposome, DaunoXome®); mitoxantrone (DHAD, Novantrone®); epirubicin (Ellence™); idarubicin (Idamycin®, Idamycin PFS®); mitomycin C (Mutamycin®); geldanamycin; herbimycin; ravidomycin; and desacetylravidomycin.

Exemplary vinca alkaloids include, e.g., vinorelbine tartrate (Navelbine®), Vincristine (Oncovin®), and Vindesine (Eldisine®)); vinblastine (also known as vinblastine sulfate, vincaleukoblastine and VLB, Alkaban-AQ® and Velban®); and vinorelbine (Navelbine®).

Exemplary proteosome inhibitors include bortezomib (Velcade®); carfilzomib (PX-171-007, (*S*)-4-Methyl-*N*-((*S*)-1-(((*S*)-4-methyl-1-((*R*)-2-methyloxiran-2-yl)-1-oxopentan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)-2-((*S*)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-pentanamide); marizomib (NPI-0052); ixazomib citrate (MLN-9708); delanzomib (CEP-18770); and *O*-Methyl-*N*-[(2-methyl-5-thiazolyl)carbonyl]-L-seryl-*O*-methyl-*N*-[(1*S*)-2-[(2*R*)-2-methyl-2-oxiranyl]-2-oxo-1-(phenylmethyl)ethyl]- L-serinamide (ONX-0912).

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with fludarabine, cyclophosphamide, and/or rituximab. In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with fludarabine, cyclophosphamide, and rituximab (FCR). In embodiments, the subject has CLL. For example, the subject has a deletion in the short arm of chromosome 17 (del(17p), e.g., in a leukemic cell). In other examples, the subject does not have a del(17p). In embodiments, the subject comprises a leukemic cell comprising a mutation in the immunoglobulin heavy-chain variable-region (IgV_H) gene. In other embodiments, the subject does not comprise a leukemic cell comprising a mutation in the immunoglobulin heavy-chain variable-region (IgV_H) gene. In embodiments, the fludarabine is administered at a dosage of about 10-50 mg/m^2 (e.g., about 10-15, 15-20, 20-25, 25-30, 30-35, 35-40, 40-45, or 45-50 mg/m^2), e.g., intravenously. In embodiments, the cyclophosphamide is administered at a dosage of about 200-300 mg/m^2 (e.g., about 200-225, 225-250, 250-275, or 275-300 mg/m^2), e.g., intravenously. In embodiments, the rituximab is administered at a dosage of about 400-600 mg/m2 (e.g., 400-450, 450-500, 500-550, or 550-600 mg/m^2), e.g., intravenously.

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with bendamustine and rituximab. In embodiments, the subject has CLL. For example, the subject has a deletion in the short arm of chromosome 17 (del(17p), e.g., in a leukemic cell). In other examples, the subject does not have a del(17p). In embodiments, the subject comprises a leukemic cell comprising a mutation in the immunoglobulin heavy-chain variable-region (IgV_H) gene. In other embodiments, the subject does not comprise a leukemic cell comprising a mutation in the immunoglobulin heavy-chain variable-region (IgV_H) gene. In embodiments, the bendamustine is administered at a dosage of about 70-110 mg/m2 (e.g., 70-80, 80-90, 90-100, or 100-110 mg/m2), e.g., intravenously. In embodiments, the rituximab is administered at a dosage of about 400-600 mg/m2 (e.g., 400-450, 450-500, 500-550, or 550-600 mg/m^2), e.g., intravenously.

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with rituximab, cyclophosphamide, doxorubicine, vincristine, and/or a corticosteroid (e.g., prednisone). In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with rituximab, cyclophosphamide, doxorubicine, vincristine, and prednisone (R-CHOP). In embodiments, the subject has diffuse large B-cell

lymphoma (DLBCL). In embodiments, the subject has nonbulky limited-stage DLBCL (e.g., comprises a tumor having a size/diameter of less than 7 cm). In embodiments, the subject is treated with radiation in combination with the R-CHOP. For example, the subject is administered R-CHOP (e.g., 1-6 cycles, e.g., 1, 2, 3, 4, 5, or 6 cycles of R-CHOP), followed by radiation. In some cases, the subject is administered R-CHOP (e.g., 1-6 cycles, e.g., 1, 2, 3, 4, 5, or 6 cycles of R-CHOP) following radiation.

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and/or rituximab. In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (EPOCH-R). In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with dose-adjusted EPOCH-R (DA-EPOCH-R). In embodiments, the subject has a B cell lymphoma, e.g., a Myc-rearranged aggressive B cell lymphoma.

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with rituximab and/or lenalidomide. Lenalidomide ((*RS*)-3-(4-Amino-1-oxo 1,3-dihydro-2*H*-isoindol- 2-yl)piperidine-2,6-dione) is an immunomodulator. In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with rituximab and lenalidomide. In embodiments, the subject has follicular lymphoma (FL) or mantle cell lymphoma (MCL). In embodiments, the subject has FL and has not previously been treated with a cancer therapy. In embodiments, lenalidomide is administered at a dosage of about 10-20 mg (e.g., 10-15 or 15-20 mg), e.g., daily. In embodiments, rituximab is administered at a dosage of about 350-550 mg/m^2 (e.g., 350-375, 375-400, 400-425, 425-450, 450-475, or 475-500 mg/m^2), e.g., intravenously.

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with brentuximab. Brentuximab is an antibody-drug conjugate of anti-CD30 antibody and monomethyl auristatin E. In embodiments, the subject has Hodgkin's lymphoma (HL), e.g., relapsed or refractory HL. In embodiments, the subject comprises CD30+ HL. In embodiments, the subject has undergone an autologous stem cell transplant (ASCT). In embodiments, the subject has not undergone an ASCT. In embodiments, brentuximab is

administered at a dosage of about 1-3 mg/kg (e.g., about 1-1.5, 1.5-2, 2-2.5, or 2.5-3 mg/kg), e.g., intravenously, e.g., every 3 weeks.

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with brentuximab and dacarbazine or in combination with brentuximab and bendamustine. Dacarbazine is an alkylating agent with a chemical name of 5-(3,3-Dimethyl-1-triazenyl)imidazole-4-carboxamide. Bendamustine is an alkylating agent with a chemical name of 4-[5-[Bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid. In embodiments, the subject has Hodgkin's lymphoma (HL). In embodiments, the subject has not previously been treated with a cancer therapy. In embodiments, the subject is at least 60 years of age, e.g., 60, 65, 70, 75, 80, 85, or older. In embodiments, dacarbazine is administered at a dosage of about 300-450 mg/m^2 (e.g., about 300-325, 325-350, 350-375, 375-400, 400-425, or 425-450 mg/m^2), e.g., intravenously. In embodiments, bendamustine is administered at a dosage of about 75-125 mg/m2 (e.g., 75-100 or 100-125 mg/m^2, e.g., about 90 mg/m^2), e.g., intravenously. In embodiments, brentuximab is administered at a dosage of about 1-3 mg/kg (e.g., about 1-1.5, 1.5-2, 2-2.5, or 2.5-3 mg/kg), e.g., intravenously, e.g., every 3 weeks.

In some embodiments, a CAR-expressing cell described herein is administered to a subject in combination with a CD20 inhibitor, e.g., an anti-CD20 antibody (e.g., an anti-CD20 mono- or bispecific antibody) or a fragment thereof. Exemplary anti-CD20 antibodies include but are not limited to rituximab, ofatumumab, ocrelizumab, veltuzumab, obinutuzumab, TRU-015 (Trubion Pharmaceuticals), ocaratuzumab, and Pro131921 (Genentech). See, e.g., Lim et al. Haematologica. 95.1(2010):135-43.

In some embodiments, the anti-CD20 antibody comprises rituximab. Rituximab is a chimeric mouse/human monoclonal antibody IgG1 kappa that binds to CD20 and causes cytolysis of a CD20 expressing cell, e.g., as described in www.accessdata.fda.gov/drugsatfda_docs/label/2010/103705s5311lbl.pdf. In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with rituximab. In embodiments, the subject has CLL or SLL.

In some embodiments, rituximab is administered intravenously, e.g., as an intravenous infusion. For example, each infusion provides about 500-2000 mg (e.g., about 500-550, 550-600, 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 900-950, 950-1000, 1000-1100,

1100-1200, 1200-1300, 1300-1400, 1400-1500, 1500-1600, 1600-1700, 1700-1800, 1800-1900, or 1900-2000 mg) of rituximab. In some embodiments, rituximab is administered at a dose of 150 mg/m^2 to 750 mg/m^2, e.g., about 150-175 mg/m^2, 175-200 mg/m^2, 200-225 mg/m^2, 225-250 mg/m^2, 250-300 mg/m^2, 300-325 mg/m^2, 325-350 mg/m^2, 350-375 mg/m^2, 375-400 mg/m^2, 400-425 mg/m^2, 425-450 mg/m^2, 450-475 mg/m^2, 475-500 mg/m^2, 500-525 mg/m^2, 525-550 mg/m^2, 550-575 mg/m^2, 575-600 mg/m^2, 600-625 mg/m^2, 625-650 mg/m^2, 650-675 mg/m^2, or 675-700 mg/m^2, where m^2 indicates the body surface area of the subject. In some embodiments, rituximab is administered at a dosing interval of at least 4 days, e.g., 4, 7, 14, 21, 28, 35 days, or more. For example, rituximab is administered at a dosing interval of at least 0.5 weeks, e.g., 0.5, 1, 2, 3, 4, 5, 6, 7, 8 weeks, or more. In some embodiments, rituximab is administered at a dose and dosing interval described herein for a period of time, e.g., at least 2 weeks, e.g., at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 weeks, or greater. For example, rituximab is administered at a dose and dosing interval described herein for a total of at least 4 doses per treatment cycle (e.g., at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or more doses per treatment cycle).

In some embodiments, the anti-CD20 antibody comprises ofatumumab. Ofatumumab is an anti-CD20 IgG1κ human monoclonal antibody with a molecular weight of approximately 149 kDa. For example, ofatumumab is generated using transgenic mouse and hybridoma technology and is expressed and purified from a recombinant murine cell line (NS0). See, e.g., www.accessdata.fda.gov/drugsatfda_docs/label/2009/125326lbl.pdf; and Clinical Trial Identifier number NCT01363128, NCT01515176, NCT01626352, and NCT01397591. In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with ofatumumab. In embodiments, the subject has CLL or SLL.

In some embodiments, ofatumumab is administered as an intravenous infusion. For example, each infusion provides about 150-3000 mg (e.g., about 150-200, 200-250, 250-300, 300-350, 350-400, 400-450, 450-500, 500-550, 550-600, 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 900-950, 950-1000, 1000-1200, 1200-1400, 1400-1600, 1600-1800, 1800-2000, 2000-2200, 2200-2400, 2400-2600, 2600-2800, or 2800-3000 mg) of ofatumumab. In embodiments, ofatumumab is administered at a starting dosage of about 300 mg, followed by 2000 mg, e.g., for about 11 doses, e.g., for 24 weeks. In some embodiments, ofatumumab is administered at a dosing interval of at least 4 days, e.g., 4, 7, 14, 21, 28, 35 days, or more. For

example, ofatumumab is administered at a dosing interval of at least 1 week, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 24, 26, 28, 20, 22, 24, 26, 28, 30 weeks, or more. In some embodiments, ofatumumab is administered at a dose and dosing interval described herein for a period of time, e.g., at least 1 week, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 24, 26, 28, 30, 40, 50, 60 weeks or greater, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months or greater, or 1, 2, 3, 4, 5 years or greater. For example, ofatumumab is administered at a dose and dosing interval described herein for a total of at least 2 doses per treatment cycle (e.g., at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 20, or more doses per treatment cycle).

In some cases, the anti-CD20 antibody comprises ocrelizumab. Ocrelizumab is a humanized anti-CD20 monoclonal antibody, e.g., as described in Clinical Trials Identifier Nos. NCT00077870, NCT01412333, NCT00779220, NCT00673920, NCT01194570, and Kappos et al. Lancet. 19.378(2011):1779-87.

In some cases, the anti-CD20 antibody comprises veltuzumab. Veltuzumab is a humanized monoclonal antibody against CD20. See, e.g., Clinical Trial Identifier No. NCT00547066, NCT00546793, NCT01101581, and Goldenberg et al. Leuk Lymphoma. 51(5)(2010):747-55.

In some cases, the anti-CD20 antibody comprises GA101. GA101 (also called obinutuzumab or RO5072759) is a humanized and glyco-engineered anti-CD20 monoclonal antibody. See, e.g., Robak. Curr. Opin. Investig. Drugs. 10.6(2009):588-96; Clinical Trial Identifier Numbers: NCT01995669, NCT01889797, NCT02229422, and NCT01414205; and www.accessdata.fda.gov/drugsatfda_docs/label/2013/125486s000lbl.pdf.

In some cases, the anti-CD20 antibody comprises AME-133v. AME-133v (also called LY2469298 or ocaratuzumab) is a humanized IgG1 monoclonal antibody against CD20 with increased affinity for the FcγRIIIa receptor and an enhanced antibody dependent cellular cytotoxicity (ADCC) activity compared with rituximab. See, e.g., Robak et al. BioDrugs 25.1(2011):13-25; and Forero-Torres et al. Clin Cancer Res. 18.5(2012):1395-403.

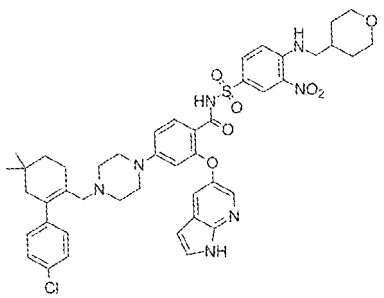
In some cases, the anti-CD20 antibody comprises PRO131921. PRO131921 is a humanized anti-CD20 monoclonal antibody engineered to have better binding to FcγRIIIa and enhanced ADCC compared with rituximab. See, e.g., Robak et al. BioDrugs 25.1(2011):13-25;

and Casulo et al. Clin Immunol. 154.1(2014):37-46; and Clinical Trial Identifier No. NCT00452127.

In some cases, the anti-CD20 antibody comprises TRU-015. TRU-015 is an anti-CD20 fusion protein derived from domains of an antibody against CD20. TRU-015 is smaller than monoclonal antibodies, but retains Fc-mediated effector functions. See, e.g., Robak et al. BioDrugs 25.1(2011):13-25. TRU-015 contains an anti-CD20 single-chain variable fragment (scFv) linked to human IgG1 hinge, CH2, and CH3 domains but lacks CH1 and CL domains.

In some embodiments, an anti-CD20 antibody described herein is conjugated or otherwise bound to a therapeutic agent, e.g., a chemotherapeutic agent (e.g., cytoxan, fludarabine, histone deacetylase inhibitor, demethylating agent, peptide vaccine, anti-tumor antibiotic, tyrosine kinase inhibitor, alkylating agent, anti-microtubule or anti-mitotic agent), anti-allergic agent, anti-nausea agent (or anti-emetic), pain reliever, or cytoprotective agent described herein.

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with a B-cell lymphoma 2 (BCL-2) inhibitor (e.g., venetoclax, also called ABT-199 or GDC-0199;) and/or rituximab. In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with venetoclax and rituximab. Venetoclax is a small molecule that inhibits the anti-apoptotic protein, BCL-2. The structure of venetoclax (4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-({3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzamide) is shown below.



In embodiments, the subject has CLL. In embodiments, the subject has relapsed CLL, e.g., the subject has previously been administered a cancer therapy. In embodiments, venetoclax is administered at a dosage of about 15-600 mg (e.g., 15-20, 20-50, 50-75, 75-100,

100-200, 200-300, 300-400, 400-500, or 500-600 mg), e.g., daily. In embodiments, rituximab is administered at a dosage of about 350-550 mg/m2 (e.g., 350-375, 375-400, 400-425, 425-450, 450-475, or 475-500 mg/m2), e.g., intravenously, e.g., monthly.

Without being bound by theory, it is believed that in some cancers, B cells (e.g., B regulatory cells) can suppress T cells. Further, it is believed that a combination of oxiplatin and the B cell depleting agent may reduce tumor size and/or eliminate tumors in a subject. In some embodiments, a CAR-expressing cell described herein (e.g., BCMA CAR) is administered in combination with a B cell depleting agent (e.g., a CD19 CAR-expressing cell, a CD20 CAR-expressing cell, rituximab, ocrelizumab, epratuzumab, or belimumab) and oxiplatin. In embodiments, the cancer cell can be CD19 negative or CD19 positive; or BCMA negative or BMCA positive. In embodiments, a CAR-expressing cell described herein (e.g., BCMA CAR) is administered in combination with a B cell depleting agent and oxiplatin to treat a cancer, e.g., a cancer described herein, e.g., solid cancer, e.g., prostate cancer, pancreatic cancer, or lung cancer.

In embodiments, a CAR-expressing cell described herein (e.g., BCMA CAR) may deplete B cells (e.g., B cells having a plasma cell-like phenotype, e.g., that express BCMA, CD19, and/or CD20) in a subject. In embodiments, the B cell can be CD19 negative or CD19 positive; or BCMA negative or BMCA positive. In some embodiments, a CAR-expressing cell described herein (e.g., BCMA CAR) is administered in combination with oxiplatin. In embodiments, a CAR-expressing cell described herein is administered in combination with oxiplatin is used to treat a cancer, e.g., solid cancer, e.g., prostate cancer, pancreatic cancer, or lung cancer.In some embodiments, a CAR-expressing cell described herein is administered in combination with an oncolytic virus. In embodiments, oncolytic viruses are capable of selectively replicating in and triggering the death of or slowing the growth of a cancer cell. In some cases, oncolytic viruses have no effect or a minimal effect on non-cancer cells. An oncolytic virus includes but is not limited to an oncolytic adenovirus, oncolytic Herpes Simplex Viruses, oncolytic retrovirus, oncolytic parvovirus, oncolytic vaccinia virus, oncolytic Sinbis virus, oncolytic influenza virus, or oncolytic RNA virus (e.g., oncolytic reovirus, oncolytic Newcastle Disease Virus (NDV), oncolytic measles virus, or oncolytic vesicular stomatitis virus (VSV)).

In some embodiments, the oncolytic virus is a virus, e.g., recombinant oncolytic virus, described in US2010/0178684 A1, which is incorporated herein by reference in its entirety. In some embodiments, a recombinant oncolytic virus comprises a nucleic acid sequence (e.g., heterologous nucleic acid sequence) encoding an inhibitor of an immune or inflammatory response, e.g., as described in US2010/0178684 A1, incorporated herein by reference in its entirety. In embodiments, the recombinant oncolytic virus, e.g., oncolytic NDV, comprises a pro-apoptotic protein (e.g., apoptin), a cytokine (e.g., GM-CSF, interferon-gamma, interleukin-2 (IL-2), tumor necrosis factor-alpha), an immunoglobulin (e.g., an antibody against ED-B firbonectin), tumor associated antigen, a bispecific adapter protein (e.g., bispecific antibody or antibody fragment directed against NDV HN protein and a T cell co-stimulatory receptor, such as CD3 or CD28; or fusion protein between human IL-2 and single chain antibody directed against NDV HN protein). See, e.g., Zamarin et al. Future Microbiol. 7.3(2012):347-67, incorporated herein by reference in its entirety. In some embodiments, the oncolytic virus is a chimeric oncolytic NDV described in US 8591881 B2, US 2012/0122185 A1, or US 2014/0271677 A1, each of which is incorporated herein by reference in their entireties.

In some embodiments, the oncolytic virus comprises a conditionally replicative adenovirus (CRAd), which is designed to replicate exclusively in cancer cells. See, e.g., Alemany et al. Nature Biotechnol. 18(2000):723-27. In some embodiments, an oncolytic adenovirus comprises one described in Table 1 on page 725 of Alemany et al., incorporated herein by reference in its entirety.

Exemplary oncolytic viruses include but are not limited to the following:

Group B Oncolytic Adenovirus (ColoAd1) (PsiOxus Therapeutics Ltd.) (see, e.g., Clinical Trial Identifier: NCT02053220);

ONCOS-102 (previously called CGTG-102), which is an adenovirus comprising granulocyte-macrophage colony stimulating factor (GM-CSF) (Oncos Therapeutics) (see, e.g., Clinical Trial Identifier: NCT01598129);

VCN-01, which is a genetically modified oncolytic human adenovirus encoding human PH20 hyaluronidase (VCN Biosciences, S.L.) (see, e.g., Clinical Trial Identifiers: NCT02045602 and NCT02045589);

Conditionally Replicative Adenovirus ICOVIR-5, which is a virus derived from wild-type human adenovirus serotype 5 (Had5) that has been modified to selectively replicate in

cancer cells with a deregulated retinoblastoma/E2F pathway (Institut Català d'Oncologia) (see, e.g., Clinical Trial Identifier: NCT01864759);

Celyvir, which comprises bone marrow-derived autologous mesenchymal stem cells (MSCs) infected with ICOVIR5, an oncolytic adenovirus (Hospital Infantil Universitario Niño Jesús, Madrid, Spain/ Ramon Alemany) (see, e.g., Clinical Trial Identifier: NCT01844661);

CG0070, which is a conditionally replicating oncolytic serotype 5 adenovirus (Ad5) in which human E2F-1 promoter drives expression of the essential E1a viral genes, thereby restricting viral replication and cytotoxicity to Rb pathway-defective tumor cells (Cold Genesys, Inc.) (see, e.g., Clinical Trial Identifier: NCT02143804); or

DNX-2401 (formerly named Delta-24-RGD), which is an adenovirus that has been engineered to replicate selectively in retinoblastoma (Rb)-pathway deficient cells and to infect cells that express certain RGD-binding integrins more efficiently (Clinica Universidad de Navarra, Universidad de Navarra/ DNAtrix, Inc.) (see, e.g., Clinical Trial Identifier: NCT01956734).

In some embodiments, an oncolytic virus described herein is administering by injection, e.g., subcutaneous, intra-arterial, intravenous, intramuscular, intrathecal, or intraperitoneal injection. In embodiments, an oncolytic virus described herein is administered intratumorally, transdermally, transmucosally, orally, intranasally, or via pulmonary administration.

In an embodiment, cells expressing a CAR described herein are administered to a subject in combination with a molecule that decreases the Treg cell population. Methods that decrease the number of (e.g., deplete) Treg cells are known in the art and include, e.g., CD25 depletion, cyclophosphamide administration, modulating GITR function. Without wishing to be bound by theory, it is believed that reducing the number of Treg cells in a subject prior to apheresis or prior to administration of a CAR-expressing cell described herein reduces the number of unwanted immune cells (e.g., Tregs) in the tumor microenvironment and reduces the subject's risk of relapse. In one embodiment, a CAR expressing cell described herein is administered to a subject in combination with a a molecule targeting GITR and/or modulating GITR functions, such as a GITR agonist and/or a GITR antibody that depletes regulatory T cells (Tregs). In embodiments, cells expressing a CAR described herein are administered to a subject in combination with cyclophosphamide. In one embodiment, the GITR binding molecules and/or molecules modulating GITR functions (e.g., GITR agonist and/or Treg

depleting GITR antibodies) are administered prior to administration of the CAR-expressing cell. For example, in one embodiment, the GITR agonist can be administered prior to apheresis of the cells. In embodiments, cyclophosphamide is administered to the subject prior to administration (e.g., infusion or re-infusion) of the CAR-expressing cell or prior to aphersis of the cells. In embodiments, cyclophosphamide and an anti-GITR antibody are administered to the subject prior to administration (e.g., infusion or re-infusion) of the CAR-expressing cell or prior to apheresis of the cells. In one embodiment, the subject has cancer (e.g., a solid cancer or a hematological cancer such as multiple myeloma, ALL or CLL). In an embodiment, the subject has CLL. In embodiments, the subject has multiple myeloma. In embodiments, the subject has a solid cancer, e.g., a solid cancer described herein. Exemplary GITR agonists include, e.g., GITR fusion proteins and anti-GITR antibodies (e.g., bivalent anti-GITR antibodies) such as, e.g., a GITR fusion protein described in U.S. Patent No.: 6,111,090, European Patent No.: 090505B1, U.S Patent No.: 8,586,023, PCT Publication Nos.: WO 2010/003118 and 2011/090754, or an anti-GITR antibody described, e.g., in U.S. Patent No.: 7,025,962, European Patent No.: 1947183B1, U.S. Patent No.: 7,812,135, U.S. Patent No.: 8,388,967, U.S. Patent No.: 8,591,886, European Patent No.: EP 1866339, PCT Publication No.: WO 2011/028683, PCT Publication No.:WO 2013/039954, PCT Publication No.: WO2005/007190, PCT Publication No.: WO 2007/133822, PCT Publication No.: WO2005/055808, PCT Publication No.: WO 99/40196, PCT Publication No.: WO 2001/03720, PCT Publication No.: WO99/20758, PCT Publication No.: WO2006/083289, PCT Publication No.: WO 2005/115451, U.S. Patent No.: 7,618,632, and PCT Publication No.: WO 2011/051726.

In one embodiment, a CAR expressing cell described herein is administered to a subject in combination with an mTOR inhibitor, e.g., an mTOR inhibitor described herein, e.g., a rapalog such as everolimus. In one embodiment, the mTOR inhibitor is administered prior to the CAR-expressing cell. For example, in one embodiment, the mTOR inhibitor can be administered prior to apheresis of the cells.

In one embodiment, a CAR expressing cell described herein is administered to a subject in combination with a GITR agonist, e.g., a GITR agonist described herein. In one embodiment, the GITR agonist is administered prior to the CAR-expressing cell. For example, in one embodiment, the GITR agonist can be administered prior to apheresis of the cells.

In one embodiment, a CAR expressing cell described herein is administered to a subject in combination with a protein tyrosine phosphatase inhibitor, e.g., a protein tyrosine phosphatase inhibitor described herein. In one embodiment, the protein tyrosine phosphatase inhibitor is an SHP-1 inhibitor, e.g., an SHP-1 inhibitor described herein, such as, e.g., sodium stibogluconate. In one embodiment, the protein tyrosine phosphatase inhibitor is an SHP-2 inhibitor.

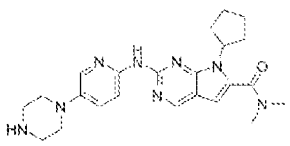
In one embodiment, a CAR-expressing cell described herein can be used in combination with a kinase inhibitor. In one embodiment, the kinase inhibitor is a CDK4 inhibitor, e.g., a CDK4 inhibitor described herein, e.g., a CDK4/6 inhibitor, such as, e.g., 6-Acetyl-8-cyclopentyl-5-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one, hydrochloride (also referred to as palbociclib or PD0332991). In one embodiment, the kinase inhibitor is a BTK inhibitor, e.g., a BTK inhibitor described herein, such as, e.g., ibrutinib. In one embodiment, the kinase inhibitor is an mTOR inhibitor, e.g., an mTOR inhibitor described herein, such as, e.g., rapamycin, a rapamycin analog, OSI-027. The mTOR inhibitor can be, e.g., an mTORC1 inhibitor and/or an mTORC2 inhibitor, e.g., an mTORC1 inhibitor and/or mTORC2 inhibitor described herein. In one embodiment, the kinase inhibitor is a MNK inhibitor, e.g., a MNK inhibitor described herein, such as, e.g., 4-amino-5-(4-fluoroanilino)-pyrazolo [3,4-*d*] pyrimidine. The MNK inhibitor can be, e.g., a MNK1a, MNK1b, MNK2a and/or MNK2b inhibitor. In one embodiment, the kinase inhibitor is a dual PI3K/mTOR inhibitor described herein, such as, e.g., PF-04695102. In one embodiment, the kinase inhibitor is a DGK inhibitor, e.g., a DGK inhibitor described herein, such as, e.g., DGKinh1 (D5919) or DGKinh2 (D5794).

In one embodiment, the kinase inhibitor is a CDK4 inhibitor selected from aloisine A; flavopiridol or HMR-1275, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-4-chromenone; crizotinib (PF-02341066; 2-(2-Chlorophenyl)-5,7-dihydroxy-8-[(2*R*,3*S*)-2-(hydroxymethyl)-1-methyl-3-pyrrolidinyl]- 4*H*-1-benzopyran-4-one, hydrochloride (P276-00); 1-methyl-5-[[2-[5-(trifluoromethyl)-1*H*-imidazol-2-yl]-4-pyridinyl]oxy]-*N*-[4-(trifluoromethyl)phenyl]-1*H*-benzimidazol-2-amine (RAF265); indisulam (E7070); roscovitine (CYC202); palbociclib (PD0332991); dinaciclib (SCH727965); N-[5-[[(5-*tert*-butyloxazol-2-yl)methyl]thio]thiazol-2-yl]piperidine-4-carboxamide (BMS 387032); 4-[[9-chloro-7-(2,6-difluorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepin-2-yl]amino]-benzoic acid

(MLN8054); 5-[3-(4,6-difluoro-1H-benzimidazol-2-yl)-1H-indazol-5-yl]-N-ethyl-4-methyl-3-pyridinemethanamine (AG-024322); 4-(2,6-dichlorobenzoylamino)-1H-pyrazole-3-carboxylic acid N-(piperidin-4-yl)amide (AT7519); 4-[2-methyl-1-(1-methylethyl)-1*H*-imidazol-5-yl]-*N*-[4-(methylsulfonyl)phenyl]- 2-pyrimidinamine (AZD5438); and XL281 (BMS908662).

In one embodiment, the kinase inhibitor is a CDK4 inhibitor, e.g., palbociclib (PD0332991), and the palbociclib is administered at a dose of about 50 mg, 60 mg, 70 mg, 75 mg, 80 mg, 90 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg (e.g., 75 mg, 100 mg or 125 mg) daily for a period of time, e.g., daily for 14-21 days of a 28 day cycle, or daily for 7-12 days of a 21 day cycle. In one embodiment, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or more cycles of palbociclib are administered.

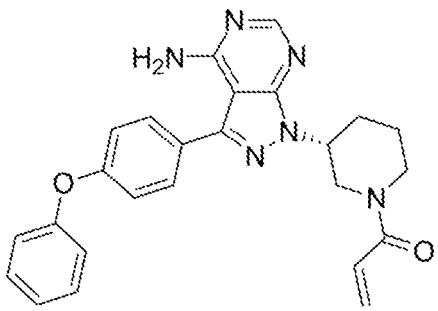
In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with a cyclin-dependent kinase (CDK) 4 or 6 inhibitor, e.g., a CDK4 inhibitor or a CDK6 inhibitor described herein. In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with a CDK4/6 inhibitor (e.g., an inhibitor that targets both CDK4 and CDK6), e.g., a CDK4/6 inhibitor described herein. In an embodiment, the subject has MCL. MCL is an aggressive cancer that is poorly responsive to currently available therapies, i.e., essentially incurable. In many cases of MCL, cyclin D1 (a regulator of CDK4/6) is expressed (e.g., due to chromosomal translocation involving immunoglobulin and Cyclin D1 genes) in MCL cells. Thus, without being bound by theory, it is thought that MCL cells are highly sensitive to CDK4/6 inhibition with high specificity (i.e., minimal effect on normal immune cells). CDK4/6 inhibitors alone have had some efficacy in treating MCL, but have only achieved partial remission with a high relapse rate. An exemplary CDK4/6 inhibitor is LEE011 (also called ribociclib), the structure of which is shown below.



Without being bound by theory, it is believed that administration of a CAR-expressing cell described herein with a CDK4/6 inhibitor (e.g., LEE011 or other CDK4/6 inhibitor described herein) can achieve higher responsiveness, e.g., with higher remission rates and/or lower relapse rates, e.g., compared to a CDK4/6 inhibitor alone.

In one embodiment, the kinase inhibitor is a BTK inhibitor selected from ibrutinib (PCI-32765); GDC-0834; RN-486; CGI-560; CGI-1764; HM-71224; CC-292; ONO-4059; CNX-774; and LFM-A13. In a preferred embodiment, the BTK inhibitor does not reduce or inhibit the kinase activity of interleukin-2-inducible kinase (ITK), and is selected from GDC-0834; RN-486; CGI-560; CGI-1764; HM-71224; CC-292; ONO-4059; CNX-774; and LFM-A13.

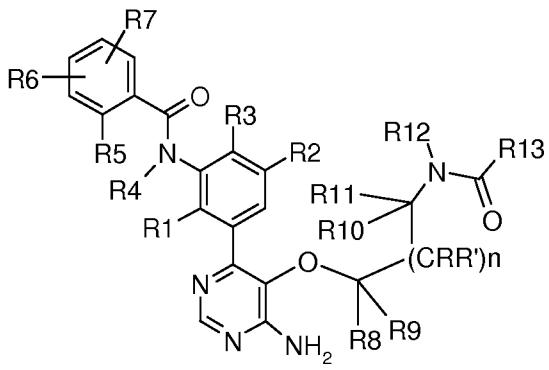
In one embodiment, the kinase inhibitor is a BTK inhibitor, e.g., ibrutinib (PCI-32765). In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with a BTK inhibitor (e.g., ibrutinib). In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with ibrutinib (also called PCI-32765). The structure of ibrutinib (1-[(3*R*)-3-[4-Amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one) is shown below.



In embodiments, the subject has CLL, mantle cell lymphoma (MCL), or small lymphocytic lymphoma (SLL). For example, the subject has a deletion in the short arm of chromosome 17 (del(17p), e.g., in a leukemic cell). In other examples, the subject does not have a del(17p). In embodiments, the subject has relapsed CLL or SLL, e.g., the subject has previously been administered a cancer therapy (e.g., previously been administered one, two, three, or four prior cancer therapies). In embodiments, the subject has refractory CLL or SLL. In other embodiments, the subject has follicular lymphoma, e.g., relapse or refractory follicular lymphoma. In some embodiments, ibrutinib is administered at a dosage of about 300-600 mg/day (e.g., about 300-350, 350-400, 400-450, 450-500, 500-550, or 550-600 mg/day, e.g., about 420 mg/day or about 560 mg/day), e.g., orally. In embodiments, the ibrutinib is administered at a dose of about 250 mg, 300 mg, 350 mg, 400 mg, 420 mg, 440 mg, 460 mg, 480 mg, 500 mg, 520 mg, 540 mg, 560 mg, 580 mg, 600 mg (e.g., 250 mg, 420 mg or 560 mg) daily for a period of time, e.g., daily for 21 day cycle cycle, or daily for 28 day cycle. In one embodiment, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or more cycles of ibrutinib are administered. In

some embodiments, ibrutinib is administered in combination with rituximab. See, e.g., Burger et al. (2013) Ibrutinib In Combination With Rituximab (iR) Is Well Tolerated and Induces a High Rate Of Durable Remissions In Patients With High-Risk Chronic Lymphocytic Leukemia (CLL): New, Updated Results Of a Phase II Trial In 40 Patients, Abstract 675 presented at 55th ASH Annual Meeting and Exposition, New Orleans, LA 7-10 Dec. Without being bound by theory, it is thought that the addition of ibrutinib enhances the T cell proliferative response and may shift T cells from a T-helper-2 (Th2) to T-helper-1 (Th1) phenotype. Th1 and Th2 are phenotypes of helper T cells, with Th1 versus Th2 directing different immune response pathways. A Th1 phenotype is associated with proinflammatory responses, e.g., for killing cells, such as intracellular pathogens/viruses or cancerous cells, or perpetuating autoimmune responses. A Th2 phenotype is associated with eosinophil accumulation and anti-inflammatory responses.

In some embodiments of the methods, uses, and compositions herein, the BTK inhibitor is a BTK inhibitor described in International Application WO/2015/079417, which is herein incorporated by reference in its entirety. For instance, in some embodiments, the BTK inhibitor is a compound of formula (I) or a pharmaceutically acceptable salt thereof;



(I)

wherein,

R1 is hydrogen, C1-C6 alkyl optionally substituted by hydroxy;

R2 is hydrogen or halogen;

R3 is hydrogen or halogen;

R4 is hydrogen;

R5 is hydrogen or halogen;

or R4 and R5 are attached to each other and stand for a bond, -CH2-, -CH2-CH2- , -CH=CH-, -CH=CH-CH2-; -CH2-CH=CH-; or -CH2-CH2-CH2-;

R6 and R7 stand independently from each other for H, C1-C6 alkyl optionally substituted by hydroxyl, C3-C6 cycloalkyl optionally substituted by halogen or hydroxy, or halogen;

R8, R9, R, R', R10 and R11 independently from each other stand for H, or C1-C6 alkyl optionally substituted by C1-C6 alkoxy; or any two of R8, R9, R, R', R10 and R11 together with the carbon atom to which they are bound may form a 3 – 6 membered saturated carbocyclic ring;

R12 is hydrogen or C1-C6 alkyl optionally substituted by halogen or C1-C6 alkoxy;

or R12 and any one of R8, R9, R, R', R10 or R11 together with the atoms to which they are bound may form a 4, 5, 6 or 7 membered azacyclic ring, which ring may optionally be substituted by halogen, cyano, hydroxyl, C1-C6 alkyl or C1-C6 alkoxy;

n is 0 or 1; and

R13 is C2-C6 alkenyl optionally substituted by C1-C6 alkyl, C1-C6 alkoxy or N,N-di-C1-C6 alkyl amino; C2-C6 alkynyl optionally substituted by C1-C6 alkyl or C1-C6 alkoxy; or C2-C6 alkylenyl oxide optionally substituted by C1-C6 alkyl.

In some embodiments, the BTK inhibitor of Formula I is chosen from: N-(3-(5-((1-Acryloylazetidin-3-yl)oxy)-6-aminopyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; (E)-N-(3-(6-Amino-5-((1-(but-2-enoyl)azetidin-3-yl)oxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; N-(3-(6-Amino-5-((1-propioloylazetidin-3-yl)oxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; N-(3-(6-Amino-5-((1-(but-2-ynoyl)azetidin-3-yl)oxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; N-(3-(5-((1-Acryloylpiperidin-4-yl)oxy)-6-aminopyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; N-(3-(6-Amino-5-(2-(N-methylacrylamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; (E)-N-(3-(6-Amino-5-(2-(N-methylbut-2-enamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; N-(3-(6-Amino-5-(2-(N-methylpropiolamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; (E)-N-(3-(6-Amino-5-(2-(4-methoxy-N-methylbut-2-enamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; N-(3-(6-Amino-5-(2-(N-methylbut-2-ynamido)ethoxy)pyrimidin-4-yl)-5-

fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; N-(2-((4-Amino-6-(3-(4-cyclopropyl-2-fluorobenzamido)-5-fluoro-2-methylphenyl)pyrimidin-5-yl)oxy)ethyl)-N-methyloxirane-2-carboxamide; N-(2-((4-Amino-6-(3-(6-cyclopropyl-8-fluoro-1-oxoisoquinolin-2(1H)-yl)phenyl)pyrimidin-5-yl)oxy)ethyl)-N-methylacrylamide; N-(3-(5-(2-Acrylamidoethoxy)-6-aminopyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; N-(3-(6-Amino-5-(2-(N-ethylacrylamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; N-(3-(6-Amino-5-(2-(N-(2-fluoroethyl)acrylamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; N-(3-(5-((1-Acrylamidocyclopropyl)methoxy)-6-aminopyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; (S)-N-(3-(5-(2-Acrylamidopropoxy)-6-aminopyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; (S)-N-(3-(6-Amino-5-(2-(but-2-ynamido)propoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; (S)-N-(3-(6-Amino-5-(2-(N-methylacrylamido)propoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; (S)-N-(3-(6-Amino-5-(2-(N-methylbut-2-ynamido)propoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; N-(3-(6-Amino-5-(3-(N-methylacrylamido)propoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; (S)-N-(3-(5-((1-Acryloylpyrrolidin-2-yl)methoxy)-6-aminopyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; (S)-N-(3-(6-Amino-5-((1-(but-2-ynoyl)pyrrolidin-2-yl)methoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; (S)-2-(3-(5-((1-Acryloylpyrrolidin-2-yl)methoxy)-6-aminopyrimidin-4-yl)-5-fluoro-2-(hydroxymethyl)phenyl)-6-cyclopropyl-3,4-dihydroisoquinolin-1(2H)-one; N-(2-((4-Amino-6-(3-(6-cyclopropyl-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)-5-fluoro-2-(hydroxymethyl)phenyl)pyrimidin-5-yl)oxy)ethyl)-N-methylacrylamide; N-(3-(5-(((2S,4R)-1-Acryloyl-4-methoxypyrrolidin-2-yl)methoxy)-6-aminopyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; N-(3-(6-Amino-5-(((2S,4R)-1-(but-2-ynoyl)-4-methoxypyrrolidin-2-yl)methoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; 2-(3-(5-(((2S,4R)-1-Acryloyl-4-methoxypyrrolidin-2-yl)methoxy)-6-aminopyrimidin-4-yl)-5-fluoro-2-(hydroxymethyl)phenyl)-6-cyclopropyl-3,4-dihydroisoquinolin-1(2H)-one; N-(3-(5-(((2S,4S)-1-Acryloyl-4-methoxypyrrolidin-2-yl)methoxy)-6-aminopyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; N-(3-(6-Amino-5-(((2S,4S)-1-(but-2-ynoyl)-4-methoxypyrrolidin-2-

yl)methoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; N-(3-(5-(((2S,4R)-1-Acryloyl-4-fluoropyrrolidin-2-yl)methoxy)-6-aminopyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; N-(3-(6-Amino-5-(((2S,4R)-1-(but-2-ynoyl)-4-fluoropyrrolidin-2-yl)methoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; (S)-N-(3-(5-((1-Acryloylazetidin-2-yl)methoxy)-6-aminopyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; (S)-N-(3-(6-Amino-5-((1-propioloylazetidin-2-yl)methoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; (S)-2-(3-(5-((1-Acryloylazetidin-2-yl)methoxy)-6-aminopyrimidin-4-yl)-5-fluoro-2-(hydroxymethyl)phenyl)-6-cyclopropyl-3,4-dihydroisoquinolin-1(2H)-one; (R)-N-(3-(5-((1-Acryloylazetidin-2-yl)methoxy)-6-aminopyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; (R)-N-(3-(5-((1-Acryloylpiperidin-3-yl)methoxy)-6-aminopyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; N-(3-(5-(((2R,3S)-1-Acryloyl-3-methoxypyrrolidin-2-yl)methoxy)-6-aminopyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; N-(3-(5-(((2S,4R)-1-Acryloyl-4-cyanopyrrolidin-2-yl)methoxy)-6-aminopyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide; or N-(3-(5-(((2S,4S)-1-Acryloyl-4-cyanopyrrolidin-2-yl)methoxy)-6-aminopyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide.

Unless otherwise provided, the chemical terms used above in describing the BTK inhibitor of Formula I are used according to their meanings as set out in International Application WO/2015/079417, which is herein incorporated by reference in its entirety.

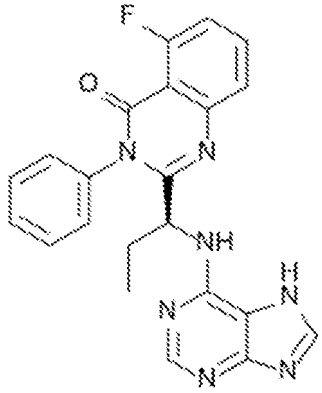
In one embodiment, the kinase inhibitor is an mTOR inhibitor selected from temsirolimus; ridaforolimus (1*R*,2*R*,4*S*)-4-[(2*R*)-2 [(1*R*,9*S*,12*S*,15*R*,16*E*,18*R*,19*R*,21*R*, 23*S*,24*E*,26*E*,28*Z*,30*S*,32*S*,35*R*)-1,18-dihydroxy-19,30-dimethoxy-15,17,21,23, 29,35-hexamethyl-2,3,10,14,20-pentaoxo-11,36-dioxa-4-azatricyclo[30.3.1.$0^{4,9}$] hexatriaconta-16,24,26,28-tetraen-12-yl]propyl]-2-methoxycyclohexyl dimethylphosphinate, also known as AP23573 and MK8669; everolimus (RAD001); rapamycin (AY22989); simapimod; (5-{2,4-bis[(3*S*)-3-methylmorpholin-4-yl]pyrido[2,3-*d*]pyrimidin-7-yl}-2-methoxyphenyl)methanol (AZD8055); 2-amino-8-[*trans*-4-(2-hydroxyethoxy)cyclohexyl]-6-(6-methoxy-3-pyridinyl)-4-methyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (PF04691502); and N^2-[1,4-dioxo-4-[[4-(4-oxo-8-

phenyl-4*H*-1-benzopyran-2-yl)morpholinium-4-yl]methoxy]butyl]-L-arginylglycyl-L-α-aspartylL-serine- (SEQ ID NO: 383), inner salt (SF1126); and XL765.

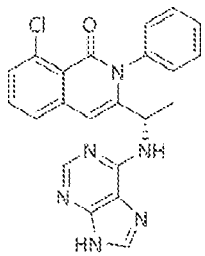
In one embodiment, the kinase inhibitor is an mTOR inhibitor, e.g., rapamycin, and the rapamycin is administered at a dose of about 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg (e.g., 6 mg) daily for a period of time, e.g., daily for 21 day cycle cycle, or daily for 28 day cycle. In one embodiment, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or more cycles of rapamycin are administered. In one embodiment, the kinase inhibitor is an mTOR inhibitor, e.g., everolimus and the everolimus is administered at a dose of about 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg (e.g., 10 mg) daily for a period of time, e.g., daily for 28 day cycle. In one embodiment, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or more cycles of everolimus are administered.

In one embodiment, the kinase inhibitor is an MNK inhibitor selected from CGP052088; 4-amino-3-(p-fluorophenylamino)-pyrazolo [3,4-*d*] pyrimidine (CGP57380); cercosporamide; ETC-1780445-2; and 4-amino-5-(4-fluoroanilino)-pyrazolo [3,4-*d*] pyrimidine.

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with a phosphoinositide 3-kinase (PI3K) inhibitor (e.g., a PI3K inhibitor described herein, e.g., idelalisib or duvelisib) and/or rituximab. In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with idelalisib and rituximab. In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with duvelisib and rituximab. Idelalisib (also called GS-1101 or CAL-101; Gilead) is a small molecule that blocks the delta isoform of PI3K. The structure of idelalisib (5-Fluoro-3-phenyl-2-[(1*S*)-1-(7*H*-purin-6-ylamino)propyl]-4(3*H*)-quinazolinone) is shown below.



Duvelisib (also called IPI-145; Infinity Pharmaceuticals and Abbvie) is a small molecule that blocks PI3K-δ,γ. The structure of duvelisib (8-Chloro-2-phenyl-3-[(1S)-1-(9H-purin-6-ylamino)ethyl]-1(2H)-isoquinolinone) is shown below.



In embodiments, the subject has CLL. In embodiments, the subject has relapsed CLL, e.g., the subject has previously been administered a cancer therapy (e.g., previously been administered an anti-CD20 antibody or previously been administered ibrutinib). For example, the subject has a deletion in the short arm of chromosome 17 (del(17p), e.g., in a leukemic cell). In other examples, the subject does not have a del(17p). In embodiments, the subject comprises a leukemic cell comprising a mutation in the immunoglobulin heavy-chain variable-region (IgV_H) gene. In other embodiments, the subject does not comprise a leukemic cell comprising a mutation in the immunoglobulin heavy-chain variable-region (IgV_H) gene. In embodiments, the subject has a deletion in the long arm of chromosome 11 (del(11q)). In other embodiments, the subject does not have a del(11q). In embodiments, idelalisib is administered at a dosage of about 100-400 mg (e.g., 100-125, 125-150, 150-175, 175-200, 200-225, 225-250, 250-275, 275-300, 325-350, 350-375, or 375-400 mg), e.g., BID. In embodiments, duvelisib is administered at a dosage of about 15-100 mg (e.g., about 15-25, 25-50, 50-75, or 75-100 mg), e.g., twice a day. In embodiments, rituximab is administered at a dosage of about 350-550

mg/m^2 (e.g., 350-375, 375-400, 400-425, 425-450, 450-475, or 475-500 mg/m^2), e.g., intravenously.

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with an anaplastic lymphoma kinase (ALK) inhibitor. Exemplary ALK kinases include but are not limited to crizotinib (Pfizer), ceritinib (Novartis), alectinib (Chugai), brigatinib (also called AP26113; Ariad), entrectinib (Ignyta), PF-06463922 (Pfizer), TSR-011 (Tesaro) (see, e.g., Clinical Trial Identifier No. NCT02048488), CEP-37440 (Teva), and X-396 (Xcovery). In some embodiments, the subject has a solid cancer, e.g., a solid cancer described herein, e.g., lung cancer.

The chemical name of crizotinib is 3-[(1*R*)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]-5-(1-piperidin-4-ylpyrazol-4-yl)pyridin-2-amine. The chemical name of ceritinib is 5-Chloro-N^2-[2-isopropoxy-5-methyl-4-(4-piperidinyl)phenyl]-N^4-[2-(isopropylsulfonyl)phenyl]-2,4-pyrimidinediamine. The chemical name of alectinib is 9-ethyl-6,6-dimethyl-8-(4-morpholinopiperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile. The chemical name of brigatinib is 5-Chloro-N^2-{4-[4-(dimethylamino)-1-piperidinyl]-2-methoxyphenyl}-N^4-[2-(dimethylphosphoryl)phenyl]-2,4-pyrimidinediamine. The chemical name of entrectinib is N-(5-(3,5-difluorobenzyl)-1H-indazol-3-yl)-4-(4-methylpiperazin-1-yl)-2-((tetrahydro-2H-pyran-4-yl)amino)benzamide. The chemical name of PF-06463922 is (10R)-7-Amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]-benzoxadiazacyclotetradecine-3-carbonitrile. The chemical structure of CEP-37440 is (S)-2-((5-chloro-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-1-methoxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-2-yl)amino)pyrimidin-4-yl)amino)-N-methylbenzamide. The chemical name of X-396 is (R)-6-amino-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)-N-(4-(4-methylpiperazine-1-carbonyl)phenyl)pyridazine-3-carboxamide.

In one embodiment, the kinase inhibitor is a dual phosphatidylinositol 3-kinase (PI3K) and mTOR inhibitor selected from 2-Amino-8-[*trans*-4-(2-hydroxyethoxy)cyclohexyl]-6-(6-methoxy-3-pyridinyl)-4-methyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (PF-04691502); *N*-[4-[[4-(Dimethylamino)-1-piperidinyl]carbonyl]phenyl]-*N*'-[4-(4,6-di-4-morpholinyl-1,3,5-triazin-2-yl)phenyl]urea (PF-05212384, PKI-587); 2-Methyl-2-{4-[3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-1*H*-imidazo[4,5-c]quinolin-1-yl]phenyl}propanenitrile (BEZ-235); apitolisib (GDC-0980, RG7422); 2,4-Difluoro-N-{2-(methyloxy)-5-[4-(4-pyridazinyl)-6-quinolinyl]-3-

pyridinyl}benzenesulfonamide (GSK2126458); 8-(6-methoxypyridin-3-yl)-3-methyl-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)-1H-imidazo[4,5-c]quinolin-2(3H)-one Maleic acid (NVP-BGT226); 3-[4-(4-Morpholinylpyrido[3',2':4,5]furo[3,2-d]pyrimidin-2-yl]phenol (PI-103); 5-(9-isopropyl-8-methyl-2-morpholino-9H-purin-6-yl)pyrimidin-2-amine (VS-5584, SB2343); and N-[2-[(3,5-Dimethoxyphenyl)amino]quinoxalin-3-yl]-4-[(4-methyl-3-methoxyphenyl)carbonyl]aminophenylsulfonamide (XL765).

Drugs that inhibit either the calcium dependent phosphatase calcineurin (cyclosporine and FK506) or inhibit the p70S6 kinase that is important for growth factor induced signaling (rapamycin). (Liu *et al.*, Cell 66:807-815, 1991; Henderson *et al.*, Immun. 73:316-321, 1991; Bierer *et al.*, Curr. Opin. Immun. 5:763-773, 1993) can also be used. In a further aspect, the cell compositions of the present invention may be administered to a patient in conjunction with (e.g., before, simultaneously or following) bone marrow transplantation, T cell ablative therapy using chemotherapy agents such as, fludarabine, external-beam radiation therapy (XRT), cyclophosphamide, and/or antibodies such as OKT3 or CAMPATH. In one aspect, the cell compositions of the present invention are administered following B-cell ablative therapy such as agents that react with CD20, e.g., Rituxan. For example, in one embodiment, subjects may undergo standard treatment with high dose chemotherapy followed by peripheral blood stem cell transplantation. In certain embodiments, following the transplant, subjects receive an infusion of the expanded immune cells of the present invention. In an additional embodiment, expanded cells are administered before or following surgery.

In one embodiment, a CAR expressing cell described herein is administered to a subject in combination with a biphosphonate, e.g., Pamidronate (Aredia®); Zoledronic acid or Zoledronate (Zometa®, Zomera®, Aclasta®, or Reclast®); Alendronate (Fosamax®); Risedronate (Actonel®); Ibandronate (Boniva®); Clondronate (Bonefos®); Etidronate (Didronel®); Tiludronate (Skelid®); Pamidronate (Aredia®); Neridronate (Nerixia®); Strontiun ranelate (Protelos®, or Protos®); and Teriparatide (Forteo®).

In one embodiment, a CAR expressing cell described herein is administered to a subject in combination with a corticosteroid, e.g., dexamethasone (e.g., Decadron®), beclomethasone (e.g., Beclovent®), hydrocortisone (also known as cortisone, hydrocortisone sodium succinate, hydrocortisone sodium phosphate, and sold under the tradenames Ala-Cort®, hydrocortisone phosphate, Solu-Cortef®, Hydrocort Acetate® and Lanacort®), prednisolone (sold under the

tradenames Delta-Cortel®, Orapred®, Pediapred® and Prelone®), prednisone (sold under the tradenames Deltasone®, Liquid Red®, Meticorten® and Orasone®), methylprednisolone (also known as 6-methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, sold under the tradenames Duralone®, Medralone®, Medrol®, M-Prednisol® and Solu-Medrol®); antihistamines, such as diphenhydramine (e.g., Benadryl®), hydroxyzine, and cyproheptadine; and bronchodilators, such as the beta-adrenergic receptor agonists, albuterol (e.g., Proventil®), and terbutaline (Brethine®).

In one embodiment, a CAR expressing cell described herein is administered to a subject in combination with an immunomodulator, e.g., Afutuzumab (available from Roche®); Pegfilgrastim (Neulasta®); Lenalidomide (CC-5013, Revlimid®); Thalidomide (Thalomid®), Actimid (CC4047); and IRX-2 (mixture of human cytokines including interleukin 1, interleukin 2, and interferon γ, CAS 951209-71-5, available from IRX Therapeutics.

In one embodiment, a CAR expressing cell described herein is administered to a subject in combination with a proteasome inhibitor, e.g., Bortezomib (Velcade®); Ixazomib citrate (MLN9708, CAS 1201902-80-8); Danoprevir (RG7227, CAS 850876-88-9); Ixazomib (MLN2238, CAS 1072833-77-2); and (S)-N-[(phenylmethoxy)carbonyl]-L-leucyl-N-(1-formyl-3-methylbutyl)- L-Leucinamide (MG-132, CAS 133407-82-6).

In one embodiment, a CAR expressing cell described herein is administered to a subject in combination with a vascular endothelial growth factor (VEGF) receptor, e.g., Bevacizumab (Avastin®), axitinib (Inlyta®); Brivanib alaninate (BMS-582664, (*S*)-((*R*)-1-(4-(4-Fluoro-2-methyl-1*H*-indol-5-yloxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yloxy)propan-2-yl)2-aminopropanoate); Sorafenib (Nexavar®); Pazopanib (Votrient®); Sunitinib malate (Sutent®); Cediranib (AZD2171, CAS 288383-20-1); Vargatef (BIBF1120, CAS 928326-83-4); Foretinib (GSK1363089); Telatinib (BAY57-9352, CAS 332012-40-5); Apatinib (YN968D1, CAS 811803-05-1); Imatinib (Gleevec®); Ponatinib (AP24534, CAS 943319-70-8); Tivozanib (AV951, CAS 475108-18-0); Regorafenib (BAY73-4506, CAS 755037-03-7); Vatalanib dihydrochloride (PTK787, CAS 212141-51-0); Brivanib (BMS-540215, CAS 649735-46-6); Vandetanib (Caprelsa® or AZD6474); Motesanib diphosphate (AMG706, CAS 857876-30-3, N-(2,3-dihydro-3,3-dimethyl-1H-indol-6-yl)-2-[(4-pyridinylmethyl)amino]-3-pyridinecarboxamide, described in PCT Publication No. WO 02/066470); Dovitinib dilactic acid (TKI258, CAS 852433-84-2); Linfanib (ABT869, CAS 796967-16-3); Cabozantinib

(XL184, CAS 849217-68-1); Lestaurtinib (CAS 111358-88-4); N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide (BMS38703, CAS 345627-80-7); (3R,4R)-4-Amino-1-((4-((3-methoxyphenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-5-yl)methyl)piperidin-3-ol (BMS690514); *N*-(3,4-Dichloro-2-fluorophenyl)-6-methoxy-7-[[(3aα,5β,6aα)-octahydro-2-methylcyclopenta[*c*]pyrrol-5-yl]methoxy]- 4-quinazolinamine (XL647, CAS 781613-23-8); 4-Methyl-3-[[1-methyl-6-(3-pyridinyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]amino]-*N*-[3-(trifluoromethyl)phenyl]-benzamide (BHG712, CAS 940310-85-0); . and Aflibercept (Eylea®).

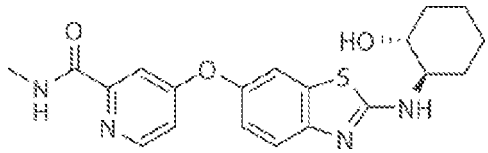
In one embodiment, a CAR expressing cell described herein is administered to a subject in combination with a CD20 antibody or a conjugate thereof, e.g.,: Rituximab (Riuxan® and MabThera®); and Tositumomab (Bexxar®); and Ofatumumab (Arzerra®), Ibritumomab tiuxetan (Zevalin®); and Tositumomab,

In one embodiment, a CAR expressing cell described herein is administered to a subject in combination with an anticonvulsant, e.g.,Anticonvulsants (antiepileptic or antiseizure drugs): aldehydes, e.g., paraldehyde; aromatic allylic alcohols, e.g., stiripentol (Diacomit®); barbiturates, e.g., phenobarbital (Luminal®), methylphenobarbital (Mebaral®), barbexaclone (Maliasin®), benzodiazepines, e.g., clobazam (Onfi®), clonazepam (Klonopin®), clorazepate (Tranxene® and Novo-Clopate®), diazepam (Valium®, Lembrol®, Diastat®), midazolam (Versed®), lorazepam (Ativan® and Orfidal®), nitrazepam (Alodorm®, Arem®, Insoma®), temazepam (restoril®, Normison®), nimetzepam (Erimin®), bromides, e.g., potassium bromide; carbamates, e.g., felbamate (Felbatol®); carboxamides, e.g., carbamazepine (Tegretol®, Equetro®), oxcarbazepine (Trileptal®, Oxcarb®), eslicarbazepine acetate (Aptiom®); fatty acids, e.g., valproates (valproic acid, sodium valproate, divalproex sodium), vigabatrin (Sabril®), progabide (Gabren®), tiagabine (Gabitril®); fructose derivatives, e.g., topiramate (Topamax®); GABA analogs, e.g., gabapentin (Neurontin®), pregabalin (Lyrica®); hydantoins, e.g., ethotoin (Peganone®), phenytoin (Dilantin®), mephenytoin (Mesantoin®), fosphenytoin (Cerebyx®, Prodilantin®); oxazolidinediones, e.g., paramethadione (Paradione®), trimethadione (Tridione®); propionates, e.g., beclamide (Choracon®, Hibicon®, Posedrine®); pyrimidinediones, e.g., primidone (Mysoline®); pyrrolidines, e.g., brivaracetam, levetiracetam, seletracetam (Keppra®); succinimides, e.g., ethosuximide (Zarontin®), phensuximide (Milontin®), mesuximide (Celontin®, Petinutin®); sulfonamides, e.g.,

acetazolamide (Diamox®), sultiame (Ospolot®), methazolamide (Neptazane®), zonisamide (Zonegran®); triazines, e.g., lamotrigine (Lamictal®); ureas, e.g., pheneturide, phenacemide (Phenurone®); valproylamides (amide derivaties of valproate), e.g., valpromide (Depamide®), valnoctamide; AMPA receptor antagonist, e.g., perampanel (Fycompa®).

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with an indoleamine 2,3-dioxygenase (IDO) inhibitor. IDO is an enzyme that catalyzes the degradation of the amino acid, L-tryptophan, to kynurenine. Many cancers overexpress IDO, e.g., prostatic, colorectal, pancreatic, cervical, gastric, ovarian, head, and lung cancer. pDCs, macrophages, and dendritic cells (DCs) can express IDO. Without being bound by theory, it is thought that a decrease in L-tryptophan (e.g., catalyzed by IDO) results in an immunosuppressive milieu by inducing T-cell anergy and apoptosis. Thus, without being bound by theory, it is thought that an IDO inhibitor can enhance the efficacy of a CAR-expressing cell described herein, e.g., by decreasing the suppression or death of a CAR-expressing immune cell. In embodiments, the subject has a solid tumor, e.g., a solid tumor described herein, e.g., prostatic, colorectal, pancreatic, cervical, gastric, ovarian, head, or lung cancer. Exemplary inhibitors of IDO include but are not limited to 1-methyl-tryptophan, indoximod (NewLink Genetics) (see, e.g., Clinical Trial Identifier Nos. NCT01191216; NCT01792050), and INCB024360 (Incyte Corp.) (see, e.g., Clinical Trial Identifier Nos. NCT01604889; NCT01685255)

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with a modulator of myeloid-derived suppressor cells (MDSCs). MDSCs accumulate in the periphery and at the tumor site of many solid tumors. These cells suppress T cell responses, thereby hindering the efficacy of CAR-expressing cell therapy. Without being bound by theory, it is thought that administration of a MDSC modulator enhances the efficacy of a CAR-expressing cell described herein. In an embodiment, the subject has a solid tumor, e.g., a solid tumor described herein, e.g., glioblastoma. Exemplary modulators of MDSCs include but are not limited to MCS110 and BLZ945. MCS110 is a monoclonal antibody (mAb) against macrophage colony-stimulating factor (M-CSF). See, e.g., Clinical Trial Identifier No. NCT00757757. BLZ945 is a small molecule inhibitor of colony stimulating factor 1 receptor (CSF1R). See, e.g., Pyonteck et al. Nat. Med. 19(2013):1264-72. The structure of BLZ945 is shown below.



In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with a CD19 CART cell (e.g., CTL019, e.g., as described in WO2012/079000, incorporated herein by reference). In embodiments, the subject has acute myeloid leukemia (AML), e.g., a CD19 positive AML or a CD19 negative AML. In embodiments, the subject has a CD19+ lymphoma, e.g., a CD19+ Non-Hodgkin's Lymphoma (NHL), a CD19+ FL, or a CD19+ DLBCL. In embodiments, the subject has a relapsed or refractory CD19+ lymphoma. In embodiments, a lymphodepleting chemotherapy is administered to the subject prior to, concurrently with, or after administration (e.g., infusion) of CD19 CART cells. In an example, the lymphodepleting chemotherapy is administered to the subject prior to administration of CD19 CART cells. For example, the lymphodepleting chemotherapy ends 1-4 days (e.g,. 1, 2, 3, or 4 days) prior to CD19 CART cell infusion. In embodiments, multiple doses of CD19 CART cells are administered, e.g., as described herein. For example, a single dose comprises about 5 x 10^8 CD19 CART cells. In embodiments, a lymphodepleting chemotherapy is administered to the subject prior to, concurrently with, or after administration (e.g., infusion) of a CAR-expressing cell described herein, e.g., a non-CD19 CAR-expresing cell. In embodiments, a CD19 CART is administered to the subject prior to, concurrently with, or after administration (e.g., infusion) of a non-CD19 CAR-expressing cell, e.g., a non-CD19 CAR-expressing cell described herein.

In some embodiments, a CAR-expressing cell described herein is administered to a subject in combination with a CD19 CAR-expressing cell, e.g., CTL019, e.g., as described in WO2012/079000, incorporated herein by reference, for treatment of a disease associated with the expression of BCMA, e.g., a cancer described herein. Without being bound by theory, it is believed that administering a CD19 CAR-expressing cell in combination with a CAR-expressing cell improves the efficacy of a CAR-expressing cell described herein by targeting early lineage cancer cells, e.g., cancer stem cells, modulating the immune response, depleting

regulatory B cells, and/or improving the tumor microenvironment. For example, a CD19 CAR-expressing cell targets cancer cells that express early lineage markers, e.g., cancer stem cells and CD19-expressing cells, while the CAR-expressing cell described herein targets cancer cells that express later lineage markers, e.g., BCMA. This preconditioning approach can improve the efficacy of the CAR-expressing cell described herein. In such embodiments, the CD19 CAR-expressing cell is administered prior to, concurrently with, or after administration (e.g., infusion) of a CAR-expressing cell described herein.

In embodiments, a CAR-expressing cell described herein also expresses a CAR targeting CD19, e.g., a CD19 CAR. In an embodiment, the cell expressing a CAR described herein and a CD19 CAR is administered to a subject for treatment of a cancer described herein, e.g., AML. In an embodiment, the configurations of one or both of the CAR molecules comprise a primary intracellular signaling domain and a costimulatory signaling domain. In another embodiment, the configurations of one or both of the CAR molecules comprise a primary intracellular signaling domain and two or more, e.g., 2, 3, 4, or 5 or more, costimulatory signaling domains. In such embodiments, the CAR molecule described herein and the CD19 CAR may have the same or a different primary intracellular signaling domain, the same or different costimulatory signaling domains, or the same number or a different number of costimulatory signaling domains. Alternatively, the CAR described herein and the CD19 CAR are configured as a split CAR, in which one of the CAR molecules comprises an antigen binding domain and a costimulatory domain (e.g., 4-1BB), while the other CAR molecule comprises an antigen binding domain and a primary intracellular signaling domain (e.g., CD3 zeta).

In some embodiments , a CAR-expressing cell described herein is administered to a subject in combination with a interleukin-15 (IL-15) polypeptide, a interleukin-15 receptor alpha (IL-15Ra) polypeptide, or a combination of both a IL-15 polypeptide and a IL-15Ra polypeptide e.g., hetIL-15 (Admune Therapeutics, LLC). hetIL-15 is a heterodimeric non-covalent complex of IL-15 and IL-15Ra. hetIL-15 is described in, e.g., U.S. 8,124,084, U.S. 2012/0177598, U.S. 2009/0082299, U.S. 2012/0141413, and U.S. 2011/0081311, incorporated herein by reference. In embodiments, het-IL-15 is administered subcutaneously. In embodiments, the subject has a cancer, e.g., solid cancer, e.g., melanoma or colon cancer. In embodiments, the subject has a metastatic cancer.

In one embodiment, the subject can be administered an agent which reduces or ameliorates a side effect associated with the administration of a CAR-expressing cell. Side effects associated with the administration of a CAR-expressing cell include, but are not limited to CRS, and hemophagocytic lymphohistiocytosis (HLH), also termed Macrophage Activation Syndrome (MAS). Symptoms of CRS include high fevers, nausea, transient hypotension, hypoxia, and the like. CRS may include clinical constitutional signs and symptoms such as fever, fatigue, anorexia, myalgias, arthalgias, nausea, vomiting, and headache. CRS may include clinical skin signs and symptoms such as rash. CRS may include clinical gastrointestinal signs and symsptoms such as nausea, vomiting and diarrhea. CRS may include clinical respiratory signs and symptoms such as tachypnea and hypoxemia. CRS may include clinical cardiovascular signs and symptoms such as tachycardia, widened pulse pressure, hypotension, increased cardac output (early) and potentially diminished cardiac output (late). CRS may include clinical coagulation signs and symptoms such as elevated d-dimer, hypofibrinogenemia with or without bleeding. CRS may include clinical renal signs and symptoms such as azotemia. CRS may include clinical hepatic signs and symptoms such as transaminitis and hyperbilirubinemia. CRS may include clinical neurologic signs and symptoms such as headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dymetria, altered gait, and seizures.

Accordingly, the methods described herein can comprise administering a CAR-expressing cell described herein to a subject and further administering one or more agents to manage elevated levels of a soluble factor resulting from treatment with a CAR-expressing cell. In one embodiment, the soluble factor elevated in the subject is one or more of IFN-γ, TNFα, IL-2 and IL-6. In an embodiment, the factor elevated in the subject is one or more of IL-1, GM-CSF, IL-10, IL-8, IL-5 and fraktalkine. Therefore, an agent administered to treat this side effect can be an agent that neutralizes one or more of these soluble factors. In one embodiment, the agent that neutralizes one or more of these soluble forms is an antibody or antibody fragment. Examples of such agents include, but are not limited to a steroid (e.g., corticosteroid), an inhibitor of TNFα, and an inhibitor of IL-6. An example of a TNFα inhibitor is an anti-TNFα antibody molecule such as, infliximab, adalimumab, certolizumab pegol, and golimumab. Another example of a TNFα inhibitor is a fusion protein such as entanercept. Small molecule inhibitors of TNFα include, but are not limited to, xanthine derivatives (e.g.

pentoxifylline) and bupropion. An example of an IL-6 inhibitor is an anti-IL-6 antibody molecule such as tocilizumab (toc), sarilumab, elsilimomab, CNTO 328, ALD518/BMS-945429, CNTO 136, CPSI-2364, CDP6038, VX30, ARGX-109, FE301, and FM101. In one embodiment, the anti-IL-6 antibody molecule is tocilizumab. An example of an IL-1R based inhibitor is anakinra.

In some embodiment, the subject is administered a corticosteroid, such as, e.g., methylprednisolone, hydrocortisone, among others.

In some embodiments, the subject is administered a vasopressor, such as, e.g., norepinephrine, dopamine, phenylephrine, epinephrine, vasopressin, or a combination thereof.

In an embodiment, the subject can be administered an antipyretic agent. In an embodiment, the subject can be administered an analgesic agent.

In one embodiment, the subject can be administered an agent that prevents trafficking of the BCMA CAR-expressing cell to the brain, e.g., natalizumab (TYSABRI®). BCMA expression, e.g., a splice variant thereof, has been detected in some parts of the brain, e.g., the cerebellum or medulla oblongata. Without being bound by any particular theory, prevention of trafficking of the BCMA CAR-expressing cells to the brain is preferred to prevent any BCMA CAR-expressing cells from interacting with or acting on BCMA-expressing brain tissue.

In one embodiment, the subject can be administered an agent which enhances the activity of a CAR-expressing cell. For example, in one embodiment, the agent can be an agent which inhibits an inhibitory molecule, e.g., the agent is a checkpoint inhibitor. Inhibitory molecules, e.g., Programmed Death 1 (PD1), can, in some embodiments, decrease the ability of a CAR-expressing cell to mount an immune effector response. Examples of inhibitory molecules include PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGFR beta. Inhibition of an inhibitory molecule, e.g., by inhibition at the DNA, RNA or protein level, can optimize a CAR-expressing cell performance. In embodiments, an inhibitory nucleic acid, e.g., an inhibitory nucleic acid, e.g., a dsRNA, e.g., an siRNA or shRNA, a clustered regularly interspaced short palindromic repeats (CRISPR), a transcription-activator like effector nuclease (TALEN), or a zinc finger

endonuclease (ZFN), e.g., as described herein, can be used to inhibit expression of an inhibitory molecule in the CAR-expressing cell. In an embodiment the inhibitor is an shRNA. In an embodiment, the inhibitory molecule is inhibited within a CAR-expressing cell. In these embodiments, a dsRNA molecule that inhibits expression of the inhibitory molecule is linked to the nucleic acid that encodes a component, e.g., all of the components, of the CAR. In embodiments, a CAR-expressing cell described herein is administered in combination with an inhibitor of an inhibitory molecule, e.g., in combination with a checkpoint inhibitor, e.g., in combination with an inhibitor of PD1 and/or PD-L1. In embodiments, a CAR- expressing cell described herein is administered in combination with an inhibitor of PD1. In embodiments, a CAR- expressing cell described herein is administered in combination with an inhibitor of PD-L1.

In an embodiment, a nucleic acid molecule that encodes a dsRNA molecule that inhibits expression of the molecule that modulates or regulates, e.g., inhibits, T-cell function is operably linked to a promoter, e.g., a H1- or a U6-derived promoter such that the dsRNA molecule that inhibits expression of the molecule that modulates or regulates, e.g., inhibits, T-cell function is expressed, e.g., is expressed within a CAR-expressing cell. See e.g., Tiscornia *G.*, "Development of Lentiviral Vectors Expressing siRNA," Chapter 3, in *Gene Transfer: Delivery and Expression of DNA and RNA* (eds. Friedmann and Rossi). Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, USA, 2007; Brummelkamp T*R, et al.* (2002*) Science* 296: 550–553; Miyagishi *M, et al.* (2002*) Nat. Biotechnol.* 19: 497–500. In an embodiment the nucleic acid molecule that encodes a dsRNA molecule that inhibits expression of the molecule that modulates or regulates, e.g., inhibits, T-cell function is present on the same vector, e.g., a lentiviral vector, that comprises a nucleic acid molecule that encodes a component, e.g., all of the components, of the CAR. In such an embodiment, the nucleic acid molecule that encodes a dsRNA molecule that inhibits expression of the molecule that modulates or regulates, e.g., inhibits, T-cell function is located on the vector, e.g., the lentiviral vector, 5'- or 3'- to the nucleic acid that encodes a component, e.g., all of the components, of the CAR. The nucleic acid molecule that encodes a dsRNA molecule that inhibits expression of the molecule that modulates or regulates, e.g., inhibits, T-cell function can be transcribed in the same or different direction as the nucleic acid that encodes a component, e.g., all of the components, of the CAR. In an embodiment the nucleic acid molecule that encodes a dsRNA

molecule that inhibits expression of the molecule that modulates or regulates, e.g., inhibits, T-cell function is present on a vector other than the vector that comprises a nucleic acid molecule that encodes a component, e.g., all of the components, of the CAR. In an embodiment, the nucleic acid molecule that encodes a dsRNA molecule that inhibits expression of the molecule that modulates or regulates, e.g., inhibits, T-cell function it transiently expressed within a CAR-expressing cell. In an embodiment, the nucleic acid molecule that encodes a dsRNA molecule that inhibits expression of the molecule that modulates or regulates, e.g., inhibits, T-cell function is stably integrated into the genome of a CAR-expressing cell. Figures 41A-41E depicts examples of vectors for expressing a component, e.g., all of the components, of the CAR with a dsRNA molecule that inhibits expression of the molecule that modulates or regulates, e.g., inhibits, T-cell function.

Examples of dsRNA molecules useful for inhibiting expression of a molecule that modulates or regulates, e.g., inhibits, T-cell function, wherein the molecule that modulates or regulates, e.g., inhibits, T-cell function is PD-1 are provided below.

Provided in Table 18 below are the names of PDCD1 (PD1) RNAi agents (derived from their position in the mouse PDCD1 gene sequence NM_008798.2), along with the SEQ ID NOs: 286-333 representing the DNA sequence. Both sense (S) and antisense (AS) sequences are presented as 19mer and 21mer sequences are in this table. Also note that the position (PoS, e.g., 176) is derived from the position number in the mouse PDCD1 gene sequence NM_008798.2. SEQ ID NOs are indicated in groups of 12 that correspond with "sense 19" SEQ ID NOs: 286-297; "sense 21" SEQ ID NOs: 298-309; "asense 21" SEQ ID NOs: 310-321; "asense 19" SEQ ID NOs: 322-333.

Table 18. Mouse PDCD1 (PD1) shRNA sequences

Position on NM_008798.2	Target region	Sense19	Sense21	Asense21	Asense19
176	CDS	GGAGGTCCCT CACCTTCTA (SEQ ID NO: 286)	CTGGAGGTCC CTCACCTTCT A (SEQ ID NO:	TAGAAGGTGA GGGACCTCCA G (SEQ ID NO:	TAGAAGGTGA GGGACCTCC (SEQ ID NO: 322)

			298)	310)	
260	CDS	CGGAGGATCTTATGCTGAA (SEQ ID NO: 287)	GTCGGAGGATCTTATGCTGAA (SEQ ID NO: 299)	TTCAGCATAAGATCCTCCGAC (SEQ ID NO: 311)	TTCAGCATAAGATCCTCCG (SEQ ID NO: 323)
359	CDS	CCCGCTTCCAGATCATACA (SEQ ID NO: 288)	TGCCCGCTTCCAGATCATACA (SEQ ID NO: 300)	TGTATGATCTGGAAGCGGGCA (SEQ ID NO: 312)	TGTATGATCTGGAAGCGGG (SEQ ID NO: 324)
528	CDS	GGAGACCTCAACAAGATAT (SEQ ID NO: 289)	CTGGAGACCTCAACAAGATAT (SEQ ID NO: 301)	ATATCTTGTTGAGGTCTCCAG (SEQ ID NO: 313)	ATATCTTGTTGAGGTCTCC (SEQ ID NO: 325)
581	CDS	AAGGCATGGTCATTGGTAT (SEQ ID NO: 290)	TCAAGGCATGGTCATTGGTAT (SEQ ID NO: 302)	ATACCAATGACCATGCCTTGA (SEQ ID NO: 314)	ATACCAATGACCATGCCTT (SEQ ID NO: 326)
584	CDS	GCATGGTCATTGGTATCAT (SEQ ID NO: 291)	AGGCATGGTCATTGGTATCAT (SEQ ID NO: 303)	ATGATACCAATGACCATGCCT (SEQ ID NO: 315)	ATGATACCAATGACCATGC (SEQ ID NO: 327)
588	CDS	GGTCATTGGTATCATGAGT (SEQ ID NO: 292)	ATGGTCATTGGTATCATGAGT (SEQ ID NO: 304)	ATGGTCATTGGTATCATGAGT (SEQ ID NO: 316)	ATGGTCATTGGTATCATGA (SEQ ID NO: 328)
609	CDS	CCTAGTGGGTATCCCTGTA (SEQ ID NO:	GCCCTAGTGGGTATCCCTGTA	GCCCTAGTGGGTATCCCTGTA	GCCCTAGTGGGTATCCCTG (SEQ ID NO:

		293)	(SEQ ID NO: 305)	(SEQ ID NO: 317)	329)
919	CDS	GAGGATGGAC ATTGTTCTT (SEQ ID NO: 294)	ATGAGGATGG ACATTGTTCTT (SEQ ID NO: 306)	ATGAGGATGG ACATTGTTCTT (SEQ ID NO: 318)	ATGAGGATGG ACATTGTTC (SEQ ID NO: 330)
1021	3'UTR	GCATGCAGGC TACAGTTCA (SEQ ID NO: 295)	GAGCATGCAG GCTACAGTTC A (SEQ ID NO: 307)	GAGCATGCAG GCTACAGTTC A (SEQ ID NO: 319)	GAGCATGCAG GCTACAGTT (SEQ ID NO: 331)
1097	3'UTR	CCAGCACATG CACTGTTGA (SEQ ID NO: 296)	TTCCAGCACA TGCACTGTTG A (SEQ ID NO: 308)	TTCCAGCACA TGCACTGTTG A (SEQ ID NO: 320)	TTCCAGCACA TGCACTGTT (SEQ ID NO: 332)
1101	3'UTR	CACATGCACT GTTGAGTGA (SEQ ID NO: 297)	AGCACATGCA CTGTTGAGTG A (SEQ ID NO: 309)	AGCACATGCA CTGTTGAGTG A (SEQ ID NO: 321)	AGCACATGCA CTGTTGAGT (SEQ ID NO: 333)

Provided in Table 19 below are the names of PDCD1 (PD1) RNAi agents (derived from their position in the human PDCD1 gene sequence, along with the SEQ ID NOs. 334-381 representing the DNA sequence. Both sense (S) and antisense (AS) sequences are presented as 19mer and 21mer sequences. SEQ ID NOs are indicated in groups of 12 that correspond with "sense 19" SEQ ID NOs: 334-345; "sense 21" SEQ ID NOs: 346-357; "asense 21" SEQ ID NOs: 358-369; "asense 19" SEQ ID NOs: 370-381.

Table 19. Human PDCD1 (PD1) shRNA sequences

Position on NM_005 018.2	Target region	Sense19	Asense19	Sense21	Asense21
145	CDS	GGCCAGGATG	TCTAAGAACC	GCGGCCAGGA	TCTAAGAACC

		GTTCTTAGA (SEQ ID NO: 334)	ATCCTGGCC (SEQ ID NO: 346)	TGGTTCTTAGA (SEQ ID NO: 358)	ATCCTGGCCGC (SEQ ID NO: 370)
271	CDS	GCTTCGTGCTAAACTGGTA (SEQ ID NO: 335)	TACCAGTTTAGCACGAAGC (SEQ ID NO: 347)	GAGCTTCGTGCTAAACTGGTA (SEQ ID NO: 359)	TACCAGTTTAGCACGAAGCTC (SEQ ID NO: 371)
393	CDS	GGGCGTGACTTCCACATGA (SEQ ID NO: 336)	TCATGTGGAAGTCACGCCC (SEQ ID NO: 348)	ACGGGCGTGACTTCCACATGA (SEQ ID NO: 360)	TCATGTGGAAGTCACGCCCGT (SEQ ID NO: 372)
1497	3'UTR	CAGGCCTAGAGAAGTTTCA (SEQ ID NO: 337)	TGAAACTTCTCTAGGCCTG (SEQ ID NO: 349)	TGCAGGCCTAGAGAAGTTTCA (SEQ ID NO: 361)	TGAAACTTCTCTAGGCCTGCA (SEQ ID NO: 373)
1863	3'UTR	CTTGGAACCCATTCCTGAA (SEQ ID NO: 338)	TTCAGGAATGGGTTCCAAG (SEQ ID NO: 350)	TCCTTGGAACCCATTCCTGAA (SEQ ID NO: 362)	TTCAGGAATGGGTTCCAAGGA (SEQ ID NO: 374)
1866	3'UTR	GGAACCCATTCCTGAAATT (SEQ ID NO: 339)	AATTTCAGGAATGGGTTCC (SEQ ID NO: 351)	TTGGAACCCATTCCTGAAATT (SEQ ID NO: 363)	AATTTCAGGAATGGGTTCCAA (SEQ ID NO: 375)
1867	3'UTR	GAACCCATTCCTGAAATTA (SEQ ID NO: 340)	TAATTTCAGGAATGGGTTC (SEQ ID NO: 352)	TGGAACCCATTCCTGAAATTA (SEQ ID NO: 364)	TAATTTCAGGAATGGGTTCCA (SEQ ID NO: 376)
1868	3'UTR	AACCCATTCCTGAAATTAT (SEQ ID NO: 341)	ATAATTTCAGGAATGGGTT (SEQ ID NO: 353)	GGAACCCATTCCTGAAATTAT (SEQ ID NO: 365)	ATAATTTCAGGAATGGGTTCC (SEQ ID NO:377)
1869	3'UTR	ACCCATTCCTGAAATTATT (SEQ ID NO: 342)	AATAATTTCAGGAATGGGT (SEQ ID NO: 354)	GAACCCATTCCTGAAATTATT (SEQ ID NO: 366)	AATAATTTCAGGAATGGGTTC (SEQ ID NO: 378)
1870	3'UTR	CCCATTCCTGAAATTATTT (SEQ ID NO: 343)	AAATAATTTCAGGAATGGG (SEQ ID NO: 355)	AACCCATTCCTGAAATTATTT (SEQ ID NO: 367)	AAATAATTTCAGGAATGGGTT (SEQ ID NO: 379)
2079	3'UTR	CTGTGGTTCTATTATATTA	TAATATAATAGAACCACAG	CCCTGTGGTTCTATTATATT	TAATATAATAGAACCACAGG

		(SEQ ID NO: 344)	(SEQ ID NO: 356)	A (SEQ ID NO: 368)	G (SEQ ID NO: 380)
2109	3'UTR	AAATATGAGA GCATGCTAA (SEQ ID NO: 345)	TTAGCATGCT CTCATATTT (SEQ ID NO: 357)	TTAAATATGA GAGCATGCTA A (SEQ ID NO: 369)	TTAGCATGCT CTCATATTTA A (SEQ ID NO: 381)

In one embodiment, the inhibitor of an inhibitory signal can be, e.g., an antibody or antibody fragment that binds to an inhibitory molecule. For example, the agent can be an antibody or antibody fragment that binds to PD1, PD-L1, PD-L2 or CTLA4 (e.g., ipilimumab (also referred to as MDX-010 and MDX-101, and marketed as Yervoy®; Bristol-Myers Squibb; Tremelimumab (IgG2 monoclonal antibody available from Pfizer, formerly known as ticilimumab, CP-675,206).). In an embodiment, the agent is an antibody or antibody fragment that binds to TIM3. In an embodiment, the agent is an antibody or antibody fragment that binds to LAG3. In embodiments, the agent that enhances the activity of a CAR-expressing cell, e.g., inhibitor of an inhibitory molecule, is administered in combination with an allogeneic CAR, e.g., an allogeneic CAR described herein (e.g., described in the Allogeneic CAR section herein).

PD-1 is an inhibitory member of the CD28 family of receptors that also includes CD28, CTLA-4, ICOS, and BTLA. PD-1 is expressed on activated B cells, T cells and myeloid cells (Agata et al. 1996 Int. Immunol 8:765-75). Two ligands for PD-1, PD-L1 and PD-L2 have been shown to downregulate T cell activation upon binding to PD-1 (Freeman et a. 2000 J Exp Med 192:1027-34; Latchman et al. 2001 Nat Immunol 2:261-8; Carter et al. 2002 Eur J Immunol 32:634-43). PD-L1 is abundant in human cancers (Dong et al. 2003 J Mol Med 81:281-7; Blank et al. 2005 Cancer Immunol. Immunother 54:307-314; Konishi et al. 2004 Clin Cancer Res 10:5094). Immune suppression can be reversed by inhibiting the local interaction of PD-1 with PD-L1. Antibodies, antibody fragments, and other inhibitors of PD-1, PD-L1 and PD-L2 are available in the art and may be used combination with a cars of the present invention described herein. For example, nivolumab (also referred to as BMS-936558 or MDX1106; Bristol-Myers Squibb) is a fully human IgG4 monoclonal antibody which specifically blocks PD-1. Nivolumab (clone 5C4) and other human monoclonal antibodies that specifically bind to PD-1 are disclosed in US 8,008,449 and WO2006/121168. Pidilizumab (CT-011; Cure Tech)

is a humanized IgG1k monoclonal antibody that binds to PD-1. Pidilizumab and other humanized anti-PD-1 monoclonal antibodies are disclosed in WO2009/101611. Pembrolizumab (formerly known as lambrolizumab, and also referred to as MK03475; Merck) is a humanized IgG4 monoclonal antibody that binds to PD-1. Pembrolizumab and other humanized anti-PD-1 antibodies are disclosed in US 8,354,509 and WO2009/114335. MEDI4736 (Medimmune) is a human monoclonal antibody that binds to PDL1, and inhibits interaction of the ligand with PD1. MDPL3280A (Genentech / Roche) is a human Fc optimized IgG1 monoclonal antibody that binds to PD-L1. MDPL3280A and other human monoclonal antibodies to PD-L1 are disclosed in U.S. Patent No.: 7,943,743 and U.S Publication No.: 20120039906. Other anti-PD-L1 binding agents include YW243.55.S70 (heavy and light chain variable regions are shown in SEQ ID NOs 20 and 21 in WO2010/077634) and MDX-1 105 (also referred to as BMS-936559, and, e.g., anti-PD-L1 binding agents disclosed in WO2007/005874). AMP-224 (B7-DCIg; Amplimmune; e.g., disclosed in WO2010/027827 and WO2011/066342), is a PD-L2 Fc fusion soluble receptor that blocks the interaction between PD-1 and B7-H1. Other anti-PD-1 antibodies include AMP 514 (Amplimmune), among others, e.g., anti-PD-1 antibodies disclosed in US 8,609,089, US 2010028330, and/or US 20120114649.

TIM3 (T cell immunoglobulin-3) also negatively regulates T cell function, particularly in IFN-g-secreting CD4+ T helper 1 and CD8+ T cytotoxic 1 cells, and plays a critical role in T cell exhaustion. Inhibition of the interaction between TIM3 and its ligands, e.g., galectin-9 (Gal9), phosphotidylserine (PS), and HMGB1, can increase immune response. Antibodies, antibody fragments, and other inhibitors of TIM3 and its ligands are available in the art and may be used combination with a CD19 or BCMA CAR described herein. For example, antibodies, antibody fragments, small molecules, or peptide inhibitors that target TIM3 binds to the IgV domain of TIM3 to inhibit interaction with its ligands. Antibodies and peptides that inhibit TIM3 are disclosed in WO2013/006490 and US20100247521. Other anti-TIM3 antibodies include humanized versions of RMT3-23 (disclosed in Ngiow et al., 2011, Cancer Res, 71:3540-3551), and clone 8B.2C12 (disclosed in Monney et al., 2002, Nature, 415:536-541). Bi-specific antibodies that inhibit TIM3 and PD-1 are disclosed in US20130156774.

In other embodiments, the agent which enhances the activity of a CAR-expressing cell is a CEACAM inhibitor (*e.g.*, CEACAM-1, CEACAM-3, and/or CEACAM-5 inhibitor). In

one embodiment, the inhibitor of CEACAM is an anti-CEACAM antibody molecule. Exemplary anti-CEACAM-1 antibodies are described in WO 2010/125571, WO 2013/082366 WO 2014/059251 and WO 2014/022332, *e.g.,* a monoclonal antibody 34B1, 26H7, and 5F4; or a recombinant form thereof, as described in, *e.g.*, US 2004/0047858, US 7,132,255 and WO 99/052552. In other embodiments, the anti-CEACAM antibody binds to CEACAM-5 as described in, *e.g.*, Zheng et al. *PLoS One*. 2010 Sep 2;5(9). pii: e12529 (DOI:10:1371/journal.pone.0021146), or crossreacts with CEACAM-1 and CEACAM-5 as described in, *e.g.*, WO 2013/054331 and US 2014/0271618.

Without wishing to be bound by theory, carcinoembryonic antigen cell adhesion molecules (CEACAM), such as CEACAM-1 and CEACAM-5, are believed to mediate, at least in part, inhibition of an anti-tumor immune response (*see e.g.*, Markel *et al. J Immunol*. 2002 Mar 15;168(6):2803-10; Markel et al. *J Immunol*. 2006 Nov 1;177(9):6062-71; Markel et al. *Immunology*. 2009 Feb;126(2):186-200; Markel et al. *Cancer Immunol Immunother*. 2010 Feb;59(2):215-30; Ortenberg et al. *Mol Cancer Ther*. 2012 Jun;11(6):1300-10; Stern et al. *J Immunol*. 2005 Jun 1;174(11):6692-701; Zheng et al. *PLoS One*. 2010 Sep 2;5(9). pii: e12529). For example, CEACAM-1 has been described as a heterophilic ligand for TIM-3 and as playing a role in TIM-3-mediated T cell tolerance and exhaustion (*see e.g.*, WO 2014/022332; Huang, *et al.* (2014) *Nature* doi:10.1038/nature13848). In embodiments, co-blockade of CEACAM-1 and TIM-3 has been shown to enhance an anti-tumor immune response in xenograft colorectal cancer models (*see e.g.*, WO 2014/022332; Huang, *et al.* (2014), *supra*). In other embodiments, co-blockade of CEACAM-1 and PD-1 reduce T cell tolerance as described, *e.g.*, in WO 2014/059251. Thus, CEACAM inhibitors can be used with the other immunomodulators described herein (*e.g.*, anti-PD-1 and/or anti-TIM-3 inhibitors) to enhance an immune response against a cancer, *e.g.*, a melanoma, a lung cancer (e.g., NSCLC), a bladder cancer, a colon cancer an ovarian cancer, and other cancers as described herein.

LAG3 (lymphocyte activation gene-3 or CD223) is a cell surface molecule expressed on activated T cells and B cells that has been shown to play a role in CD8+ T cell exhaustion. Antibodies, antibody fragments, and other inhibitors of LAG3 and its ligands are available in the art and may be used combination with a CD19 or BCMA CAR described herein. For example, BMS-986016 (Bristol-Myers Squib) is a monoclonal antibody that targets LAG3. IMP701 (Immutep) is an antagonist LAG3 antibody and IMP731 (Immutep and

GlaxoSmithKline) is a depleting LAG3 antibody. Other LAG3 inhibitors include IMP321 (Immutep), which is a recombinant fusion protein of a soluble portion of LAG3 and Ig that binds to MHC class II molecules and activates antigen presenting cells (APC). Other antibodies are disclosed, e.g., in WO2010/019570.

In some embodiments, the agent which enhances the activity of a CAR-expressing cell can be, e.g., a fusion protein comprising a first domain and a second domain, wherein the first domain is an inhibitory molecule, or fragment thereof, and the second domain is a polypeptide that is associated with a positive signal, e.g., a polypeptide comrpsing an antracellular signaling domain as described herein. In some embodiments, the polypeptide that is associated with a positive signal can include a costimulatory domain of CD28, CD27, ICOS, e.g., an intracellular signaling domain of CD28, CD27 and/or ICOS, and/or a primary signaling domain, e.g., of CD3 zeta, e.g., described herein. In one embodiment, the fusion protein is expressed by the same cell that expressed the CAR. In another embodiment, the fusion protein is expressed by a cell, e.g., a T cell or NK cell that does not express an anti-BCMA CAR.

In one embodiment, the agent which enhances activity of a CAR-expressing cell described herein is miR-17-92.

In one embodiment, the agent which enhances activity of a CAR-described herein is a cytokine. Cytokines have important functions related to T cell expansion, differentiation, survival, and homeostatis. Cytokines that can be administered to the subject receiving a CAR-expressing cell described herein include: IL-2, IL-4, IL-7, IL-9, IL-15, IL-18, and IL-21, or a combination thereof. In preferred embodiments, the cytokine administered is IL-7, IL-15, or IL-21, or a combination thereof. The cytokine can be administered once a day or more than once a day, e.g., twice a day, three times a day, or four times a day. The cytokine can be administered for more than one day, e.g. the cytokine is administered for 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, or 4 weeks. For example, the cytokine is administered once a day for 7 days.

In embodiments, the cytokine is administered in combination with CAR-expressing T cells. The cytokine can be administered simultaneously or concurrently with the CAR-expressing T cells, e.g., administered on the same day. The cytokine may be prepared in the same pharmaceutical composition as the CAR-expressing T cells, or may be prepared in a

separate pharmaceutical composition. Alternatively, the cytokine can be administered shortly after administration of the CAR-expressing T cells, e.g., 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, or 7 days after administration of the CAR-expressing T cells. In embodiments where the cytokine is administered in a dosing regimen that occurs over more than one day, the first day of the cytokine dosing regimen can be on the same day as administration with the CAR-expressing T cells, or the first day of the cytokine dosing regimen can be 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, or 7 days after administration of the CAR-expressing T cells. In one embodiment, on the first day, the CAR-expressing T cells are administered to the subject, and on the second day, a cytokine is administered once a day for the next 7 days. In a preferred embodiment, the cytokine to be administered in combination with CAR-expressing T cells is IL-7, IL-15, or IL-21.

In other embodiments, the cytokine is administered a period of time after administration of CAR-expressing cells, e.g., at least 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or 1 year or more after administration of CAR-expressing cells. In one embodiment, the cytokine is administered after assessment of the subject's response to the CAR-expressing cells. For example, the subject is administered CAR-expressing cells according to the dosage and regimens described herein. The response of the subject to CAR-expressing cell therapy is assessed at 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or 1 year or more after administration of CAR-expressing cells, using any of the methods described herein, including inhibition of tumor growth, reduction of circulating tumor cells, or tumor regression. Subjects that do not exhibit a sufficient response to CAR-expressing cell therapy can be administered a cytokine. Administration of the cytokine to the subject that has sub-optimal response to the CAR-expressing cell therapy improves CAR-expressing cell efficacy or anti-cancer activity. In a preferred embodiment, the cytokine administered after administration of CAR-expressing cells is IL-7.

COMBINATION WITH A LOW, IMMUNE ENHANCING, DOSE OF AN MTOR INHIBITOR

Methods described herein use low, immune enhancing, doses of mTOR inhibitors, e.g., allosteric mTOR inhibitors, including rapalogs such as RAD001. Administration of a low,

immune enhancing, dose of an mTOR inhibitor (e.g., a dose that is insufficient to completely suppress the immune system, but sufficient to improve immune function) can optimize the performance of immune effector cells, e.g., T cells or CAR-expressing cells, in the subject. Methods for measuring mTOR inhibition, dosages, treatment regimens, and suitable pharmaceutical compositions are described in U.S. Patent Application No. 2015/01240036, hereby incorporated by reference.

In an embodiment, administration of a low, immune enhancing, dose of an mTOR inhibitor results in one or more of the following:

i) a decrease in the number of PD-1 positive immune effector cells;

ii) an increase in the number of PD-1 negative immune effector cells;

iii) an increase in the ratio of PD-1 negative immune effector cells / PD-1 positive immune effector cells;

iv) an increase in the number of naive T cells;

v) an increase in the expression of one or more of the following markers: $CD62L^{high}$, $CD127^{high}$, $CD27^{+}$, and BCL2, e.g., on memory T cells, e.g., memory T cell precursors;

vi) a decrease in the expression of KLRG1, e.g., on memory T cells, e.g., memory T cell precursors; or

vii) an increase in the number of memory T cell precursors, e.g., cells with any one or combination of the following characteristics: increased $CD62L^{high}$, increased $CD127^{high}$, increased $CD27^{+}$, decreased KLRG1, and increased BCL2;

and wherein any of the foregoing, e.g., i), ii), iii), iv), v), vi), or vii), occurs e.g., at least transiently, e.g., as compared to a non-treated subject.

In another embodiment, administration of a low, immune enhancing, dose of an mTOR inhibitor results in increased or prolonged proliferation or persistence of CAR-expressing cells, e.g., in culture or in a subject, e.g., as compared to non-treated CAR-expressing cells or a non-treated subject. In embodiments, increased proliferation or persistence is associated with in an increase in the number of CAR-expressing cells. Methods for measuring increased or prolonged proliferation are described in Examples 15 and 16. In another embodiment, administration of a low, immune enhancing, dose of an mTOR inhibitor results in increased killing of cancer cells by CAR-expressing cells, e.g., in culture or in a subject, e.g., as compared to non-treated CAR-expressing cells or a non-treated subject. In embodiments,

increased killing of cancer cells is associated with in a decrease in tumor volume. Methods for measuring increased killing of cancer cells are described herein, e.g., in Examples 2, 5-6, 8, and 13.In one embodiment, the cells expressing a CAR molecule, e.g., a CAR molecule described herein, are administered in combination with a low, immune enhancing dose of an mTOR inhibitor, e.g., an allosteric mTOR inhibitor, e.g., RAD001, or a catalytic mTOR inhibitor. For example, administration of the low, immune enhancing, dose of the mTOR inhibitor can be initiated prior to administration of a CAR-expressing cell described herein; completed prior to administration of a CAR-expressing cell described herein; initiated at the same time as administration of a CAR-expressing cell described herein; overlapping with administration of a CAR-expressing cell described herein; or continuing after administration of a CAR-expressing cell described herein.

Alternatively or in addition, administration of a low, immune enhancing, dose of an mTOR inhibitor can optimize immune effector cells to be engineered to express a CAR molecule described herein. In such embodiments, administration of a low, immune enhancing, dose of an mTOR inhibitor, e.g., an allosteric inhibitor, e.g., RAD001, or a catalytic inhibitor, is initiated or completed prior to harvest of immune effector cells, e.g., T cells or NK cells, to be engineered to express a CAR molecule described herein, from a subject.

In another embodiment, immune effector cells, e.g., T cells or NK cells, to be engineered to express a CAR molecule described herein, e.g., after harvest from a subject, or CAR-expressing immune effector cells, e.g., T cells or NK cells, e.g., prior to administration to a subject, can be cultured in the presence of a low, immune enhancing, dose of an mTOR inhibitor.

In an embodiment, administering to the subject a low, immune enhancing, dose of an mTOR inhibitor comprises administering, e.g., once per week, e.g., in an immediate release dosage form, 0.1 to 20, 0.5 to 10, 2.5 to 7.5, 3 to 6, or about 5, mgs of RAD001, or a bioequivalent dose thereof. In an embodiment, administering to the subject a low, immune enhancing, dose of an mTOR inhibitor comprises administering, e.g., once per week, e.g., in a sustained release dosage form, 0.3 to 60, 1.5 to 30, 7.5 to 22.5, 9 to 18, or about 15 mgs of RAD001, or a bioequivalent dose thereof.

In an embodiment, a dose of an mTOR inhibitor is associated with, or provides, mTOR inhibition of at least 5 but no more than 90%, at least 10 but no more than 90%, at least 15, but no more than 90%, at least 20 but no more than 90%, at least 30 but no more than 90%, at least 40 but no more than 90%, at least 50 but no more than 90%, at least 60 but no more than 90%, at least 70 but no more than 90%, at least 5 but no more than 80%, at least 10 but no more than 80%, at least 15, but no more than 80%, at least 20 but no more than 80%, at least 30 but no more than 80%, at least 40 but no more than 80%, at least 50 but no more than 80%, at least 60 but no more than 80%, at least 5 but no more than 70%, at least 10 but no more than 70%, at least 15, but no more than 70%, at least 20 but no more than 70%, at least 30 but no more than 70%, at least 40 but no more than 70%, at least 50 but no more than 70%, at least 5 but no more than 60%, at least 10 but no more than 60%, at least 15, but no more than 60%, at least 20 but no more than 60%, at least 30 but no more than 60%, at least 40 but no more than 60%, at least 5 but no more than 50%, at least 10 but no more than 50%, at least 15, but no more than 50%, at least 20 but no more than 50%, at least 30 but no more than 50%, at least 40 but no more than 50%, at least 5 but no more than 40%, at least 10 but no more than 40%, at least 15, but no more than 40%, at least 20 but no more than 40%, at least 30 but no more than 40%, at least 35 but no more than 40%, at least 5 but no more than 30%, at least 10 but no more than 30%, at least 15, but no more than 30%, at least 20 but no more than 30%, or at least 25 but no more than 30%.

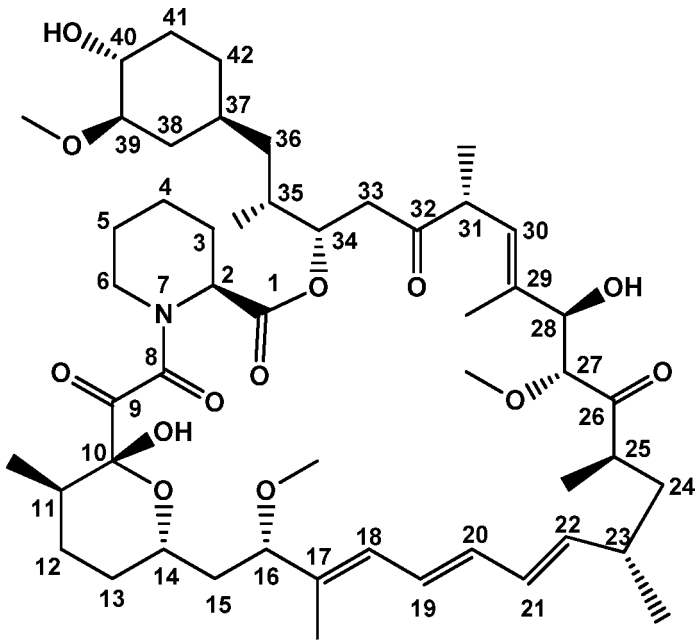
In an embodiment, administering to the subject a low, immune enhancing, dose of an mTOR inhibitor comprises administering, e.g., once per week, e.g., in an immediate release dosage form, 0.1 to 20, 0.5 to 10, 2.5 to 7.5, 3 to 6, or about 5, mgs of RAD001, or a bioequivalent dose thereof. In an embodiment, administering to the subject a low, immune enhancing, dose of an mTOR inhibitor comprises administering, e.g., once per week, e.g., in a sustained release dosage form, 0.3 to 60, 1.5 to 30, 7.5 to 22.5, 9 to 18, or about 15 mgs of RAD001, or a bioequivalent dose thereof.

The extent of mTOR inhibition can be conveyed as, or corresponds to, the extent of P70 S6 kinase inhibition, e.g., the extent of mTOR inhibition can be determined by the level of decrease in P70 S6 kinase activity, e.g., by the decrease in phosphorylation of a P70 S6 kinase substrate. The level of mTOR inhibition can be evaluated by various methods, such as measuring P70 S6 kinase activity by the Boulay assay, as described in U.S. Patent Application

No. 2015/01240036, hereby incorporated by reference, or as described in U.S. Patent No. 7,727,950, hereby incorporated by reference; measuring the level of phosphorylated S6 by western blot; or evaluating a change in the ratio of PD1 negative immune effector cells to PD1 positive immune effector cells.

As used herein, the term "mTOR inhibitor" refers to a compound or ligand, or a pharmaceutically acceptable salt thereof, which inhibits the mTOR kinase in a cell. In an embodiment, an mTOR inhibitor is an allosteric inhibitor. Allosteric mTOR inhibitors include the neutral tricyclic compound rapamycin (sirolimus), rapamycin-related compounds, that is compounds having structural and functional similarity to rapamycin including, e.g., rapamycin derivatives, rapamycin analogs (also referred to as rapalogs) and other macrolide compounds that inhibit mTOR activity. In an embodiment, an mTOR inhibitor is a catalytic inhibitor.

Rapamycin is a known macrolide antibiotic produced by Streptomyces hygroscopicus having the structure shown in Formula A.



(A)

See, e.g., McAlpine, J.B., et al., J. Antibiotics (1991) 44: 688; Schreiber, S.L., et al., J. Am. Chem. Soc. (1991) 113: 7433; U.S. Patent No. 3,929,992. There are various numbering schemes proposed for rapamycin. To avoid confusion, when specific rapamycin analogs are named herein, the names are given with reference to rapamycin using the numbering scheme of formula A.

Rapamycin analogs useful in the invention are, for example, O-substituted analogs in which the hydroxyl group on the cyclohexyl ring of rapamycin is replaced by OR_1 in which R_1 is hydroxyalkyl, hydroxyalkoxyalkyl, acylaminoalkyl, or aminoalkyl; e.g. RAD001, also known as everolimus, as described in US 5,665,772 and WO94/09010, the contents of each are incorporated by reference.

Other suitable rapamycin analogs include those substituted at the 26- or 28-position. The rapamycin analog may be an epimer of an analog mentioned above, particularly an epimer of an analog substituted in position 40, 28 or 26, and may optionally be further hydrogenated, e.g. as described in US 6,015,815, WO95/14023 and WO99/15530 the contents of which are incorporated by reference, e.g. ABT578 also known as zotarolimus or a rapamycin analog described in US 7,091,213, WO98/02441 and WO01/14387 the contents of which are incorporated by reference, e.g. AP23573 also known as ridaforolimus.

Examples of rapamycin analogs suitable for use in the present invention from US 5,665,772 include, but are not limited to, 40-O-benzyl-rapamycin, 40-O-(4'-hydroxymethyl)benzyl-rapamycin, 40-O-[4'-(1,2-dihydroxyethyl)]benzyl-rapamycin, 40-O-allyl-rapamycin, 40-O-[3'-(2,2-dimethyl-1,3-dioxolan-4(S)-yl)-prop-2'-en-1'-yl]-rapamycin, (2'E,4'S)-40-O-(4',5'-dihydroxypent-2'-en-1'-yl)-rapamycin, 40-O-(2-hydroxy)ethoxycarbonylmethyl-rapamycin, 40-O-(2-hydroxy)ethyl-rapamycin , 40-O-(3-hydroxy)propyl-rapamycin, 40-O-(6-hydroxy)hexyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, 40-O-[(3S)-2,2-dimethyldioxolan-3-yl]methyl-rapamycin, 40-O-[(2S)-2,3-dihydroxyprop-1-yl]-rapamycin, 40-O-(2-acetoxy)ethyl-rapamycin, 40-O-(2-nicotinoyloxy)ethyl-rapamycin, 40-O-[2-(N-morpholino)acetoxy]ethyl-rapamycin, 40-O-(2-N-imidazolylacetoxy)ethyl-rapamycin, 40-O-[2-(N-methyl-N'-piperazinyl)acetoxy]ethyl-rapamycin, 39-O-desmethyl-39,40-O,O-ethylene-rapamycin, (26R)-26-dihydro-40-O-(2-hydroxy)ethyl-rapamycin, 40-O-(2-aminoethyl)-rapamycin, 40-O-(2-acetaminoethyl)-rapamycin, 40-O-(2-nicotinamidoethyl)-rapamycin, 40-O-(2-(N-methyl-imidazo-2'-ylcarbethoxamido)ethyl)-rapamycin, 40-O-(2-ethoxycarbonylaminoethyl)-rapamycin, 40-O-(2-tolylsulfonamidoethyl)-rapamycin and 40-O-[2-(4',5'-dicarboethoxy-1',2',3'-triazol-1'-yl)-ethyl]-rapamycin.

Other rapamycin analogs useful in the present invention are analogs where the hydroxyl group on the cyclohexyl ring of rapamycin and/or the hydroxy group at the 28 position is

replaced with an hydroxyester group are known, for example, rapamycin analogs found in US RE44,768, e.g. temsirolimus.

Other rapamycin analogs useful in the preset invention include those wherein the methoxy group at the 16 position is replaced with another substituent, preferably (optionally hydroxy-substituted) alkynyloxy, benzyl, orthomethoxybenzyl or chlorobenzyl and/or wherein the mexthoxy group at the 39 position is deleted together with the 39 carbon so that the cyclohexyl ring of rapamycin becomes a cyclopentyl ring lacking the 39 position methyoxy group; e.g. as described in WO95/16691 and WO96/41807, the contents of which are incorporated by reference. The analogs can be further modified such that the hydroxy at the 40-position of rapamycin is alkylated and/or the 32-carbonyl is reduced.

Rapamycin analogs from WO95/16691 include, but are not limited to, 16-demthoxy-16-(pent-2-ynyl)oxy-rapamycin, 16-demthoxy-16-(but-2-ynyl)oxy-rapamycin, 16-demthoxy-16-(propargyl)oxy-rapamycin, 16-demethoxy-16-(4-hydroxy-but-2-ynyl)oxy-rapamycin, 16-demthoxy-16-benzyloxy-40-O-(2-hydroxyethyl)-rapamycin, 16-demthoxy-16-benzyloxy-rapamycin, 16-demethoxy-16-ortho-methoxybenzyl-rapamycin, 16-demethoxy-40-O-(2-methoxyethyl)-16-pent-2-ynyl)oxy-rapamycin, 39-demethoxy-40-desoxy-39-formyl-42-nor-rapamycin, 39-demethoxy-40-desoxy-39-hydroxymethyl-42-nor-rapamycin, 39-demethoxy-40-desoxy-39-carboxy-42-nor-rapamycin, 39-demethoxy-40-desoxy-39-(4-methyl-piperazin-1-yl)carbonyl-42-nor-rapamycin, 39-demethoxy-40-desoxy-39-(morpholin-4-yl)carbonyl-42-nor-rapamycin, 39-demethoxy-40-desoxy-39-[N-methyl, N-(2-pyridin-2-yl-ethyl)]carbamoyl-42-nor-rapamycin and 39-demethoxy-40-desoxy-39-(p-toluenesulfonylhydrazonomethyl)-42-nor-rapamycin.

Rapamycin analogs from WO96/41807 include, but are not limited to, 32-deoxo-rapamycin, 16-O-pent-2-ynyl-32-deoxo-rapamycin, 16-O-pent-2-ynyl-32-deoxo-40-O-(2-hydroxy-ethyl)-rapamycin, 16-O-pent-2-ynyl-32-(S)-dihydro-40-O-(2-hydroxyethyl)-rapamycin, 32(S)-dihydro-40-O-(2-methoxy)ethyl-rapamycin and 32(S)-dihydro-40-O-(2-hydroxyethyl)-rapamycin.

Another suitable rapamycin analog is umirolimus as described in US2005/0101624 the contents of which are incorporated by reference.

RAD001, otherwise known as everolimus (Afinitor®), has the chemical name (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-

15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.04,9]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone, as described in US 5,665,772 and WO94/09010, the contents of each are incorporated by reference.

Further examples of allosteric mTOR inhibitors include sirolimus (rapamycin, AY-22989), 40-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate]-rapamycin (also called temsirolimus or CCI-779) and ridaforolimus (AP-23573/MK-8669). Other examples of allosteric mTor inhibtors include zotarolimus (ABT578) and umirolimus.

Alternatively or additionally, catalytic, ATP-competitive mTOR inhibitors have been found to target the mTOR kinase domain directly and target both mTORC1 and mTORC2. These are also more effective inhibitors of mTORC1 than such allosteric mTOR inhibitors as rapamycin, because they modulate rapamycin-resistant mTORC1 outputs such as 4EBP1-T37/46 phosphorylation and cap-dependent translation.

Catalytic inhibitors include: BEZ235 or 2-methyl-2-[4-(3-methyl-2-oxo-8-quinolin-3-yl-2,3-dihydro-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile, or the monotosylate salt form (the synthesis of BEZ235 is described in WO2006/122806); CCG168 (otherwise known as AZD-8055, Chresta, C.M., et al., Cancer Res, 2010, 70(1), 288-298) which has the chemical name {5-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3d]pyrimidin-7-yl]-2-methoxy-phenyl}-methanol; 3-[2,4-bis[(3S)-3-methylmorpholin-4-yl]pyrido[2,3-d]pyrimidin-7-yl]-N-methylbenzamide (WO09104019); 3-(2-aminobenzo[d]oxazol-5-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (WO10051043 and WO2013023184); A N-(3-(N-(3-((3,5-dimethoxyphenyl)amino)quinoxaline-2-yl)sulfamoyl)phenyl)-3-methoxy-4-methylbenzamide (WO07044729 and WO12006552); PKI-587 (Venkatesan, A.M., J. Med.Chem., 2010, 53, 2636-2645) which has the chemical name 1-[4-[4-(dimethylamino)piperidine-1-carbonyl]phenyl]-3-[4-(4,6-dimorpholino-1,3,5-triazin-2-yl)phenyl]urea; GSK-2126458 (ACS Med. Chem. Lett., 2010, 1, 39-43) which has the chemical name 2,4-difluoro-N-{2-methoxy-5-[4-(4-pyridazinyl)-6-quinolinyl]-3-pyridinyl}benzenesulfonamide; 5-(9-isopropyl-8-methyl-2-morpholino-9H-purin-6-yl)pyrimidin-2-amine (WO10114484); and (E)-N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (WO12007926).

Further examples of catalytic mTOR inhibitors include 8-(6-methoxy-pyridin-3-yl)-3-methyl-1-(4-piperazin-1-yl-3-trifluoromethyl-phenyl)-1,3-dihydro-imidazo[4,5-c]quinolin-2-one (WO2006/122806) and Ku-0063794 (Garcia-Martinez JM, et al.,Biochem J., 2009, 421(1),

29-42. Ku-0063794 is a specific inhibitor of the mammalian target of rapamycin (mTOR).) WYE-354 is another example of a catalytic mTOR inhibitor (Yu K, et al. (2009). Biochemical, Cellular, and In vivo Activity of Novel ATP-Competitive and Selective Inhibitors of the Mammalian Target of Rapamycin. Cancer Res. 69(15): 6232-6240).

mTOR inhibitors useful according to the present invention also include prodrugs, derivatives, pharmaceutically acceptable salts, or analogs thereof of any of the foregoing.

mTOR inhibitors, such as RAD001, may be formulated for delivery based on well-established methods in the art based on the particular dosages described herein. In particular, US Patent No. 6,004,973 (incorporated herein by reference) provides examples of formulations useable with the mTOR inhibitors described herein.

Methods and Biomarkers for Evaluating CAR-Effectiveness or Sample Suitability

In another aspect, the invention features a method of evaluating or monitoring the effectiveness of a CAR-expressing cell therapy (e.g., a BCMACAR therapy), in a subject (e.g., a subject having a cancer, e.g., a hematological cancer), or the suitability of a sample (e.g., an apheresis sample) for a CAR therapy (e.g., a BCMACAR therapy). The method includes acquiring a value of effectiveness to the CAR therapy, or sample suitability, wherein said value is indicative of the effectiveness or suitability of the CAR-expressing cell therapy.

In embodiments, the value of effectiveness to the CAR therapy, or sample suitability, comprises a measure of one, two, three, four, five, six or more (all) of the following:

(i) the level or activity of one, two, three, or more (*e.g.*, all) of resting T_{EFF} cells, resting T_{REG} cells, younger T cells (*e.g.*, younger CD4 or CD8 cells, or gamma/delta T cells), or early memory T cells, or a combination thereof, in a sample (e.g., an apheresis sample or a manufactured CAR-expressing cell product sample);

(ii) the level or activity of one, two, three, or more (*e.g.*, all) of activated T_{EFF} cells, activated T_{REG} cells, older T cells (*e.g.*, older CD4 or CD8 cells), or late memory T cells, or a combination thereof, in a sample (e.g., an apheresis sample or a manufactured CAR-expressing cell product sample);

(iii) the level or activity of an immune cell exhaustion marker, *e.g.*, one, two or more immune checkpoint inhibitors (e.g., PD-1, PD-L1, TIM-3 and/or LAG-3) in a sample (e.g., an apheresis sample or a manufactured CAR-expressing cell product sample). In one

embodiment, an immune cell has an exhausted phenotype, *e.g.*, co-expresses at least two exhaustion markers, *e.g.*, co-expresses PD-1 and TIM-3. In other embodiments, an immune cell has an exhausted phenotype, *e.g.*, co-expresses at least two exhaustion markers, *e.g.*, co-expresses PD-1 and LAG-3;

(iv) the level or activity of CD27 and/or CD45RO- (e.g., CD27+ CD45RO-) immune effector cells, e.g., in a CD4+ or a CD8+ T cell population, in a sample (e.g., an apheresis sample or a manufactured CAR-expressing cell product sample);

(v) the level or activity of one, two, three, four, five, ten, twenty or more of the biomarkers chosen from CCL20, IL-17a and/or IL-6, PD-1, PD-L1, LAG-3, TIM-3, CD57, CD27, CD122, CD62L, KLRG1;

(vi) a cytokine level or activity (*e.g.*, quality of cytokine reportoire) in a CAR-expressing cell product sample, e.g., BCMA- expressing cell product sample; or

(vii) a transduction efficiency of a CAR-expressing cell in a manufactured CAR-expressing cell product sample.

In some embodiments of any of the methods disclosed herein, the CAR-expressing cell therapy comprises a plurality (e.g., a population) of CAR-expressing immune effector cells, e.g., a plurality (e.g., a population) of T cells or NK cells, or a combination thereof. In one embodiment, the CAR-expressing cell therapy is a BCMACAR therapy.

In some embodiments of any of the methods disclosed herein, the measure of one or more of (i)-(vii) is obtained from an apheresis sample acquired from the subject. The apheresis sample can be evaluated prior to infusion or re-infusion.

In some embodiments of any of the methods disclosed herein, the measure of one or more of (i)-(vii) is obtained from a manufactured CAR-expressing cell product sample, e.g., BCMACAR- expressing cell product sample. The manufactured CAR-expressing cell product can be evaluated prior to infusion or re-infusion.

In some embodiments of any of the methods disclosed herein, the subject is evaluated prior to receiving, during, or after receiving, the CAR-expressing cell therapy.

In some embodiments of any of the methods disclosed herein, the measure of one or more of (i)-(vii) evaluates a profile for one or more of gene expression, flow cytometry or protein expression.

In some embodiments of any of the methods disclosed herein, the method further comprises identifying the subject as a responder, a non-responder, a relapser or a non-relapser, based on a measure of one or more of (i)-(vii).

In some embodiments of any of the methods disclosed herein, a responder (e.g., a complete responder) has, or is identified as having, a greater level or activity of one, two, or more (all) of GZMK, PPF1BP2, or naïve T cells as compared to a non-responder.

In some embodiments of any of the methods disclosed herein, a non-responder has, or is identified as having, a greater level or activity of one, two, three, four, five, six, seven, or more (e.g., all) of IL22, IL-2RA, IL-21, IRF8, IL8, CCL17, CCL22, effector T cells, or regulatory T cells, as compared to a responder.

In an embodiment, a relapser is a patient having, or who is identified as having, an increased level of expression of one or more of (e.g., 2, 3, 4, or all of) the following genes, compared to non relapsers: MIR199A1, MIR1203, uc021ovp, ITM2C, and HLA-DQB1 and/or a decreased levels of expression of one or more of (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or all of) the following genes, compared to non relapsers: PPIAL4D, TTTY10, TXLNG2P, MIR4650-1, KDM5D, USP9Y, PRKY, RPS4Y2, RPS4Y1, NCRNA00185, SULT1E1, and EIF1AY.

In some embodiments of any of the methods disclosed herein, a complete responder has, or is identified as having, a greater, e.g., a statistically significant greater, percentage of CD8+ T cells compared to a reference value, e.g., a non-responder percentage of CD8+ T cells.

In some embodiments of any of the methods disclosed herein, a complete responder has, or is identified as having, a greater percentage of CD27+ CD45RO- immune effector cells, e.g., in the CD8+ population, compared to a reference value, e.g., a non-responder number of CD27+ CD45RO- immune effector cells.

In some embodiments of any of the methods disclosed herein, a complete responder or a partial responder has, or is identified as having, a greater, e.g., a statistically significant greater, percentage of CD4+ T cells compared to a reference value, e.g., a non-responder percentage of CD4+ T cells.

In some embodiments of any of the methods disclosed herein, a complete responder has, or is identified as having, a greater percentage of one, two, three, or more (*e.g.*, all) of resting T_{EFF} cells, resting T_{REG} cells, younger T cells (*e.g.*, younger CD4 or CD8 cells, or gamma/delta T cells), or early memory T cells,, or a combination thereof, compared to a reference value, e.g., a non-responder number of resting T_{EFF} cells, resting T_{REG} cells, younger T cells (*e.g.*, younger CD4 or CD8 cells), or early memory T cells.

In some embodiments of any of the methods disclosed herein, a non-responder has, or is identified as having, a greater percentage of one, two, three, or more (*e.g.*, all) of activated T_{EFF} cells, activated T_{REG} cells, older T cells (*e.g.*, older CD4 or CD8 cells), or late memory T cells, or a combination thereof, compared to a reference value, e.g., a responder number of activated T_{EFF} cells, activated T_{REG} cells, older T cells (*e.g.*, older CD4 or CD8 cells), or late memory T cells.

In some embodiments of any of the methods disclosed herein, a non-responder has, or is identified as having, a greater percentage of an immune cell exhaustion marker, *e.g.*, one, two or more immune checkpoint inhibitors (e.g., PD-1, PD-L1, TIM-3 and/or LAG-3). In one embodiment, a non-responder has, or is identified as having, a greater percentage of PD-1, PD-L1, or LAG-3 expressing immune effector cells (e.g., CD4+ T cells and/or CD8+ T cells) (e.g., CAR-expressing CD4+ cells and/or CD8+ T cells) compared to the percentage of PD-1 or LAG-3 expressing immune effector cells from a responder.

In one embodiment, a non-responder has, or is identified as having, a greater percentage of immune cells having an exhausted phenotype, *e.g.*, immune cells that co-express at least two exhaustion markers, *e.g.*, co-expresses PD-1, PD-L1 and/or TIM-3. In other embodiments, a non-responder has, or is identified as having, a greater percentage of immune cells having an exhausted phenotype, *e.g.*, immune cells that co-express at least two exhaustion markers, *e.g.*, co-expresses PD-1 and LAG-3.

In some embodiments of any of the methods disclosed herein, a non-responder has, or is identified as having, a greater percentage of PD-1/ PD-L1+/LAG-3+ cells in the CAR-expressing cell population (e.g., a BCMACAR+ cell population) compared to a responder (e.g., a complete responder) to the CAR-expressing cell therapy.

In some embodiments of any of the methods disclosed herein, a partial responder has, or is identified as having, a higher percentages of PD-1/ PD-L1+/LAG-3+ cells, than a responder, in the CAR-expressing cell population (e.g., a BCMACAR+ cell population).

In some embodiments of any of the methods disclosed herein, a non-responder has, or is identified as having, an exhausted phenotype of PD1/ PD-L1+ CAR+ and co-expression of LAG3 in the CAR-expressing cell population (e.g., a BCMACAR + cell population).

In some embodiments of any of the methods disclosed herein, a non-responder has, or is identified as having, a greater percentage of PD-1/ PD-L1+/TIM-3+ cells in the CAR-expressing cell population (e.g., a BCMACAR + cell population) compared to the responder (e.g., a complete responder).

In some embodiments of any of the methods disclosed herein, a partial responders has, or is identified as having, a higher percentage of PD-1/ PD-L1+/TIM-3+ cells, than responders, in the CAR-expressing cell population (e.g., a BCMACAR + cell population).

In some embodiments of any of the methods disclosed herein, the presence of CD8+ CD27+ CD45RO- T cells in an apheresis sample is a positive predictor of the subject response to a CAR-expressing cell therapy (e.g., a BCMACAR therapy).

In some embodiments of any of the methods disclosed herein, a high percentage of PD1+ CAR+ and LAG3+ or TIM3+ T cells in an apheresis sample is a poor prognostic predictor of the subject response to a CAR-expressing cell therapy (e.g., a BCMACAR therapy).

In some embodiments of any of the methods disclosed herein, the responder (e.g., the complete or partial responder) has one, two, three or more (or all) of the following profile:

(i) has a greater number of CD27+ immune effector cells compared to a reference value, e.g., a non-responder number of CD27+ immune effector cells;

(ii) (i) has a greater number of CD8+ T cells compared to a reference value, e.g., a non-responder number of CD8+ T cells;

(iii) has a lower number of immune cells expressing one or more checkpoint inhibitors, e.g., a checkpoint inhibitor chosen from PD-1, PD-L1, LAG-3, TIM-3, or KLRG-1, or a combination, compared to a reference value, e.g., a non-responder number of cells expressing one or more checkpoint inhibitors; or

(iv) has a greater number of one, two, three, four or more (all) of resting T_{EFF} cells, resting T_{REG} cells, naïve CD4 cells, unstimulated memory cells or early memory T cells, or a combination thereof, compared to a reference value, e.g., a non-responder number of resting T_{EFF} cells, resting T_{REG} cells, naïve CD4 cells, unstimulated memory cells or early memory T cells.

In some embodiments of any of the methods disclosed herein, the cytokine level or activity of (vi) is chosen from one, two, three, four, five, six, seven, eight, or more (or all) of cytokine CCL20/MIP3a, IL17A, IL6, GM-CSF, IFNγ, IL10, IL13, IL2, IL21, IL4, IL5, IL9 or TNFα, or a combination thereof. The cytokine can be chosen from one, two, three, four or more (all) of IL-17a, CCL20, IL2, IL6, or TNFa. In one embodiment, an increased level or activity of a cytokine is chosen from one or both of IL-17a and CCL20, is indicative of increased responsiveness or decreased relapse.

In some embodiments of any of the methods disclosed herein, a transduction efficiency of 15% or higher in (vii) is indicative of increased responsiveness or decreased relapse.

In some embodiments of any of the methods disclosed herein, a transduction efficiency of less than 15% in (vii) is indicative of decreased responsiveness or increased relapse.

In embodiments, the responder, a non-responder, a relapser or a non-relapser identified by the methods herein can be further evaluated according to clinical criteria. For example, a complete responder has, or is identified as, a subject having a disease, e.g., a cancer, who exhibits a complete response, e.g., a complete remission, to a treatment. A complete response may be identified, e.g., using the NCCN Guidelines®, or Cheson et al, J Clin Oncol 17:1244 (1999) and Cheson et al., "Revised Response Criteria for Malignant Lymphoma", J Clin Oncol 25:579-586 (2007) (both of which are incorporated by reference herein in their entireties), as described herein. A partial responder has, or is identified as, a subject having a disease, e.g., a cancer, who exhibits a partial response, e.g., a partial remission, to a treatment. A partial response may be identified, e.g., using the NCCN Guidelines®, or Cheson criteria as described herein. A non-responder has, or is identified as, a subject having a disease, e.g., a cancer, who does not exhibit a response to a treatment, e.g., the patient has stable disease or progressive disease. A non-responder may be identified, e.g., using the NCCN Guidelines®, or Cheson criteria as described herein.

Alternatively, or in combination with the methods disclosed herein, responsive to said value, performing one, two, three four or more of:

administering e.g., to a responder or a non-relapser, a CAR-expressing cell therapy;

administered an altered dosing of a CAR-expressing cell therapy;

altering the schedule or time course of a CAR-expressing cell therapy;

administering, e.g., to a non-responder or a partial responder, an additional agent in combination with a CAR-expressing cell therapy, e.g., a checkpoint inhibitor, e.g., a checkpoint inhibitor described herein;

administering to a non-responder or partial responder a therapy that increases the number of younger T cells in the subject prior to treatment with a CAR-expressing cell therapy;

modifying a manufacturing process of a CAR-expressing cell therapy, e.g., enriching for younger T cells prior to introducing a nucleic acid encoding a CAR, or increasing the transduction efficiency, e.g., for a subject identified as a non-responder or a partial responder;

administering an alternative therapy, e.g., for a non-responder or partial responder or relapser; or

if the subject is, or is identified as, a non-responder or a relapser, decreasing the T_{REG} cell population and/or T_{REG} gene signature, *e.g.*, by one or more of CD25 depletion, administration of cyclophosphamide, anti-GITR antibody, or a combination thereof.

In certain embodiments, the subject is pre-treated with an anti-GITR antibody. In certain embodiment, the subject is treated with an anti-GITR antibody prior to infusion or re-infusion.

Biopolymer delivery methods

In some embodiments, one or more CAR-expressing cells as disclosed herein can be administered or delivered to the subject via a biopolymer scaffold, e.g., a biopolymer implant. Biopolymer scaffolds can support or enhance the delivery, expansion, and/or dispersion of the CAR-expressing cells described herein. A biopolymer scaffold comprises a biocompatible (e.g., does not substantially induce an inflammatory or immune response) and/or a biodegradable polymer that can be naturally occurring or synthetic.

Examples of suitable biopolymers include, but are not limited to, agar, agarose, alginate, alginate/calcium phosphate cement (CPC), beta-galactosidase (β-GAL), (1 ,2,3,4,6-pentaacetyl a-D-galactose), cellulose, chitin, chitosan, collagen, elastin, gelatin, hyaluronic acid collagen, hydroxyapatite, poly(3-hydroxybutyrate-co-3-hydroxy-hexanoate) (PHBHHx), poly(lactide), poly(caprolactone) (PCL), poly(lactide-co-glycolide) (PLG), polyethylene oxide

(PEO), poly(lactic-co-glycolic acid) (PLGA), polypropylene oxide (PPO), polyvinyl alcohol (PVA), silk, soy protein, and soy protein isolate, alone or in combination with any other polymer composition, in any concentration and in any ratio. The biopolymer can be augmented or modified with adhesion- or migration-promoting molecules, e.g., collagen-mimetic peptides that bind to the collagen receptor of lymphocytes, and/or stimulatory molecules to enhance the delivery, expansion, or function, e.g., anti-cancer activity, of the cells to be delivered. The biopolymer scaffold can be an injectable, e.g., a gel or a semi-solid, or a solid composition.

In some embodiments, CAR-expressing cells described herein are seeded onto the biopolymer scaffold prior to delivery to the subject. In embodiments, the biopolymer scaffold further comprises one or more additional therapeutic agents described herein (e.g., another CAR-expressing cell, an antibody, or a small molecule) or agents that enhance the activity of a CAR-expressing cell, e.g., incorporated or conjugated to the biopolymers of the scaffold. In embodiments, the biopolymer scaffold is injected, e.g., intratumorally, or surgically implanted at the tumor or within a proximity of the tumor sufficient to mediate an anti-tumor effect. Additional examples of biopolymer compositions and methods for their delivery are described in Stephan et al., *Nature Biotechnology*, 2015, 33:97-101; and WO2014/110591.

Pharmaceutical compositions and treatments

Pharmaceutical compositions of the present invention may comprise a CAR-expressing cell, e.g., a plurality of CAR-expressing cells, as described herein, in combination with one or more pharmaceutically or physiologically acceptable carriers, diluents or excipients. Such compositions may comprise buffers such as neutral buffered saline, phosphate buffered saline and the like; carbohydrates such as glucose, mannose, sucrose or dextrans, mannitol; proteins; polypeptides or amino acids such as glycine; antioxidants; chelating agents such as EDTA or glutathione; adjuvants (e.g., aluminum hydroxide); and preservatives. Compositions of the present invention are in one aspect formulated for intravenous administration.

Pharmaceutical compositions of the present invention may be administered in a manner appropriate to the disease to be treated (or prevented). The quantity and frequency of administration will be determined by such factors as the condition of the patient, and the type and severity of the patient's disease, although appropriate dosages may be determined by clinical trials.

In one embodiment, the pharmaceutical composition is substantially free of, e.g., there are no detectable levels of a contaminant, e.g., selected from the group consisting of endotoxin, mycoplasma, replication competent lentivirus (RCL), p24, VSV-G nucleic acid, HIV gag, residual anti-CD3/anti-CD28 coated beads, mouse antibodies, pooled human serum, bovine serum albumin, bovine serum, culture media components, vector packaging cell or plasmid components, a bacterium and a fungus. In one embodiment, the bacterium is at least one selected from the group consisting of Alcaligenes faecalis, Candida albicans, Escherichia coli, Haemophilus influenza, Neisseria meningitides, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pneumonia, and Streptococcus pyogenes group A.

When "an immunologically effective amount," "an anti-tumor effective amount," "a tumor-inhibiting effective amount," or "therapeutic amount" is indicated, the precise amount of the compositions of the present invention to be administered can be determined by a physician with consideration of individual differences in age, weight, tumor size, extent of infection or metastasis, and condition of the patient (subject). It can generally be stated that a pharmaceutical composition comprising the T cells described herein may be administered at a dosage of 10^4 to 10^9 cells/kg body weight, in some instances 10^5 to 10^6 cells/kg body weight, including all integer values within those ranges. T cell compositions may also be administered multiple times at these dosages. The cells can be administered by using infusion techniques that are commonly known in immunotherapy (see, e.g., Rosenberg et al., New Eng. J. of Med. 319:1676, 1988)..

In certain aspects, it may be desired to administer activated T cells to a subject and then subsequently redraw blood (or have an apheresis performed), activate T cells therefrom according to the present invention, and reinfuse the patient with these activated and expanded T cells. This process can be carried out multiple times every few weeks. In certain aspects, T cells can be activated from blood draws of from 10cc to 400cc. In certain aspects, T cells are activated from blood draws of 20cc, 30cc, 40cc, 50cc, 60cc, 70cc, 80cc, 90cc, or 100cc.

The administration of the subject compositions may be carried out in any convenient manner, including by aerosol inhalation, injection, ingestion, transfusion, implantation or transplantation. The compositions described herein may be administered to a patient trans arterially, subcutaneously, intradermally, intratumorally, intranodally, intramedullary, intramuscularly, by intravenous (i.v.) injection, or intraperitoneally. In one aspect, the T cell

compositions of the present invention are administered to a patient by intradermal or subcutaneous injection. In one aspect, the CAR-expressing cell (e.g., T cell or NK cell) compositions of the present invention are administered by i.v. injection. The compositions of CAR-expressing cells (e.g., T cells or NK cells) may be injected directly into a tumor, lymph node, or site of infection.

In a particular exemplary aspect, subjects may undergo leukapheresis, wherein leukocytes are collected, enriched, or depleted ex vivo to select and/or isolate the cells of interest, e.g., immune effector cells (e.g., T cells or NK cells). These immune effector cell (e.g., T cell or NK cell) isolates may be expanded by methods known in the art and treated such that one or more CAR constructs of the invention may be introduced, thereby creating a CAR-expressing cell (e.g., CAR T cell or CAR-expressing NK cell)of the invention. Subjects in need thereof may subsequently undergo standard treatment with high dose chemotherapy followed by peripheral blood stem cell transplantation. In certain aspects, following or concurrent with the transplant, subjects receive an infusion of the expanded CAR-expressing cells (e.g., CAR T cells or NK cells) of the present invention. In an additional aspect, expanded cells are administered before or following surgery.

In embodiments, lymphodepletion is performed on a subject, e.g., prior to administering one or more cells that express a CAR described herein, e.g., a BCMA-binding CAR described herein. In embodiments, the lymphodepletion comprises administering one or more of melphalan, cytoxan, cyclophosphamide, and fludarabine.

The dosage of the above treatments to be administered to a patient will vary with the precise nature of the condition being treated and the recipient of the treatment. The scaling of dosages for human administration can be performed according to art-accepted practices. The dose for CAMPATH, for example, will generally be in the range 1 to about 100 mg for an adult patient, usually administered daily for a period between 1 and 30 days. The preferred daily dose is 1 to 10 mg per day although in some instances larger doses of up to 40 mg per day may be used (described in U.S. Patent No. 6,120,766).

In one embodiment, the CAR is introduced into immune effector cells (e.g., T cells or NK cells), e.g., using in vitro transcription, and the subject (e.g., human) receives an initial administration of CAR immune effector cells (e.g., T cells or NK cells)of the invention, and

one or more subsequent administrations of the CAR immune effector cells (e.g., T cells or NK cells) of the invention, wherein the one or more subsequent administrations are administered less than 15 days, e.g., 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, or 2 days after the previous administration. In one embodiment, more than one administration of the CAR immune effector cells (e.g., T cells or NK cells) of the invention are administered to the subject (e.g., human) per week, e.g., 2, 3, or 4 administrations of the CAR immune effector cells (e.g., T cells or NK cells) of the invention are administered per week. In one embodiment, the subject (e.g., human subject) receives more than one administration of the CAR immune effector cells (e.g., T cells or NK cells) per week (e.g., 2, 3 or 4 administrations per week) (also referred to herein as a cycle), followed by a week of no CAR immune effector cells (e.g., T cells or NK cells) administrations, and then one or more additional administration of the CAR immune effector cells (e.g., T cells or NK cells) (e.g., more than one administration of the CAR immune effector cells (e.g., T cells or NK cells) per week) is administered to the subject. In another embodiment, the subject (e.g., human subject) receives more than one cycle of CAR immune effector cells (e.g., T cells or NK cells), and the time between each cycle is less than 10, 9, 8, 7, 6, 5, 4, or 3 days. In one embodiment, the CAR immune effector cells (e.g., T cells or NK cells) are administered every other day for 3 administrations per week. In one embodiment, the CAR immune effector cells (e.g., T cells or NK cells) of the invention are administered for at least two, three, four, five, six, seven, eight or more weeks.

In one aspect, BCMA CAR-expressing cells (e.g., BCMA CARTs or BCMA CAR-expressing NK cells) are generated using lentiviral viral vectors, such as lentivirus. CAR-expressing cells (e.g., CARTs or CAR-expressing NK cells) generated that way will have stable CAR expression.

In one aspect, CAR-expressing cells, e.g., CARTs, are generated using a viral vector such as a gammaretroviral vector, e.g., a gammaretroviral vector described herein. CARTs generated using these vectors can have stable CAR expression.

In one aspect, CAR-expressing cells (e.g., CARTs or CAR-expressing NK cells) transiently express CAR vectors for 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 days after transduction. Transient expression of CARs can be effected by RNA CAR vector delivery. In one aspect, the CAR RNA is transduced into the cell, e.g., T cell or NK cell, by electroporation.

A potential issue that can arise in patients being treated using transiently expressing CAR-expressing cells (e.g., CARTs or CAR-expressing NK cells) (particularly with murine scFv bearing CAR-expressing cells (e.g., CARTs or CAR-expressing NK cells)) is anaphylaxis after multiple treatments.

Without being bound by this theory, it is believed that such an anaphylactic response might be caused by a patient developing humoral anti-CAR response, i.e., anti-CAR antibodies having an anti-IgE isotype. It is thought that a patient's antibody producing cells undergo a class switch from IgG isotype (that does not cause anaphylaxis) to IgE isotype when there is a ten to fourteen day break in exposure to antigen.

If a patient is at high risk of generating an anti-CAR antibody response during the course of transient CAR therapy (such as those generated by RNA transductions), CAR-expressing cell (e.g., CART or CAR-expressing NK cell) infusion breaks should not last more than ten to fourteen days.

EXAMPLES

The invention is further described in detail by reference to the following experimental examples. These examples are provided for purposes of illustration only, and are not intended to be limiting unless otherwise specified. Thus, the invention should in no way be construed as being limited to the following examples, but rather, should be construed to encompass any and all variations which become evident as a result of the teaching provided herein.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. The following working examples specifically point out various aspects of the present invention, and are not to be construed as limiting in any way the remainder of the disclosure.

Example 1: BCMA is expressed in Myeloma cell lines and primary samples

Analysis of BCMA expression in Myeloma cell lines by quantitative PCR

16 cell lines of human cancers were screened for BCMA RNA expression by quantitative RT-PCR. RNA was extracted with RNAqueos-4PCR Kit (Ambion, AM-1914) and

cDNA was synthesized with iScript Reverse Transcription Supermix for RT-qPCR (BioRad, 170-8841). The relative BCMA cDNA copies were quantified by relative qPCR (qPCR) with ABI TaqMan BCMA-specific primers and probe set (ABI, Hs03045080, lot:1139777) ;TaqMan GUSB (ABI, Hs99999908_M1, lot: 1093869) primers and probe set for normalization.

Analysis of the qPCR showed that all MM cell lines (U266, NCI H929 and RPMI 8226) tested express BCMA. BCMA was also detected in BJAB and LCL cells (B-cell lymphoblastoid cell lines) and CEM cells (a T-lymphoblastoid cell line). None of the other non-MM cell lines exhibited detectable expression of BCMA. This RNA analysis compliments protein detection by flow cytometry for the selection of positive BCMA expressing cell lines used in evaluations. Detailed results are provided in Figure 1A.

Comparison by RNA analysis of BCMA expression in plasma cells and in the different multiple myeloma samples from patients is provided in Figure 1B.

Analysis of BCMA expression in multiple myeloma cells lines and primary samples by flow cytometry

Multiple Myeloma (MM) cell lines U266, NCI H929 or RPMI 8226 or primary samples from MM patients (PB or BM) were stained with Human BCMA/TNFRSF17 Phycoerythrin Affinity Purified PAb, Goat IgG (R&D, FAB193P). Primary samples from multiple myeloma patients were also stained with Live/dead dye (LifeTechnologies, L34960), CD45-BV421 (Biolegend, 304032), CD38-APCeF780 (eBioscience 47-0389-42), CD138-APC (eBioscience 17-1389-42), CD19-PECY7 (eBioscience, E10328-1632), lambda chain-PerCP-eF710 (eBioscience 46-9990-42) and Kappa light chain (eBioscience, 11-9970-42). Data from staoined samplse were collected using a BD Fortessa cytometer. Flow cytometric analysis performed using Flowjo v10 (Tree Star Inc).

BCMA was detected on the surface of all the 3 MM cell lines as shown in Figure 2A, 2B, and 2C. Moreover, BCMA was homogenously expressed on majority of clonal (kappa or lambda restricted) plasma cells in most of the MM patients analyzed (9 of 10). (Fig. 2D and 2E). These results provide strong support for the relevance of BCMA as a target in MM.

Flow cytometric analysis of BCMA expression in normal peripheral blood cells, CD3/CD28 expanded T cells and bone marrow stem cells

In order to rule out possible off-target expression of BCMA in normal tissues and on T cells, BCMA expression in two bone marrow (BM) and peripheral blood (PB) specimens from voluntary healthy donors, were evaluated by flow cytometry. Mononuclear cells were obtained

through Ficoll-Paque (GE healthcare) gradient separation. BM cells were marked with Live/dead dye (LifeTechnologies, L34960) then stained with monoclonal antibodies against, CD34-APC (eBioscience, 17-0349-42 , CD38-PECY7(eBioscience, 25-0389-42), human hemopoietic lineage markers mix-FITC (eBioscience, 22-7778-72), CD45RA-APC-eF780 (eBioscience, 47-0458-42, CD90-PerCPCy5.5 (eBioscience, 45-0909-41, CD10-BV421 (Biolegend, 312218) and BCMA-PE (R&D, FAB193P). Fresh PB cells were stained at baseline and following stimulation and expansion with CD3/CD28 beads. PB was stained with monoclonal antibodies against CD14-V500 (BD, 561391), CD45-BV421 (Biolegend, 304032), CD3-AF700 (56-0038-42), CD19-PECY7 (eBioscience, E10328-1632, and BCMA-PE (R&D, FAB193P). Cells were washed twice and staining data acquired in a BD Fortessa cytometer. Flow cytometric analysis was carried out by using FlowJo v10 (Tree Star Inc).

No evidence of BCMA expression was observed on PBMC. Importantly, T cells remained negative for BCMA during expansion. (Fig. 3A) Analysis of different stem cells subsets in the BM revealed no expression of BCMA on immature, lineage negative CD34 positive stem cells. In particular, the Common Lymphocyte Progenitor and the Hemopoietic Stem Cells were negative. (Fig. 3B)

Analysis of BCMA expression in normal tissues by immunohistochemistry

Three commercially available antibodies (Novus, Sigma) for immunohistochemistry were selected and titrated in paraffin-fixed normal splenic tissue. Tissue micro arrays (TMA) including 27 healthy human tissues were stained by immunohistochemistry.

All 3 antibodies showed positive staining on normal plasma cells in lymph nodes, spleen and tonsil, whereas normal lung, pancreas and thyroid tested negative. Staining, likely non-specific due to the polyclonal nature of the available antibodies, was observed in the following organs: stomach, salivary gland, kidney, adrenal gland, cerebellum, heart and appendix. Selected results are shown in Figures 4A-4E and summarized in Table 11.

Table 11. BCMA expression by immunohistochemistry staining in normal tissues

Site	n=	Staining
Placenta	2	neg
Adipose	2	neg
Urinary bladder	2	neg
Cerebral cortex	2	neg
Cerebellum	2	pos
breast	0	N/A
cervix	1	neg
colon	2	pos
diaphragm	2	neg
Duodenum	2	pos
Esophagus	2	pos
Gallbladder	2	neg
Heart	2	neg
Ileum	2	pos
Jejunum	2	pos
Kidney	2	neg
Liver	2	neg
Lung	2	neg
Ovary	2	neg
pancreas	2	neg
Thyroid	1	neg
Rectum	2	pos
Skin	2	neg
Skeletal muscle	2	neg
Spleen	2	pos
Stomach	2	pos
Testes	2	neg
Thymus	2	neg
Smooth muscle	2	neg
Tonsil	1	pos
Uterus	2	neg

These results led to further analysis of expression, in particular using RNAscope in situ hybridization to confirm the lack of BCMA expression in these tissues. Selected results are shown in Figure 4F.

Example 2: *In vitro* evaluation of CARs containing humanized anti-BCMA scFv

BCMA CAR constructs generated from humanized mouse anti-BCMA antibody

Four distinct anti-BCMA CARs constructs were designed using the VL and VH sequences disclosed in PCT Publication WO 2012/163805 (the contents of which are hereby incorporated by reference in its entirety). In order to create the anti-BCMA CARs, the VH and VL sequences were synthesized and joined with a [Gly-Gly-Gly-Gly-Ser] x 4 linker (SEQ ID NO: 27) creating two single-chain variable fragments (scFvs) in which the VH precedes the VL (H2L, SEQ ID NO: 255) or the VL precedes the VH (L2H, SEQ ID NO: 257). The CD8 leader was also synthesized and fused to the 5' end of each scFv with a BamHI site Restriction sites for XbaI and BspE1 were included at the 5' and 3' ends, respectively, at the time of synthesis to

facilitate cloning of the CD8 leader-scFvs into the pTRPE lentiviral vector containing the hinge and CD8TM regions with 4-1BB and CD3z cytoplasmic domains. Two separate CAR backbone constructs were used for the cloning, one containing a human CD8 hinge and the other containing a human IgG4 hinge to generate the 4 anti-BCMA CAR constructs shown schematically in Figure 5, designated pBCMA 1, pBCMA 2, pBCMA 3, and pBCMA 4. To produce infectious lentiviral vector supernatants, 293-T cells were transfected with the following plasmids: pTRP –VSV-G (encoding the vesicular stomatitis virus (VSV-G) envelope), pTRP gag/pol (encoding gag and pol) and pTRP-Rev with either of the four BCMA CAR constructs utilizing lipofectamine 2000 (Invitrogen).

The nucleic acid sequence of humanized anti-BCMA scFv in which VH precedes the VL (H2L, e.g., pBCMA 2 and pBCMA 4) is as follows:

CAGGTGCAGCTGGTCCAGAGCGGCGCCGAAGTGAAGAAGCCCGGCAGCTCCGTGAAAGTGAGCTGCAAG
GCCAGCGGCGGCACCTTCAGCAACTACTGGATGCACTGGGTGAGGCAGGCCCCCGGACAGGGCCTGGAG
TGGATGGGCGCCACCTACAGGGGCCACAGCGACACCTACTACAACCAGAAGTTCAAGGGCCGGGTGACC
ATCACCGCCGACAAGAGCACCAGCACCGCCTACATGGAACTGAGCAGCCTCAGGAGCGAGGACACCGCT
GTGTATTACTGCGCCAGGGGCGCCATCTACAACGGCTACGACGTGCTGGACAACTGGGGCCAGGGCACA
CTAGTGACCGTGTCCAGCGGTGGAGGAGGTAGCGGAGGAGGCGGGAGCGGTGGAGGTGGCTCTGGAGGT
GGCGGAAGCGACATCCAGATGACCCAGAGCCCTAGCTCACTGAGCGCCAGCGTGGGCGACAGGGTGACC
ATTACCTGCTCCGCCAGCCAGGACATCAGCAACTACCTGAACTGGTACCAGCAGAAGCCCGGCAAGGCC
CCCAAGCTGCTGATCTACTACACCTCCAACCTGCACTCCGGCGTGCCCAGCAGGTTCAGCGGAAGCGGC
AGCGGCACCGATTTCACCCTGACCATCTCCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAG
CAGTACAGGAAGCTCCCCTGGACTTTCGGCCAGGGCACCAAACTGGAGATCAAGCGT
(SEQ ID NO: 272)

The corresponding amino acid sequence for the humanized anti-BCMA scFv in which Vh precedes the VL (H2L, e.g., pBCMA 2 and pBCMA 4) is as follows:

Q V Q L V Q S G A E V K K P G S S V K V S C K A S G G T F S N Y W M H W V R
Q A P G Q G L E W M G A T Y R G H S D T Y Y N Q K F K G R V T I T A D K S T
S T A Y M E L S S L R S E D T A V Y Y C A R G A I Y N G Y D V L D N W G Q G
T L V T V S S G G G G S G G G G S G G G G S G G G G S D I Q M T Q S P S S L
S A S V G D R V T I T C S A S Q D I S N Y L N W Y Q Q K P G K A P K L L I Y
Y T S N L H S G V P S R F S G S G S G T D F T L T I S S L Q P E D F A T Y Y
C Q Q Y R K L P W T F G Q G T K L E I K R (SEQ ID NO: 271)

The nucleic acid sequence of humanized anti-BCMA scFv in which VL precedes the VH (L2H, e.g., pBCMA1 and pBCMA3) is as follows:

GACATCCAGATGACCCAGAGCCCTAGCTCACTGAGCGCCAGCGTGGGCGACAGGGTGACCATTACCTGC
TCCGCCAGCCAGGACATCAGCAACTACCTGAACTGGTACCAGCAGAAGCCCGGCAAGGCCCCCAAGCTG
CTGATCTACTACACCTCCAACCTGCACTCCGGCGTGCCCAGCAGGTTCAGCGGAAGCGGCAGCGGCACC
GATTTCACCCTGACCATCTCCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGTACAGG
AAGCTCCCCTGGACTTTCGGCCAGGGCACCAAACTGGAGATCAAGCGTGGTGGAGGAGGTAGCGGAGGA
GGCGGGAGCGGTGGAGGTGGCTCTGGAGGTGGCGGAAGCCAGGTGCAGCTGGTCCAGAGCGGCGCCGAA

GTGAAGAAGCCCGGCAGCTCCGTGAAAGTGAGCTGCAAGGCCAGCGGCGGCACCTTCAGCAACTACTGG
ATGCACTGGGTGAGGCAGGCCCCCGGACAGGGCCTGGAGTGGATGGGCGCCACCTACAGGGGCCACAGC
GACACCTACTACAACCAGAAGTTCAAGGGCCGGGTGACCATCACCGCCGACAAGAGCACCAGCACCGCC
TACATGGAACTGAGCAGCCTCAGGAGCGAGGACACCGCTGTGTATTACTGCGCCAGGGGCGCCATCTAC
AACGGCTACGACGTGCTGGACAACTGGGGCCAGGGCACACTAGTGACCGTGTCCAGC
(SEQ ID NO: 274) The corresponding amino acid sequence of humanized anti-BCMA scFv in which VL precedes the VH (L2H, e.g., pBCMA1 and pBCMA3) is as follows:

DIQMTQSPSS LSASVGDRVT ITCSASQDIS NYLNWYQQKP GKAPKLLIYY TSNLHSGVPSRFSGSGSGTD FTLTISSLQP EDFATYYCQQ YRKLPWTFGQ GTKLEIKRGG GGSGGGGSGGGGSGGGGSQV QLVQSGAEVK KPGSSVKVSC KASGGTFSNY WMHWVRQAPG QGLEWMGATYRGHSDTYYNQ KFKGRVTITA DKSTSTAYME LSSLRSEDTA VYYCARGAIYNGYDVLDNWGQGTLVTVSS (SEQ ID NO: 273)

These pBCMA-CARs containing humanized anti-BCMA scFvs are utilized in the experiments detailed below and in Example 3.

Efficient expression of BCMA-CARs on T cells

Fresh isolated human T cells from healthy donors were transduced with lentiviral vector supernatants encoding the pBCMA 1 to 4 CARs, and anti-BCMA CAR expression was evaluated by flow cytometry. Briefly, T cells were cultured in RPMI 1640 medium with 10% FBS and stimulated with anti-CD3/anti-CD28 Dynabeads (Invitrogen). 24 hrs after stimulation, T cells were transduced with the four different pBCMA CAR lentiviral vector supernatants. T cells transduced with an anti-mesothelin CAR (SS1) vector were used as a positive control. Mock-transduced T cells (NTD) were used as a negative control. 4-6 days after lentiviral transduction T cells were stained with biotinylated Protein L antibody followed by strepavidin FITC (BD Biosciences) or Biotin Goat-anti mouse and CAR expression was evaluated by flow cytometry (FACS Calibur, BD). Flow cytometric analysis was carried out by using Flowjo (Tree Star Inc).

After transduction it was observed that pBCMA CARs were efficiently expressed on the cell surface of the transduced T cells as shown in Figure 6.

Cytokine production from anti-BCMA CAR-expressing T cells (BCMA CARTs)

K562 cells ectopically expressing human BCMA (K562-BCMA) were generated by lentiviral transduction using a vector supplied by GeneCopoeia followed by puromycin selection. K562-BCMA specific target cells were utilized *in vitro* to evaluate cytotoxic and cytokine production from pBCMA 1-4 CAR-transduced T cells. Anti-pBCMA CAR T cells or control T cells were expanded until the end of log-phase growth and subsequently co-cultured

for 16 hrs with either K562-BCMA specific target cells, K562-Mesothelin target cells as positive control or no target cells as negative control at a 3 to 1 ratio of effector cells to target cells. Culture supernatants were harvested and IFN-gamma and IL-2 concentration was measured by specific ELISA following manufacturer instructions (R&D).

T cells expressing all four anti-pBCMA CARs produced similar levels of IFN-gamma and IL-2 when co-cultured with BCMA-expressing target cells but not with BCMA-negative target cells as shown in Figure 7A and 7B.

Cytotoxic activity of BCMA CARTs on Myeloma cell lines

The ability of pBCMA CAR T cells to kill BCMA-expressing target cells was evaluated using a ^{51}Cr release-assay. Briefly, target MM cells were labeled with ^{51}Cr (Sodium Dichromate salt), washed and co-cultured with effector pBCMA CAR T cells at different effector/target ratios. Supernatants were collected at 4-hrs, and placed into 96 well Lumaplates (Perkin Elmer). The amount of ^{51}Cr released from the labeled target cells was measured on a liquid scintillation counter (MicroBeta trilux, Perkin Elmer). Target cells incubated in medium alone or with 1% SDS were used to determine spontaneous (S) or maximum (M) ^{51}Cr release. Percentage of specific lysis was calculated as follow: 100x (cpm experimental release- cpm S release)/ (cpm M release- cpm S release).

All four pBCMA-CAR-transduced T cells were able to induce lysis of K562-BCMA cells and BCMA-expressing multiple myeloma cells lines with little activity towards the BCMA negative cell lines as shown in Figures 8A, 8B, 8C, and 8D. pBCMA-CARs with a CD8 hinge (pBCMA 3 and 4) exhibited greater cytotoxicity compared with pBCMA CARs containing the IgG4 hinge, suggesting that the hinge is an important factor in the CAR design for optimal function.

Example 3: *In vivo* evaluation of pBCMA-CARTs for Multiple Myeloma

Based upon in vitro data supporting enhanced function of pBCMA 3 and pBCMA 4 CAR-modified T cells, the anti-tumor activity of these CARTs was evaluated in a preclinical animal model of multiple myeloma using the RPMI 8226 cell line. RPMI 8226 cells were engineered to express Click-beetle Green luciferase (CB-G Luc$^+$) to track tumor progression by bioluminescent *in vivo* imaging (IVIS) and Living Image software (Perkin Elmer). 4 weeks after injection of CB-G Luc$^+$ RPMI 8226 cells were IV injected in NSG recipients, T cells expressing pBCMA 3 CAR, pBCMA 4 CAR, CD19 CAR (FMC63 anti-CD19 scFv with

human CD8 hinge, 4-1BB and CD3z cytoplasmic domain) or SS1 CAR (SS1 anti-mesothelin scFv with human CD8 hinge, 4-1BB and CD3z cytoplasmic domain) were IV injected and the tumor burden was evaluated by optical imaging as well as by the appearance of clinical signs of disease (Table 12 below). Scoring was performed as follows: 1- no clinical signs; 2- minor gait change/minor tumor mass; 3- decreased mobility/tumor mass/still ambulatory; 4- hind limb paralysis/big tumor mass/END POINT; and 5- complete limb paralysis.

Table 12. Treatment Groups and Clinical Scoring.

Groups	Scoring Day 50
BCMA3	2
BCMA4	2
SS1	3
CD19	4
CTL	4

T cells expressing either the pBCMA-3 and pBCMA 4 CAR T cells induce a significant reduction in the tumor burden of mice bearing RPMI 8226 as well as improved clinical disease activity compared with control T cells targeting mesothelin (designated SS1) or CD19 as shown in Figure 9A and 9B.

The experiments described in Examples 2 and 3 provided the rationale to identify human scFv binding domains for additional CAR constructs, which are described and assessed in Examples 4-7.

Example 4: Generating human anti-BCMA CAR constructs

Human BCMA-specific scFvs for CAR constructs were identified by 3 rounds of bead-based Bio-BCMA panning. In Arm 1, SBAL-1Sk Phage Library (8.4E13) was used. In Arm 2, SBAL-3Sk(G1+G2+G4+G5) Phage Library (1E13) was used. The phage lysates were screened for BCMA reactivity by ELISA. 319 positive hits were identified, representing 135 unique sequences. The phage sequences were converted to soluble scFv that can be expressed in *E. coli*. The *E. coli* lysates were next screened by ELISA, and the periplasm was screened by FACs. 15 hits were identified by the FACs analysis. Next, the scFvs were purified from the *E. coli* and the purified scFvs were tested by FACs. 15 scFvs were confirmed, and were designated BCMA-1, BCMA-2, BCMA-3, BCMA-4, BCMA-5, BCMA-6, BCMA-7, BCMA-

8, BCMA-9, BCMA-10, BCMA-11, BCMA-12, BCMA-13, BCMA-14, and BCMA-15. The sequences of human anti-BCMA scFv fragments (SEQ ID NOS: 39-52), are provided in Table 1 (and the name designations are provided in Table 2). Full BCMA CAR constructs (SEQ ID NOs: 99-113) were generated using the human scFv fragments (SEQ ID NOs: 39-52) in combination with the additional sequences shown in the Detailed Description, e.g., leader, CD8 hinge, CD8 transmembrane, 4-1BB intracellular domain, CD27 intracellular domain, CD28 intracellular domain, ICOS domain, CD3zeta domain (mutant), human CD3zeta domain, IgG4 hinge, Gly/Ser sequences, and/or Poly(A) sequences.

The CAR scFv fragments were then cloned into lentiviral vectors to create a full length CAR construct in a single coding frame, and using the EF1 alpha promoter for expression (SEQ ID NO: 11).

The amino acid and nucleic acid sequences of the BCMA scFv domains and BCMA CAR molecules are provided in Table 1 in the Detailed Description. Table 2 in the Detailed Description designates the nicknames for the BCMA CAR constructs with respect to the DNA ID number, also listed in Table 1.

Additional tool BCMA CAR constructs were also generated using the VH and VL sequences from PCT Publication WO2012/0163805 (the contents of which are hereby incorporated by reference in its entirety), and are based upon the results from the pBCMA3 and pBCMA4 CARs described in Examples 2 and 3. A schematic of the tool BCMA constructs (BCMA-3NP and BCMA-4NP) is shown in Figure 10A. The two constructs differ in the orientation of the VH and VL chains (Fig. 10B). The tool BCMA CAR constructs and their corresponding DNA ID are shown below.

Table 3. Tool CAR construct IDs

Nickname	Novartis ID	DNA2.0 ID
BCMA-3NP		126022
BCMA-4NP		126021

Additional BCMA CAR constructs can also be generated using the VH and VL sequences found in Table 16 in the Detailed Description. The amino acid sequences of exemplary scFv domains comprising the VH and VL domains and a linker sequence, and full-length CARs are also found in Table 16.

Production and calculation of viral titer for BCMA CAR constructs

Lentiviral supernatants were generated from 15 BCMA-specific CAR constructs obtained from scFv phage screening (Table 2). Lentiviral supernatants for 2 BCMA tool CAR constructs, BCMA-3NP and BCMA-4NP, were also generated. The tool constructs described in this example are based on the pBCMA3 and pBCMA4 constructs previously described in Examples 2 and 3.

To generate lentiviral supernatants, LentiX-293T cells were seeded on Day 0 and transfected on Day 1 with Lipofectamine 2000 transfection reagent (Life Technologies). For each construct, the plasmid DNA used was: pRSV.REV (Rev expression plasmid), pMDLg/p.RRE (Gag/Pol expression plasmid), pVSV-G (VSV glycoprotein expression plasmid), and CAR transfer vector. The transfection mixture was replaced with fresh medium on Day 2, and viral supernatant were collected on Days 3 and 4.

Viral supernatants were concentrated using Lenti-X Concentrator reagent (Clontech), and the resulting pellets were resuspended in growth medium at 1/10 to 1/100 of the original volume. Concentrated viral supernatants were aliquoted and stored at -80°C.

Calculation of viral titer was determined by transducing SupT1 cells and assessing CAR expression. SupT1 cells were transduced on Day 1 with a 3-fold serial dilution series of viral supernatants with a starting concentration of 1:300. CAR expression was assessed on Day 5 with BCMA-Fc antigen (R&D Systems) and Biotin-Protein L reagent (GenScript). Viral titer was calculated according to the following formula:

(% CAR+) x (# SupT1 cells) / (Amount of Virus (ml)) x (Dilution)

Average viral titer was calculated from dilution points in the linear range between 1 and 20% CAR-positive. Titer calculations for BCMA CAR clones are shown in Table 4.

Table 4: Titer of lentiviral supernatants from LentiX-293T cells transduced with BCMA-targeting CARs as measured by either BCMA-Fc or Protein L.

Clone	BCMA-Fc titer (TU/ml)	Protein L titer (TU/ml)
BCMA-1	1.27E+08	7.54E+06
BCMA-2	1.02E+08	1.43E+08
BCMA-4	1.46E+08	1.58E+08

BCMA-5	9.98E+07	9.64E+07
BCMA-6	1.41E+08	4.82E+06
BCMA-7	6.41E+07	5.53E+07
BCMA-8	6.15E+07	6.98E+07
BCMA-9	8.57E+07	7.75E+07
BCMA-10	6.73E+07	8.77E+07
BCMA-11	4.60E+07	5.43E+06
BCMA-12	4.88E+07	5.97E+07
BCMA-13	9.96E+07	5.52E+07
BCMA-14	9.88E+07	1.20E+08
BCMA-15	7.39E+07	7.41E+07
BCMA-3NP	5.38E+07	6.11E+07
BCMA-4NP	5.35E+07	5.37E+07

All BCMA CAR clones were detected with BCMA-Fc antigen, but detection was weaker with Biotin-Protein L for a number of clones (BCMA-1, BCMA-6, BCMA-11). Titers based on BCMA-Fc detection were used to calculate MOI for transduction in primary T cells. The BCMA CAR constructs containing human anti-BCMA scFvs described in this example are used throughout the experiments in Examples 4 and 5. The tool BCMA CAR constructs described in this example are also used in the experiments described in Examples 5, 6, and 7.

Example 5: *In vitro* characterization of tool BCMA CAR constructs

JNL reporter assay for tool BCMA CAR constructs

Jurkat-NFAT-luciferase (JNL) cells transduced with the tool BCMA CAR constructs were evaluated for activation in response to BCMA-expressing target cell lines. On Day 0, JNL cells were transduced with BCMA-3NP and BCMA-4NP. Virus concentrations were adjusted to a MOI of 3 and incubated overnight. On Day 6 following transduction, BCMA CAR-transduced JNL cells were incubated with target cells at effector-to-target (E:T) ratios ranging from 0 to 27. Target cell lines were: K562 (BCMA negative control), and BCMA positive multiple myeloma cell lines, NCI-H929, KMS26, and RPMI 8226. JNL activation was measured using Bright-Glo substrate (Promega) on Day 7. CAR expression on transduced JNL was assessed on Day 6 with BCMA-Fc antigen (Table 5). This reporter assay demonstrates that the tool BCMA-targeting CAR clones are activated in a target-specific manner (Figure 11).

Table 5: Percent CAR expression on JNL cells

	BCMA-Fc detection
Clone	% CAR+
BCMA-3NP	31.2
BCMA-4NP	41.9

Schedule for isolation, transduction and activation of primary T cells with BCMA-targeting tool CARs is shown in Table 6. On Day 0, healthy human donor PBMCs (Novartis Employee Blood Donor program) were isolated from whole blood by Ficoll extraction, and T cells were isolated from PBMC by negative selection using the Pan T Cell Isolation Kit II (Miltenyi Biotec). Isolated T cells were stimulated overnight with Dynabeads Human T-Expander CD3/CD28 beads (Life Technologies) at a 3:1 ratio of beads-to-cells. T cells were also stained to assess relative amounts of CD4+ and CD8+ cells (Figure 12).

Table 6: Schedule for T cell expansion of BCMA CAR transduced clones

Day #	*Activity*
0	Isolate and activate T cells
1	Transduce T cells (MOI=5)
2	Add medium - 0.5 ml/well
3	
4	Split 1:2
5	
6	Split 1:2 (Split UTD control 1:2.5)
7	
8	
9	Split 1:2
10	
11	De-bead and freeze aliquots

On Day 1, T cells were transduced with BCMA-3NP and BCMA-4NP. Virus concentrations were adjusted to a MOI of 5 and incubated overnight. On Day 11, transduced CART cells were de-beaded and frozen in aliquots in 90% FBS, 10% DMSO. Following transduction and expansion, T cells were again stained to assess relative amounts of CD4+ and CD8+ cells. In addition, CAR expression was assessed with BCMA-Fc antigen (Figure 13).

BCMA Proliferation Assay

BCMA CART cell proliferation in response to BCMA-expressing target cells was evaluated. CART cells were thawed on Day 0 and incubated overnight to recover. On Day 1, CART cells were labeled with CellTrace CFSE (Life Technologies) and incubated with irradiated target cells at an E:T ratio of 1:1. Dynabeads Human T-Expander CD3/CD28 beads at a bead-to-cell ratio of 3:1 were included as a positive control. On Day 5, CFSE levels were measured in CART cells (Figure 14). In addition, CART cells were stained with CD3, CD4, CD8, and BCMA-Fc antigen and measured by flow cytometry relative to CountBright Absolute Counting Beads (Life Technologies) to determine relative cell counts (Figure 15). Specific proliferation in response to BCMA observed for both BCMA-3NP and BCMA-4NP.

BCMA CART luciferase cell killing assay

BCMA CART cell killing in response to BCMA-expressing target cells was evaluated. CART cells were thawed on Day 0 and incubated overnight to recover. On Day 1, CART cells were incubated with either BCMA expressing KMS11-luciferase or MM1-S-luciferase target cells at E:T ratios ranging from 0 to 20. Loss of luciferase signal resulting from cell killing was measured using Bright-Glo substrate on Day 2 and specific lysis was calculated according to the following formula:

Specific lysis (%) = 100 - (sample luminescence / average maximal luminescence) * 100

Results of cell killing are showing in Figure 16 demonstrating tool CART clones have specific killing response.

BCMA CART CFSE cell killing assay

BCMA CART cell killing in response to BCMA-expressing target cells was evaluated. CART cells were thawed on Day 0 and incubated overnight to recover. On Day 1, target cells were labeled with CellTrace CFSE (Life Technologies) and incubated with BCMA CAR T cells at E:T ratios ranging from 0 to 10. Target cell lines were: K562-BCMA (engineered to stably express BCMA), K562 (parental line), and BCMA positive multiple myeloma cell lines, NCI-H929, KMS26, and RPMI 8226. Loss of CFSE-positive cells resulting from cell killing was measured on Day 2 by flow cytometry relative to CountBright Absolute Counting Beads (Life Technologies) to determine relative cell counts (Figure 17). Specific cell killing was observed for both BCMA-3NP and BCMA-4NP.

Based on in vitro characterization of BCMA tool CAR clones, BCMA-3NP and BCMA-4NP, were selected for in vivo evaluation in KMS11-luciferase disseminated tumor model. UTD (untransduced) T cells were selected as a negative control. The results from the *in vivo* characterization is further described in Example 5.

Example 6: *In vitro* characterization of BCMA CART

The experiments described in this example utilize CAR constructs containing human anti-BCMA scFvs from Table 1, and the tool BCMA CAR contructs.

JNL reporter assay for BCMA CAR constructs

Jurkat-NFAT-luciferase (JNL) cells transduced with BCMA CAR constructs were evaluated for activation in response to BCMA-expressing target cell lines. Small-scale viral supernatant samples were generated in HEK293T cells for transduction of JNL cells. On Day 3 following transduction, BCMA CAR-transduced JNL cells were incubated with target cells at an effector-to-target (E:T) ratio of 6:1. Target cell lines were: K562-BCMA (engineered to stably express BCMA), K562 (parental line), and BCMA positive multiple myeloma cell lines, NCI-H929 and RPMI 8226. JNL activation was measured using Bright-Glo substrate (Promega) on Day 4. CAR expression on transduced JNL was assessed on Day 7 with BCMA-Fc antigen and Biotin-Protein L reagent (Table 7). This reporter assay demonstrates that several BCMA-targeting CAR clones are activated in a target-specific manner (Figure 18).

Table 7: Percent CAR expression on JNL cells

	BCMA-Fc detection
Clone	% CAR+
BCMA-1	72.1
BCMA-2	32.0
BCMA-3	0.0
BCMA-4	49.5
BCMA-5	28.9
BCMA-6	44.4
BCMA-7	30.4
BCMA-8	32.4
BCMA-9	54.7
BCMA-10	29.5
BCMA-11	42.7

BCMA-12	23.4
BCMA-13	32.7
BCMA-14	31.8
BCMA-15	36.9
BCMA-3NP	6.7
BCMA-4NP	28.3

JNL activity was not correlated with % CAR expression. Based on BCMA-specific activation, the following BCMA CAR clones were selected for characterization in primary T cells: BCMA-1, BCMA-4, BCMA-5, BCMA-7, BCMA-8, BCMA-10, BCMA-12, BCMA-13, BCMA-14, and BCMA-15. Based on the non-specific activation observed, BCMA-6 was selected as a negative control. Based on the absence of activity observed, BCMA-9 was also selected as a negative control.

BCMA CAR transduction of primary human T cells

Schedule for isolation, transduction and activation of primary T cells with BCMA-targeting CARs is shown in Table 8. On Day 0, healthy human donor PBMCs (Novartis Employee Blood Donor program) were isolated from whole blood by Ficoll extraction, and T cells were isolated from PBMC by negative selection using the Pan T Cell Isolation Kit II (Miltenyi Biotec). Isolated T cells were stimulated overnight with Dynabeads Human T-Expander CD3/CD28 beads (Life Technologies) at a 3:1 ratio of beads-to-cells. T cells were also stained to assess relative amounts of CD4+ and CD8+ cells (Figure 19).

Table 8: Schedule for T cell expansion of BCMA CAR transduced clones

Day #	*Activity*
0	Isolate and activate T cells
1	Transduce T cells (MOI=5)
2	Add medium - 0.5 ml/well
3	
4	Split 1:3
5	
6	Split 1:2
7	
8	Split 1:2.25
9	
10	
11	De-bead and freeze aliquots

On Day 1, T cells were transduced with the following BCMA CAR clones: BCMA-1, BCMA-4, BCMA-5, BCMA-6, BCMA-7, BCMA-8, BCMA-9, BCMA-10, BCMA-12, BCMA-13, BCMA-14, BCMA-15, BCMA-3NP, and BCMA-4NP. Virus concentrations were adjusted to a MOI of 5 (Table 9) and incubated overnight.

Table 9: Calculation of T cells added per well for each clone to obtain an MOI of 5.

Clone	TU/ml	MOI:5 per well
BCMA-1	1.27E+08	39.4
BCMA-4	1.46E+08	34.3
BCMA-5	9.98E+07	50.1
BCMA-6	1.41E+08	35.5
BCMA-7	6.41E+07	78.0
BCMA-8	6.15E+07	81.4
BCMA-9	8.57E+07	58.3
BCMA-10	6.73E+07	74.3
BCMA-12	4.88E+07	102.5
BCMA-13	9.96E+07	50.2
BCMA-14	9.88E+07	50.6
BCMA-15	7.39E+07	67.6
BCMA-3NP	5.38E+07	92.9
BCMA-4NP	5.35E+07	93.5

On Day 11, transduced CART cells were de-beaded and frozen in aliquots in 90% FBS, 10% DMSO. Following transduction and expansion, T cells were again stained to assess relative amounts of CD4+ and CD8+ cells. In addition, CAR expression was assessed with BCMA-Fc antigen (Figure 20).

BCMA CART proliferation assay

BCMA CART cell proliferation in response to BCMA-expressing target cells was evaluated. CART cells were thawed on Day 0 and incubated overnight to recover. On Day 1, CART cells were labeled with CellTrace CFSE (Life Technologies) and incubated with irradiated target cells at an E:T ratio of 1:1. On Day 6, CFSE levels were measured in CART cells (Figure 21).

In addition, CART cells were stained with CD3, CD4, and CD8 and measured by flow cytometry relative to CountBright Absolute Counting Beads (Life Technologies) to

determine relative cell counts (Figure 22A, 22B, and 22C). Specific proliferation in response to BCMA observed for the following CART clones: BCMA-4, BCMA-10, BCMA-12, BCMA-13, BCMA-14, and BCMA-15.

BCMA CART killing assay

BCMA CART cell killing in response to BCMA-expressing target cells was evaluated. CART cells were thawed on Day 0 and incubated overnight to recover. On Day 1, CART cells were incubated with BCMA expressing KMS11-luciferase target cells at E:T ratios ranging from 0 to 10. Loss of luciferase signal resulting from cell killing was measured using Bright-Glo substrate on Day 2 and specific lysis was calculated according to the following formula:

Specific lysis (%) = 100 - (sample luminescence / average maximal luminescence) * 100

Results of the cell killing assay are shown in Figure 23A, comparing each BCMA CAR construct to BCMA-3NP and BCMA-4NP. These results demonstrate thatseveral CART clones (expressing the human anti-BCMA scFvs) have a greater killing response than the control BCMA-3NP and BCMA-4NP constructs. The results from select candidate BCMA CARs (BCMA-4, BCMA-9, BCMA-10, BCMA-13, and BCMA-15) are presented in graph in Figure 23B to compare the killing capacity between the candidate CARs. Untransduced T cells and T cells transduced with BCMA-4NP construct were used as negative and positive controls, respectively. The percentage of cell killing of the select BCMA CART clones (BCMA-4, BCMA-9, BCMA-10, BCMA-13, and BCMA-15) were normalized to the percent of CAR expression for each CART and presented in Figure 23C. The results show that BCMA-4, BCMA-9, BCMA-10, BCMA-13, and BCMA-15 CART clones all had cell killing capacity similar to that of BCMA-4NP.

A summary of the in vitro assays of BCMA CART clones described above is shown in Table 10. Based on the *in vitro* characterization of BCMA CART clones, BCMA-4, BCMA-10, BCMA-13, and BCMA-15 were selected for *in vivo* evaluation in KMS11-luciferase disseminated tumor model, as described in Example 7. BCMA-4NP was selected a positive control. BCMA-9 and UTD (untransduced) were selected as negative controls.

Table 10: Summary of *in vitro* characterization of BCMA CART clones

	JNL binding assay			Cell Killing	Proliferation					
	Ratio to K562			EC50	CD3 Ratio to no target					
	K562-BCMA	NCI-H929	RPMI 8226	KMS11-luc	K562	K562-BCMA	NCI-H929	KMS11-luc	RPMI 8226	
BCMA-3NP	1.39	[illegible]	1.86	0.18	1.70	[illegible]	[illegible]	[illegible]	[illegible]	BCMA-3NP
BCMA-4NP	3.15	2.27	3.04	0.12	1.00	5.02	3.52	5.41	5.53	BCMA-4NP
BCMA-1	4.00	4.85	[illegible]	[illegible]	1.35	1.56	4.07	1.86	2.98	BCMA-1
BCMA-4	4.67	3.31	[illegible]	0.13	1.30	7.07	[illegible]	[illegible]	[illegible]	BCMA-4
BCMA-5	2.34	2.34	2.40	0.21	[illegible]	1.82	1.72	1.81	1.73	BCMA-5
BCMA-6	[illegible]	[illegible]	[illegible]	0.29	2.04	3.14	3.03	2.39	3.17	BCMA-6
BCMA-7	2.85	2.38	2.77	0.15	[illegible]	1.72	1.80	1.71	1.82	BCMA-7
BCMA-8	3.17	2.67	3.87	0.14	[illegible]	2.55	2.17	2.46	2.56	BCMA-8
BCMA-9	1.56	1.29	1.54	[illegible]	1.10	1.41	4.53	1.85	2.50	BCMA-9
BCMA-10	3.29	2.70	3.26	0.16	1.31	5.86	5.57	4.20	5.80	BCMA-10
BCMA-12	3.17	2.78	3.56	0.22	[illegible]	2.93	2.58	2.76	3.27	BCMA-12
BCMA-13	3.74	2.69	3.88	[illegible]	[illegible]	3.47	3.46	3.20	3.48	BCMA-13
BCMA-14	2.81	2.65	3.31	[illegible]	1.24	4.12	3.88	3.42	3.83	BCMA-14
BCMA-15	2.91	2.79	3.49	[illegible]	1.13	3.94	4.08	3.51	3.73	BCMA-15

Proliferation										
CD8 Ratio to no target					CD4 Ratio to no target					
K562	K562-BCMA	NCI-H929	KMS11-luc	RPMI 8226	K562	K562-BCMA	NCI-H929	KMS11-luc	RPMI 8226	
1.54	5.79	7.08	[illegible]	5.83	1.79	8.42	10.89	8.45	10.82	BCMA-3NP
1.24	3.00	4.31	5.36	3.49	1.65	5.50	9.38	5.04	9.05	BCMA-4NP
1.13	1.81	4.14	1.56	3.58	1.51	1.57	5.57	1.24	2.43	BCMA-1
1.18	5.26	7.42	4.74	6.19	1.50	8.21	9.95	8.00	10.12	BCMA-4
[illegible]	0.99	1.11	1.27	1.25	0.57	2.18	2.23	1.49	2.15	BCMA-5
2.01	2.13	2.28	2.23	2.39	4.39	4.70	4.34	2.60	4.35	BCMA-6
0.77	1.08	1.18	1.35	1.18	[illegible]	2.17	2.29	1.08	1.81	BCMA-7
0.81	1.59	1.41	1.83	1.81	1.15	3.59	2.98	3.11	3.38	BCMA-8
1.05	1.48	4.79	1.55	2.78	1.31	1.33	4.45	1.48	2.34	BCMA-9
1.09	3.01	4.60	3.84	4.33	1.37	[illegible]	7.06	4.35	3.91	BCMA-10
[illegible]	1.61	1.78	2.11	2.12	1.32	3.42	3.41	2.94	3.65	BCMA-12
[illegible]	2.34	2.53	2.78	3.90	1.26	5.40	5.06	3.04	4.44	BCMA-13
1.30	2.65	2.73	2.83	3.03	1.46	5.73	5.07	3.97	4.84	BCMA-14
[illegible]	1.88	2.42	2.78	2.91	1.28	4.87	4.82	3.52	4.24	BCMA-15

Example 7: *In vivo* characterization of BCMA CART

KMS-11 is a human multiple myeloma cell line derived from an IgGκ pleural effusion, and can be grown as a xenograft in immune compromised mice. This xenograft will mimic disease in the bone marrow as seen in humans, establishing a model with which to test the efficacy of therapies on multiple myeloma in the bone. These mice can be used to test the efficacy of chimeric antigen receptor (CAR) T cells specific for cellular markers found on plasma cells and multiple myeloma cells, such as the B Cell Maturation Antigen (BCMA). KMS-11 cells were tagged with a firefly luciferase reporter gene and used in an orthotopic model of multiple myeloma in NOD.Cg-*Prkdc*^{scid}*Il2rg*^{tm1Wjl}/SzJ (NSG) mice to test the efficacy of CAR T cells specific for BCMA.

BCMA expression was tested on KMS-11 cells and these cells were used in *in vitro* assays to look at the ability of BCMA-specific CAR T cells to recognize and respond to the target. *In vivo* KMS-11 cells grow when implanted intravenously via the tail vein and growth is limited primarily to the bone marrow. One week after the tumor cells are implanted, the disease shifts fully to the bones and begins to grow at an exponential rate. Left untreated, mice will start to display clinical symptoms and hind limb paralysis 5-6 weeks after tumor implantation. Tool BCMA CAR T cells were first tested in this model in an efficacy study to determine if the model is an appropriate *in vivo* model to test the efficacy and anti-tumor activity of BCMA CAR T cells. Following this, lead BCMA scFvs from an *in vitro* screen have been tested in this *in vivo* model and are now being confirmed in a repeat efficacy study.

Materials and Methods:

KMS-11 cell line: The KMS-11 human multiple myeloma cell line was developed from the pleural effusion of a patient with multiple myeloma. The cells were then tagged with firefly luciferase. These suspension cells grow in RPMI supplemented with 10% heat inactivated fetal bovine serum.

Mice: 6 week old NSG (NOD.Cg-*Prkdc*^{scid}*Il2rg*^{tm1Wjl}/SzJ) mice were received from the Jackson Laboratory (stock number 005557). Animals were allowed to acclimate to the Novartis NIBRI animal facility for at least 3 days prior to experimentation. Animals were handled in accordance with Novartis ACUC regulations and guidelines.

Tumor implantation: KMS-11-luc cells were grown and expanded *in vitro* in RPMI supplemented with 10% heat inactivated fetal bovine serum. The cells were then transferred to a 15 ml conical tube and washed twice with cold sterile PBS. KMS-11-luc cells were then counted and resuspended at a concentration of $10x10^6$ cells per milliliter of PBS. The cells were placed on ice and immediately (within one hour) implanted in the mice. KMS-11 cells were injected intravenously via the tail vein in a 100 µl volume, for a total of $1x10^6$ cells per mouse.

CAR T cell dosing: Mice were administered $5x10^6$ T cells 7-8 days after tumor implantation. Cells were partially thawed in a 37 degree Celsius water bath and then completely thawed by the addition of 1 ml of cold sterile PBS to the tube containing the cells. The thawed cells were transferred to a 15 ml falcon tube and adjusted to a final volume of 10 mls with PBS. The cells were washed twice at 1000rpm for 10 minutes each time and then counted on a hemocytometer.

The CAR T cells were normalized for CAR transduction so that each group has the same percentage of CAR^+ T cells. The total of the $5x10^6$ cells were then resuspended at a concentration of $50x10^6$ cells per ml of cold PBS and kept on ice until the mice were dosed. The mice were injected intravenously via the tail vein with 100 µl of the CAR T cells for a dose of $5x10^6$ T cells per mouse.

Five to seven mice per group were treated either with 100 µl of PBS alone (PBS), untransduced T cells (Mock), tool BCMA CAR T cells (BCMA-3NP or BCMA-4NP), or novel BCMA CAR T cells (BCMA-4, BCMA-9, BCMA-10, BCMA-13, BCMA-15). The T cells were all prepared from the same human donor in parallel.

Animal monitoring: The health status of the mice was monitored daily, including twice weekly body weight measurements. The percent change in body weight was calculated as $(BW_{current} - BW_{initial})/(BW_{initial}) \times 100\%$. Tumor burden was monitored twice weekly by bioluminescent imaging. Mice were intraperitoneally injected with D-luciferin 10 minutes prior to anesthetizing and imaging the mice with a Xenogen. Disease burden was calculated by calculating the bioluminescence of the tumor cells (photons/second).

Bioluminescence Analysis: Percent treatment/control (T/C) values were calculated using the following formula:

$$\% \text{ T/C} = 100 \times \Delta T/\Delta C \text{ if } \Delta T \geq 0 ;$$

$$\% \text{ Regression} = 100 \times \Delta T/T_{initial} \text{ if } \Delta T < 0 ;$$

where T = mean bioluminescence of the drug-treated group on the final day of the study; $T_{initial}$ = = mean bioluminescence of the drug-treated group on initial day of dosing; ΔT = = mean bioluminescence of the drug-treated group on the final day of the study – = mean bioluminescence of the drug treated group on the initial day of dosing; C = = mean bioluminescence of the control group on the final day of the study; and ΔC = = mean bioluminescence of the control group on the final day of the study – = mean bioluminescence of the control group on the initial day of dosing.

T/C values in the range of 100% to 42% are interpreted to have no or minimal anti-tumor activity; T/C values that are ≤ 42% and > 10% are interpreted to have anti-tumor activity or tumor growth inhibition. T/C values ≤ 10% or regression values ≥ -10% are interpreted to be tumor stasis. Regression values < -10% are reported as regression.

Peripheral blood FACS analysis: T cells in the peripheral blood of the mice were also monitored. Mice were bled weekly via the tail vein into EDTA coated tubes that were kept on ice. 10-20µl of blood was plated from the tubes into 96 well plates on ice. Red blood cells were lysed with ACK red blood cell lysis buffer (Life Technologies, catalog number A10492-01) and then washed twice with cold PBS. The cells were incubated with an Fc blocking mix of human and mouse Fc block (Miltenyi Biotec, catalog numbers 130-059-901 and 130-092-575) for 30 minutes and then incubated with anti-mouse CD11b antibody (BD Biosciences, catalog number 557960), anti-human CD4 antibody (BD Biosciences catalog number 563550), anti-human CD8 antibody (BD Biosciences catalog number 560347), and BCMA-Fc antibody (R&D Systems, catalog number 193-BC-050) , followed by an Ig secondary (Jackson ImmunoResearch). The cells were fixed with a 2% paraformaldehyde solution for 20 minutes, washed and stored in PBS + 2% FBS overnight prior to analysis on a BD Fortessa, followed by further analysis using the FlowJo FACS analysis software. The cells were analyzed to determine the number of CAR^+ $CD4^+$ and $CD8^+$ T cells per milliliter of blood in the KMS-11-luc tumor-bearing NSG mice. T cell numbers in the blood are reported as the mean ± standard error of the mean (SEM).

Results:

The anti-tumor activity of the tool BCMA CAR T cells (BCMA-3NP and BCMA 4-NP) were evaluated and directly compared in the KMS-11 model of human multiple myeloma. Following tumor implantation on day 0, mice were randomized into treatment groups and treated with $5x10^6$ T cells intravenously on day 7. Multiple myeloma disease burden and animal health were monitored until animals achieved endpoint. The mice in all the groups were euthanized on day 14 post-CAR T cell dosing (day 21 post-tumor implantation) when disease burden in the control groups nearing maximum luminescence via imaging.

A clear difference in disease burden can be seen between the control groups and the groups treated with either of the tool CAR T cells with $P<0.01$ on day 14 post-CAR T cell dosing. Both of the tool BCMA CAR T cells demonstrate a similar ability to control human multiple myeloma growth in NSG mice. The % T/C value for the mock transduced T cell group is 212.13%, demonstrating that the mock transduced T cells have no anti-tumor activity.

The percent delta T/C values for the BCMA-3NP and BCMA-4P groups are 1.10% and 2.17% respectively, demonstrating tumor stasis after treatment with the tool BCMA CAR

T cells. The bioluminescence imaging results are shown in Figure 24. The PBS treatment group, which did not receive any T cells, demonstrates baseline KMS-11 tumor growth kinetics in intravenously implanted NSG mice. The Mock treatment group received untransduced T cells that underwent the same *in vitro* expansion process as the CAR T cells. These cells serve as a T cell control to show the non-specific response of the T cells in this tumor model. Both the PBS and Mock transduced T cell treatment groups demonstrate continuous tumor progression throughout the experiment. Both the tool BCMA CAR T cells control the progression of disease after the $5x10^6$ T cell injections.

Following confirmation that the KMS-11-luc model responds to targeting via BCMA CAR T cells, a study to evaluate novel scFv leads was initiated. Following tumor implantation, mice were again randomized into treatment groups and treated with $5x10^6$ T cells intravenously on day 7. Multiple myeloma disease burden and animal health were monitored until animals achieved endpoint. The mice in each of the groups were euthanized when disease burden in the group neared maximum luminescence via imaging.

A clear difference in disease burden can be seen between the control groups and some of the groups treated with the BCMA CAR T cells. The tool BCMA CAR T cells (BMCA-4NP) did not control the KMS-11 tumor growth as they had been shown to do so previously. However, some of the novel BCMA CAR T cells did show varying levels of efficacy in this multiple myeloma model. The % T/C values calculated at the endpoint for each group show stasis in tumor growth for the BCMA-10 and BCMA-13 groups. The mock transduced T cell group has a %T/C value of 61.56%, demonstrating that the mock transduced T cells have minimal to no anti-tumor activity. The percent delta T/C values for the BCMA-4P group is 32.03%, demonstrating some minimal anti-tumor efficacy after treatment with the tool BCMA CAR T cells. Both the BCMA-10 and BCMA-13 groups show stasis in tumor growth with T/C values of 0.07% and 6.04% respectively. The BCMA-4 shows an initial control in tumor growth, but with only one T cell dose given to each group, the tumors in this group start to grow out. The bioluminescence imaging results from a first experiment are shown in Figures 25A. The PBS treatment group, which did not receive any T cells, demonstrates baseline KMS-11 tumor growth kinetics in intravenously implanted NSG mice. The Mock treatment group received untransduced T cells that underwent the same *in vitro* expansion process as the CAR T cells. These cells serve as a T cell control to show the non-specific response of the T cells in this tumor model. Both the PBS and Mock transduced T cell treatment groups

demonstrate continuous tumor progression throughout the experiment. Among the BCMA CAR T cell groups, BCMA-4, BCMA-10, and BCMA-13 show anti-tumor activity, while the tool BCMA CAR T cells (BCMA-4NP) and BCMA-9 and BCMA-15 show no anti-tumor efficacy. A second experiment was performed and the bioluminescence imaging results are provided in Figure 25B. Mice receiving untransduced T cells show the baseline KMS-11 tumor growth kinetics. BCMA-4NP* represents the results from the BCMA-4NP CART clones in the first experiment. In the second experiment, BCMA-10, BCMA-13, and BCMA-15 showed robust anti-tumor activity.

In addition to monitoring the disease burden via bioluminescence, the CAR^+ T cell numbers in each group was also monitored vial peripheral blood FACS analysis. The FACS results of this study are shown in Figure 26. The groups that show anti-tumor effects on the KMS-11 tumors also show $CD4^+CAR^+$ and $CD8^+CAR^+$ T cells expanding in the peripheral blood. The BCMA-4, BCMA-10, and BCMA-13 groups show a peak of $CD4^+CAR^+$ proliferation between days 10 and 20 post T cell treatment. These same groups also show a prolonged $CD8^+CAR^+$ T cell expansion.

The anti-tumor activity of novel BCMA CAR transduced T cells was assessed in an efficacy study in NSG mice bearing a xenograft model of human multiple myeloma. These studies show that the KMS-11-luc model recapitulates human multiple myeloma in the NSG mouse and is capable of being targeted by BCMA CAR T cells (Figure 24). Following the confirmation that this model is suitable to test BCMA CAR T cells, novel human BCMA CARs were tested in an efficacy study. This study demonstrated that several of the novel BCMA CARs (BCMA-4, BCMA-10, and BCMA-13) mounted an anti-tumor response in a xenograft model of multiple myeloma (Figures 25A). The tumor experiment was repeated, testing BCMA-4, BCMA-10, BCMA-13, and BCMA-15. BCMA-4, BCMA-10, BCMA-13, and BCMA-15 demonstrated anti-tumor efficacy by inhibiting or reducing tumor growth for at least 4 weeks (28 days) after implantation (Figure 25B).

In addition, the anti-tumor response correlates with the expansion of $CD4^+CAR^+$ and $CD8^+CAR^+$ T cells in the peripheral blood of these mice (Figures 26A, B, C, and D). No anti-tumor efficacy was observed for any of the BCMA CARs when this T cell expansion is not observed. BCMA-10, which shows the greatest anti-tumor efficacy in this model, also shows the most sustained $CD8^+CAR^+$ T cell expansion. The BCMA-4, BCMA-10 and BCMA-13 groups all show a significant change in tumor growth as compared to the control groups. The

lack of efficacy seen with the tool BCMA CAR (BCMA-4NP) and BCMA-9 and BCMA-15 in the first tumor experiment (Figure 25A) correlates with a lack of T cell expansion in the peripheral blood in the mice in these groups. Similarly, the lack of efficacy seen with BCMA-4NP in the second tumor experiment (Figure 25B) correlates with the lack of T cell expansion in the peripheral blood in the mice.

Terminal bone marrow and spleen samples were also analyzed at the end of the *in vivo* tumor experiment to determine if the CART clones that demonstrated anti-tumor efficacy show a difference in being able to establish a bone marrow population compared to the groups that did not show anti-tumor efficacy. The number of CAR-expressing CD4+ and CD8+ T cells was determined in the bone marrow (Figures 27A and 27C) and the spleen (Figures 27B and 27D) of the mice from the first experiment. The results show that administration of BCMA-9 CART resulted in the highest number of CAR+ T cells (both CD4+ and CD8+ T cells) in the bone marrow and spleen, indicating that BCMA-9 CART cells undergo efficient expansion *in vivo*, but does not have killing capacity, or anti-tumor activity. BCMA-10 CART cells showed the next most consistent establishment of T cells in the bone marrow and spleen. BCMA-4 and BCMA-15 CART cells were also found in the spleen.

Example 8: Identifying lead BCMA CAR constructs for therapy

To identify the lead BCMA CAR constructs, the results of several *in vitro* and *in vivo* assays. The experimental assays, the Examples in which the details of the assays are described, and the number of lead BCMA CARs resulting after analysis of the assay are summarized in the following table (Table 13). The results of the assays were analyzed in the order as listed in Table 13 to select the candidate BCMA CARs that exhibited specificity, expression in immune effector cells, and *in vitro* and/or *in vivo* activity.

Table 13. Assays for selecting BCMA CARs

Assay	Example where assay is described	Criteria	BCMA CARs (out of 15)
CAR expression (Jurkat and/or primary T cells lentivirally transduced)	Examples 5 and 6	Yes	14
JNL NFAT reporter activation	Example 5	> 2-fold over negative control	10
T-cell expansion (Cell size, total cell count)	Examples 5 and 6	Size: 10 microns Cell count: > 20-fold over T =0	10

		cell number	
T-cell proliferation (CFSE stained cells FACS)		≥ 1 log shift relative to negative control	10
Target cell killing (CFSE or luciferase)	Examples 5 and 6	> 90% killing at E:T 3-fold < negative control	7
Tumor regression (single dose administration; 1.5 x 10^6 CAR+ T cells)	Example 7	Sustained tumor regression > 2 weeks Evidence of CAR+ T cell expansion	4 or 2
Lentiviral titer	Example 8	Reproducibly high viral titers	4 or 2

Based on *in vitro* assays, e.g., lentivirally transduced CAR expression, JNL NFAT activation, T cell expansion, T cell proliferation, and target cell killing (as described in Examples 5, 6 and 7), 7 BCMA CARs were identified as lead CARs to be tested for therapeutic efficacy *in vivo*, and 5 BCMA CARs (BCMA-4, BCMA-9, BCMA-10, BCMA-13, and BCMA-15) were tested in Example 8. As described in Example 8, BCMA-4, BCMA-10, BCMA-13, and BCMA-15 all demonstrated anti-tumor efficacy, with BCMA-10 and BCMA-13 reproducibly demonstrating anti-tumor efficacy in two separate *in vivo* experiments.

Lentiviral titer was compared between the candidate BCMA CARs after automated viral production and automated transduction of SupT1 cells. Two independent lentiviral titer assays were run. The first titer test run analyzed two independent DNA preps (A and B) of BMCA-4, BCMA-10, BCMA-13, and BCMA-15 CARs. The second titer test run analyzed three independent DNA preps (A, B and C) of BMCA-4, BCMA-10, BCMA-13, and BCMA-15 CARs. Viral production was produced in an automated 96-well format. SupT1 cell transduction was also performed via an automated 96-well format. CAR expression was manually analyzed by FACs and the results are shown in Figures 28A and 28B. All tested BCMA CARs showed comparable levels and consistency of viral titer.

Thus, taking together the results from the *in vitro* and *in vivo* experiments as outlined in Table 13, BMCA-4, BCMA-10, BCMA-13, and BCMA-15 were identified as having met the criteria for each assay and are good prospects for further testing for therapeutic use. When more stringent criteria was used in the tumor regression analysis, in which only CAR constructs that reproducibly demonstrated anti-tumor efficacy in both experiments were analyzed further, then BCMA-10 and BCMA-13 were identified for further therapeutic testing.

Example 9: Characterization of lead BCMA CAR constructs

Additional assays were performed to characterize properties of the lead BCMA CAR constructs BMCA-4, BCMA-10, BCMA-13, and BCMA-15 CARs that have demonstrated *in vitro* and *in vivo* efficacy in various assays described in Examples 5-8. Sequence alignment of BCMA-10 and BCMA-13 showed that the two CARs have identical heavy chain CDRs and high homology in the light chain CDRs. A competition assay was performed between four lead candidates BMCA-4, BCMA-10, BCMA-13, and BCMA-15 CARs and BCMA-4NP (tool CAR) as the control. BCMA-4NP was incubated with BCMA substrate, and binds between 50 and 300 seconds after incubation, as shown in Figure 29. The four BCMA CAR constructs are added and binding to the substrate was monitored. As shown in Figure 29, all four BCMA CAR constructs were competitive with the BCMA-4NP control, indicating that all four candidate BCMA CARs bind to the same epitope as the BCMA-4NP tool CAR. At the given concentrations, if the candidate CARs were binding to a different epitope, the expected RU change would be about 70 RU. The small RU change observed during binding of the candidate BCMA CARs was due to the slight dissociation of the BCMA-4NP control sample from BCMA.

Antibody affinity was also assessed for the candidate BCMA CARs: BCMA-4, BCMA-10, BCMA-13, and BMCA-15. The results are shown in Figure 30, and summarized in the table below.

Table 14. BCMA CAR binding affinity

Sample	Fit	ka	kd	KD
BCMA-10	1:1 Binding	7.10E+04	2.39E-03	33.6
BCMA-13	1:1 Binding	6.56E+04	1.61E-03	24.5
BCMA-15	1:1 Binding	2.01E+05	1.87E-03	9.3
BCMA-4	1:1 Binding	6.17E+05	6.00E-04	1.0
BCMA-4NP	1:1 Binding	1.58E+06	1.72E-04	0.1

BCMA-10 and BCMA-13 have similar affinities and are the lowest affinities of the tested candidates.

Selective binding of the candidate BCMA CARs was also tested. BCMA is one receptor in the TNF receptor family, includes closely related family members BaffR and TACI. BCMA has about 41% homology to BaffR and about 22% homology to TACI. T cells expressing the candidate BCMA CARs BCMA-4, BCMA-10, BCMA-13, and BCMA-15 were

incubated with recombinant BCMA, BaffR, or TACI fused to Fc regions. Binding was assessed by staining CAR+ cells (Figure 31). The results indicate that specific binding was only observed between all of the BCMA-expressing T cells and recombinant BCMA-Fc, demonstrating that the BCMA CAR constructs selectively bind to BCMA.

Example 10: BCMA expression in the brain

The tissue microarray results shown in Table 11 indicated that by immunohistochemical analysis, BCMA expression was detected in the cerebellum. Human and non-human primate formalin fixed paraffin embedded (FFPE) brain tissues were stained with anti-BCMA antibodies, e.g., USBio rabbit polyclonal antibody (0807-50G) raised to a BCMA intracellular epitope, and J6MO rabbit chimera antibody recognizing a BCMA extracellular epitope. Staining with the UsBio rabbit polyclonal antibody in non-primate human (cynomolgus macaque) brain tissue resulted in positive staining of the cerebellar climbing fibers (Figure 32A) and the cell bodies in the inferior olivary nucleus (Figure 32B) of the cerebellum. Staining of non-human primate brain tissue with J6MO resulted in BCMA positive staining only in the inferior olivary nucleus (Figure 32C; Ig control staining in Figure 32E). Similarly, staining of human brain tissue with J6MO also resulted in BCMA positive staining only in the inferior olivary nucleus (Figure 32D; Ig control staining in Figure 32F).

The immunohistochemistry results were confirmed by RNA analysis. In situ hybridization of non-human primate and human brain tissue was performed. Both the cerebellum and medulla oblongata was BCMA negative by mRNA detection by in situ hybridization (Figures 33A and 33B). Quantitative PCR was also performed on cerebellum, medulla oblongata, stomach, and kidney tissues from non-human primate (cynomolgus macaque) and human. The qPCR results indicate that BCMA mRNA was not detected in the cerebellum and the medulla oblongata of human (Figure 33C) or non-human primate (Figure 33D). The potential discrepancy between the immunohistochemical and RNA analysis may be due to the different BCMA splice variants known in the art (Smirnova et al., *Mol Immunol*, 2008, 45:1179-83).

RNAseq analysis, which would detect all BCMA isoforms and splice variants, was performed on normal tissues. The results show that little or no expression of BCMA was detected by RNAseq in normal tissue (Figure 33E).

Further analysis is performed to determine whether the BCMA detected protein would be accessible to BCMA CART cells, and the implications for BCMA CART therapy. PCR probes are redesigned and BCMA splice variant expression is re-assessed. Single cell RNAseq in cerebellum samples is performed. Confocal microscopy analysis is performed to visualize intracellular staining. Mice are also evaluated for effects on the brain in efficacious CARTs, e.g., BCMA-10 and BCMA-13. To prevent potential trafficking of BCMA CART cells to the brain, natalizumab can be administered to subjects.

Example 11: BCMA CART therapy in relapsed/refractory myeloma

This example provides a single cohort, open-label pilot study to assess the safety and feasibility of infusion of autologous T cells expressing BCMA-specific CARs in relapsed and/or refractory multiple myeloma. The BCMA-CARs comprise tandem TCRζ and 4-1BB (TCRζ /4-1BB) costimulatory domains, and the T cells expressing the BCMA-CARs are referred to as BCMA CAR T cells.

Study Objectives

The primary objective of the study is to determine the safety and tolerability of BCMA CAR T cells in MM patients. The secondary objectives include: describe outcomes, including response rates, minimal residual disease (MRD) rates, progression-free and overall survival; and assess the feasibility of manufacturing BCMA CAR T cells. The exploratory objectives include: characterize BCMA CAR T cells with respect to their expansion, persistence, homing, phenotype and function; evaluate for development of cellular and/or humoral immunity against BCMA CAR T cells; evaluate effect of BCMA CAR T cells on B cell and plasma cell compartments, including immunoglobulin levels; determine the impact of BCMA CAR T cells on systemic soluble immune factors in patients; assess BCMA expression on MM cells pre- and post-treatment; and evaluate safety and efficacy of re-treatment with BCMA CAR T cells in patients who progress after prior clinical benefit

Study Duration

The duration of active intervention and monitoring is approximately 2 years. After 2 years, monitoring for delayed adverse events will transition to a separate long term follow-up protocol in accordance with FDA guidelines. The protocol will require approximately 12-18 months to complete enrollment.

Diagnosis and Main Inclusion Criteria

Up to 12 evaluable subjects will be enrolled.

Inclusion criteria include adult patients aged >18 with relapsed and/or refractory multiple myeloma after at least 3 prior lines of therapy that must include a prior alkylator, a proteasome inhibitor (PI) and immunomodulatory drug (IMiD) (or 2 priors if double-refractory to an IMiD (immunomodulatory drug, thalidomide and lenalidomide), and proteasome inhibitor). The patients have relapsed, defined as meeting IMWG (International Myeloma Working Group) criteria for PD) or are refractory, as defined as achieving <PR) after the most recent regimen. The patients have a limited prognosis (≤2 year expected survival) with currently available therapies.

Study product, Dose, Route, Regimen

Single infusion of BCMA CAR T cells administered by intravenous infusion. Cohort 1 will receive 1-5x10^8 BCMA CAR T cells alone, calculated as a range of 2-50% transduced cells in total cells (The cell dose in Cohort 1 may be decreased to 1-5x10^7 BCMA CAR T cells (Cohort -1) if there is unexpected severe toxicity). Cohort 2 will receive cyclophosphamide (cytoxan) 1.5 g/m^2, administered by i.v. infusion, 1-3 days prior to infusion of 1-5x10^7 BCMA CAR T cells. Cohort 3 will receive cyclophosphamide 1.5 g/m^2, administered by i.v. infusion, 1-3 days prior to infusion of 1-5x10^8 BCMA CAR T cells.

Based on the total volume to be infused and the recommended infusion rate of 10-20mL per minute. The dosage and regimens for each cohort is summarized in the table below and a schematic diagram is shown in Figure 34.

Table 15. Summary of cohorts and dosages

Cohort	Lymphodepleting chemo	BCMA-CAR T cell dose
-1	-	1 to 5 x 10^7
1 (n=3)	-	1 to 5 x 10^8
2 (n=3)	Cytoxan 1.5 g/m^2	1 to 5 x 10^7
3 (n=6)	Cytoxan 1.5 g/m^2	1 to 5 x 10^8

To prevent potential trafficking of T-cells to the brain, patients can be administered natalizumab (TYSABRI®).

Patient Monitoring

Tumor response will be measured by serum and urine protein electrophoresis and immunofixation; bone marrow biopsy; and imaging if skeletal lesions are present prior to

treatment. Neural exams will also be performed before and after therapy to ensure no neural changes.

Statistical Methodology

The statistical analysis will be primarily descriptive in keeping with the exploratory nature of the study. Descriptive statistics will be applied to determine the relative engraftment, persistence and trafficking of the study drug components to blood and bone marrow. All adverse events will be described and exact 95% confidence intervals will be produced for adverse event rates, both overall and within major categories. Analysis of other secondary endpoints such as anti-tumor activity will also be primarily descriptive and may include summary statistics such as means and standard deviations or Kaplan-Meier curves for survival information.

Example 12: Cytokine secretion from CART cells

The ability of CART cells to secrete cytokines in response to target was determined. CART cells containing BCMA-10 CAR or untransduced T-cells were co-cultured with BCMA-positive (KMS11-luc) or BCMA negative (U87-luc) target cells, and the secretion of IL-2, IFNγ, and TNFα into the media was measured. Specifically, thawed CAR T cells containing either BCMA-10 CAR or untransduced were co-cultured with target cells for 20 h at an effector:target ratio of 2.5:1. Target cells included BCMA positive luciferized KMS-11 (KMS11-luc) or BCMA negative luciferized U87 cells (U87-luc). Effector cells were cultured in 96-well U-bottom plates with $3x10^4$ target cells in a total volume of 200 µL/well in complete T cell media. After 20 h, supernatants were removed from the cultures, and IFNγ, IL-2, and TNFα secretion were quantified by cytometric bead array (BD Bioscience) on FACS according to manufacturer's instructions. Measurements were in duplicate. Error bars represent the standard deviation (Figures 35A-35B). The results show that the BCMA-10 CARTs but not untransduced T-cells were stimulated to produce cytokines by BCMA-expressing but not BCMA-negative target cells (Figures 35A-35B).

Example 13: Function of BCMA-CART in multiple myeloma

Multiple Myeloma (MM) is a malignancy of plasma cells in the bone marrow with clinical features that include anemia, skin lesions, bone tenderness or pain, tiredness, osteolytic lesions, hypercalcemia, kidney failure and recurrent bacterial infection as most

common. Despite the fact that recent treatments with drugs such as lenalidomide produce a significant increase in survival of relapsed MM, the disease is almost always incurable. The median 5-year survival rate is about 35%. Due to poor prognosis, an effective targeted therapy is needed.

Treatments using T-cells engineered to express chimeric antigen receptors (CAR) can result in promising immunotherapies for hematologic malignancies such as ALL. CARs contain a fusion protein that recognizes a cell-surface target protein expressed on a tumor cell. Differential gene expression studies have identified B-cell maturation antigen (BCMA, CD269) as a highly specific target antigen for malignant plasma cells and normal plasma cells; thus, BCMA is a potentially useful target antigen for CAR T cell therapy. See, e.g., Carpenter et al. Clin Cancer Res. 19.8(2013):2048-60.

BCMA is a member of the TNF-receptor superfamily. The protein is encoded by *TNFRSF17* gene. BCMA is expressed in mature B lymphocytes. It binds to the tumor necrosis factor (ligand) superfamily, member 13b (TNFSF13B/TALL-1/BAFF), APRIL and to various TRAF family members. Interaction with their ligands leads to NF-kappaB and MAPK8/JNK signals that are linked to B cell development, long term plasma survival, and cell proliferation.

This example describes a preclinical study to evaluate the *in vitro* and *in vivo* function of huBCMA-BBz CAR-transduced T cells (CART-BCMA or BCMA-CART) that incorporates the BCMA10 scFv.

Materials

T cells. T cells from healthy donors were obtained from the University of Pennsylvania CFAR Human Immunology Core (Philadelphia, PA). Cells were prepared from the leukapheresis of healthy volunteer donors.

Medium. RPMI medium (Gibco) supplemented with 10% Fetal Bovine serum and filtered (Valley Biomedical), 2mM GlutaMax, (Invitrogen), 10mM HEPES (Invitrogen), 100U/ml Pencillin and 100 ug/ml Streptomycin (Gibco) was used.

CD3/28 beads. CD3/28 beads (GMP-grade) were manufactured by Clinical Cell and Vaccine Production Facility at University of Pennsylvania.

Plasmids. The huBCMA-BBz CAR construct cloned in the pELPS lentiviral vector NVP- MCM998 was generated by Novartis.

Antibodies. The antibodies, goat anti-human BCMA PE labeled (Biolegend cat# 357504), and streptavidin (BD Biosciences), were used to detect BCMA expression on

multiple myeloma cell lines. For CAR T cell expression, BCMA fc fusion protein (R&D Systems, cat#193-BC-050) was used followed by anti-human IgG fc-PE antibody (Biolengend, cat# 409304).

PBS. PBS was from Gibco.

Lentiviral package. PCL USUG, PRSV Rev, PGAG pol plasmids (Nature Technology corp. cat# NTC RP20) were used for huBCMA-BBz lentiviral preparation by transfecting with Lipofectamine 2000 (Invitrogen Cat# 11668027) on 293T cells.

Cell lines. Human embryonic kidney 293T cells (ATCC cat# CRL-3216) were used for lentiviral preparation. Multiple Myeloma cell lines RPMI 8226 (ATCC cat# CCL-155), MM1S (ATCC cat# CRL-2974), U266 (ATCC cat# CRL-3216), NCI H929 (ATCC cat# CRL-9068) and OPM2 (DSMZ cat# ACC-50); and K562 (ATCC cat# CCL-256), or K562- BCMA cells (BCMA Lentiviral vector from Genecopoeia cat# Lv105) were used for functional experiments on CART-BCMA cells.

Methods

Lentiviral production protocol and titer determination. 293T cells were seeded at 8.10^6 cells/per flask in a T150 flask (Corning Costar Cat. #430825) with RPMI1640 medium (Gibco Cat. #11875-080) supplemented with 10% FBS (ATCC cat # 30-2020) and strep/penicillin (Invitrogen cat # 10378-016) and transfected with packing plasmids mix (Nature Technology corp.) plus huBCMA-BBz encoding pELPS lentiviral vector for 24hrs. The resulting viral preparation was stored at -80°C. Recombinant lentivirus was titered on CD4 T.

Transduction protocol. T cells obtained from the Human Immunology Core were washed once in media, re-suspended at 10^6 cells/ml, and stimulated with CD3/28 beads at a cell:bead ratio of 1:3. Lentivirus transduction was performed on day 2 by mixing the lentivirus vector into the cell cultures at an MOI of 3.

T cell expansion. Stimulated T cells were fed and split every 2-3 days to $0.8x10^6$ cells/ml for 7-9 days or until cells were rested as determined by decreased rate of cell division and a decrease in mean cellular volume to < ~300fl.

Cell cultures. Multiple Myeloma cell lines and K562, K562 BCMA cell lines were cultured in RPMI with 10% FBS and antibiotics.

Cell counting. Cells were counted every 3 days during the expansion by gently mixing cultures and collecting 40ul of cells from culture volume and placed into accuvettes (Beckman

Coulter) with 20ml Isoton II Diluent Buffer for counting using a Coulter Multisizer 3 (Beckman Coulter). The results of this test (absolute cell count and cell volume) were used to determine cell concentration, total cell numbers, growth rates, and dilution volumes.

^{51}Cr release-assay. The ability of CART-BCMA cells to kill BCMA-expressing target cells was evaluated using a ^{51}Cr release-assay. Briefly, target K562-BCMA cells (or control K562 cells) and multiple myeloma cell lines were labeled with ^{51}Cr (Sodium Dichromate salt), washed and co-cultured with effector CART-BCMA or control non-transduced T cells (NTD) at different effector/target ratios. Supernatants were collected a 4-hrs, and placed into 96 well Lumaplates (Perkin Elmer). The amount of ^{51}Cr released from the labeled target cells was measured on a liquid scintillation counter (MicroBeta trilux, Perkin Elmer). Target cells incubated in medium alone or with 1% SDS were used to determine spontaneous (S) or maximum (M) ^{51}Cr release. Percentage of specific lysis was calculated as follow: 100x (cpm experimental release- cpm S release)/ (cpm M release- cpm S release).

CAR detection on transduced T cells. To evaluate transduction of CART-BCMA, T cells were stained with BCMA-Fc fusion protein (R&D Systems) followed by anti-human IgG Fc-PE antibody (Biolengend).

Flow cytometry. For anti-BCMA staining, human myeloma cell lines were stained with goat anti-human-PE BCMA antibody (Bioloegend) followed by streptavidin (BD Biosciences). Flow cytometry analysis for all experiments was carried out by using FlowJo (Tree Star, Inc.).

ELISA. Target K562-BCMA cells (or control K562 cells) or multiple myeloma cell lines were combined with CAR-transduced T cells at a target:effector ratio 1:3 in duplicate wells of a 96 well flat bottom plate. ELISA assay was performed in a 1:10 dilution of supernatant collected after 16hr of incubation by using the human IFNγ or IL2 Duoset ELISA kit (R&D) as recommended by the manufacturer.

Results

huBCMA-BBz was highly expressed on transduced T cells.

Freshly purified negatively selected normal human T cells were activated *in vitro* using CD3/28 beads (cell:bead ratio 1:3) and allowed to expand. On day 1 post-activation, cells were transduced with the preclinical lentiviral vector expressing huBMCA-BBz or mock transduced (NTD control). Figure 36A shows the increase of total T cells during culture. BCMA-CART cells were counted every 3 days and adjusted for the ratio of split cells. T cells were enumerated using a Coulter Counter Multisizer III and fed every 2 days until the end of the

expansion cycle (Day 7-9). On day 6 of ex vivo expansion, 200ul of CART- BCMA or control NTD T cells were stained as described in the Methods section above. The live cell populations were gated using FCS vs. SSC. The flow acquisition was performed on a BC FACS Canto instrument and the flow analysis was performed using FlowJo software (TreeStar, Inc).

No differences in the proliferation rates of non transduced (NTD) and CART-BCMA cells were observed, indicating that lentiviral expression did not affect the proliferative potential of T cells (Figure 36A). Transduction efficiency was evaluated at day 6 post-transduction as described in the methods section above. Figure 36B shows that huBCMA-BBz transduction efficiency was 49%. These results demonstrate that huBCMA-BBz CAR was efficiently expressed on the surface of human T cells.

BCMA was expressed at different levels on multiple myeloma cell lines.

BCMA surface expression on multiple myeloma cell lines was determined using flow cytometry staining. The live cell populations were gated by FCS/SCC parameters. The flow acquisition was done on a canto instrument and the flow analysis with FlowJo software. Most multiple myeloma cell lines tested showed strong BCMA expression, whereas RPMI 8226 and control K562-BCMA cells expressed lower levels of surface BCMA (Figure 37). For all plots, the orange solid peak represents isotype control and the blue solid peak staining with BCMA antibody (Figure 37). Flow cytometry staining revealed BCMA expression on the surface of the multiple myeloma cell lines NCI H929, U266, RPMI 8226, OPM2 and MM1S, as well as by K562- BCMA cells. BCMA was not detected on the surface of K562 cell line (Figure 37). These results demonstrate that BCMA was expressed by several multiple myeloma cell lines with expression levels varying by about 1 log.

CART-BCMA cells produced cytokines and showed cytotoxic properties specifically in response to different BCMA-expressing, multiple myeloma cell lines.

The ability of CART-BCMA cells to produce cytokines and kill BCMA+ target cells was determined. CART-BCMA cells (huBCMA-BBz transduced T cells) or control non transduced T cells (NTD) were co-cultured in duplicates for 16hrs with K562, K562-BCMA or multiple myeloma cell lines (MM1S, OPM2, or U266). Cells were co-cultured at a 3:1 ratio of T cell to target cells. Cell-free supernatant was harvested and the production of IL2 or IFNγ was evaluated as described in the Methods section above.

CART-BCMA cells specifically produced IL2 or IFNγ in the presence of K562 engineered to express BCMA (K562-BCMA) compared to non-antigen-expressing, wildtype

K562 cells. CART-BCMA cells were also able to produce cytokines in the presence of U266, OPM2 and MM1S multiple myeloma cell lines (Figures 38A-38B). These results demonstrate that in the presence of BCMA+ target cell lines, CART-BCMA cells produced pro-inflammatory cytokines.

Another *in vitro* measure for the anti-tumor effectiveness of CART-BCMA cells is their ability to kill BCMA+ target cells. T cells were activated and transduced, as described above, e.g., in relation to Figures 36A-36B. BCMA10 CAR T cells were co-cultured with ^{51}Cr-labeled K562-BCMA, RPMI 8226 or MM1S cell lines for 4 hrs at the effector to target ratios (E:T Ratio) indicated in Figures 39A-39C (E:T of 0, 10, 20, or 30) and percentage of lysis was calculated as described in the Methods section above. Figure 39A shows that CART-BCMA cells specifically killed K562-BCMA cells. CART-BCMA cells also efficiently killed the BCMA^{high} multiple myeloma cell line MM1S and the BCMA^{low} RPMI 8226 cell line in a 4-hr cytotoxicity assay (Figures 39B, 39C). These results demonstrate that CART-BCMA displayed enhanced cytotoxic activity (^{51}Cr assay) against multiple myeloma cell lines.

Antitumor activity of CART-BCMA cells in vivo

Using RPMI 8226 cells, which show lower levels of BCMA expression compared to many other myeloma cells lines, a mouse model was established to evaluate the capacity of CART-BCMA to recognize and eliminate tumors produced by the BCMA^{low} RPMI 8226 cell line engineered to express Click-beetle green luciferase (CBG) for bioluminenscence imaging (BLI). NOD/SCID/γ- chain$^{-/-}$ (NSG) mice with established intravenous RPMI 8226 tumors received intravenous injections of CART-BCMA cells (N=10) or non transduced control T cells (NTD) (N=10) on day 30 following tumor cell inoculation. NSG mice engrafted with RPMI-8226 cells were treated with 5x10^6 CART-BCMA T cells at day 30 following tumor cell injection. Myeloma tumor progression was followed by *in vivo* BLI (BLI of ventral and dorsal mouse areas once per week) up to 9 weeks post-T cell infusion (14 weeks post-tumor injection).

Non-transduced T cells failed to control the tumors, and all mice had to be euthanized due to disease progression 10-11 weeks after tumor injection (Figure 40A and 40C). In contrast, mice receiving CART-BCMA cells showed control of tumor growth in most mice resulting in 80% survival of CART-BCMA- treated mice at 10 weeks post-tumor cell inoculation compared with 0% survival of the NTD control-treated mice (Figures 40B and

40C). These results demonstrate that intramedullary RPMI 8226 tumors were inhibited by CART-BCMA treatment.

Example 14: BCMA-CART dosing scheme

A BCMA CART cell therapy, e.g., a BCMA CART cell therapy described herein, can be administered to patients, e.g., multiple myeloma patients, according to a dosing regimen described herein, e.g., a dosing regimen described as follows.

Leukopheresis is performed on the patient prior to receiving a BCMA CART therapy to obtain autologous T cells. Manufacturing and/or cryopreservation of the BCMA lentiCAR T cells is performed. Patients may receive therapy during manufacturing to maintain disease control. Some patients may receive a lympho-depleting therapy (e.g., cytoxan) before CART cell administration. For example, a lympho-depleting chemotherapy, e.g., cytoxan (e.g., at 1.5 g/m^2) is administered to the patient. In other dosing regimens, a lympho-depleting chemotherapy is not administered to the patient. Patients are then treated with BCMA CART cells according to a dosing regimen described herein.

A dosing regimen involves dose fractionation, e.g., where a certain percentage of the total dose of cells is delivered on a first day of treatment, a different percentage of the total dose of cells is delivered on a subsequent day of treatment, and a different percentage of the total dose of cells is delivered on a yet subsequent day of treatment. For example, 10% of the total dose of cells is delivered on the first day, 30% of the total dose of cells is delivered on the second day, and the remaining 60% of the total dose of cells is delivered on the third day of treatment. For example, a total cell dose includes 1 to 5 x 10^7 or 1 to 5 x 10^8 BCMA-CART cells.

In one dosing regimen, no lympho-depleting chemotherapy is administered, and a total BCMA-CART cell dose of 1 to 5 x 10^7 is administered (e.g., by infusion) with 10% of the cell dose on day 1 of treatment, 30% on day 2 of treatment, and 60% on day 3 of treatment. In another dosing regimen, no lympho-depleting chemotherapy is administered, and a total BCMA-CART cell dose of 1 to 5 x 10^8 is administered (e.g., by infusion) with 10% of the cell dose on day 1 of treatment, 30% on day 2 of treatment, and 60% on day 3 of treatment. In another dosing regimen, a lympho-depleting chemotherapy (cytoxan at 1.5 g/m^2) is administered three days before BCMA-CART cell administration, and then a total BCMA-

CART cell dose of 1 to 5 x 10^7 is administered (e.g., by infusion) with 10% of the cell dose on day 1 of treatment, 30% on day 2 of treatment, and 60% on day 3 of treatment. In yet another dosing regimen, a lympho-depleting chemotherapy (cytoxan at 1.5 g/m^2) is administered three days before BCMA-CART cell administration, and then a total BCMA-CART cell dose of 1 to 5 x 10^8 is administered (e.g., by infusion) with 10% of the cell dose on day 1 of treatment, 30% on day 2 of treatment, and 60% on day 3 of treatment.

Clinical lab assessments are performed on days 1, 2, 4, 7, 14, 21, 28, every 4 weeks, after CART cell administration (with day 0 being the first day of CART dosing). Multiple myeloma assessments are performed pre-CART dosing, on the first day of CART dosing (day 0), and days 14, 28, and every 4 weeks. Bone marrow aspirate/biopsy (bx) is performed pre-CART dosing, and on days 28 and 90 after CART dosing. After the first 28 days of CART treatment, follow-up is performed every 4 weeks up to 6 months, then every 3 months, up to 2 years.

Example 15: Low dose RAD001 stimulates CART proliferation in a cell culture model

The effect of low doses of RAD001 on CAR T cell proliferation in vitro was evaluated by co-culturing CART-expressing cells with target cells in the presence of different concentrations of RAD001.

Materials and Methods

Generation of CAR-transduced T cells

A humanized, anti-human CD19 CAR (huCART19) lentiviral transfer vector was used to produce the genomic material packaged into VSVg pseudotyped lentiviral particles. The amino acid and nucleotide sequence of the humanized anti-human CD19 CAR (huCART19) is CAR 1, ID 104875 described in PCT publication, WO2014/153270, filed March 15, 2014, and is designated SEQ ID NOs. 85 and 31 therein.

Lentiviral transfer vector DNA is mixed with the three packaging components VSVg env, gag/pol and rev in combination with lipofectamine reagent to transfect Lenti-X 293T cells. Medium is changed after 24h and 30h thereafter, the virus-containing media is collected, filtered and stored at -80°C. CARTs are generated by transduction of fresh or frozen naïve T cells obtained by negative magnetic selection of healthy donor blood or leukopak. T cells are activated by incubation with anti-CD3/anti-CD28 beads for 24h, after which viral supernatant or concentrated virus (MOI=2 or 10, respectively) is added to the cultures. The modified T cells are allowed to expand for about 10 days.

The percentage of cells transduced (expressing the CARs on the cell surface) and the level of CAR expression (relative fluorescence intensity, Geo Mean) are determined by flow cytometric analysis between days 7 and 9. The combination of slowing growth rate and T cell size approaching ~350 fL determines the state for T cells to be cryopreserved for later analysis.

Evaluating proliferation of CARTs

To evaluate the functionality of CARTs, the T cells are thawed and counted, and viability is assessed by Cellometer. The number of CAR-positive cells in each culture is normalized using non-transduced T cells (UTD). The impact of RAD001 on CARTs was tested in titrations with RAD001, starting at 50nM. The target cell line used in all co-culture experiments is Nalm-6, a human pre-B cell acute lymphoblastic leukemia (ALL) cell line expressing CD19 and transduced to express luciferase.

For measuring the proliferation of CARTs, T cells are cultured with target cells at a ratio of 1:1. The assay is run for 4 days, when cells are stained for CD3, CD4, CD8 and CAR expression. The number of T cells is assessed by flow cytometry using counting beads as reference.

Results

The proliferative capacity of CART cells was tested in a 4 day co-culture assay. The number of CAR-positive CD3-positive T cells (dark bars) and total CD3-positive T cells (light bars) was assessed after culturing the CAR-transduced and non-transduced T cells with Nalm-6 (Fig. 43). huCART19 cells expanded when cultured in the presence of less than 0.016 nM of RAD001, and to a lesser extent at higher concentrations of the compound. Importantly, both at 0.0032 and 0.016 nM RAD001 the proliferation was higher than observed without the addition of RAD001. The non-transduced T cells (UTD) did not show detectable expansion.

Example 16: Low dose RAD001 stimulates CART expansion in vivo

This example evaluates the ability of huCAR19 cells to proliferate *in vivo* with different concentrations of RAD001.

Materials and Methods:

NALM6-luc cells: The NALM6 human acute lymphoblastic leukemia (ALL) cell line was developed from the peripheral blood of a patient with relapsed ALL. The cells were then tagged with firefly luciferase. These suspension cells grow in RPMI supplemented with 10% heat inactivated fetal bovine serum.

Mice: 6 week old NSG (NOD.Cg-*Prkdc*^{scid}*Il2rg*^{tm1Wjl}/SzJ) mice were received from the Jackson Laboratory (stock number 005557).

Tumor implantation: NALM6-luc cells were grown and expanded *in vitro* in RPMI supplemented with 10% heat inactivated fetal bovine serum. The cells were then transferred to a 15 ml conical tube and washed twice with cold sterile PBS. NALM6-luc cells were then counted and resuspended at a concentration of $10x10^6$ cells per milliliter of PBS. The cells were placed on ice and immediately (within one hour) implanted in the mice. NALM6-luc cells were injected intravenously via the tail vein in a 100 µl volume, for a total of $1x10^6$ cells per mouse.

CAR T cell dosing: Mice were administered $5x10^6$ CAR T cells 7 days after tumor implantation. Cells were partially thawed in a 37 degree Celsius water bath and then completely thawed by the addition of 1 ml of cold sterile PBS to the tube containing the cells. The thawed cells were transferred to a 15 ml falcon tube and adjusted to a final volume of 10 mls with PBS. The cells were washed twice at 1000rpm for 10 minutes each time and then counted on a hemocytometer. T cells were then resuspended at a concentration of $50x10^6$ CAR T cells per ml of cold PBS and kept on ice until the mice were dosed. The mice were injected intravenously via the tail vein with 100 µl of the CAR T cells for a dose of $5x10^6$ CAR T cells per mouse. Eight mice per group were treated either with 100 µl of PBS alone (PBS), or humanized CD19 CAR T cells.

RAD001 dosing: A concentrated micro-emulsion of 50mg equal to 1mg RAD001 was formulated and then resuspended in D5W (dextrose 5% in water) at the time of dosing. Mice were orally dosed daily (via oral gavage) with 200 µl of the desired doses of RAD001.

PK analysis: Mice were dosed daily with RAD001 starting 7 days post tumor implantation. Dosing groups were as follows: 0.3 mg/kg, 1 mg/kg, 3 mg/kg, and 10 mg/kg. Mice were bled on days 0 and 14 following the first and last dose of RAD001, at the following time points for PK analysis: 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, and 24 hours.

Results:

The expansion and pharmacokinetics of RAD001 was tested in NSG mice with NALM6-luc tumors. Daily oral dosing of RAD001 alone did not have an impact on the growth of NALM6-luc tumors (Figure 44). The pharmacokinetic analysis of RAD001 shows that it is fairly stable in the blood of tumor bearing mice (Figure 45A and 45B). Both the day 0 and day 14 PK analyses show that the RAD001 concentrations in the blood is above 10nm even 24 hours after dosing at the lowest dose tested (0.3 mg/kg).

Based on these doses, huCAR19 CAR T cells were dosed with and without RAD001 to determine the proliferative ability of these cells. The highest dose used was 3 mg/kg based on the levels of RAD001 in the blood 24 hours after dosing. As the concentration of RAD001 was

above 10nM 24 hours after the final dose of RAD001, several lower doses of RAD001 were used in the *in vivo* study with CAR T cells. The CAR T cells were dosed IV one day prior to the start of the daily oral RAD001 dosing. Mice were monitored via FACS for T cell expansion.

The lowest doses of RAD001 show an enhanced proliferation of the CAR T cells (Figure 46). This enhanced proliferation is more evident and prolonged with the $CD4^+$ CAR T cells than the $CD8^+$ CAR T cells. However, with the $CD8^+$ CAR T cells, enhanced proliferation can be seen at early time points following the CAR T cell dose.

Example 17: CD19 CAR T cells for use in treating multiple myeloma

Even with current regimens of chemotherapy, targeted therapies, and autologous stem cell transplant, myeloma is considered an incurable disease. The present example describes treating multiple myeloma (MM) with autologous T cells directed to CD19 with a chimeric antigen receptor (lentivirus/CD19:4-1BB:CD3zeta; also known as "CART19" or CTL019). This example demonstrates that CD19-directed CAR therapies have the potential to establish deep, long-term durable remissions based on targeting the myeloma stem cell and/or tumor cells that express very low (undetectable by most methods) levels of CD19.

In treating a patient with an aggressive secondary plasma cell leukemia, we found that CART19 administered two days after a salvage autologous stem cell transplant resulted in rapid clearance of plasma cell leukemia and a very good partial response in a patient who had progressed through multiple lines of chemotherapy. This patient was transfusion-dependent for months prior to the treatment; at two months after the treatment, she has recovered her blood counts (with normal-range platelet counts and white blood cell counts) and has not required transfusions since she was discharged from the hospital from her treatment.

Because myeloma cells do not naturally express CD19, the finding that CART19 treatment induced a rapid and significant tumor response in this tumor was surprising. Without wishing to be bound by a particular theory, it was reasoned that CART19 could be used to treat myeloma because: (1) while myeloma cells are traditionally thought to be negative for CD19 expression by flow cytometry, there are data indicating that myeloma cells may express very low levels of CD19, such that expression is detectable by RNA but not by flow cytometry or immunohistochemistry; and (2) the concept of targeting the clonotypic B cell, which is thought

to be the cancerous stem cell that gives rise to multiple myeloma, and is particularly resistant to chemotherapy. There is a clonal relationship between B cells and myeloma tumor cells, but traditional myeloma therapy is aimed at the malignant plasma cells rather than B cells. CART19 for treating myeloma therefore targets a different cell population than most myeloma therapies.

In our single patient experience, the patient had circulating plasma cells, and we were able to test her tumor cells for the expression of CD19. Approximately 1-2% of her tumor cells expressed the CD19 antigen. (FIG. 47). Thus, it was reasoned that CART19 may have a direct effect on a very small population of her tumor cells; a very good partial response, though would not have been predicted based on targeting only the very small population of CD19+ tumor cells.

In this case, CART19 was administered following autologous stem cell transplant rescue after high-dose melphalan. Although this is a standard therapy in myeloma, it is not curative. Furthermore, this patient had previously undergone tandem autologous stem cell transplants and relapsed early (<6 months) after transplant. Without wishing to be bound by a particular theory, use of CART19 cells as described in the present example may have a non-overlapping mechanism in the treatment of myeloma when combined with a salvage autologous stem cell transplant.

A patient with refractory multiple myeloma was treated with CTL019 after myeloablative chemotherapy and ASCT. Remission was maintained despite loss of detectable CTL019 and reconstitution of normal CD19-positive B cells, indicating that this response did not require sustained CTL019 activity. Moreover, this patient's response was realized even though the vast majority (99.95%) of the neoplastic plasma cells were CD19-negative by both flow cytometry and RT-PCR.

The absence of detectable CD19 expression in this patient's dominant neoplastic plasma cell population suggests that the clinically relevant target of CTL019 resided outside this dominant CD19-negative population. Neoplastic plasma cells in multiple myeloma patients exhibit genetic, immunophenotypic, and functional heterogeneity. Particular subpopulations may be required for survival of the clone through anti-myeloma therapy. In the patient reported here, for example, the small CD19-expressing subset of plasma cells might have been relatively melphalan-resistant but sensitive to CTL019. This finding suggests that therapeutically

targeting a small subset of the clone can lead to durable clinical benefit when coupled with conventional anti-myeloma therapy.

Alternatively, the clinically relevant target of CTL019 in this patient may have resided outside the neoplastic plasma cell population. For instance, the CTL019 may target a stem cell population that is relatively small but gives rise to neoplastic plasma cells. Multiple myeloma may therefore be a disease of multiple late B-lineage cell types, not just terminally differentiated plasma cells, such that therapies like CTL019 that target B lymphocytes might be useful adjuncts to therapies that directly target plasma cells.

Ten additional multiple myeloma patients will be treated with CART19 in a Phase I trial, at least three patients have been treated to date.

Dose Rationale

With the first 3 patients, we have observed clinical activity at doses ranging from 1.4 x 10^7 to 1.1 x 10^9 CART-19 cells. This observation demonstrates, at least in the first 3 patients treated, that there is not an obvious dose response relationship. A complete response was observed in patients administered with two log fold difference in dose. Thus, unlike standard drugs that are metabolized, CAR T cells can have a wide dose response range. This is most likely because the CAR T cells are able to proliferate extensively in the patients. We therefore set a dose range of 1-5 x 10^8 CART-19 cells for infusion. In this single-patient study offered on a compassionate use basis, the patient was offered up to 5 x 10^8 CART19 cells, with no lower dose limit. For the ten patient trial, patients will be offered 1-5 x 10^7 CART-19 cells.

General Design

This was single patient-study offered on a compassionate use basis; it was modeled after a Phase I study to determine if the infusion of autologous T cells transduced to express CART-19 is safe. The primary goals of the study were to determine the safety, tolerability and engraftment potential of CART -19 T cells in patients undergoing salvage ASCT after early relapse following first ASCT. The protocol consists of an open label pilot study.

At entry subjects will undergo a bone marrow biopsy and routine laboratory and imaging assessment of their MM. Eligible subjects will undergo steady-state apheresis to obtain large numbers of peripheral blood mononuclear cells (PBMC) for CART-19 manufacturing. The T cells will be purified from the PBMC, transduced with TCRζ/4-1BB lentiviral vector, expanded in vitro and then frozen for future administration. The number of patients who have inadequate T cell collections, expansion or manufacturing compared to the number of patients

who have T cells successfully manufactured will be recorded; feasibility of product manufacturing is not expected to be problematic in this patient population.

Subjects will generally have had adequate peripheral blood stem cells remaining stored from the mobilization/collection performed in preparation for their first ASCT to conduct two additional ASCT. Those who do not will undergo a second mobilization/collection procedure either before or after their steady-state apheresis with a regimen according to the treating physician's preference. Approximately two weeks after the initial leukapheresis, subjects will be admitted to the hospital and receive high-dose melphalan (day -2) followed by infusion of autologous stem cells two days later (day 0), and all subjects will receive infusion of CART-19 cells twelve to fourteen days later (day +12-14). Up to 10 patients will be enrolled.

All subjects will have blood tests to assess safety, and engraftment and persistence of the CART-19 cells at regular intervals through week 4 of the study. At day +42 and day +100, subjects will undergo bone marrow aspirates/biopsies to assess the bone marrow plasma cell burden and trafficking of CART-19 cells to the bone marrow. A formal response assessment will be made at day 100 according to International Myeloma Working Group (IMWG) criteria136, and TTP will be monitored according to routine clinical practice for patients with multiple myeloma. The main efficacy outcome measured in this study will be a comparison of TTP after a patient's initial ASCT to TTP after the ASCT on this study.

Treatment Regimen

Therapy for Relapsed/Progressive Multiple Myeloma

Patients may receive, prior to enrollment, therapy for relapsed/progressive multiple myeloma according to the preference of their treating physicians. Therapy may continue upon enrollment.

Patients must stop all therapy for two weeks prior to apheresis and for two weeks prior to high-dose melphalan. If more than two weeks are expected to lapse between apheresis and high-dose melphalan, patients may resume therapy after apheresis at the discretion of their treating physicians.

High-dose Melphalan (day -2)

Patients will be admitted to the hospital on day -3 or -2 and will undergo examination by the attending physician and routine laboratory tests, which will include monitoring parameters for tumor lysis syndrome, prior to commencement of the treatment protocol. Blood for MM monitoring laboratory tests (SPEP, quantitative immunoglobulins, and serum free light

chain analysis), will be drawn prior to initiation of therapy if such tests had not been drawn within 7 days of admission.

High-dose therapy will consist of melphalan at a dose of 200 mg/m^2 administered intravenously over approximately 20 minutes on day -2. The dose of melphalan will be reduced to 140 mg/m^2 for patients >70 years of age or for patients of any age whom, at the discretion of the treating physician, may not tolerate a dose of 200 mg/m^2 All patients will receive standard anti-emetic prophylaxis, which may include dexamethasone, and standard antibiotic prophylaxis.

Stem-cell Re-infusion (day 0)

Stem cell infusion will take place on day 0, at least 18 hours after the administration of the high-dose melphalan. Stem cells will be infused intravenously over approximately 20-60 minutes following premedication according to standard institutional practice. At least 2 x 10^6 CD34+ progenitors/kg body weight should be infused. In addition, at least 1 x 10^6 CD34+ progenitors/kg body weight should be available as a back-up stem-cell product to be infused in the event of delayed engraftment or late graft failure. G-CSF should be administered SQ beginning on day +5, dosed according to standard institutional practice. Other supportive care measures such as transfusion support will be done in accordance with standard institutional guidelines.

CART19 Cell Infusion (day +12-14)

A single dose of CART-19 transduced T cells will be given consisting of up to 5 x 10^7 CART-19 cells. The minimal acceptable dose for infusion of cells transduced with the CD19 TCRζ4-1BB vector is 1 x 10^7. CART-19 cells will be given as a single dose by rapid i.v. infusion on day +12-14 after stern cell infusion. If patient fails to meet any of the inclusion criteria described herein in the 12-14 day window, the CART-19 infusion may be delayed beyond day +12-14 until the criteria is satisfied.

Maintenance Lenalidomide

Subjects who received and tolerated maintenance lenalidomide after their first ASCT will re-initiate lenalidomide maintenance therapy at approximately day + 100, assuming there are no contraindications in the judgment of the treating physician. The starting dose will be 10 mg daily unless prior experience dictates an alternative starting dose for a particular patient. Maintenance therapy will continue until disease progression or intolerance.

Administration of Study Drug

The infusion will take place in an isolated room in Rhoads, using precautions for immunosuppressed patients. The transduced T cells will be administered by rapid intravenous infusion at a flow rate of approximately 10mL to 20 ml per minute through an 18-gauge latex free Y-type blood set with a 3-way stopcock. The duration of the infusion will be based on the total volume to be infused and the recommended infusion rate. Each infusion bag will have affixed to it a label containing the following: "FOR AUTOLOGOUS USE ONLY." In addition the label will have at least two unique identifiers such as the subject's initials, birth date, and study number. Prior to the infusion, two individuals will independently verify all this information in the presence of the subject and so confirm that the information is correctly matched to the participant.

Packaging

Infusion will be comprised of a single dose of 1-5 x 10^7 CA T19-transduced cells, with a minimal acceptable dose of 1 x 10^7 CART-19 cells for infusion. Each bag will contain an aliquot (volume dependent upon dose) of cryomedia containing the following infusible grade reagents (% v/v): 31.25% plasmalyte-A, 31.25% dextrose (5%), 0.45% NaCl, up to 7.5% DMSO, 1% dextran 40, 5% human serum albumin.

Apheresis

A large volume (12-15 liters or 4-6 blood volumes) apheresis procedure is carried out at the apheresis center. PBMC are obtained for CART-19 during this procedure. From a single leukapheresis, the intention is to harvest at least 5 x 10^9 white blood cells to manufacture CART-19 T cells. Baseline blood leukocytes for FDA look-back requirements and for research are also obtained and cryopreserved. The cell product is expected to be ready for release approximately 2-4 weeks later. Flow cytometry lymphocyte subset quantitation, including CD19 and CD20 B cell determination. Baseline assessment is made for human anti-VSV-G and anti-murine antibody (HAMA). If a subject has previously had an adequate apberesis collection banked according to current Good Manufacturing Practices at the Clinical Cell and Vaccine Production Facility these cells may be used as the source of cells for CART -19 manufacturing. Using a banked apheresis product would avert the expense, time, and risk to the subject of undergoing an additional apheresis collection.

Cytoreductive Chemotherapy

The lymphodepleting chemotherapy will be high-dose melphalan as described herein.

CART-19 Infusion

Infusion will begin on day +12-14 after stem-cell reinfusion.

On day + 12-14 prior to the first infusion, patients will have a CBC with differential, and assessment of CD3, CD4 and CD8 counts since chemotherapy is given in part to induce lymphopenia.

The first dose will be administered using a single dose. The cells are thawed at the patient's bedside. The thawed cells will be given at as rapid an infusion rate as tolerated such that the duration of the infusion will be approximately l 0-15 minutes. In order to facilitate mixing, the cells will be administered simultaneously using a Y -adapter. Subjects will be infused and premedicated as described herein. Subjects' vital signs will be assessed and pulse oxymetry done prior to dosing, at the end of the infusion, and every 15 minutes thereafter for 1 hour and until these are stable and satisfactory. A blood sample for determination of a baseline CART-19 level is obtained any time prior to the first infusion and 20 minutes to 4 hours after each infusion (and sent to TCSL).

Results

Three treatment-refractory, advanced multiple myeloma patients have now been treated with CTL019 in this ongoing trial. Results for two of these patients show that both have had substantial anti-tumor effects from the CTL019 therapy based on the primary efficacy assessment at the three-month time-point. The third patient has not yet reached the three-month time point. The results for the two patients are described in more detail below.

The first myeloma patient has completed her +100 day response assessment and she had a very good response to the CART19 therapy. The following tests were performed with the following results:

-SPEP/immunofixation: negative

-urine immunofixation: faint unmeasurable kappa light chain band on her immunofixation (also present at day 38, so not new)

Otherwise, the patient met the criteria for stringent complete remission including:

-serum free light chain ratio: normal

-bone marrow biopsy: negative

-IgA immunophenotyping: IgA is below the limit of detection

Other than the faint unmeasurable kappa light chain result from urine immunofixation, the patient met all criteria for “stringent complete remission”. The summary of the plasma cell immunophenotyping at 3 time points (day -2, day +38, day +103) is shown in Figure 39, and

demonstrates that the patient's IgA is below the limit of detection. The summary shows heavy myeloma burden at day -2 and none detectable at day +38 and +103, which classifies the patient as "MRD negative" by flow analysis. At day +103, the summary shows recovery of normal, polyclonal, CD19+ plasma cells and B cells. The patient had no symptoms of disease or therapy and is functioning like a normal person.

The second patient treated has not yet reached the +100 day time point. However, at this time point, she is doing well but it is too early to determine the effect of the CTL019 infusion.

EQUIVALENTS

The disclosures of each and every patent, patent application, and publication cited herein are hereby incorporated herein by reference in their entirety. While this invention has been disclosed with reference to specific aspects, it is apparent that other aspects and variations of this invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The appended claims are intended to be construed to include all such aspects and equivalent variations.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An isolated nucleic acid molecule encoding a chimeric antigen receptor (CAR), wherein the CAR comprises an anti-BCMA binding domain, a transmembrane domain, and an intracellular signaling domain, wherein said anti-BCMA binding domain comprises:

(i) a heavy chain complementary determining region 1 (HC CDR1) comprising the amino acid sequence of SEQ ID NO: 394, a heavy chain complementary determining region 2 (HC CDR2) comprising the amino acid sequence of SEQ ID NO: 434, a heavy chain complementary determining region 3 (HC CDR3) comprising the amino acid sequence of SEQ ID NO: 474, a light chain complementary determining region 1 (LC CDR1) comprising the amino acid sequence of SEQ ID NO: 514, a light chain complementary determining region 2 (LC CDR2) comprising the amino acid sequence of SEQ ID NO: 554, and a light chain complementary determining region 3 (LC CDR3) comprising the amino acid sequence of SEQ ID NO: 594;

(ii) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 634, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 674, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 714, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 754, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 794, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 834;

(iii) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 874, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 914, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 954, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 994, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 1034, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 1074;

(iv) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 436, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 476, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 516, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 556, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 596;

(v) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 636, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 676, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 716, a LC CDR1 comprising the amino acid

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sequence of SEQ ID NO: 756, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 796, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 836;

(vi) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 876, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 916, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 956, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 996, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 1036, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 1076;

(vii) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 398, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 438, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 478, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 518, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 558, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 598;

(viii) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 638, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 678, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 718, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 758, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 798, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 838; or

(ix) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 878, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 918, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 958, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 998, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 1038, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 1078.

2. The isolated nucleic acid molecule of claim 1, wherein the CAR comprises:

(i) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 79 (or an amino acid sequence with 95-99% identity thereto) and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 94 (or an amino acid sequence with 95-99% identity thereto);

(ii) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 81 (or an amino acid sequence with 95-99% identity thereto) and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 96 (or an amino acid sequence with 95-99% identity thereto); or

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(iii) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 83 (or an amino acid sequence with 95-99% identity thereto) and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 98 (or an amino acid sequence with 95-99% identity thereto).

3. The isolated nucleic acid molecule of claim 1 or 2, wherein the CAR comprises:

(i) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 79 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 94;

(ii) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 81 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 96; or

(iii) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 83 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 98.

4. The isolated nucleic acid molecule of any of claims 1-3, wherein the anti-BCMA binding domain comprises:

(i) an amino acid sequence selected from the group consisting of SEQ ID NO: 49, SEQ ID NO: 51, and SEQ ID NO: 53;

(ii) an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications to any of SEQ ID NO: 49, SEQ ID NO: 51, or SEQ ID NO: 53; or

(iii) an amino acid sequence with 95-99% identity to any of SEQ ID NO: 49, SEQ ID NO: 51, or SEQ ID NO: 53.

5. The isolated nucleic acid molecule of any of claims 1-4, comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO: 64, SEQ ID NO: 66, and SEQ ID NO: 68, or a sequence with 95-99% identity thereto.

6. The isolated nucleic acid molecule of any of claims 1-5, wherein:

(i) the transmembrane domain comprises a transmembrane domain of a protein selected from the group consisting of the alpha, beta or zeta chain of the T-cell receptor,

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CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 and CD154;

(ii) the transmembrane domain comprises the amino acid sequence of SEQ ID NO: 6, an amino acid sequence comprising at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:6, or an amino acid sequence with 95-99% identity to the amino acid sequence of SEQ ID NO:6; or

(iii) the nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:17, or a nucleotide sequence with 95-99% identity thereto.

7. The isolated nucleic acid molecule of any of claims 1-6, wherein the anti-BCMA binding domain is connected to the transmembrane domain by a hinge region.

8. The isolated nucleic acid molecule of claim 7, wherein:

(i) the hinge region comprises the amino acid sequence of SEQ ID NO:2, or an amino acid sequence with 95-99% identity thereto; or

(ii) the nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO: 13, or a nucleotide sequence with 95-99% identity thereto.

9. The isolated nucleic acid molecule of any of claims 1-8, wherein the intracellular signaling domain comprises a costimulatory domain.

10. The isolated nucleic acid molecule of claim 9, wherein the costimulatory domain comprises a functional signaling domain derived from a protein selected from the group consisting of MHC class I molecule, TNF receptor proteins, Immunoglobulin-like proteins, cytokine receptors, integrins, signaling lymphocytic activation molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, 4-1BB (CD137), B7-H3, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile),

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CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, and a ligand that specifically binds with CD83.

11. The isolated nucleic acid molecule of claim 9, wherein the costimulatory domain comprises:

(i) the amino acid sequence of SEQ ID NO:7;

(ii) an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:7; or

(iii) an amino acid sequence with 95-99% identity to the amino acid sequence of SEQ ID NO:7.

12. The isolated nucleic acid molecule of claim 9, wherein the nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:18, or a nucleotide sequence with 95-99% identity thereto.

13. The isolated nucleic acid molecule of any of claims 1-12, wherein the intracellular signaling domain comprises a functional signaling domain of 4-1BB and/or a functional signaling domain of CD3 zeta.

14. The isolated nucleic acid molecule of any of claims 1-13, wherein the intracellular signaling domain comprises:

(i) the amino acid sequence of SEQ ID NO: 7 and/or the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10;

(ii) an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:7 and/or an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10; or

(iii) an amino acid sequence with 95-99% identity to the amino acid sequence of SEQ ID NO:7 and/or an amino acid sequence with 95-99% identity to the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10.

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15. The isolated nucleic acid molecule of any of claims 1-14, wherein the intracellular signaling domain comprises the amino acid sequence of SEQ ID NO:7 and the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain.

16. The isolated nucleic acid molecule of any of claims 1-15, wherein the nucleic acid molecule comprises:

(i) the nucleotide sequence of SEQ ID NO:18, or a nucleotide sequence with 95-99% identity thereto, and/or

(ii) the nucleotide sequence of SEQ ID NO:20 or SEQ ID NO:21, or a nucleotide sequence with 95-99% identity thereto.

17. The isolated nucleic acid molecule of any of claims 1-16, further comprising a leader sequence which encodes the amino acid sequence of SEQ ID NO: 1.

18. The isolated nucleic acid molecule of any of claims 1-17, which encodes a CAR comprising:

(i) the amino acid sequence of SEQ ID NO: 109, SEQ ID NO: 111, or SEQ ID NO: 113;

(ii) an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications to any of SEQ ID NO: 109, SEQ ID NO: 111, or SEQ ID NO: 113; or

(iii) an amino acid sequence with 95-99% identity to any of SEQ ID NO: 109, SEQ ID NO: 111, or SEQ ID NO: 113,

without a leader sequence comprising the amino acid of SEQ ID NO: 1.

19. The isolated nucleic acid molecule of any of claims 1-17, comprising the nucleotide sequence of any of SEQ ID NO: 124, SEQ ID NO: 126, or SEQ ID NO: 128, or a nucleotide sequence with 95-99% identity to any of SEQ ID NO: 124, SEQ ID NO: 126, or SEQ ID NO: 128.

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20. An isolated nucleic acid molecule encoding a chimeric antigen receptor (CAR), wherein the CAR comprises:

(i) an anti-BCMA binding domain comprising:

(a) a heavy chain complementary determining region 1 (HC CDR1) comprising the amino acid sequence of SEQ ID NO: 394, a heavy chain complementary determining region 2 (HC CDR2) comprising the amino acid sequence of SEQ ID NO: 434, a heavy chain complementary determining region 3 (HC CDR3) comprising the amino acid sequence of SEQ ID NO: 474, a light chain complementary determining region 1 (LC CDR1) comprising the amino acid sequence of SEQ ID NO: 514, a light chain complementary determining region 2 (LC CDR2) comprising the amino acid sequence of SEQ ID NO: 554, and a light chain complementary determining region 3 (LC CDR3) comprising the amino acid sequence of SEQ ID NO: 594;

(b) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 634, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 674, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 714, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 754, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 794, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 834; or

(c) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 874, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 914, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 954, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 994, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 1034, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 1074,

(ii) a transmembrane domain comprising the amino acid sequence of SEQ ID NO: 6,

(iii) a costimulatory domain comprising the amino acid sequence of SEQ ID NO: 7, and

(iv) a primary signaling domain comprising the amino acid sequence of SEQ ID NO: 9.

21. The isolated nucleic acid molecule of claim 20, wherein the anti-BCMA binding domain comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 79 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 94.

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22. The isolated nucleic acid molecule of claim 20 or 21, wherein the anti-BCMA binding domain comprises the amino acid sequence of SEQ ID NO: 49.

23. An isolated nucleic acid molecule encoding a chimeric antigen receptor (CAR), wherein the CAR comprises an anti-B-cell maturation antigen (BCMA) binding domain, a transmembrane domain, and an intracellular signaling domain, wherein the CAR comprises the amino acid sequence of SEQ ID NO: 109 without a leader sequence comprising the amino acid of SEQ ID NO: 1.

24. An isolated polypeptide molecule encoded by the nucleic acid molecule of any one of claims 1-23.

25. An isolated chimeric antigen receptor (CAR) polypeptide, wherein the CAR polypeptide comprises an anti-BCMA binding domain, a transmembrane domain, and an intracellular signaling domain, wherein said anti-BCMA binding domain comprises:

(i) a heavy chain complementary determining region 1 (HC CDR1) comprising the amino acid sequence of SEQ ID NO: 394, a heavy chain complementary determining region 2 (HC CDR2) comprising the amino acid sequence of SEQ ID NO: 434, a heavy chain complementary determining region 3 (HC CDR3) comprising the amino acid sequence of SEQ ID NO: 474, a light chain complementary determining region 1 (LC CDR1) comprising the amino acid sequence of SEQ ID NO: 514, a light chain complementary determining region 2 (LC CDR2) comprising the amino acid sequence of SEQ ID NO: 554, and a light chain complementary determining region 3 (LC CDR3) comprising the amino acid sequence of SEQ ID NO: 594;

(ii) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 634, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 674, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 714, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 754, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 794, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 834;

(iii) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 874, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 914, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 954, a LC CDR1 comprising the amino acid

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sequence of SEQ ID NO: 994, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 1034, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 1074;

(iv) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 436, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 476, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 516, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 556, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 596;

(v) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 636, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 676, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 716, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 756, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 796, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 836;

(vi) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 876, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 916, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 956, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 996, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 1036, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 1076;

(vii) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 398, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 438, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 478, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 518, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 558, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 598;

(viii) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 638, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 678, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 718, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 758, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 798, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 838; or

(ix) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 878, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 918, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 958, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 998, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 1038, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 1078.

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26. The isolated CAR polypeptide of claim 25, comprising:

(i) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 79 (or an amino acid sequence with 95-99% identity thereto) and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 94 (or an amino acid sequence with 95-99% identity thereto);

(ii) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 81 (or an amino acid sequence with 95-99% identity thereto) and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 96 (or an amino acid sequence with 95-99% identity thereto); or

(iii) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 83 (or an amino acid sequence with 95-99% identity thereto) and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 98 (or an amino acid sequence with 95-99% identity thereto).

27. The isolated CAR polypeptide of claim 25 or 26, comprising:

(i) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 79 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 94;

(ii) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 81 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 96; or

(iii) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 83 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 98.

28. The isolated CAR polypeptide of any of claims 25-27, comprising:

(i) an amino acid sequence selected from the group consisting of SEQ ID NO: 49, SEQ ID NO: 51, and SEQ ID NO: 53;

(ii) an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications to any of SEQ ID NO: 49, SEQ ID NO: 51, or SEQ ID NO: 53; or

(iii) an amino acid sequence with 95-99% identity to any of SEQ ID NO: 49, SEQ ID NO: 51, or SEQ ID NO: 53.

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29. The isolated CAR polypeptide of any of claims 25-28, wherein the transmembrane domain comprises:

(i) a transmembrane domain from a protein selected from the group consisting of the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 and CD154;

(ii) the amino acid sequence of SEQ ID NO: 6;

(iii) an amino acid sequence comprising at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO: 6; or

(iv) an amino acid sequence with 95-99% identity to the amino acid sequence of SEQ ID NO: 6.

30. The isolated CAR polypeptide of any one of claims 25-29, wherein the anti-BCMA binding domain is connected to the transmembrane domain by a hinge region, wherein the hinge region comprises the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:36, or an amino acid sequence with 95-99% identity thereto.

31. The isolated CAR polypeptide of any of claims 25-30, wherein the intracellular signaling domain comprises a costimulatory domain, wherein the costimulatory domain comprises:

(i) a functional signaling domain derived from a protein selected from the group consisting of MHC class I molecule, TNF receptor proteins, Immunoglobulin-like proteins, cytokine receptors, integrins, signaling lymphocytic activation molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, 4-1BB (CD137), B7-H3, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8),

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SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, and a ligand that specifically binds with CD83;

(ii) the amino acid sequence of SEQ ID NO: 7;

(iii) an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO: 7; or

(iv) an amino acid sequence with 95-99% identity to the amino acid sequence of SEQ ID NO: 7.

32. The isolated CAR polypeptide of any of claims 25-31, wherein the intracellular signaling domain comprises:

(i) a functional signaling domain of 4-1BB and/or a functional signaling domain of CD3 zeta;

(ii) the amino acid sequence of SEQ ID NO: 7 and/or the amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 10;

(iii) an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:7 and/or an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10;

(iv) an amino acid sequence with 95-99% identity to the amino acid sequence of SEQ ID NO:7 and/or an amino acid sequence with 95-99% identity to the amino acid sequence of SEQ ID NO:9 or SEQ ID NO:10; or

(v) the amino acid sequence of SEQ ID NO: 7 and the amino acid sequence of SEQ ID NO: 9 or SEQ ID NO:10, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain.

33. The isolated CAR polypeptide of any of claims 25-32, further comprising a leader sequence which comprises the amino acid sequence of SEQ ID NO: 1.

34. The isolated CAR polypeptide of any of claims 25-32, comprising:

(i) the amino acid sequence of any of SEQ ID NO: 109, SEQ ID NO: 111, or SEQ ID NO: 113;

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(ii) an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications to any of SEQ ID NO: 109, SEQ ID NO: 111, or SEQ ID NO: 113; or

(iii) an amino acid sequence with 95-99% identity to any of SEQ ID NO: 109, SEQ ID NO: 111, or SEQ ID NO: 113,

without a leader sequence comprising the amino acid of SEQ ID NO: 1.

35. An isolated anti-BCMA binding domain comprising:

(i) a heavy chain complementary determining region 1 (HC CDR1) comprising the amino acid sequence of SEQ ID NO: 394, a heavy chain complementary determining region 2 (HC CDR2) comprising the amino acid sequence of SEQ ID NO: 434, a heavy chain complementary determining region 3 (HC CDR3) comprising the amino acid sequence of SEQ ID NO: 474, a light chain complementary determining region 1 (LC CDR1) comprising the amino acid sequence of SEQ ID NO: 514, a light chain complementary determining region 2 (LC CDR2) comprising the amino acid sequence of SEQ ID NO: 554, and a light chain complementary determining region 3 (LC CDR3) comprising the amino acid sequence of SEQ ID NO: 594;

(ii) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 634, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 674, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 714, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 754, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 794, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 834;

(iii) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 874, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 914, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 954, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 994, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 1034, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 1074;

(iv) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 436, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 476, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 516, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 556, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 596;

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(v) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 636, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 676, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 716, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 756, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 796, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 836;

(vi) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 876, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 916, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 956, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 996, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 1036, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 1076;

(vii) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 398, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 438, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 478, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 518, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 558, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 598;

(viii) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 638, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 678, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 718, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 758, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 798, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 838; or

(ix) a HC CDR1 comprising the amino acid sequence of SEQ ID NO: 878, a HC CDR2 comprising the amino acid sequence of SEQ ID NO: 918, a HC CDR3 comprising the amino acid sequence of SEQ ID NO: 958, a LC CDR1 comprising the amino acid sequence of SEQ ID NO: 998, a LC CDR2 comprising the amino acid sequence of SEQ ID NO: 1038, and a LC CDR3 comprising the amino acid sequence of SEQ ID NO: 1078.

36. The isolated anti-BCMA binding domain of claim 35, comprising:

(i) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 79 or an amino acid sequence with 95-99% identity thereto and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 94 or an amino acid sequence with 95-99% identity thereto;

(ii) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 81 or an amino acid sequence with 95-99% identity thereto and a light chain variable

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region comprising the amino acid sequence of SEQ ID NO: 96 or an amino acid sequence with 95-99% identity thereto; or

(iii) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 83 or an amino acid sequence with 95-99% identity thereto and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 98 or an amino acid sequence with 95-99% identity thereto.

37. The isolated anti-BCMA binding domain of claim 35 or 36, comprising:

(i) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 79 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 94;

(ii) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 81 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 96; or

(iii) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 83 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 98.

38. The isolated anti-BCMA binding domain of any of claims 35-37, comprising:

(i) an amino acid sequence selected from the group consisting of SEQ ID NO: 49, SEQ ID NO: 51, and SEQ ID NO: 53;

(ii) an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications to any of SEQ ID NO: 49, SEQ ID NO: 51, or SEQ ID NO: 53; or

(iii) an amino acid sequence with 95-99% identity to any of SEQ ID NO: 49, SEQ ID NO: 51, or SEQ ID NO: 53.

39. A vector comprising the nucleic acid molecule of any of claims 1-23 or a nucleic acid molecule encoding the CAR polypeptide of any of claims 25-34, wherein the vector is selected from the group consisting of a DNA vector, a RNA vector, a plasmid, a lentivirus vector, an adenoviral vector, and a retrovirus vector.

40. The vector of claim 39, further comprising an EF-1 promoter comprising the nucleotide sequence of SEQ ID NO: 11.

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41. A cell, e.g., an immune effector cell, comprising the nucleic acid molecule of any of claims 1-23, the polypeptide molecule of claim 24, the CAR polypeptide of any of claims 25-34, the anti-BCMA binding domain of any of claims 35-38, or the vector of claim 39 or 40.

42. A method of making a cell, e.g., an immune effector cell, comprising transducing an immune effector cell with the vector of claim 39 or 40.

43. A method of generating a population of RNA-engineered cells comprising introducing an *in vitro* transcribed RNA or synthetic RNA into a cell, where the RNA comprises the nucleic acid molecule of any of claims 1-23 or a nucleic acid encoding the CAR polypeptide of any of claims 25-34.

44. A method of providing an anti-tumor immunity in a mammal having a disease associated with the expression of BCMA, the method comprising administering to the mammal an effective amount of a cell, e.g., a population of immune effector cells, comprising the nucleic acid molecule of any of claims 1-23, the polypeptide molecule of claim 24, the CAR polypeptide of any of claims 25-34, the anti-BCMA binding domain of any of claims 35-38, or the vector of claim 39 or 40, wherein the disease associated with the expression of BCMA is a cancer or malignancy, or a precancerous condition chosen from one or more of a myelodysplasia, a myelodysplastic syndrome or a pre-leukemia.

45. Use of a composition comprising an effective amount of a cell, e.g., a population of immune effector cells, comprising the nucleic acid molecule of any of claims 1-23, the polypeptide molecule of claim 24, the CAR polypeptide of any of claims 25-34, the anti-BCMA binding domain of any of claims 35-38, or the vector of claim 39 or 40 in the manufacture of a medicament for providing anti-tumor immunity in a mammal having a disease associated with the expression of BCMA, wherein the disease associated with the expression of BCMA is a cancer or malignancy, or a precancerous condition chosen from one or more of a myelodysplasia, a myelodysplastic syndrome or a pre-leukemia.

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46. The method of claim 44 or the use of claim 45, wherein the cell is an autologous T cell or an allogeneic T cell.

47. A method of treating a mammal having a disease associated with expression of BCMA comprising administering to the mammal an effective amount of a cell, e.g., a population of immune effector cells, comprising the nucleic acid molecule of any of claims 1-23, the polypeptide molecule of claim 24, the CAR polypeptide of any of claims 25-34, the anti-BCMA binding domain of any of claims 35-38, or the vector of claim 39 or 40, wherein the disease associated with expression of BCMA is:

(i) a cancer or malignancy, or a precancerous condition chosen from one or more of a myelodysplasia, a myelodysplastic syndrome or a pre-leukemia, or

(ii) a non-cancer related indication associated with expression of BCMA.

48. Use of a composition comprising an effective amount of a cell, e.g., a population of immune effector cells, comprising the nucleic acid molecule of any of claims 1-23, the polypeptide molecule of claim 24, the CAR polypeptide of any of claims 25-34, the anti-BCMA binding domain of any of claims 35-38, or the vector of claim 39 or 40 in the manufacture of a medicament for treating a mammal having a disease associated with expression of BCMA, wherein the disease associated with expression of BCMA is:

(i) a cancer or malignancy, or a precancerous condition chosen from one or more of a myelodysplasia, a myelodysplastic syndrome or a pre-leukemia, or

(ii) a non-cancer related indication associated with expression of BCMA.

49. The method of claim 44 or 47 or the use of claim 45or 48, wherein the disease is a hematologic cancer.

50. The method of any of claims 44, 47, or 49or the use of any of claims 45 or 48-49 -, wherein the disease is an acute leukemia chosen from B-cell acute lymphoid leukemia ("BALL"), T-cell acute lymphoid leukemia ("TALL"), acute lymphoid leukemia (ALL); chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL); B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT

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lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia; a prostate cancer (e.g., castrate-resistant or therapy-resistant prostate cancer, or metastatic prostate cancer), pancreatic cancer, lung cancer; or a plasma cell proliferative disorder (e.g., asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), monoclonal gammapathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia, plasmacytomas (e.g., plasma cell dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, and POEMS syndrome (also known as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome), or a combination thereof.

51. The method of any of claims 44or 47, or 49-50-or the use of any of claims 45 or 48-50-, wherein the cell, e.g., the population of immune effector cells, is to be administered in combination with one or more of:

(i) an agent that increases the efficacy of the cell comprising the nucleic acid molecule or CAR polypeptide;

(ii) an agent that ameliorates one or more side effects associated with administration of the cell comprising the nucleic acid molecule or CAR polypeptide; or

(iii) an agent that treats the disease associated with expression of BCMA.

52. The method of any of claims 44, 47or 49-51or the use of any of claims 45 or 48-51, wherein the cell, e.g., a population of immune effector cells, is to be administered in combination with a PD-L1 inhibitor, e.g., an anti-PD-L1 antibody.

53. Use of the isolated nucleic acid molecule of any of claims 1-23, the isolated polypeptide molecule of claim 24, the isolated CAR polypeptide of any of claims 25-34, the isolated anti-BCMA binding domain of any of claims 35-38, the vector of claims 39 or 40, or the cell of claim 41 in the manufacture of a medicament for the treatment of a disease associated with the expression of BCMA, wherein the disease associated with expression of BCMA is:

(i) a cancer or malignancy, or a precancerous condition chosen from one or more of a myelodysplasia, a myelodysplastic syndrome or a pre-leukemia, or

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(ii) a non-cancer related indication associated with expression of BCMA.

54. The cell, e.g., a population of immune effector cells, of claim 41, further expressing an inhibitory molecule that comprises a first polypeptide that comprises at least a portion of an inhibitory molecule, associated with a second polypeptide that comprises a positive signal from an intracellular signaling domain.

55. The cell of claim 55, wherein the inhibitory molecule comprises a first polypeptide that comprises at least a portion of PD1 and a second polypeptide comprising a costimulatory domain and a primary signaling domain.

56. The method or use of claim 52, wherein the agent is an mTOR inhibitor and the subject is to be administered a low, immune enhancing, dose of an mTOR inhibitor, e.g., RAD001 or rapamycin.

57. The method or use of claim 57, wherein the mTOR inhibitor is to be administered for an amount of time sufficient to decrease the proportion of PD-1 positive T cells, increase the proportion of PD-1 negative T cells, or increase the ratio of PD-1 negative T cells/ PD-1 positive T cells, in the peripheral blood of the subject, or in a preparation of T cells isolated from the subject.

58. The method of any of claims 47, 49-53, 57 or 58 or the use of any of claims 48-53, 57, or 58, wherein the cell is to be administered in combination with a cell comprising a CD19 CAR molecule.

59. The method of any of claims 47, 49-53, or 57-59 or the use of any of claims 48-53 or 57-59, wherein the disease associated with expression of BCMA is multiple myeloma, e.g., CD19-negative multiple myeloma.

60. The method or the use of claim 60, wherein:

(i) the cell expressing the BCMA CAR molecule is to be administered before, subsequent to, or simultaneously with administration of the cell comprising the CD19 CAR molecule;

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(ii) the BCMA CAR molecule and the CD19 CAR molecule are expressed in the same cell; or

(iii) the BCMA CAR molecule and the CD19 CAR molecule are the same, said CAR molecules defining a bispecific CAR having an immunoglobulin variable domain sequence specific to CD19.

61. The method of any of claims 47, 49-53, or 57-61 or the use of any of claims 48-53 or 57-61, wherein the cell is to be administered to the subject by dose fractionation, e.g., one, two, three, or more separate administrations of a partial dose.

62. The method or the use of claim 61, wherein a first percentage of the total dose is to be administered on a first day of treatment, a second percentage of the total dose is to be administered on a subsequent (e.g., second, third, fourth, fifth, sixth, or seventh or later) day of treatment, and optionally, a third percentage (e.g., the remaining percentage) of the total dose is to be administered on a yet subsequent (e.g., third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, or later) day of treatment.

63. The method or use of claim 62 or claim 63, wherein 10% of the total dose of cells is to be administered on the first day, 30% of the total dose of cells is to be administered on the second day, and the remaining 60% of the total dose of cells is to be administered on the third day of treatment.

64. The method or use of any of claims 62 to 64, wherein the total cell dose comprises 1 to 5 x 10^7 or 1 to 5 x 10^8 cells.

65. A pharmaceutical composition comprising a population of cells in combination with one or more pharmaceutically or physiologically acceptable carriers, diluents or excipients, wherein the population of cells comprises the cell of claim 41.

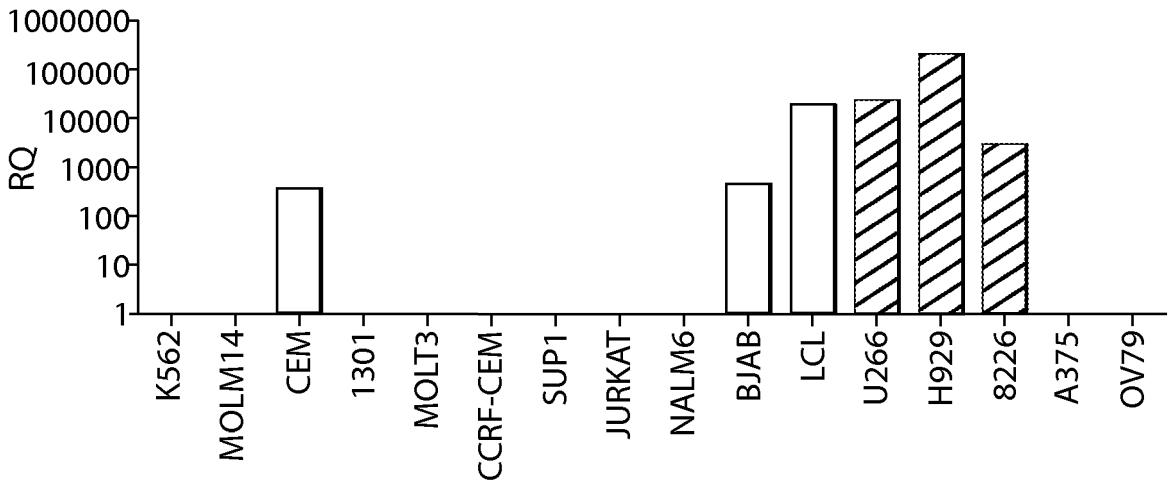

1000000
100000
10000
1000
100
10
1
RQ
K562
MOLM14
CEM
1301
MOLT3
CCRF-CEM
SUP1
JURKAT
NALM6
BJAB
LCL
U266
H929
8226
A375
OV79

FIG. 1A

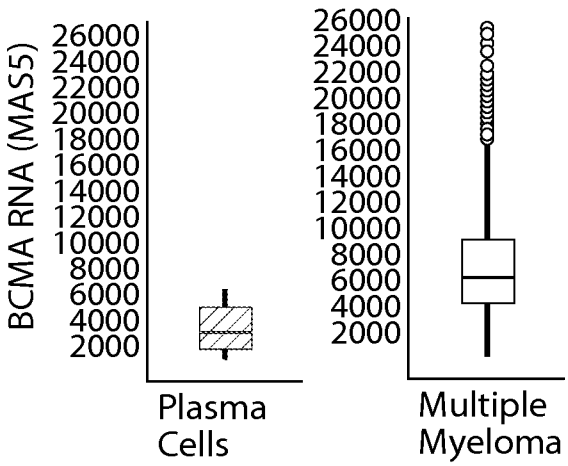

BCMA RNA (MAS5)
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
Plasma Cells
Multiple Myeloma

FIG. 1B

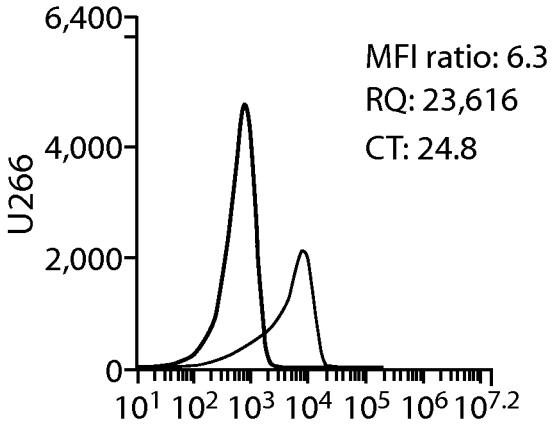


FIG. 2A

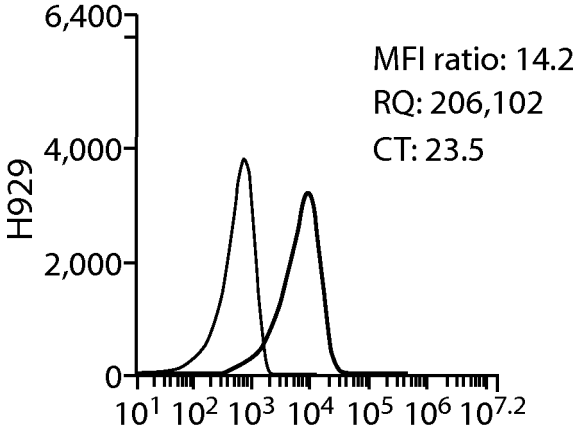


FIG. 2B

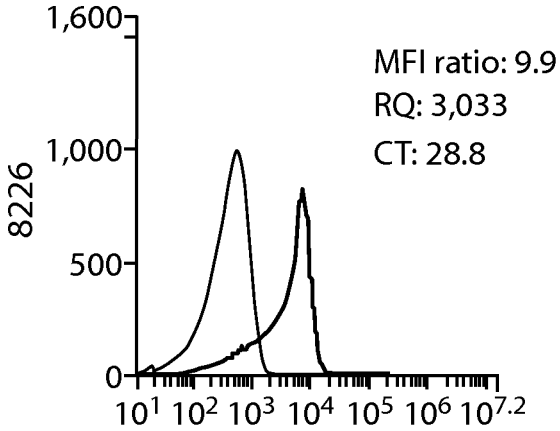


FIG. 2C

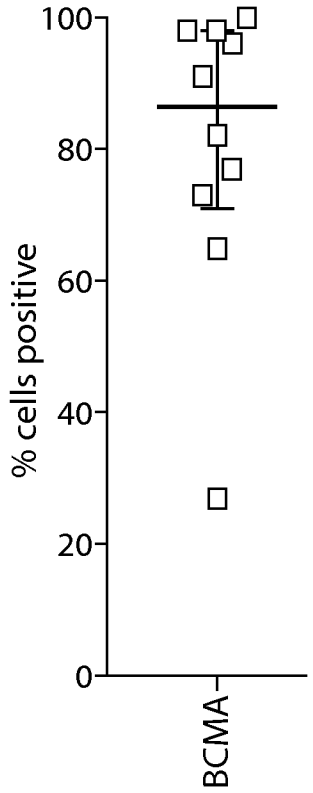

100
80
60
40
20
0
% cells positive
BCMA

FIG. 2D

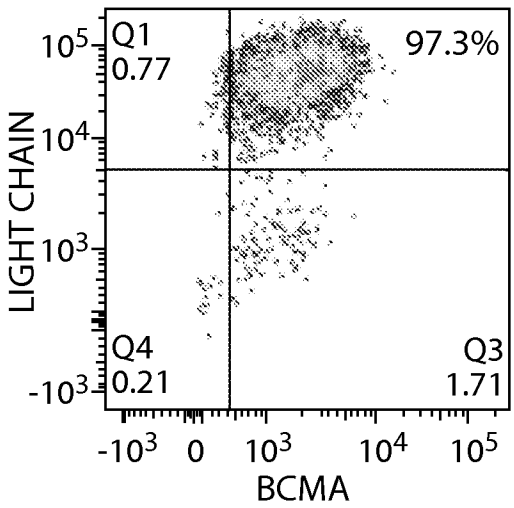

Q1
0.77
97.3%
Q4
0.21
Q3
1.71
LIGHT CHAIN
BCMA
10^5
10^4
10^3
-10^3
0
10^3
10^4
10^5

FIG. 2E

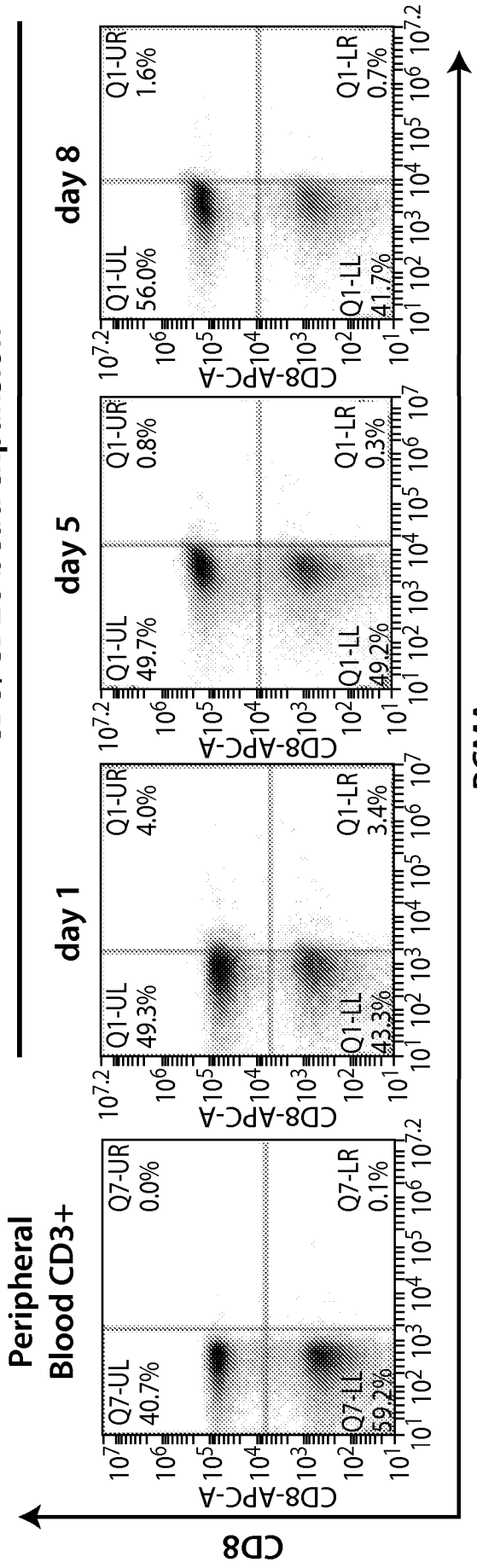

CD3/CD28 bead expansion
day 1
day 5
day 8
Peripheral Blood CD3+
Q7-UL 40.7%
Q7-UR 0.0%
Q7-LL 59.2%
Q7-LR 0.1%
Q1-UL 49.3%
Q1-UR 4.0%
Q1-LL 43.3%
Q1-LR 3.4%
Q1-UL 49.7%
Q1-UR 0.8%
Q1-LL 49.2%
Q1-LR 0.3%
Q1-UL 56.0%
Q1-UR 1.6%
Q1-LL 41.7%
Q1-LR 0.7%
CD8-APC-A
CD8
BCMA

FIG. 3A

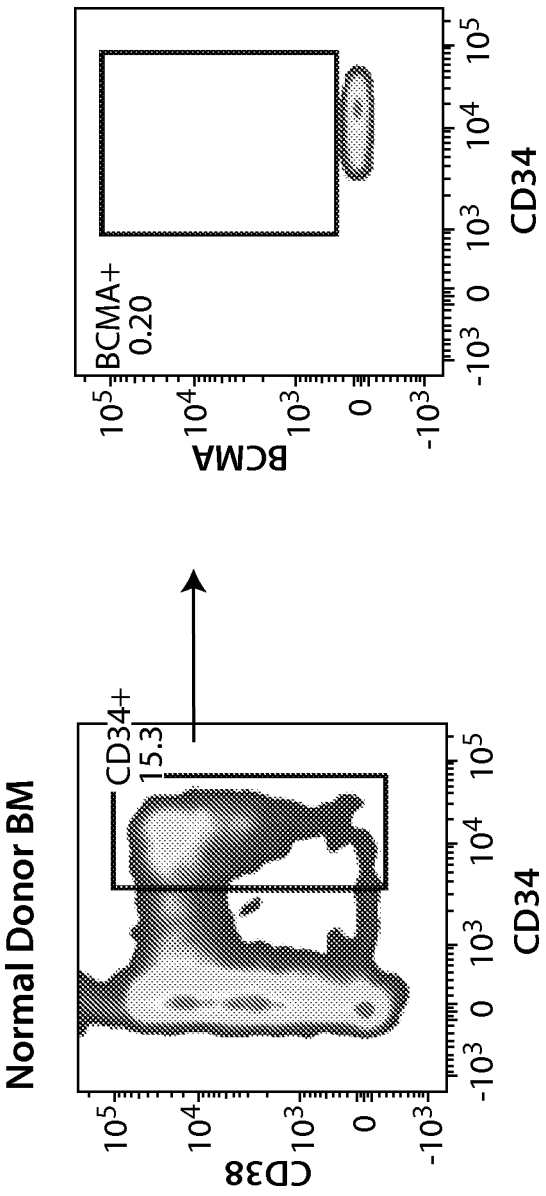


FIG. 3B

Lymph node

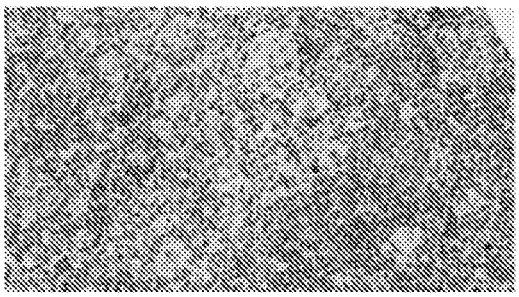


FIG. 4A

Tonsil

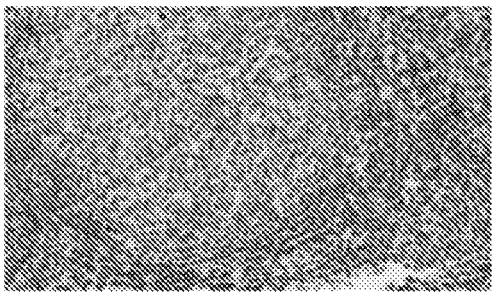


FIG. 4B

Lung

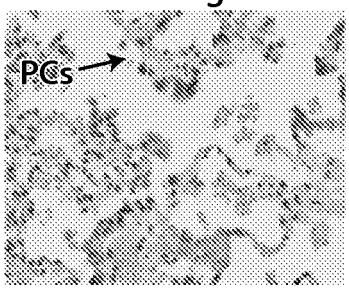


FIG. 4C

Pancreas

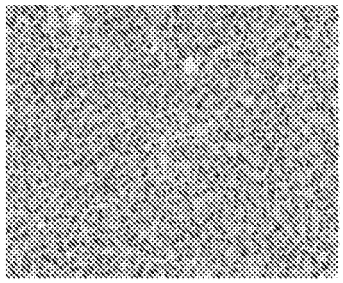


FIG. 4D

Thyroid

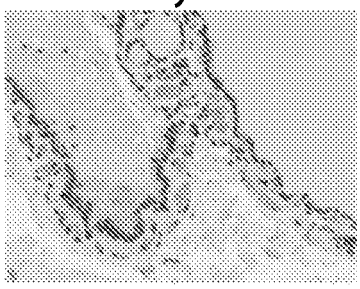


FIG. 4E

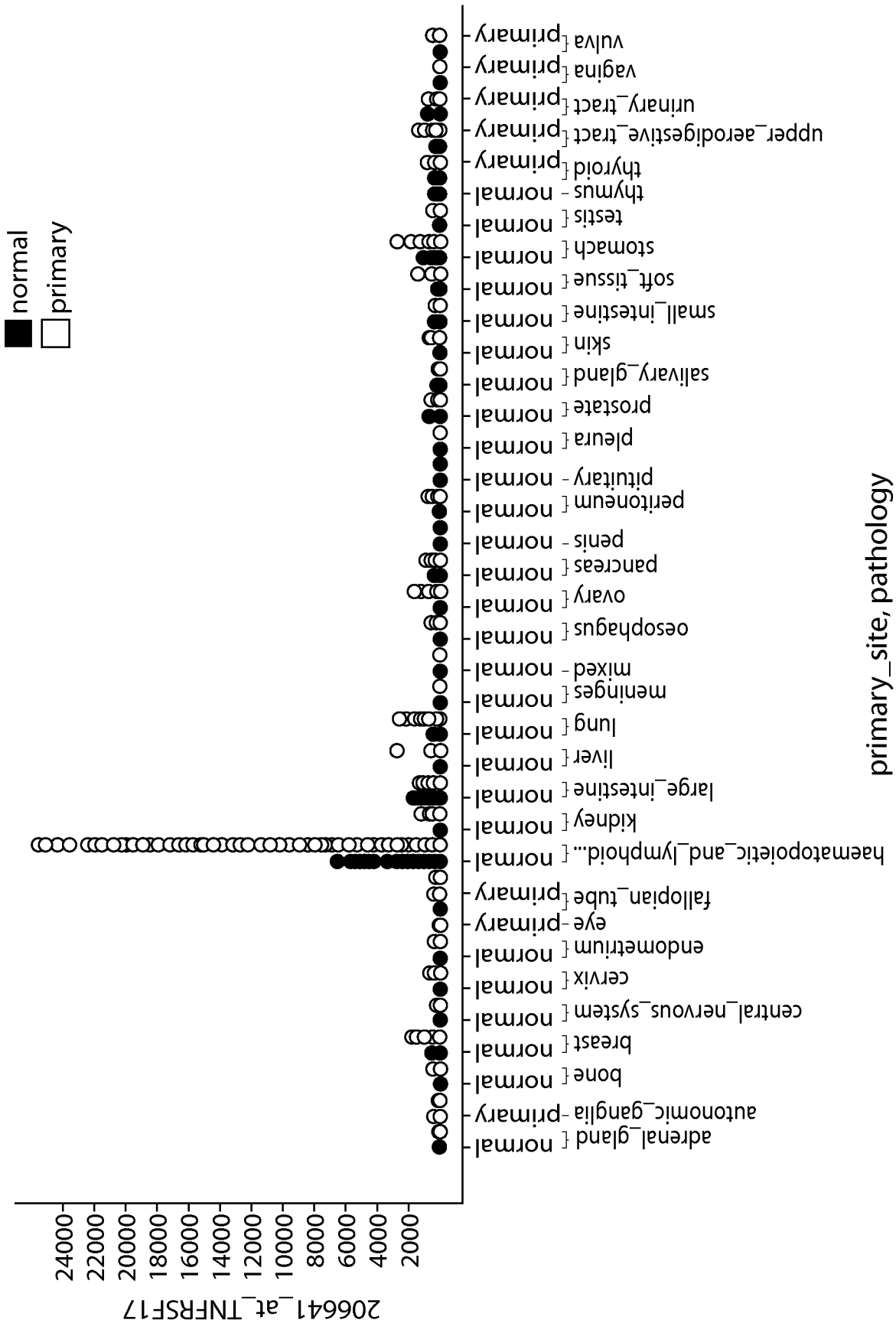

normal
primary
2066 41_at_TNFRSF17
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
adrenal_gland [normal
autonomic_ganglia - primary
bone [normal
breast [normal
central_nervous_system [normal
cervix [normal
endometrium [normal
eye - primary
fallopian_tube [primary
haematopoietic_and_lymphoid... [normal
kidney [normal
large_intestine [normal
liver [normal
lung [normal
meninges [normal
mixed - normal
oesophagus [normal
ovary [normal
pancreas [normal
penis - normal
peritoneum [normal
pituitary - normal
pleura [normal
prostate [normal
salivary_gland [normal
skin [normal
small_intestine [normal
soft_tissue [normal
stomach [normal
testis [normal
thymus - normal
thyroid [primary
upper_aerodigestive_tract [primary
urinary_tract [primary
vagina [primary
vulva [primary
primary_site, pathology

FIG. 4F

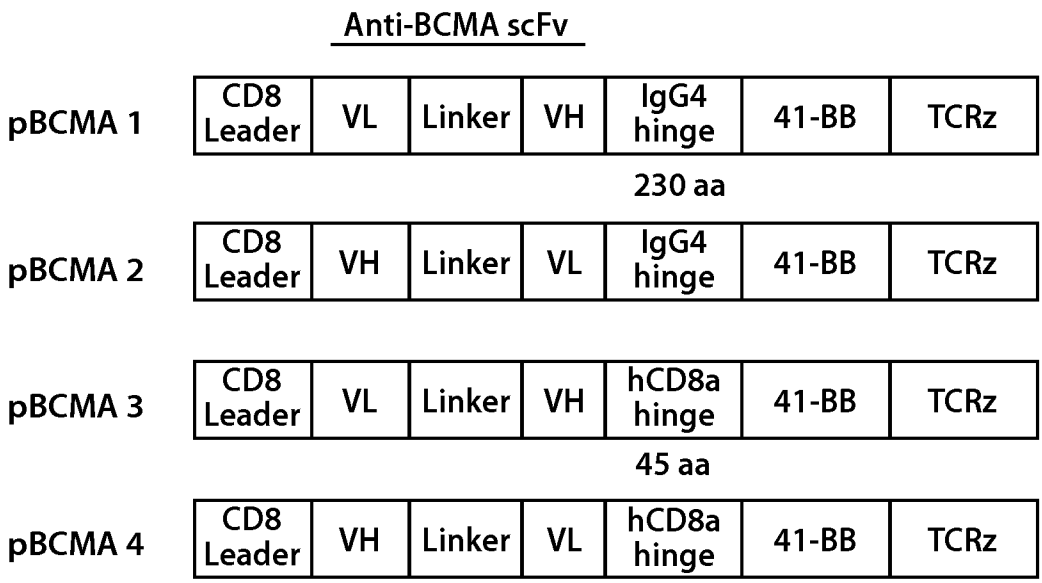

Anti-BCMA scFv
pBCMA 1
CD8 Leader
VL
Linker
VH
IgG4 hinge
41-BB
TCRz
230 aa
pBCMA 2
CD8 Leader
VH
Linker
VL
IgG4 hinge
41-BB
TCRz
pBCMA 3
CD8 Leader
VL
Linker
VH
hCD8a hinge
41-BB
TCRz
45 aa
pBCMA 4
CD8 Leader
VH
Linker
VL
hCD8a hinge
41-BB
TCRz

FIG. 5

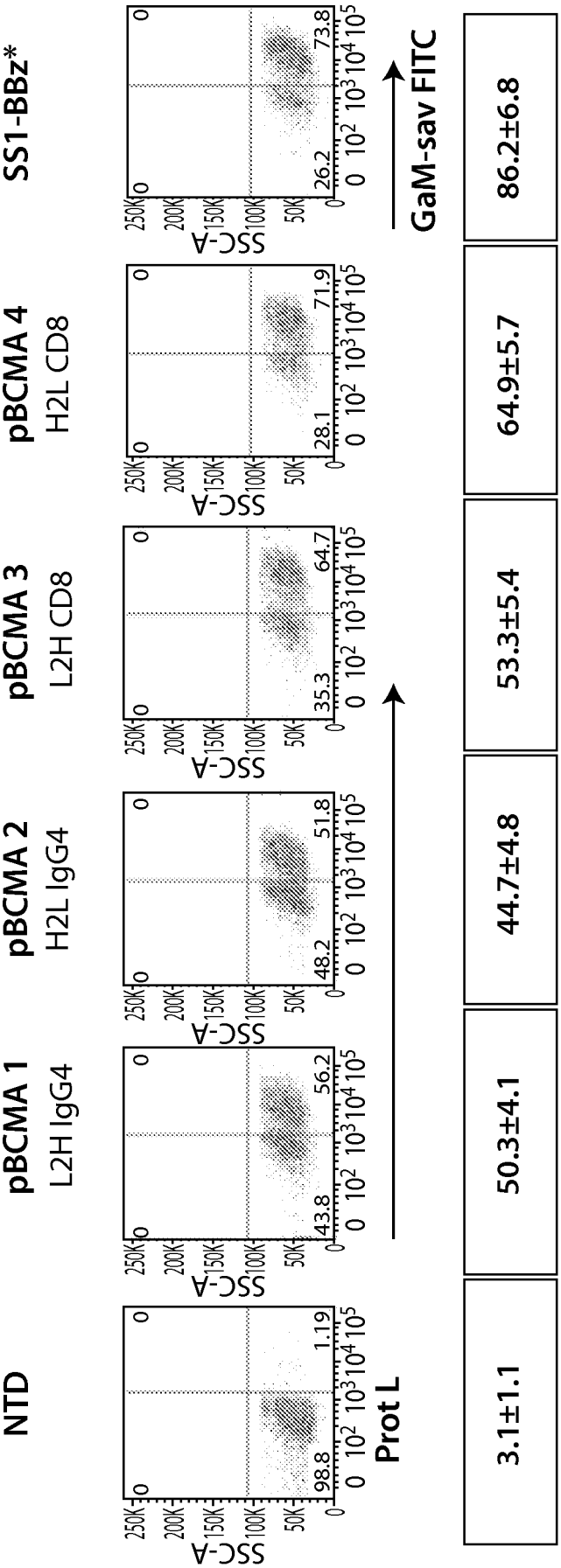

NTD
pBCMA 1
L2H IgG4
pBCMA 2
H2L IgG4
pBCMA 3
L2H CD8
pBCMA 4
H2L CD8
SS1-BBz*
SSC-A
Prot L
GaM-sav FITC
98.8
1.19
43.8
56.2
48.2
51.8
35.3
64.7
28.1
71.9
26.2
73.8
3.1±1.1
50.3±4.1
44.7±4.8
53.3±5.4
64.9±5.7
86.2±6.8

FIG. 6

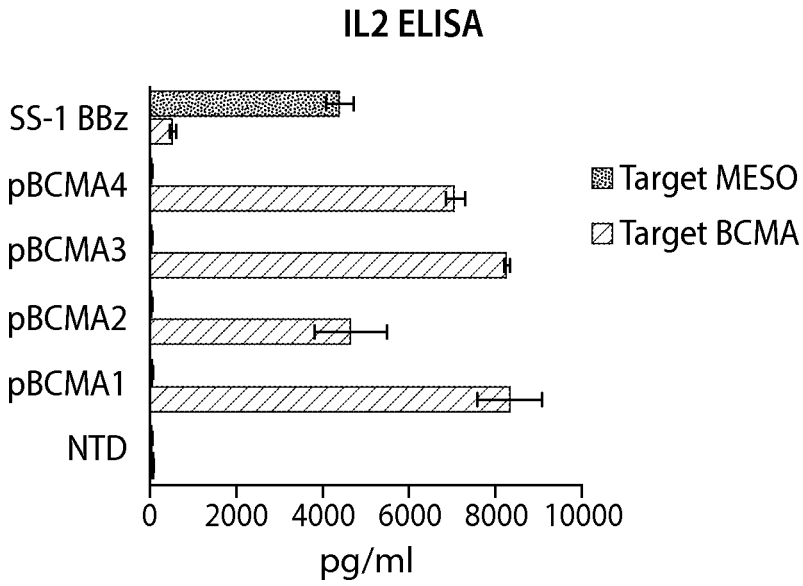

IL2 ELISA
SS-1 BBz
pBCMA4
pBCMA3
pBCMA2
pBCMA1
NTD
Target MESO
Target BCMA
0
2000
4000
6000
8000
10000
pg/ml

FIG. 7A

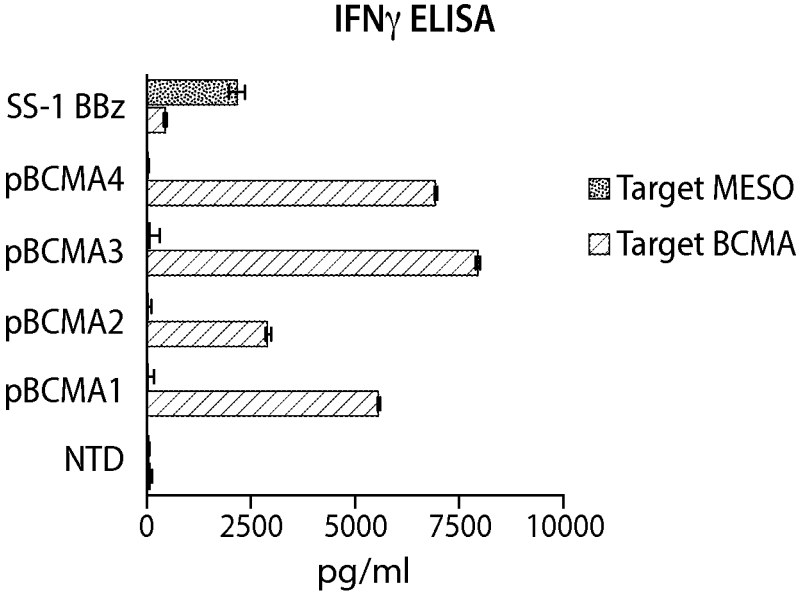

IFNγ ELISA
SS-1 BBz
pBCMA4
pBCMA3
pBCMA2
pBCMA1
NTD
Target MESO
Target BCMA
0
2500
5000
7500
10000
pg/ml

FIG. 7B

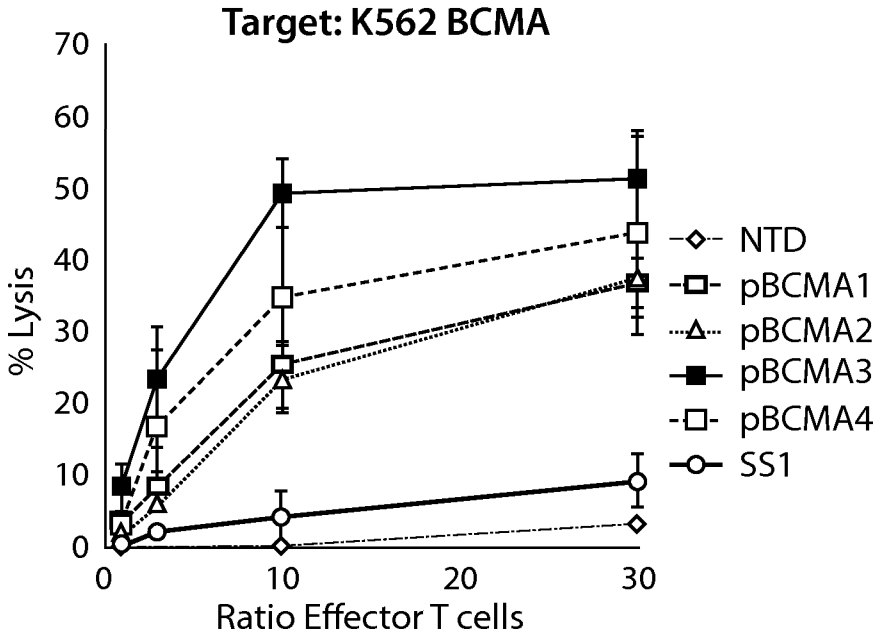

Target: K562 BCMA
% Lysis
70
60
50
40
30
20
10
0
0
10
20
30
Ratio Effector T cells
NTD
pBCMA1
pBCMA2
pBCMA3
pBCMA4
SS1

FIG. 8A

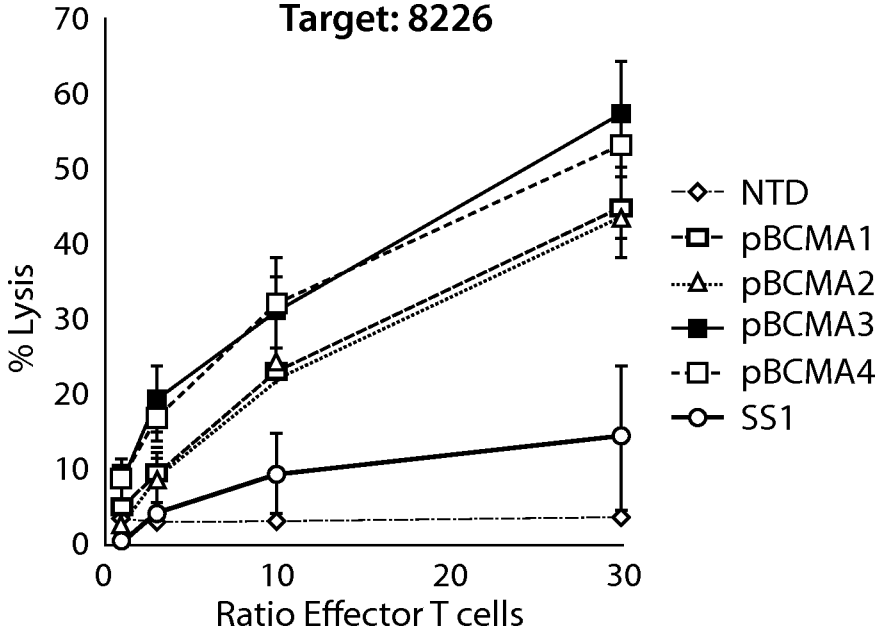

Target: 8226
% Lysis
70
60
50
40
30
20
10
0
0
10
20
30
Ratio Effector T cells
NTD
pBCMA1
pBCMA2
pBCMA3
pBCMA4
SS1

FIG. 8B

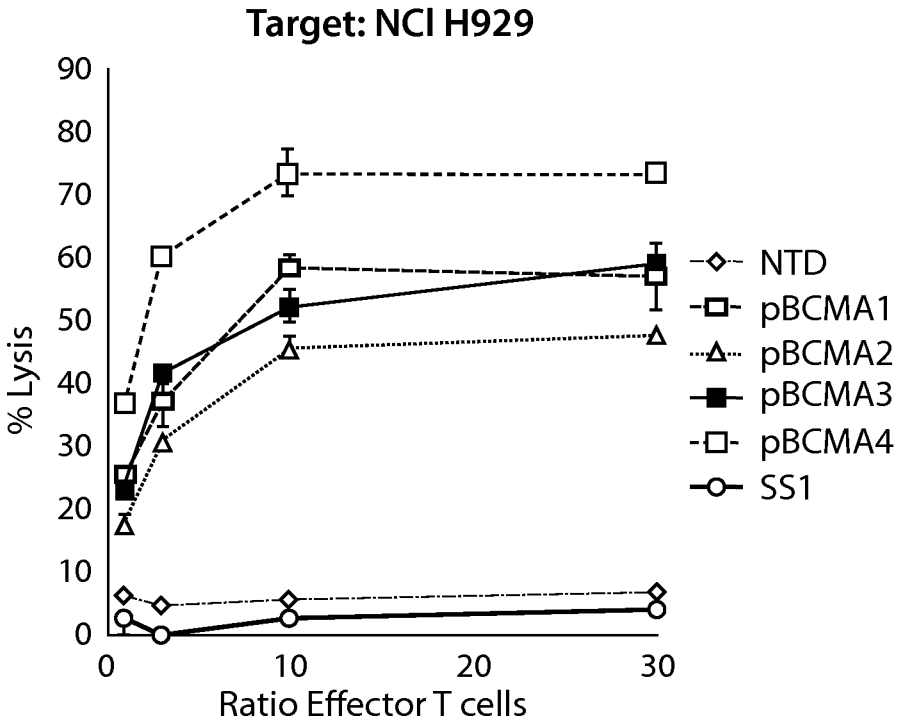

Target: NCl H929
% Lysis
Ratio Effector T cells
NTD
pBCMA1
pBCMA2
pBCMA3
pBCMA4
SS1

FIG. 8C

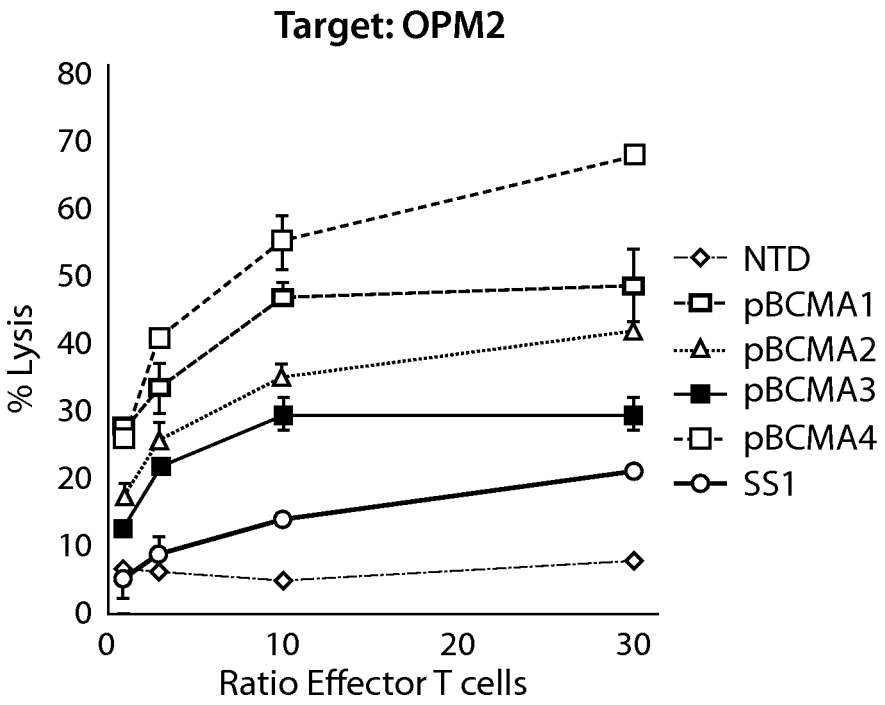

Target: OPM2
% Lysis
Ratio Effector T cells
NTD
pBCMA1
pBCMA2
pBCMA3
pBCMA4
SS1

FIG. 8D

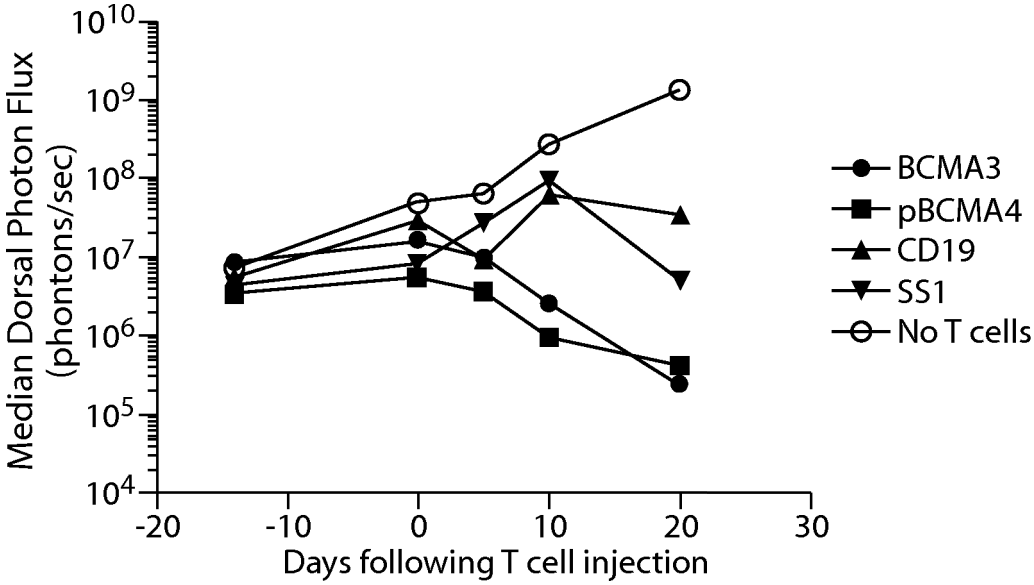

Median Dorsal Photon Flux (phontons/sec)
10^{10}
10^{9}
10^{8}
10^{7}
10^{6}
10^{5}
10^{4}
-20
-10
0
10
20
30
Days following T cell injection
BCMA3
pBCMA4
CD19
SS1
No T cells

FIG. 9A

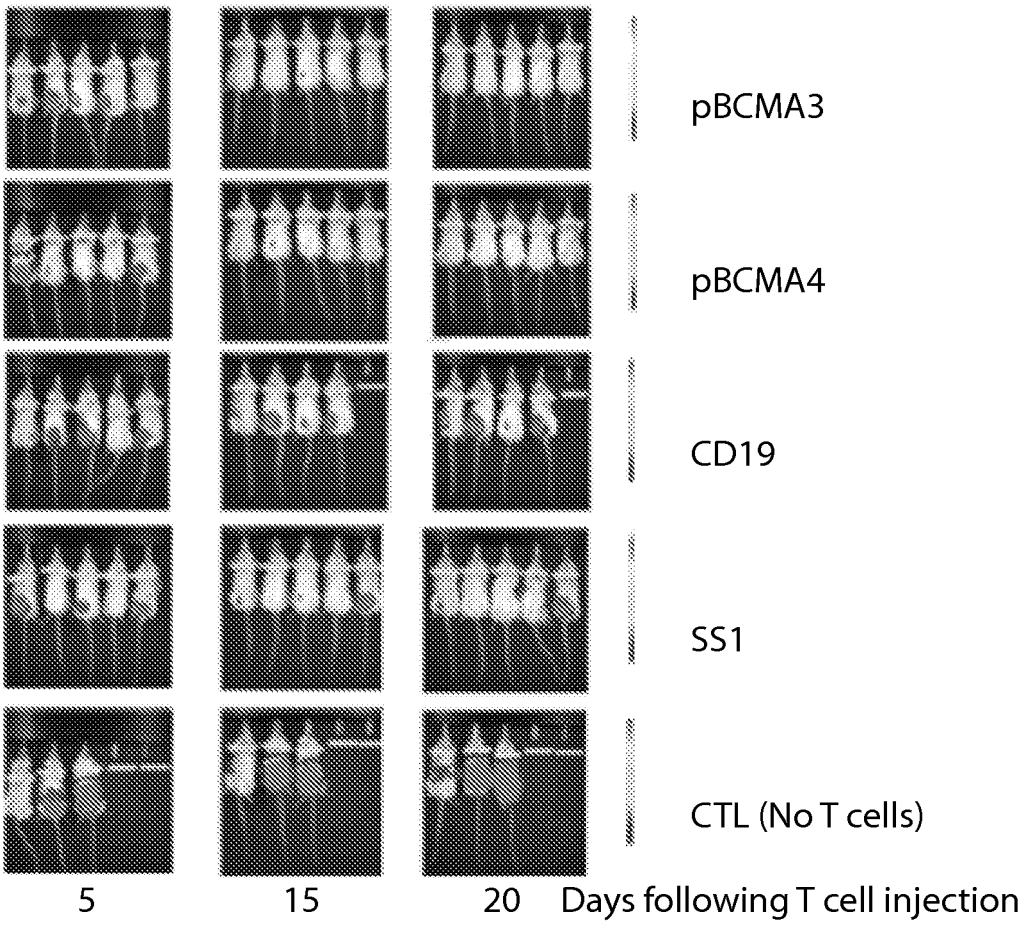

pBCMA3
pBCMA4
CD19
SS1
CTL (No T cells)
5
15
20
Days following T cell injection

FIG. 9B

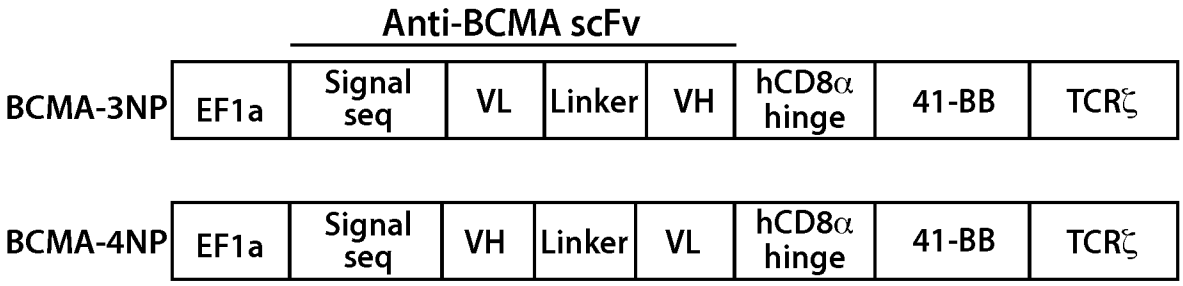


FIG. 10A

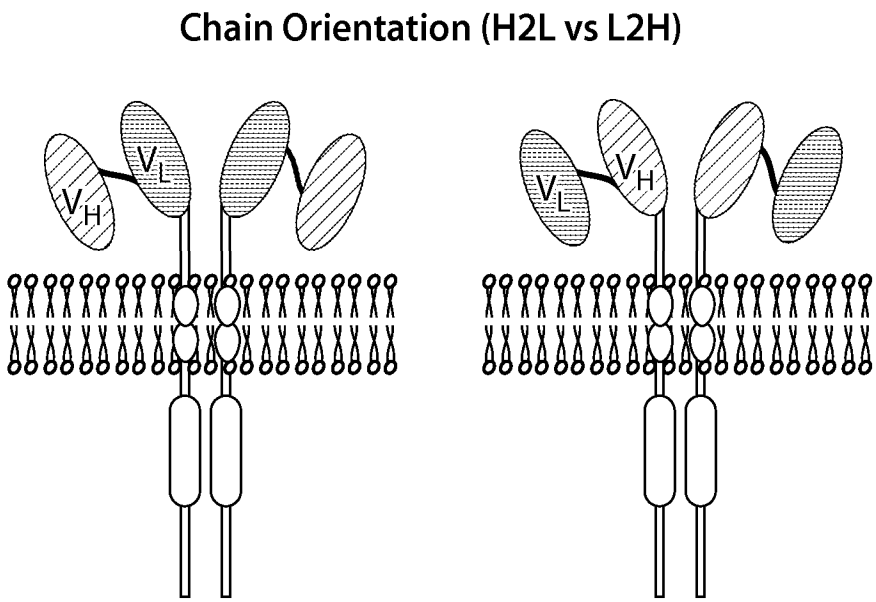


FIG. 10B

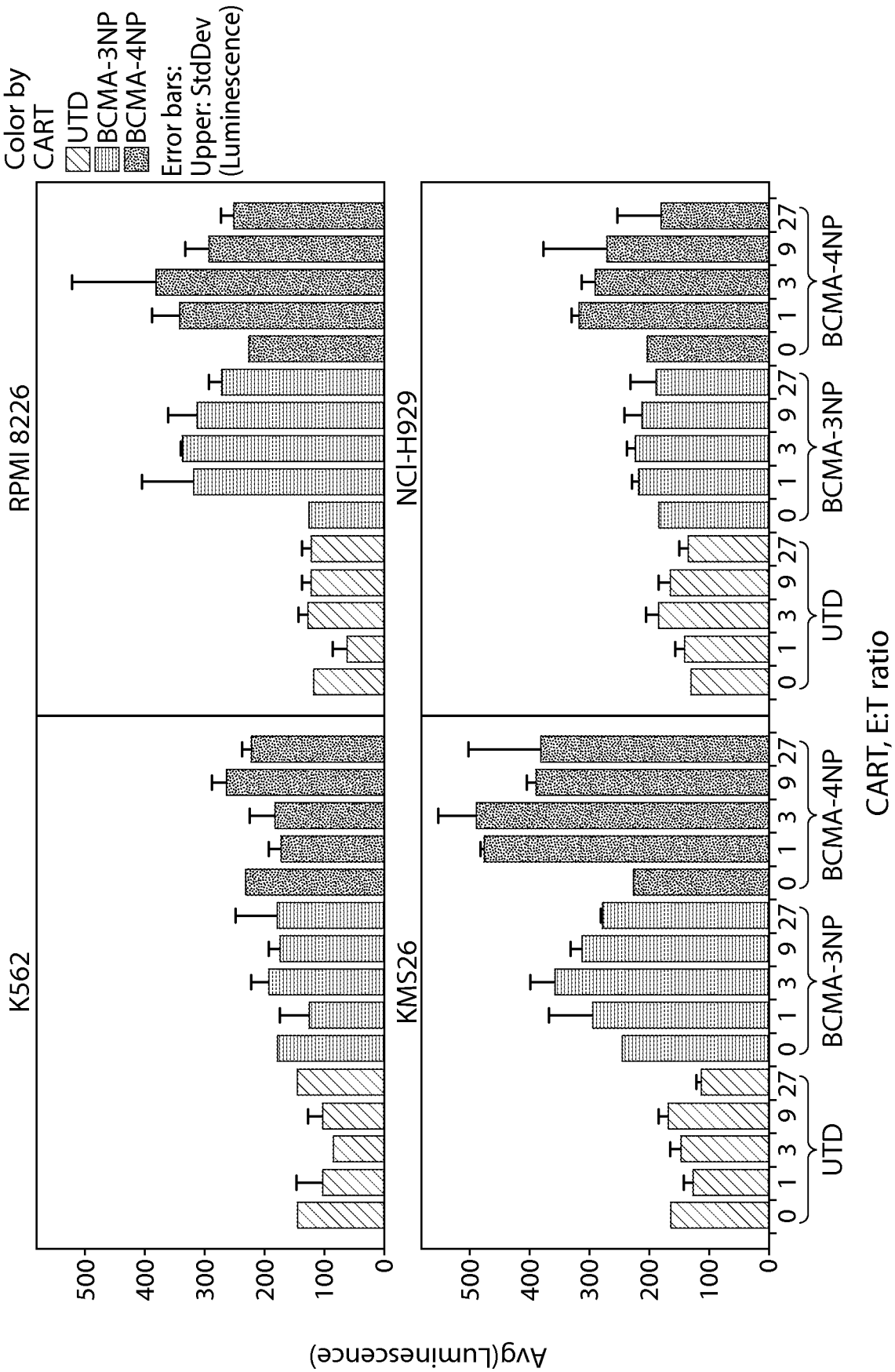

Color by CART
UTD
BCMA-3NP
BCMA-4NP
Error bars: Upper: StdDev (Luminescence)
K562
RPMI 8226
KMS26
NCI-H929
Avg(Luminescence)
0
100
200
300
400
500
0 1 3 9 27
UTD
BCMA-3NP
BCMA-4NP
CART, E:T ratio

FIG. 11

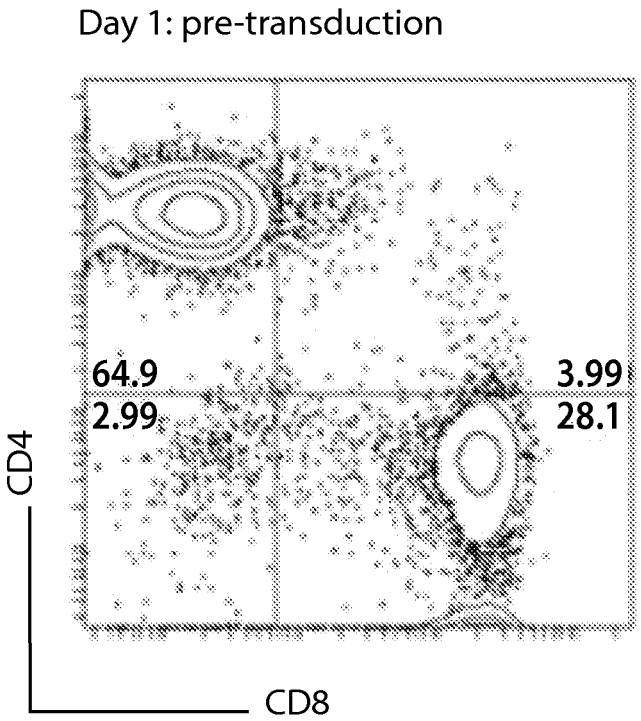


FIG. 12

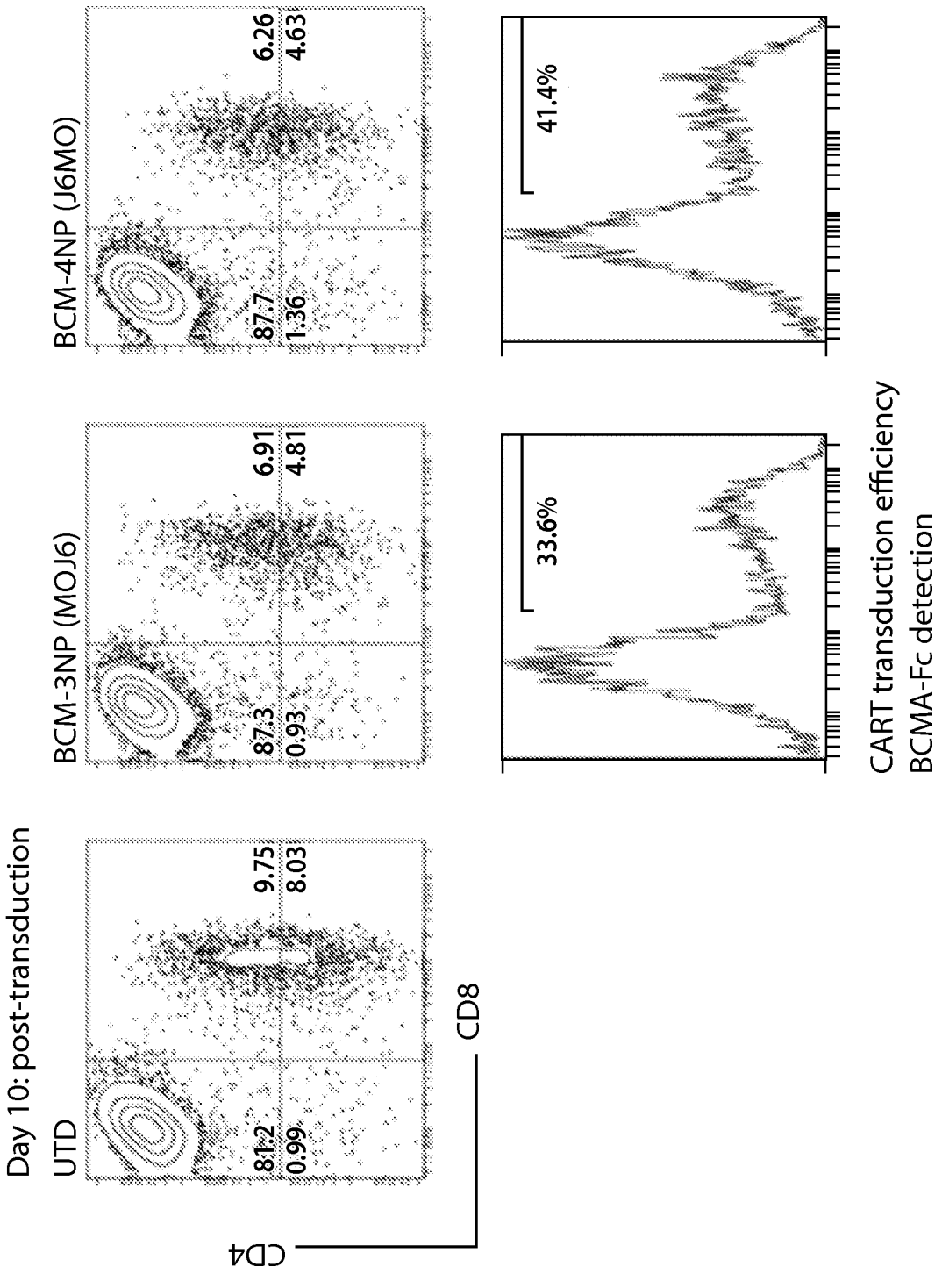

Day 10: post-transduction
UTD
BCM-3NP (MOJ6)
BCM-4NP (J6MO)
CD4
CD8
81.2
0.99
9.75
8.03
87.3
0.93
6.91
4.81
87.7
1.36
6.26
4.63
33.6%
41.4%
CART transduction efficiency
BCMA-Fc detection

FIG. 13

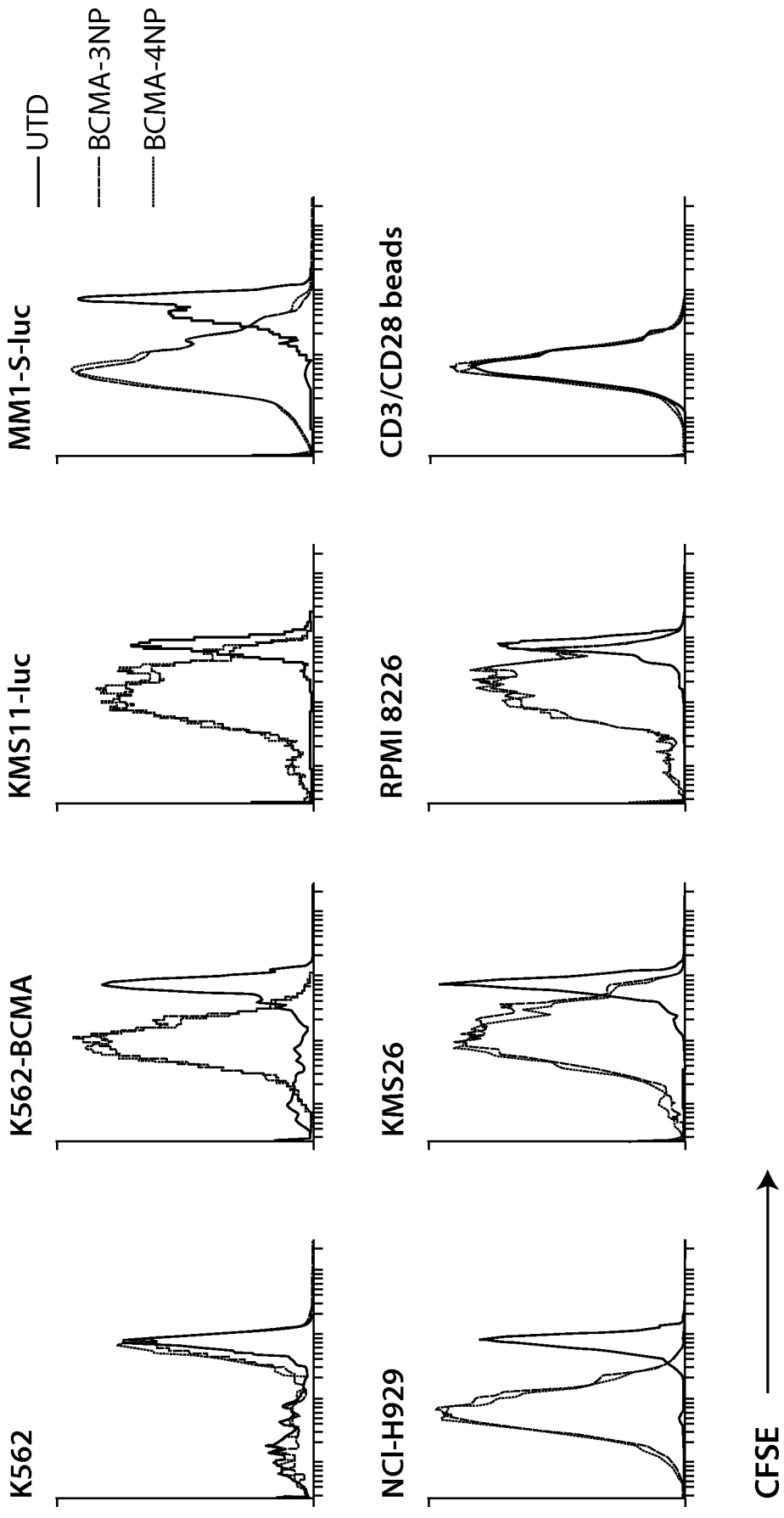

UTD
BCMA-3NP
BCMA-4NP
MM1-S-luc
KMS11-luc
RPMI 8226
CD3/CD28 beads
K562
K562-BCMA
KMS26
NCI-H929
CFSE

FIG. 14

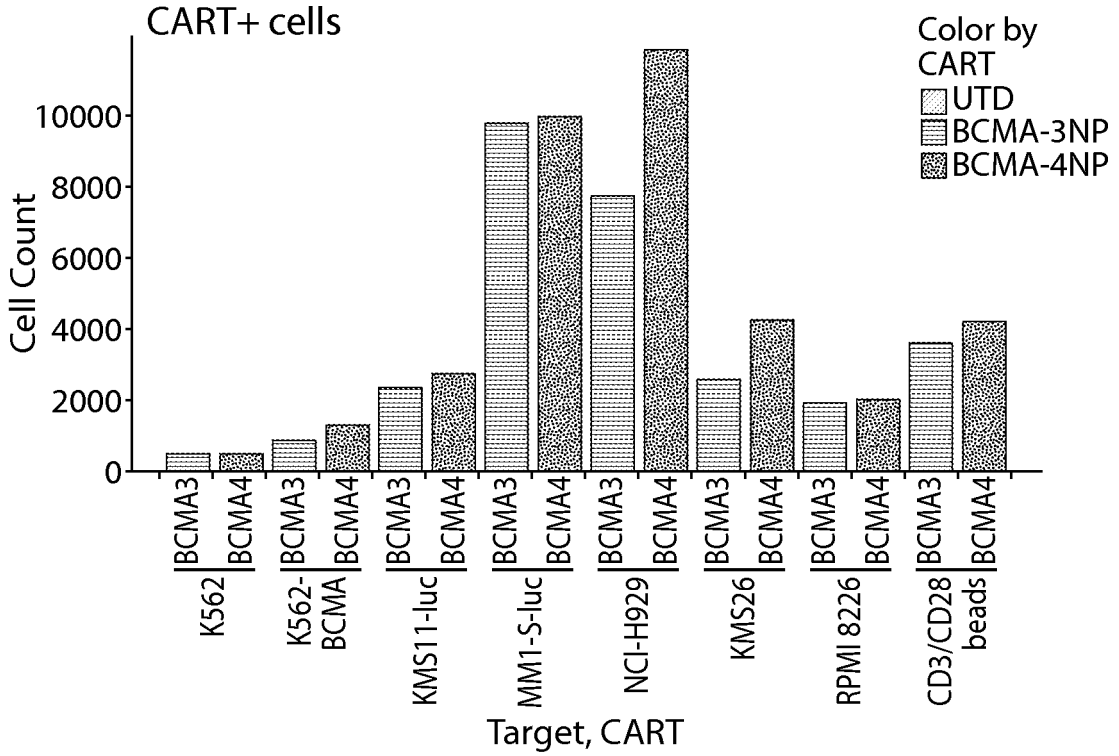


FIG. 15A

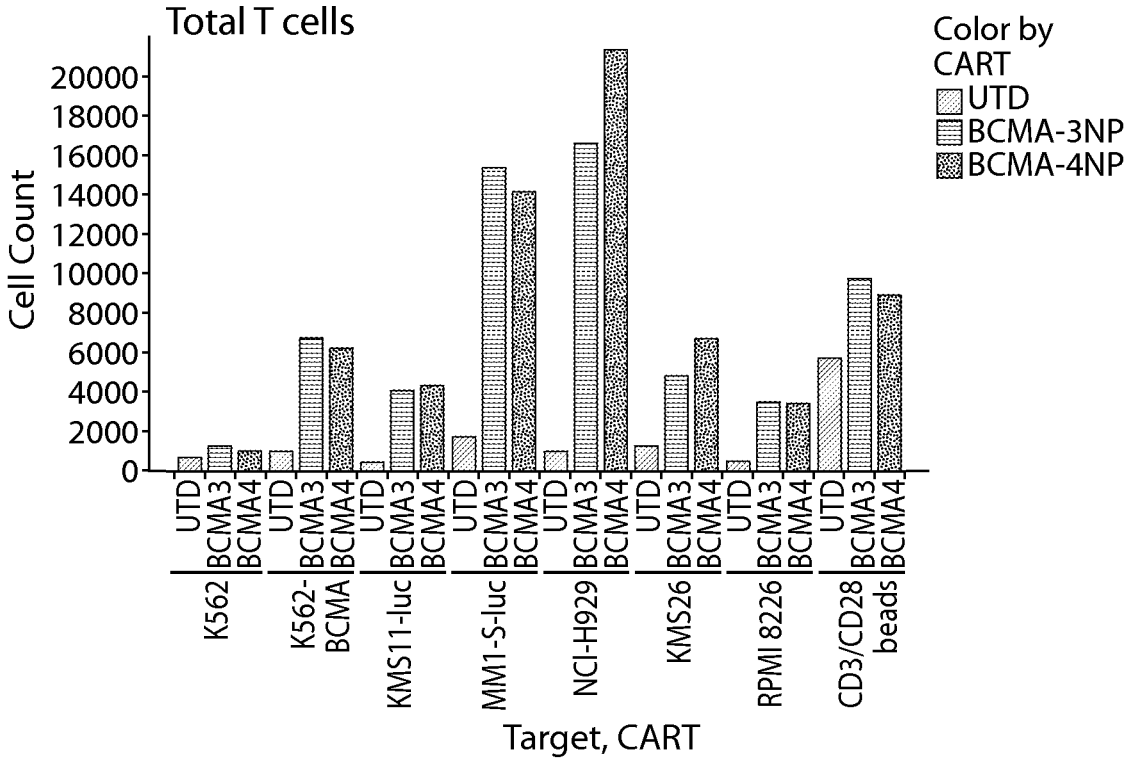


FIG. 15B

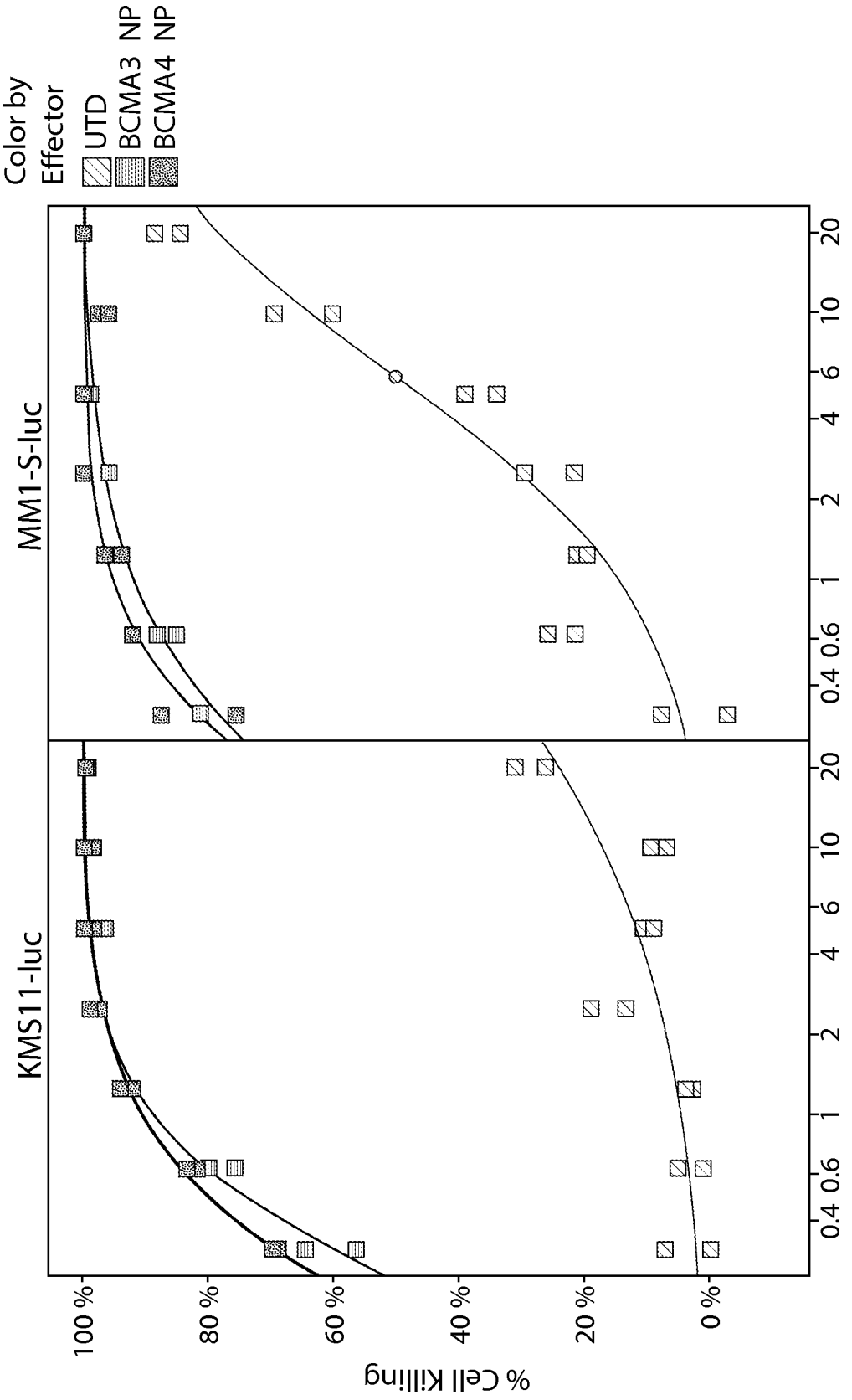

Color by
Effector
UTD
BCMA3 NP
BCMA4 NP
KMS11-luc
MM1-S-luc
% Cell Killing
100 %
80 %
60 %
40 %
20 %
0 %
0.4 0.6 1 2 4 6 10 20
E:T ratio

FIG. 16

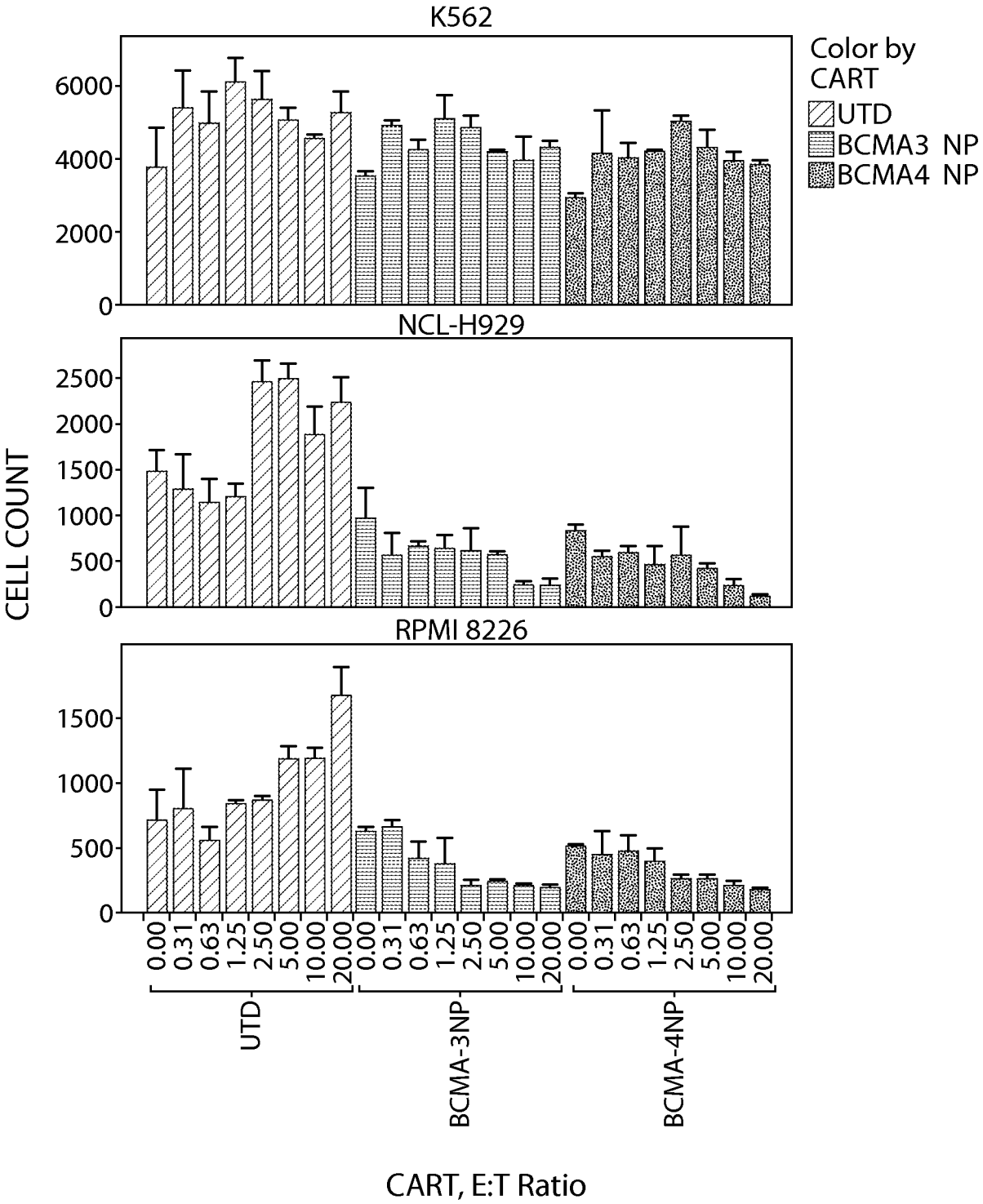

K562
NCL-H929
RPMI 8226
CELL COUNT
6000
4000
2000
0
2500
1500
1000
500
Color by CART
UTD
BCMA3 NP
BCMA4 NP
0.00
0.31
0.63
1.25
2.50
5.00
10.00
20.00
UTD
BCMA-3NP
BCMA-4NP
CART, E:T Ratio

FIG. 17

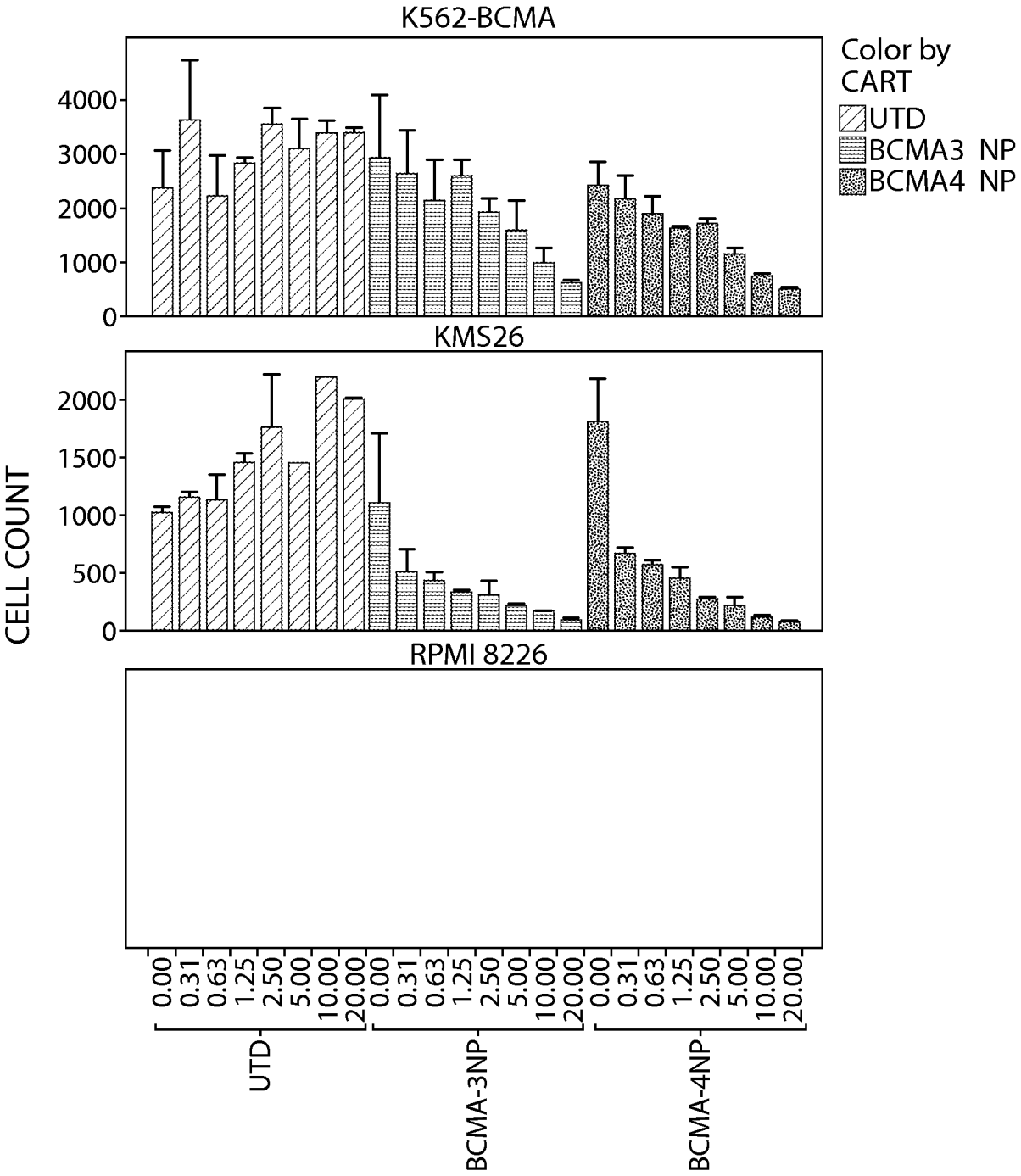

K562-BCMA
KMS26
RPMI 8226
CELL COUNT
4000
3000
2000
1000
0
2000
1500
1000
500
0
Color by CART
UTD
BCMA3 NP
BCMA4 NP
0.00
0.31
0.63
1.25
2.50
5.00
10.00
20.00
UTD
BCMA-3NP
BCMA-4NP
CART, E:T Ratio

FIG. 17 cont.

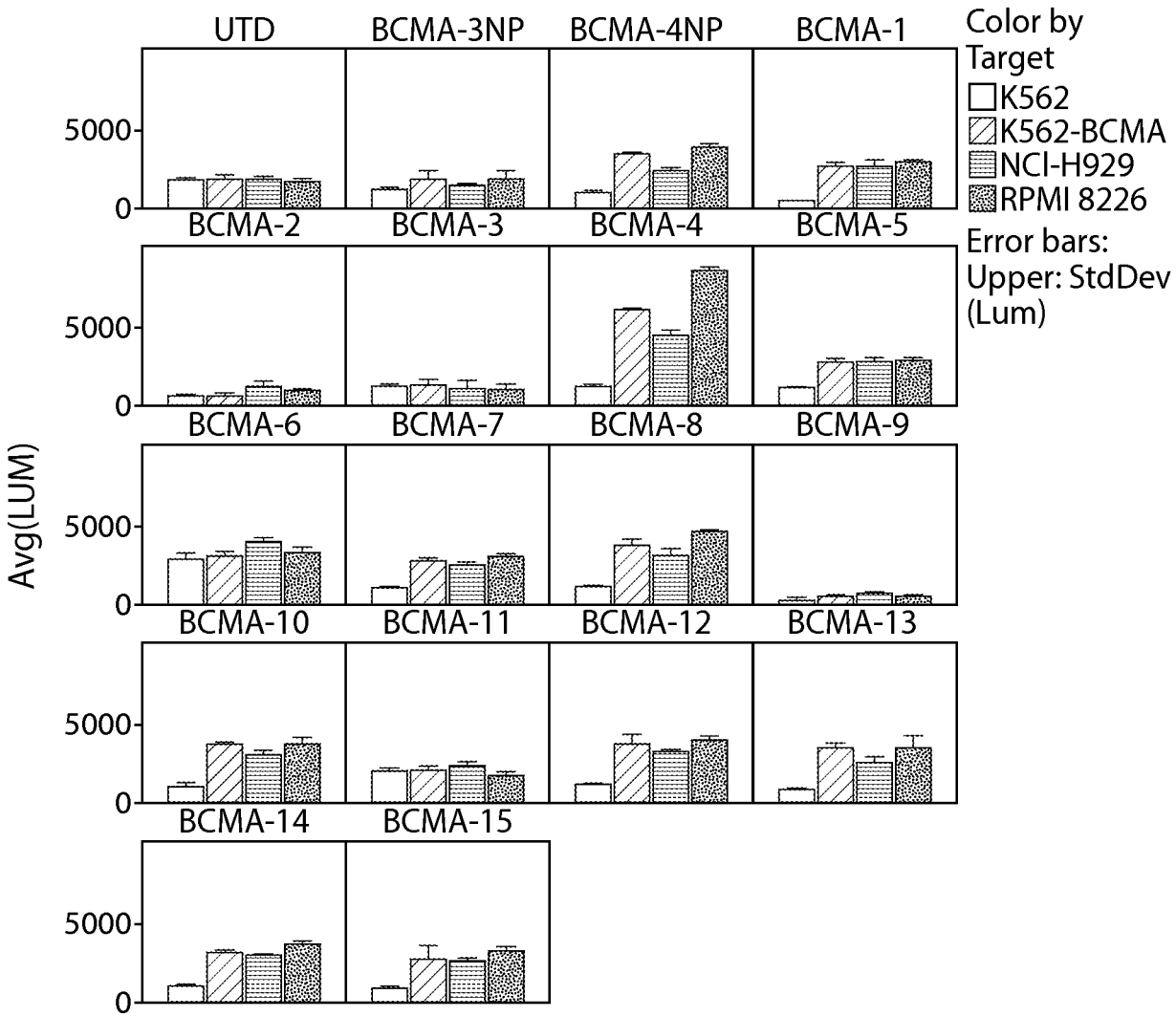

UTD
BCMA-3NP
BCMA-4NP
BCMA-1
BCMA-2
BCMA-3
BCMA-4
BCMA-5
BCMA-6
BCMA-7
BCMA-8
BCMA-9
BCMA-10
BCMA-11
BCMA-12
BCMA-13
BCMA-14
BCMA-15
Avg(LUM)
5000
0
Color by Target
K562
K562-BCMA
NCI-H929
RPMI 8226
Error bars: Upper: StdDev (Lum)

FIG. 18

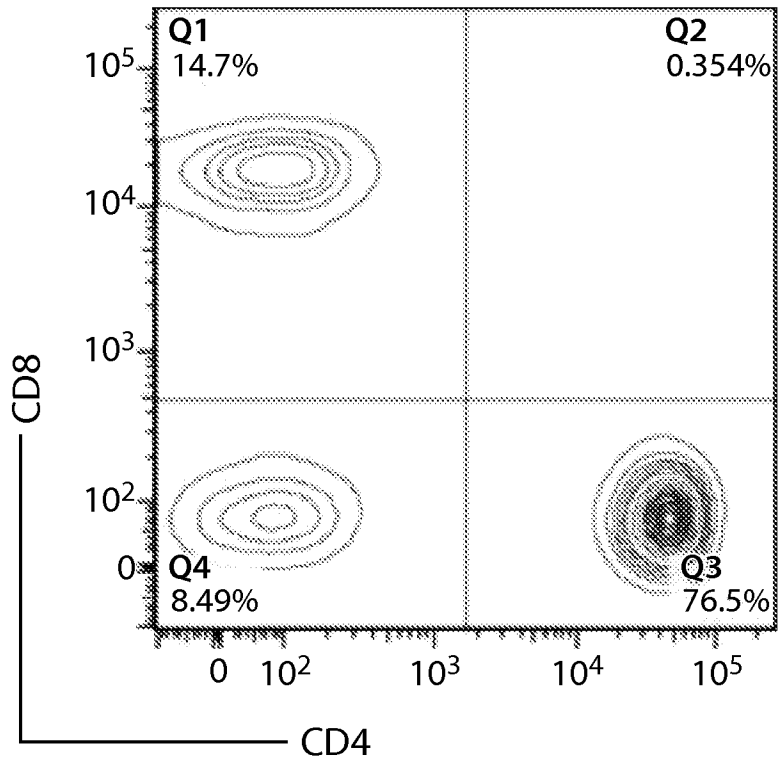

Q1
14.7%
Q2
0.354%
Q4
8.49%
Q3
76.5%
10^5
10^4
10^3
10^2
0
0
10^2
10^3
10^4
10^5
CD8
CD4

FIG. 19

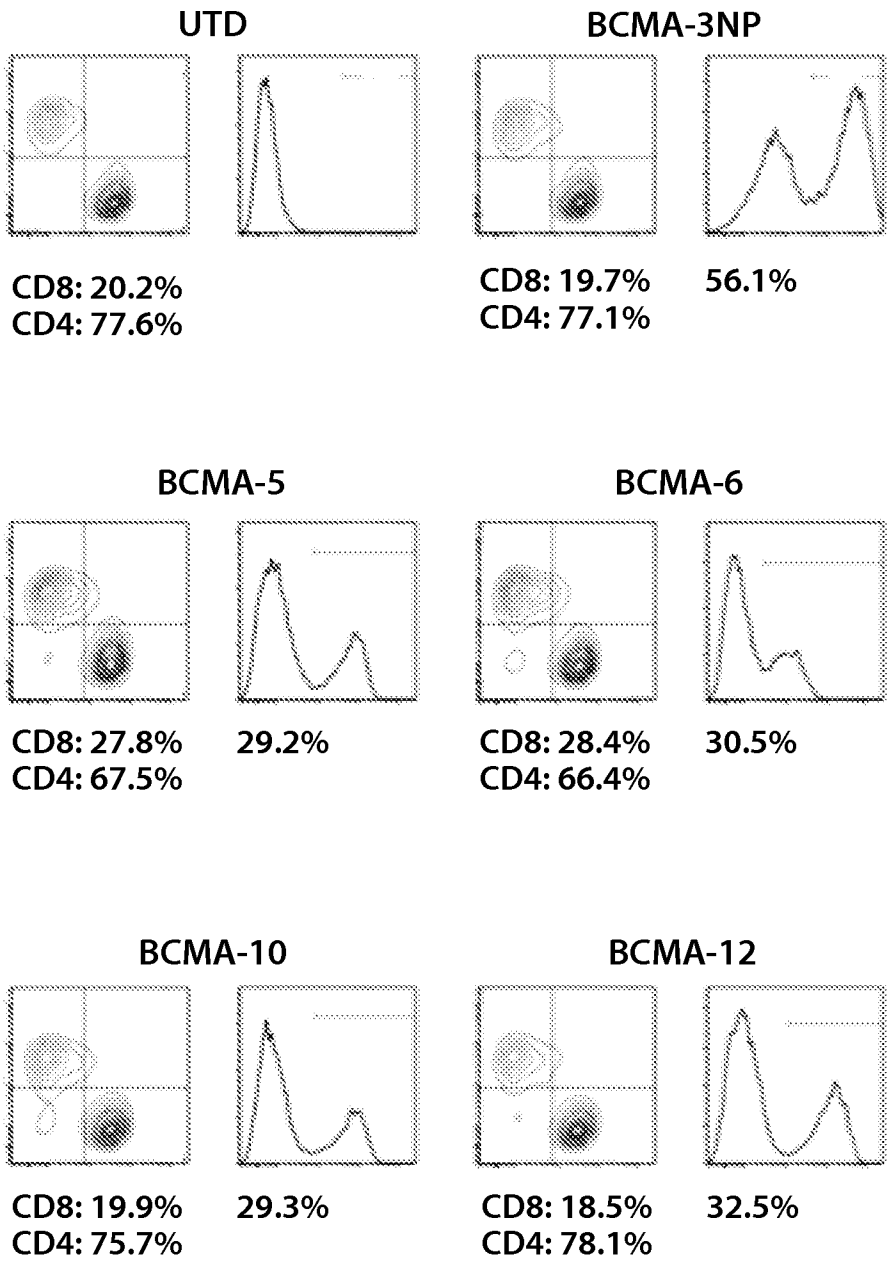

UTD
CD8: 20.2%
CD4: 77.6%
BCMA-3NP
CD8: 19.7%
CD4: 77.1%
56.1%
BCMA-5
CD8: 27.8%
CD4: 67.5%
29.2%
BCMA-6
CD8: 28.4%
CD4: 66.4%
30.5%
BCMA-10
CD8: 19.9%
CD4: 75.7%
29.3%
BCMA-12
CD8: 18.5%
CD4: 78.1%
32.5%

FIG. 20-1

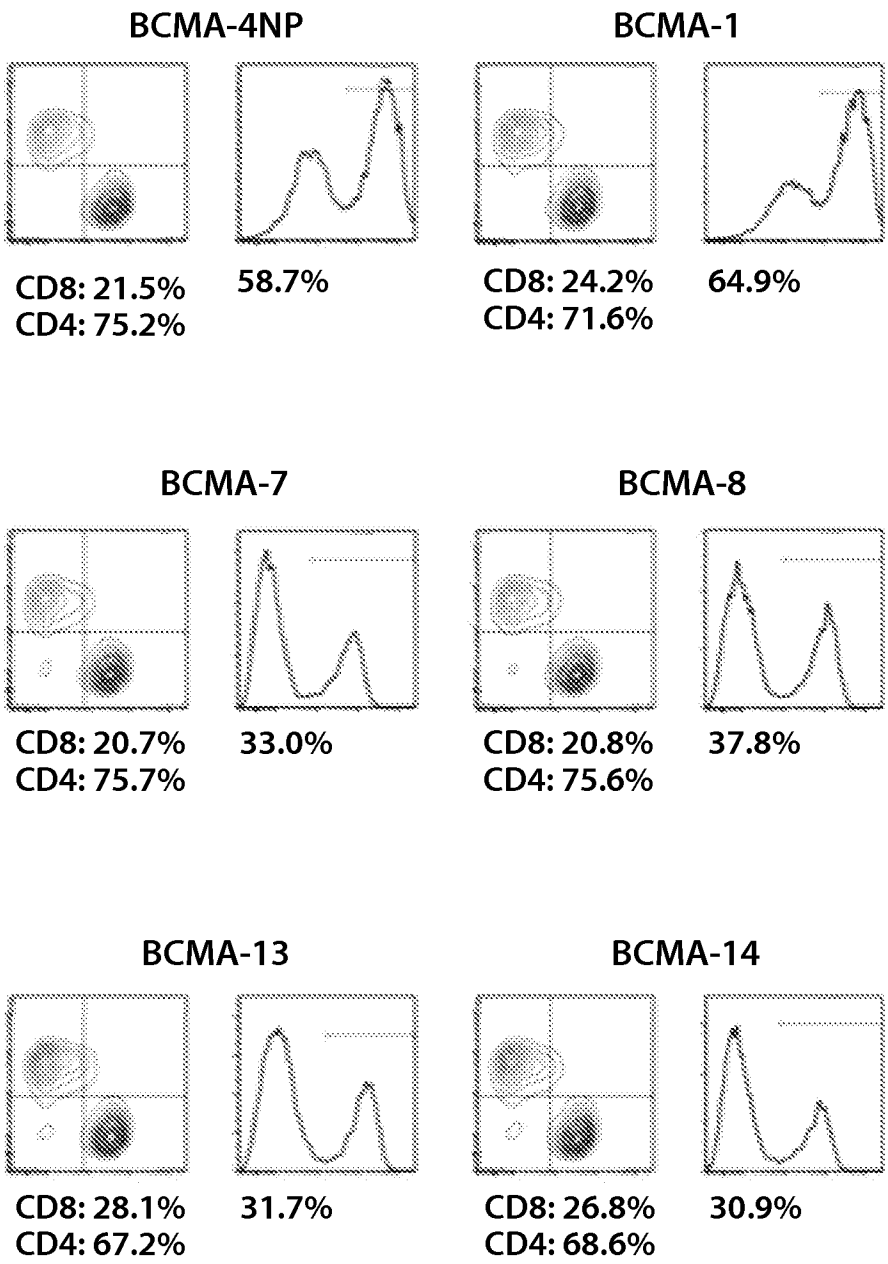
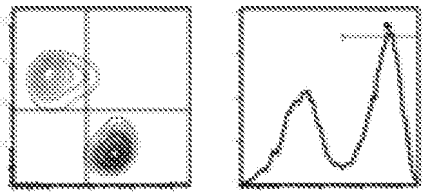

BCMA-4NP
CD8: 21.5%
CD4: 75.2%
58.7%
BCMA-1
CD8: 24.2%
CD4: 71.6%
64.9%
BCMA-7
CD8: 20.7%
CD4: 75.7%
33.0%
BCMA-8
CD8: 20.8%
CD4: 75.6%
37.8%
BCMA-13
CD8: 28.1%
CD4: 67.2%
31.7%
BCMA-14
CD8: 26.8%
CD4: 68.6%
30.9%

FIG. 20-2

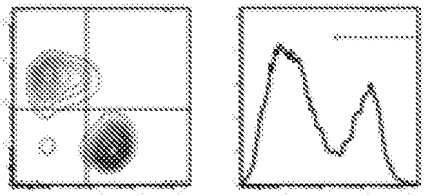
BCMA-4



CD8: 22.4%
CD4: 74.3%

56.3%

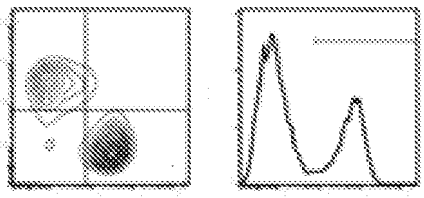
BCMA-9



CD8: 27.5%
CD4: 68.2%

31.4%

BCMA-15



CD8: 21.2%
CD4: 74.4%

34.2%

FIG. 20-3

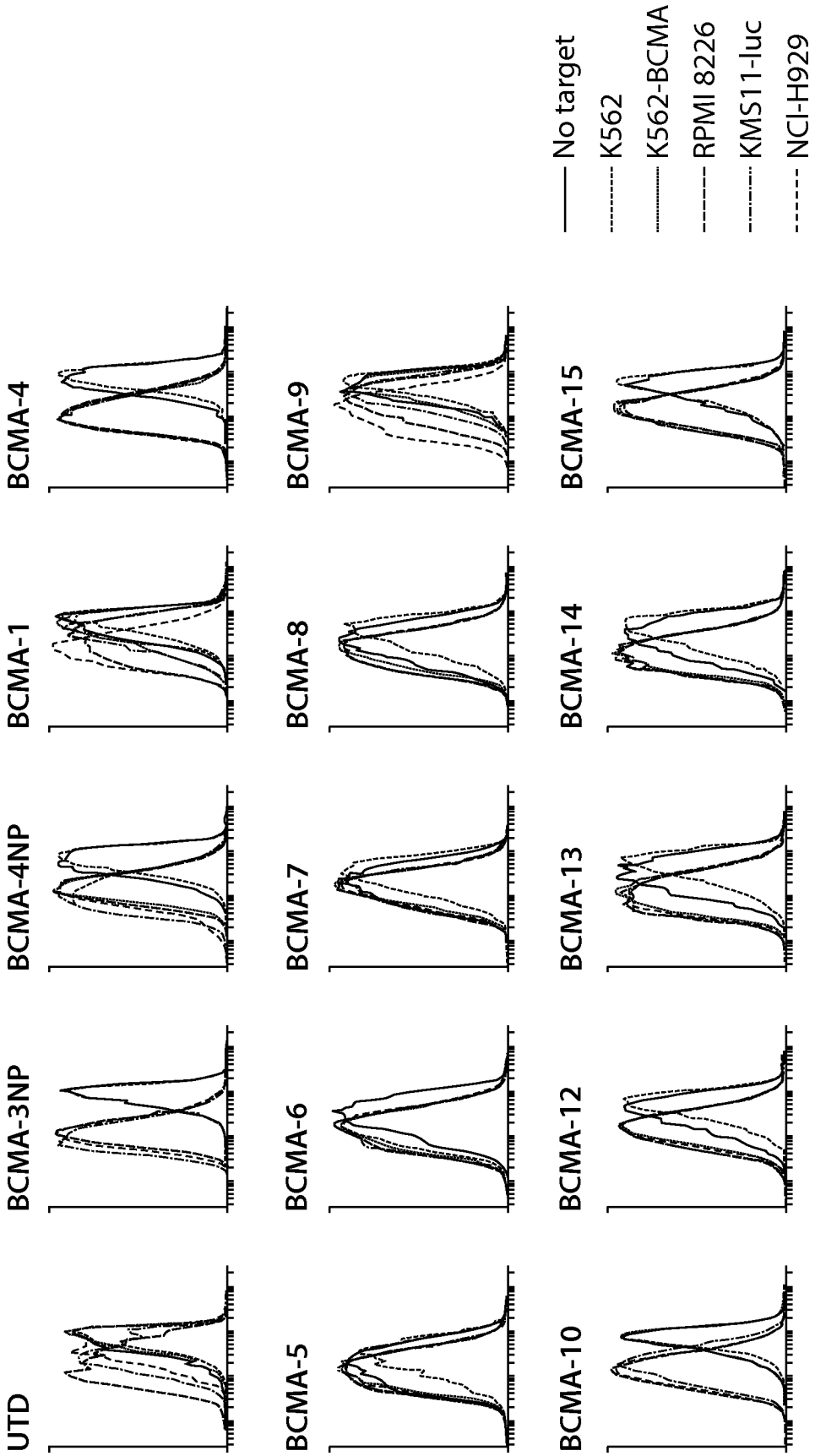

UTD
BCMA-3NP
BCMA-4NP
BCMA-1
BCMA-4
BCMA-5
BCMA-6
BCMA-7
BCMA-8
BCMA-9
BCMA-10
BCMA-12
BCMA-13
BCMA-14
BCMA-15
No target
K562
K562-BCMA
RPMI 8226
KMS11-luc
NCI-H929

FIG. 21

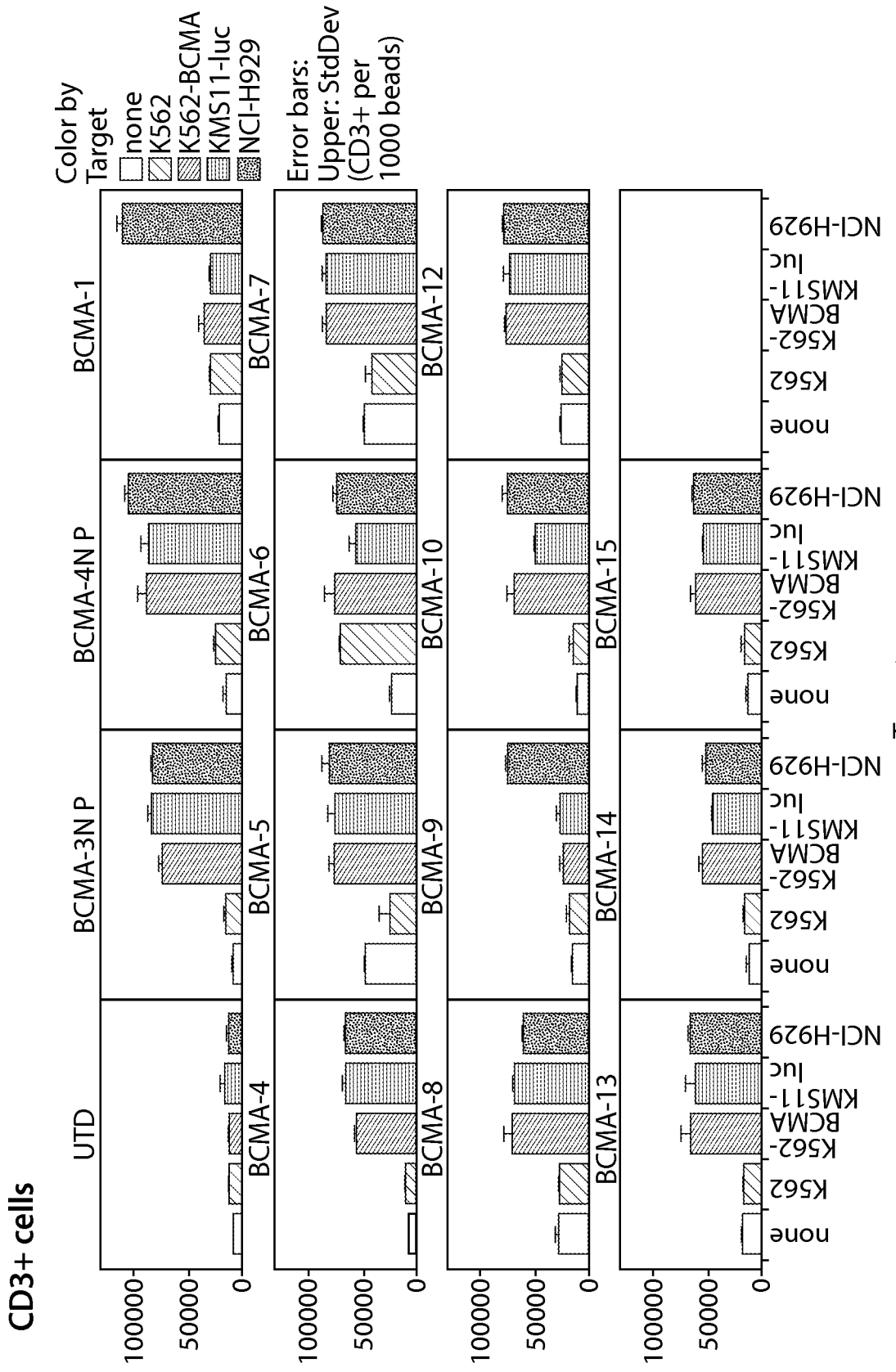

CD3+ cells
UTD
BCMA-3N P
BCMA-4N P
BCMA-1
Color by Target
none
K562
K562-BCMA
KMS11-luc
NCI-H929
Error bars: Upper: StdDev (CD3+ per 1000 beads)
BCMA-4
BCMA-5
BCMA-6
BCMA-7
BCMA-8
BCMA-9
BCMA-10
BCMA-12
BCMA-13
BCMA-14
BCMA-15
100000
50000
0
Avg(CD3+ per 1000 beads)
none
K562
K562-BCMA
KMS11-luc
NCI-H929
Target

FIG. 22A

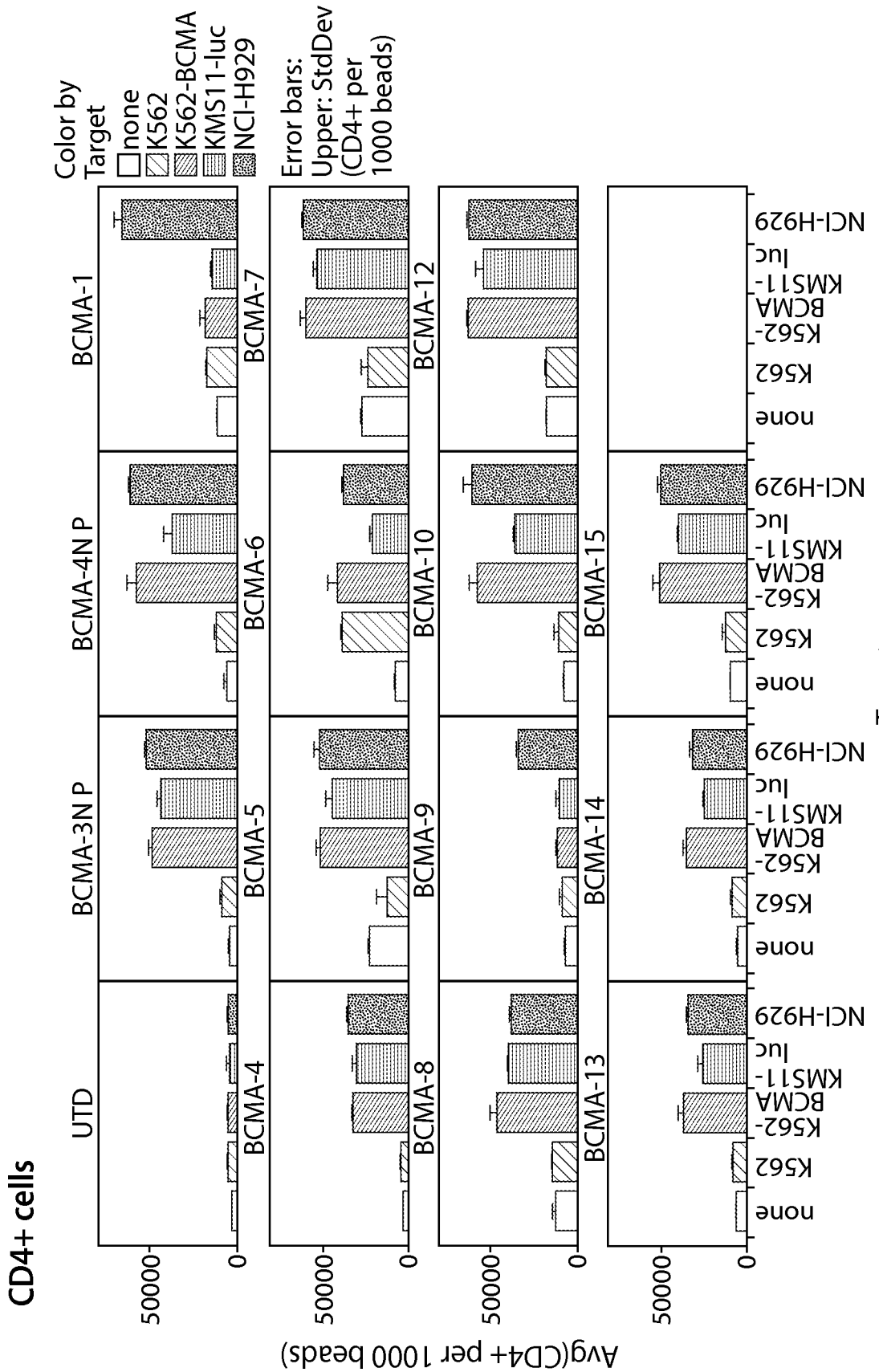

CD4+ cells
UTD
BCMA-3N P
BCMA-4N P
BCMA-1
Color by Target
none
K562
K562-BCMA
KMS11-luc
NCI-H929
Error bars: Upper: StdDev (CD4+ per 1000 beads)
BCMA-4
BCMA-5
BCMA-6
BCMA-7
BCMA-8
BCMA-9
BCMA-10
BCMA-12
BCMA-13
BCMA-14
BCMA-15
50000
0
Avg(CD4+ per 1000 beads)
none
K562
K562-BCMA
KMS11-luc
NCI-H929
Target

FIG. 22B

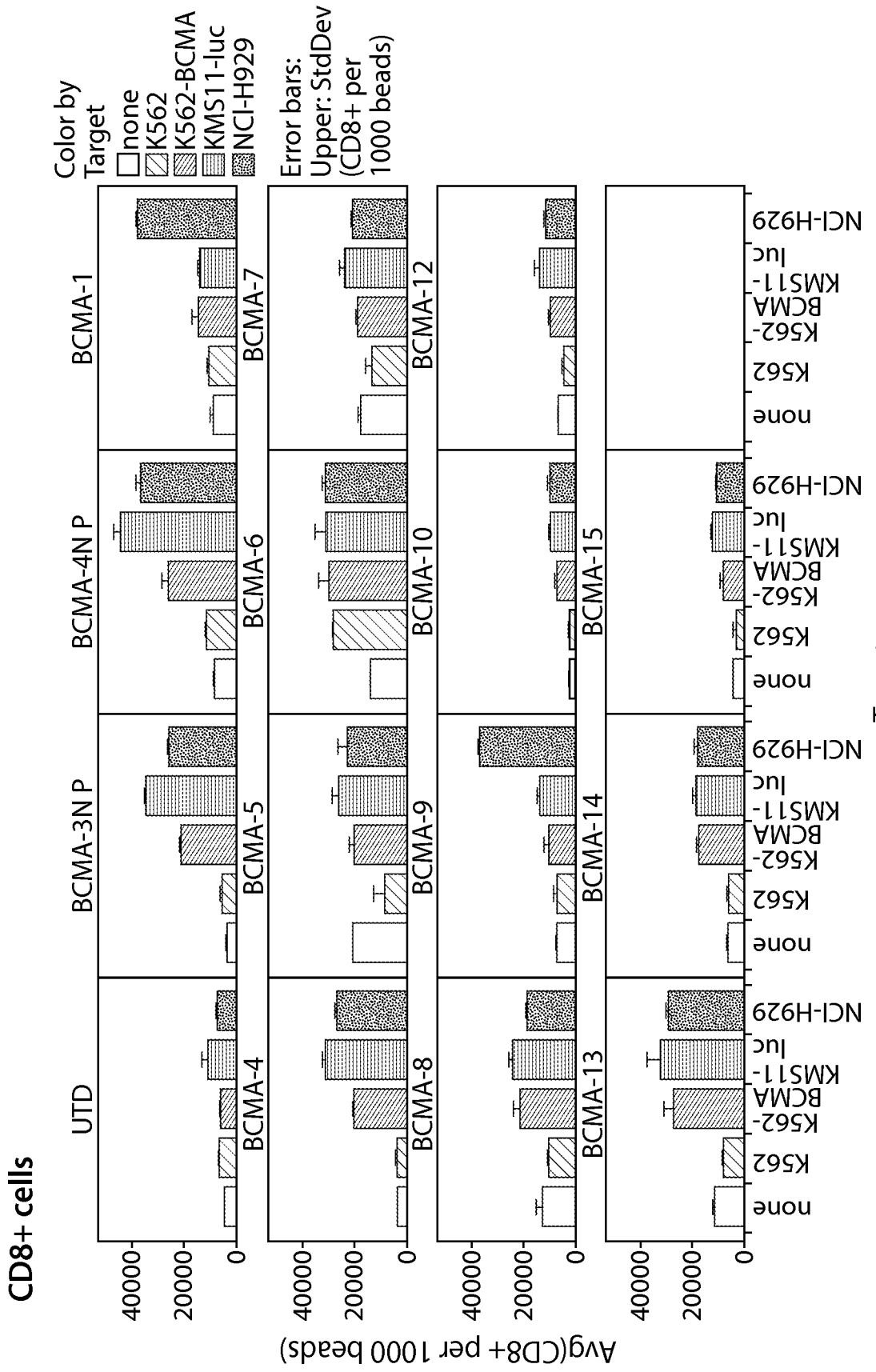

CD8+ cells
UTD
BCMA-3N P
BCMA-4N P
BCMA-1
Color by Target
none
K562
K562-BCMA
KMS11-luc
NCI-H929
Error bars: Upper: StdDev (CD8+ per 1000 beads)
BCMA-4
BCMA-5
BCMA-6
BCMA-7
BCMA-8
BCMA-9
BCMA-10
BCMA-12
BCMA-13
BCMA-14
BCMA-15
Avg(CD8+ per 1000 beads)
40000
20000
0
none
K562
K562-BCMA
KMS11-luc
NCI-H929
Target

FIG. 22C

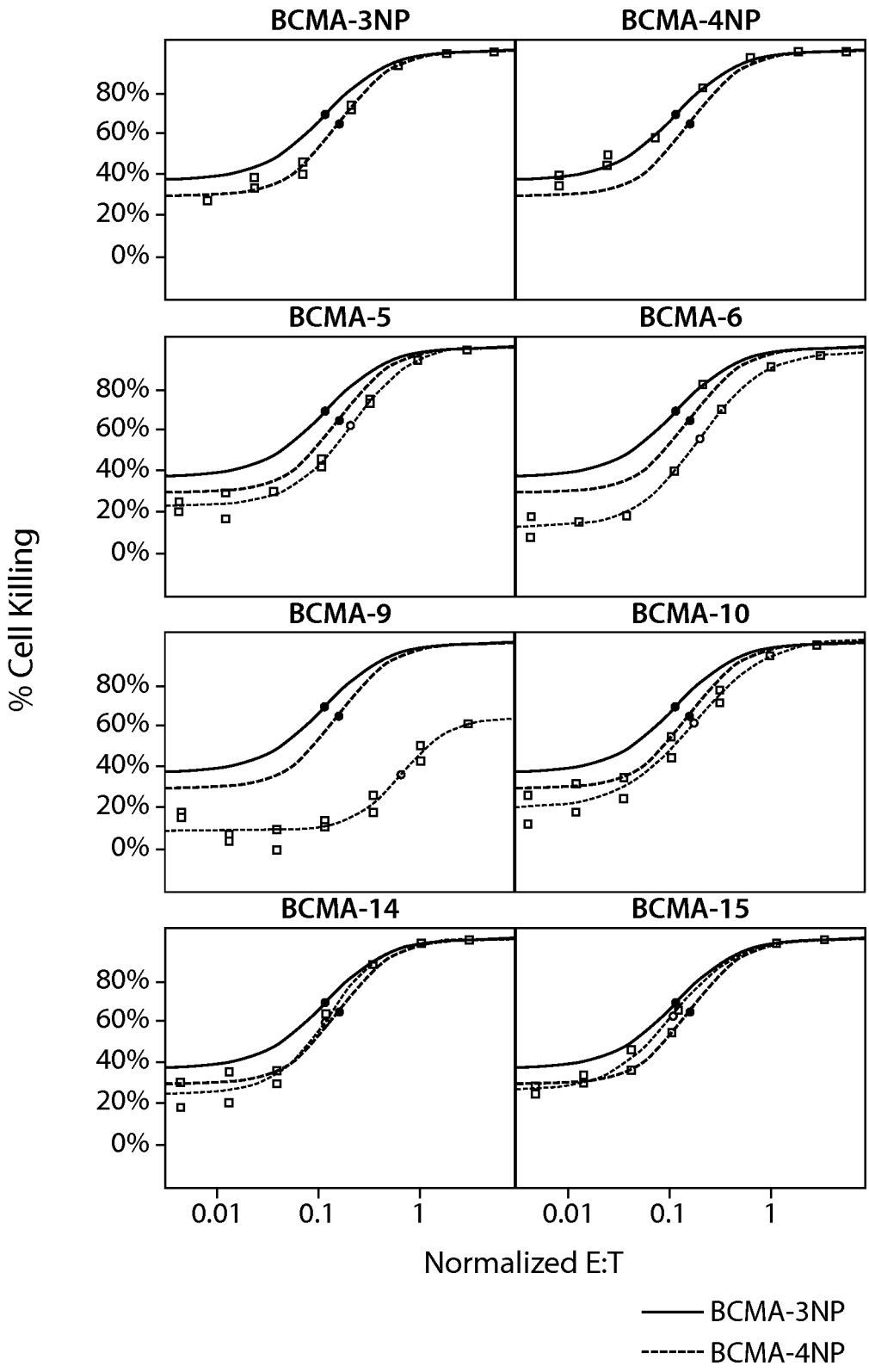

BCMA-3NP
BCMA-4NP
BCMA-5
BCMA-6
BCMA-9
BCMA-10
BCMA-14
BCMA-15
% Cell Killing
80%
60%
40%
20%
0%
0.01
0.1
1
Normalized E:T
BCMA-3NP
BCMA-4NP

FIG. 23A-1

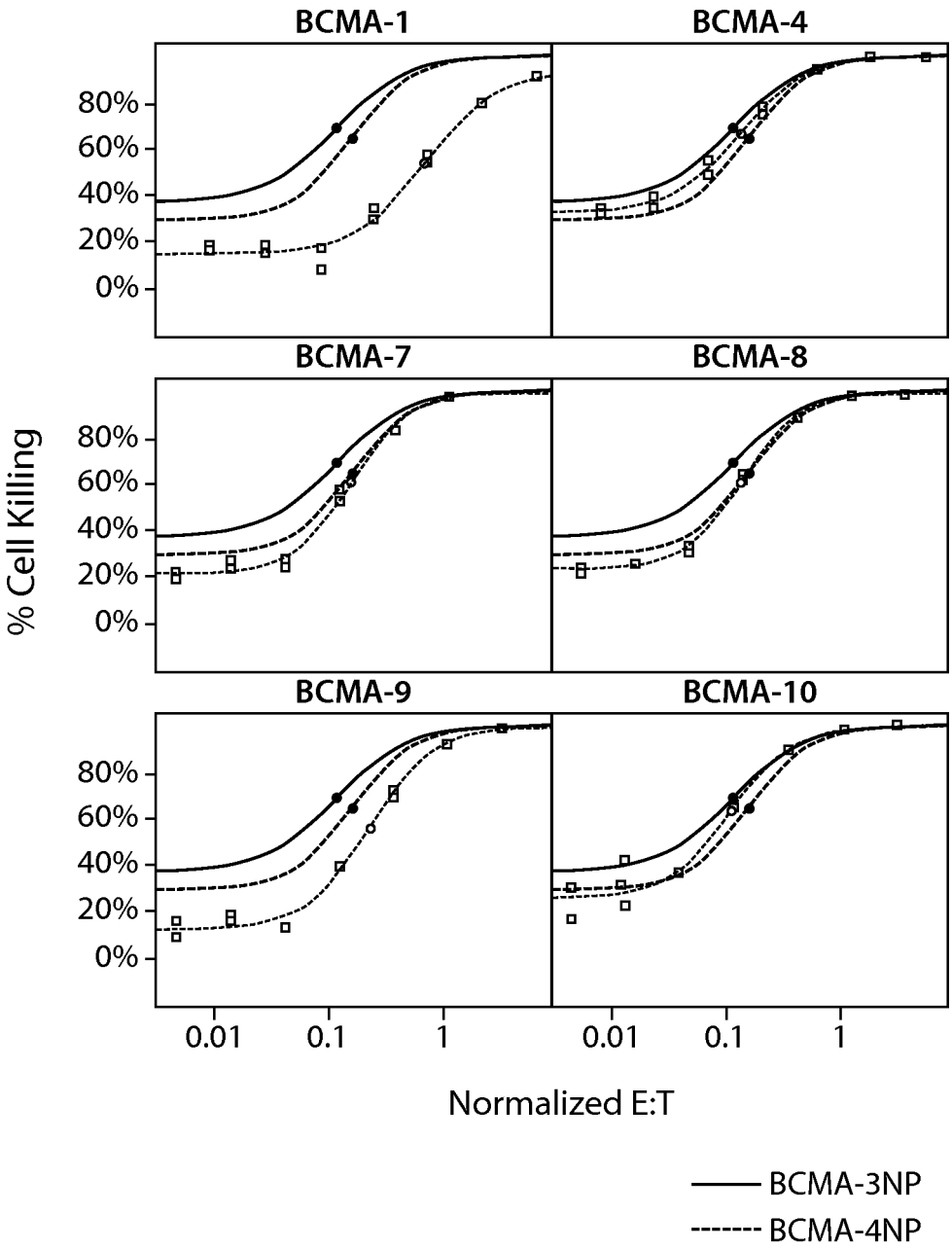

BCMA-1
BCMA-4
BCMA-7
BCMA-8
BCMA-9
BCMA-10
% Cell Killing
80%
60%
40%
20%
0%
0.01
0.1
1
Normalized E:T
BCMA-3NP
BCMA-4NP

FIG. 23A-2

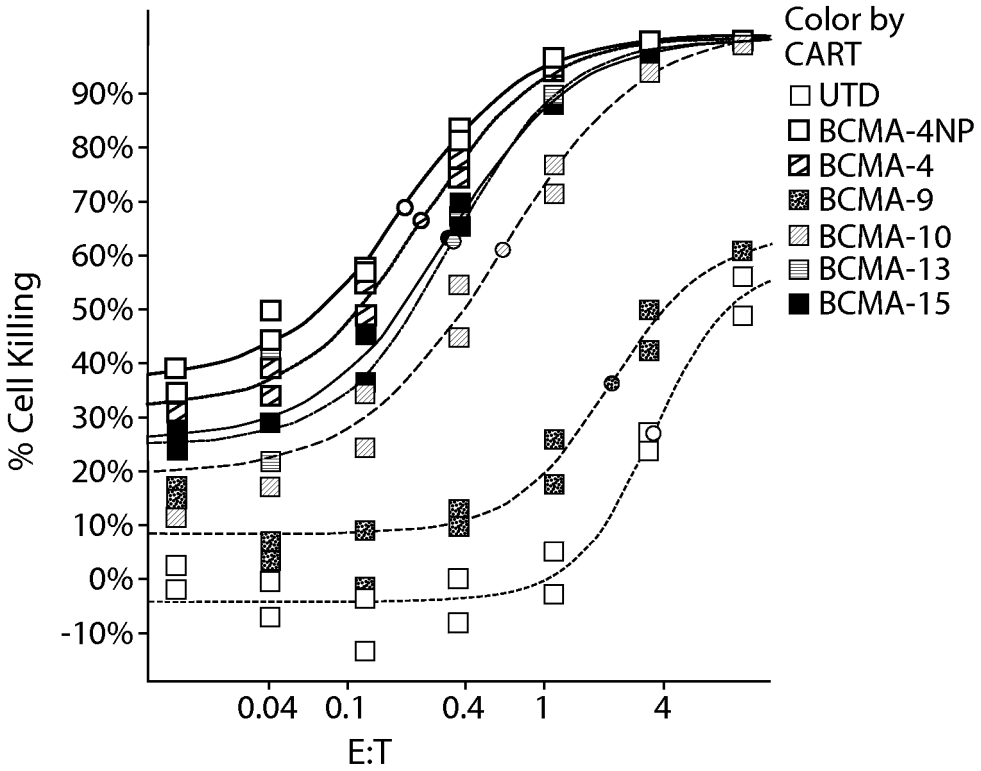


FIG. 23B

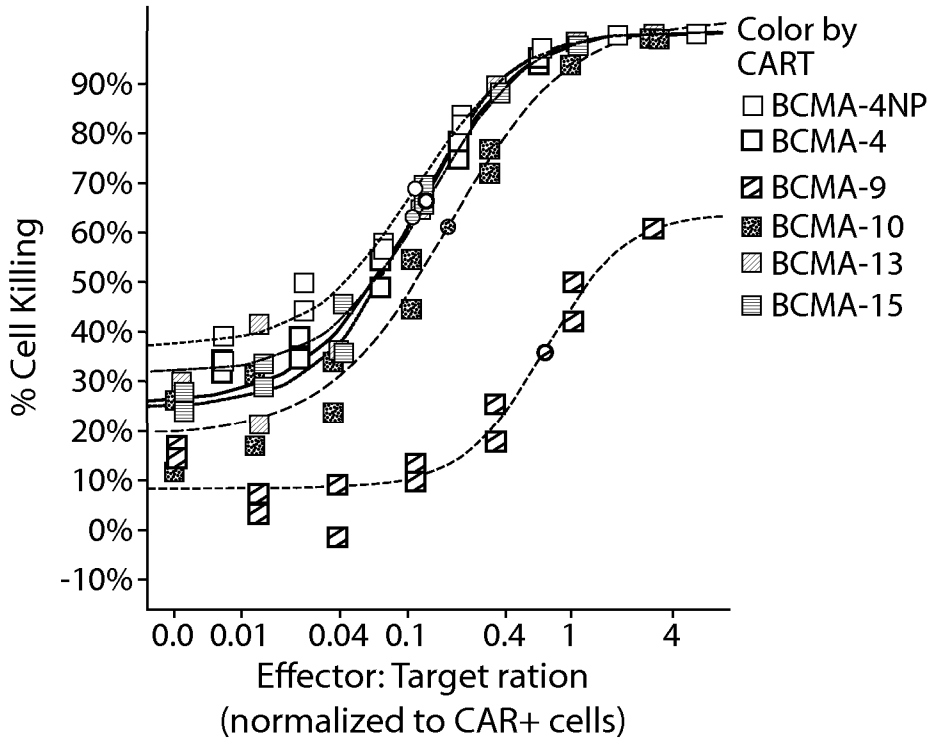


FIG. 23C

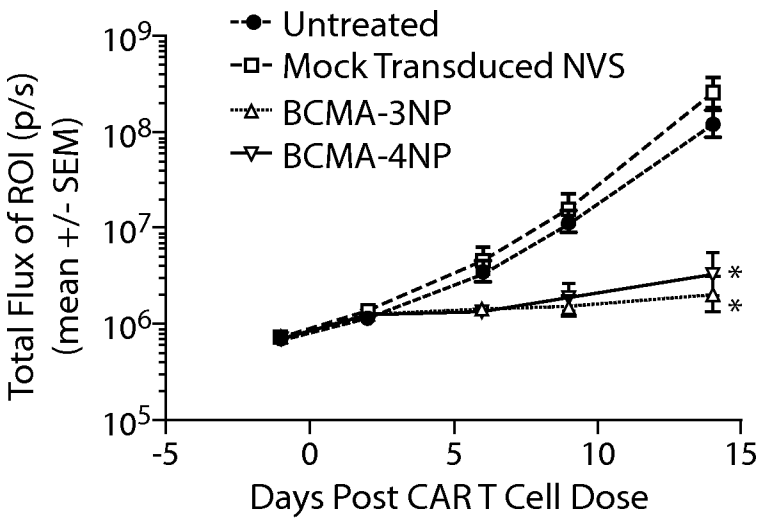

Untreated
Mock Transduced NVS
BCMA-3NP
BCMA-4NP
Total Flux of ROI (p/s)
(mean +/- SEM)
10^9
10^8
10^7
10^6
10^5
-5
0
5
10
15
Days Post CAR T Cell Dose
*
*

FIG. 24

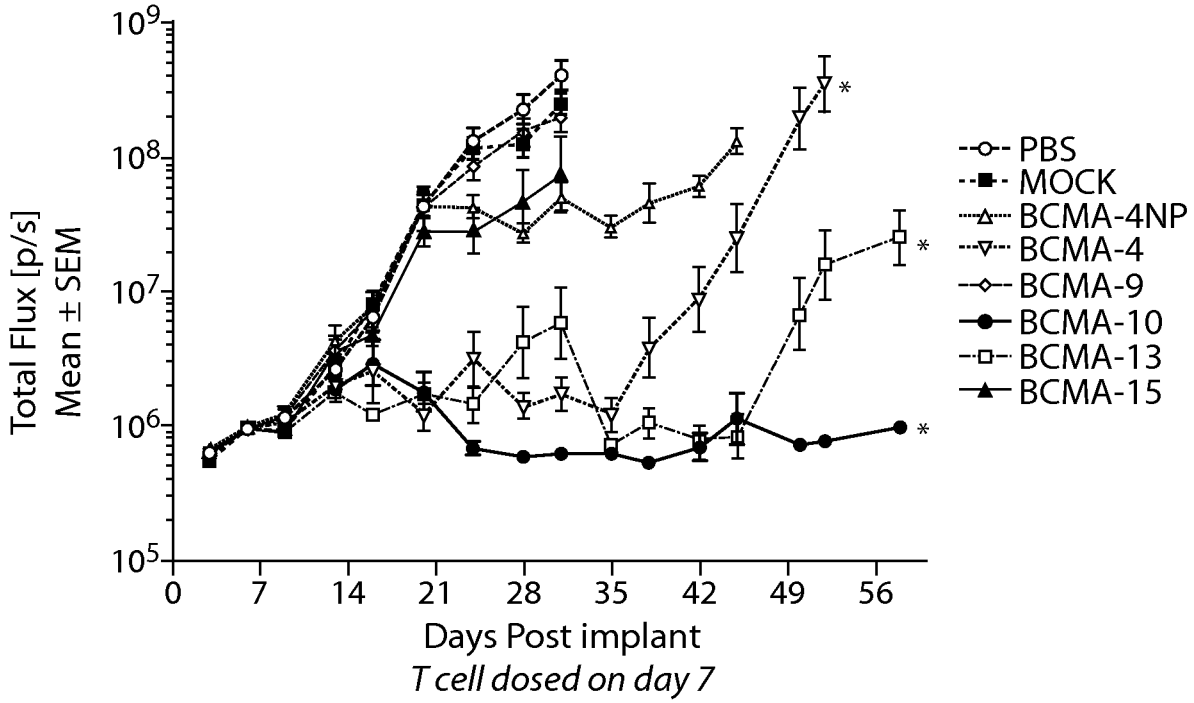


FIG. 25A

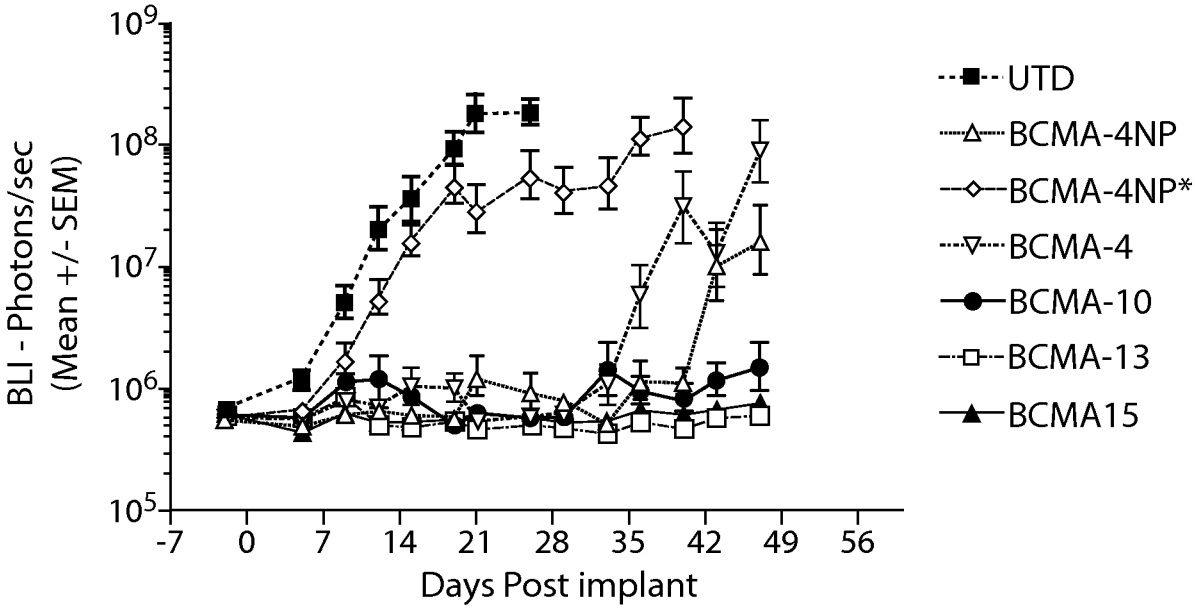


FIG. 25B

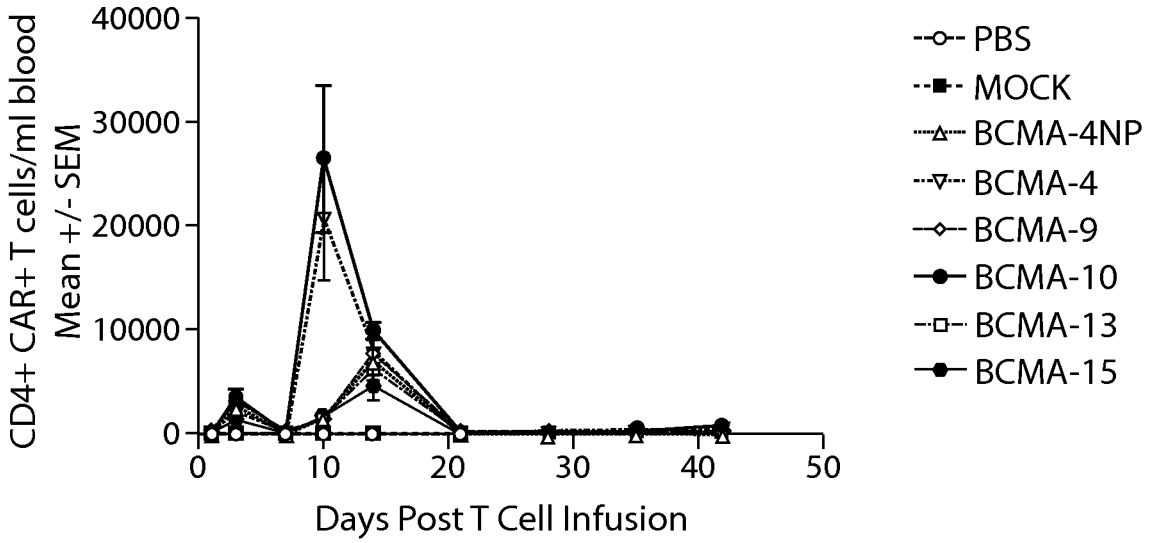


FIG. 26A

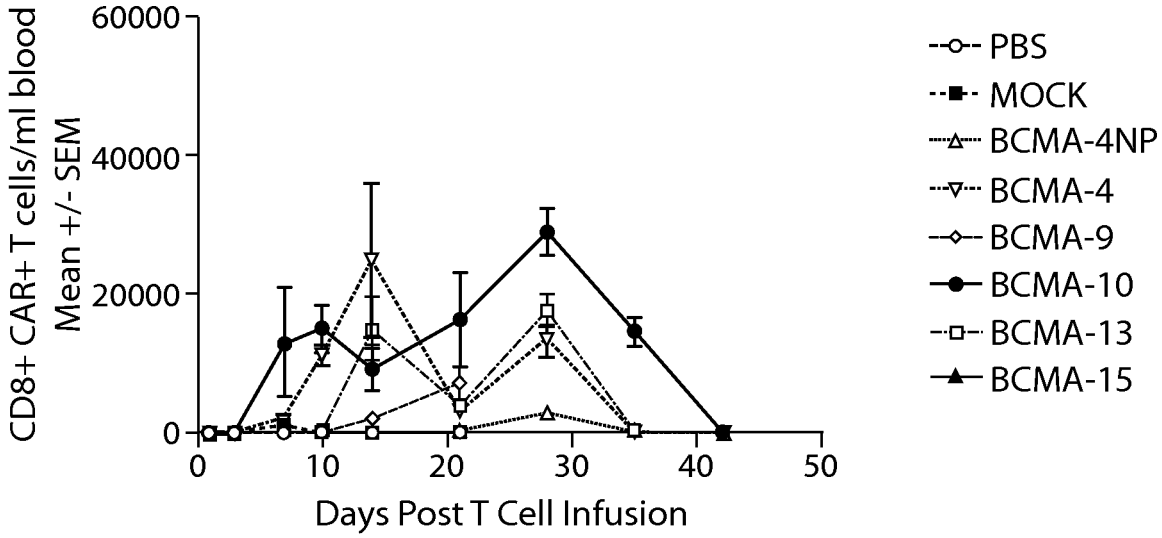


FIG. 26B

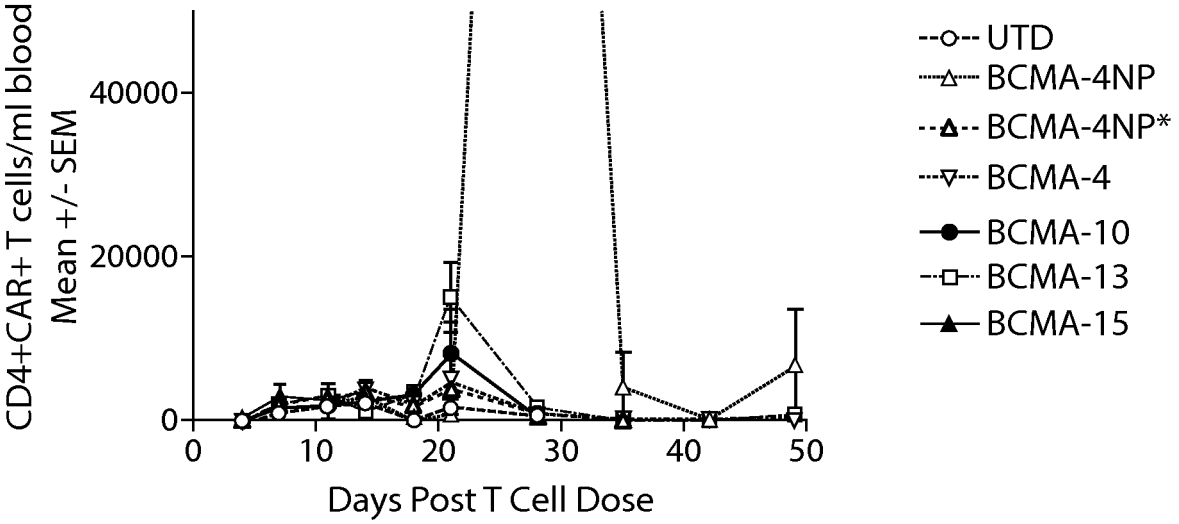


FIG. 26C

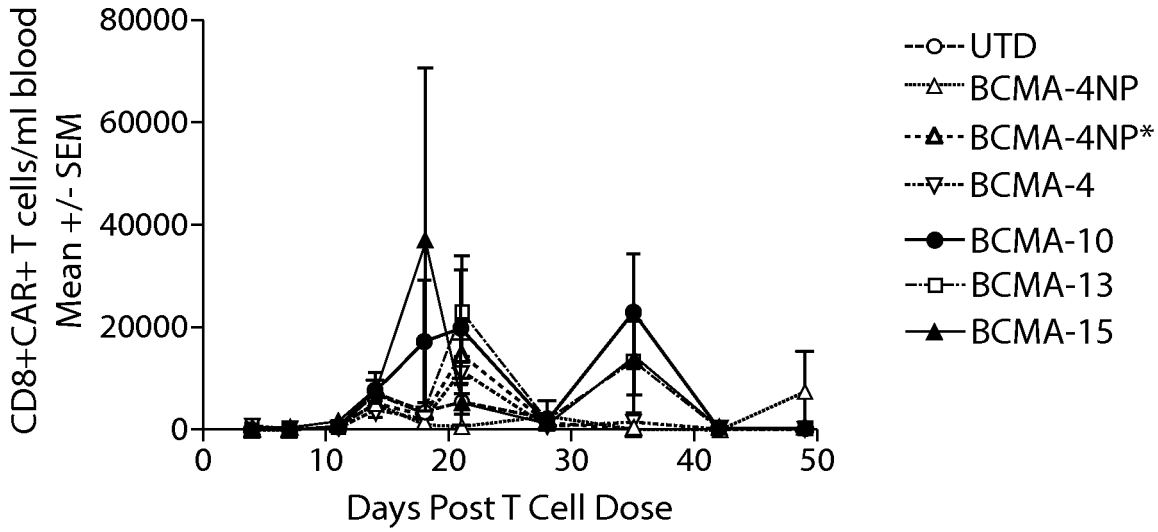


FIG. 26D

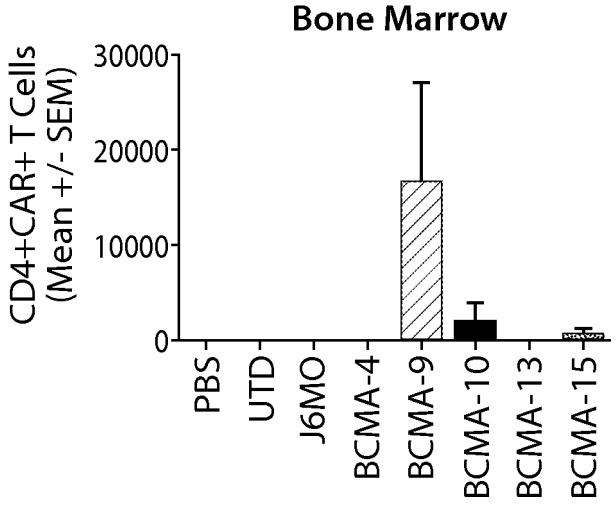


FIG. 27A

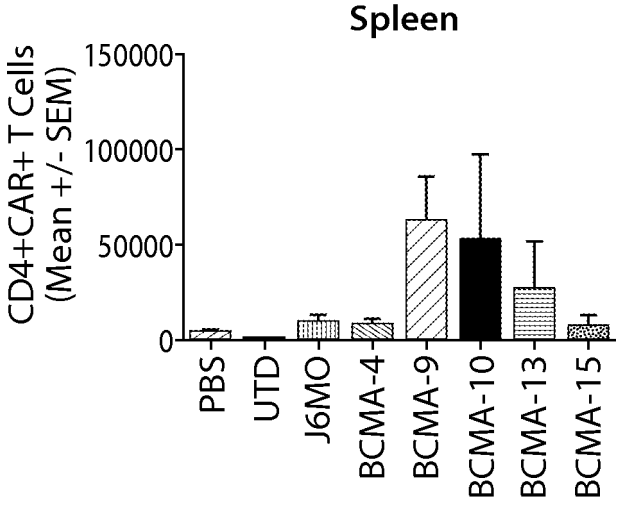


FIG. 27B

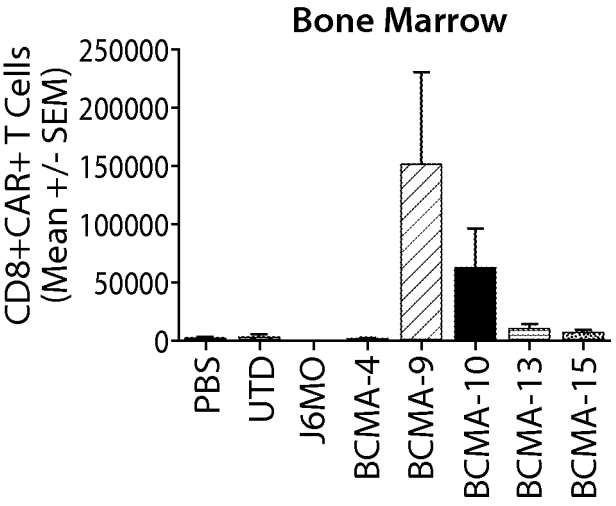


FIG. 27C

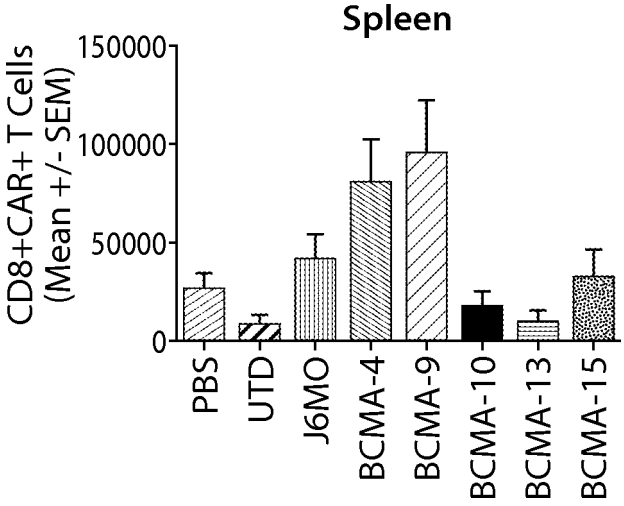


FIG. 27D

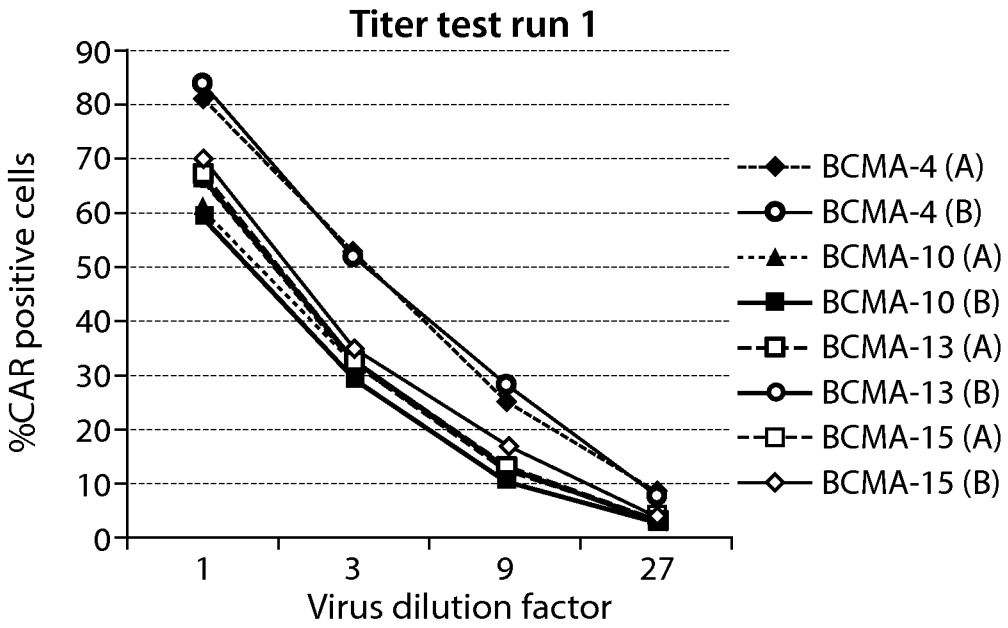


FIG. 28A

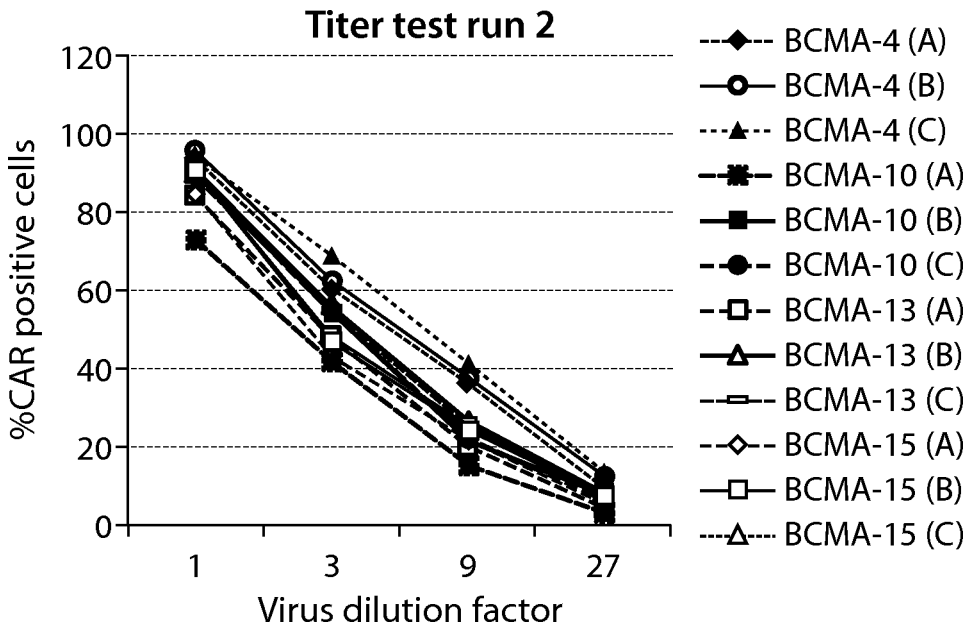


FIG. 28B

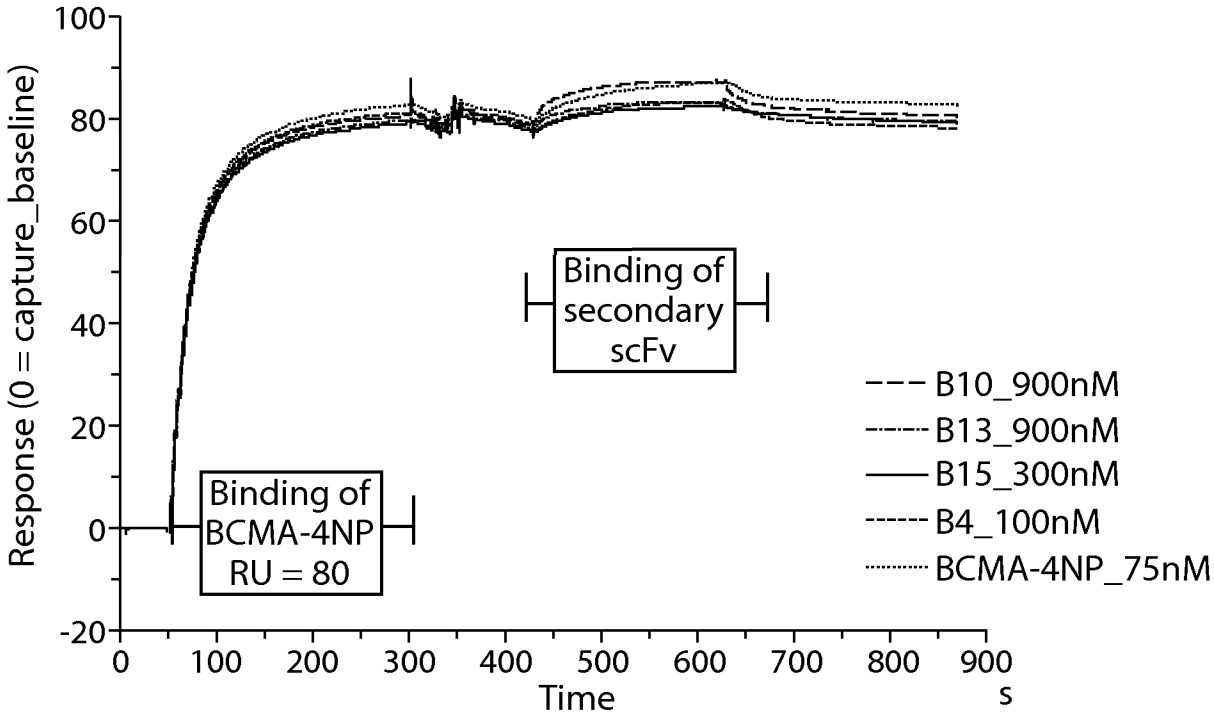

Response (0 = capture_baseline)
100
80
60
40
20
0
-20
0
100
200
300
400
500
600
700
800
900
Time
s
Binding of BCMA-4NP RU = 80
Binding of secondary scFv
B10_900nM
B13_900nM
B15_300nM
B4_100nM
BCMA-4NP_75nM

FIG. 29

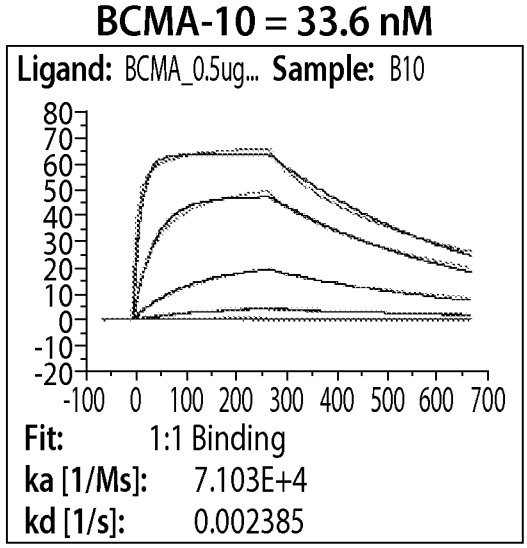


FIG. 30A

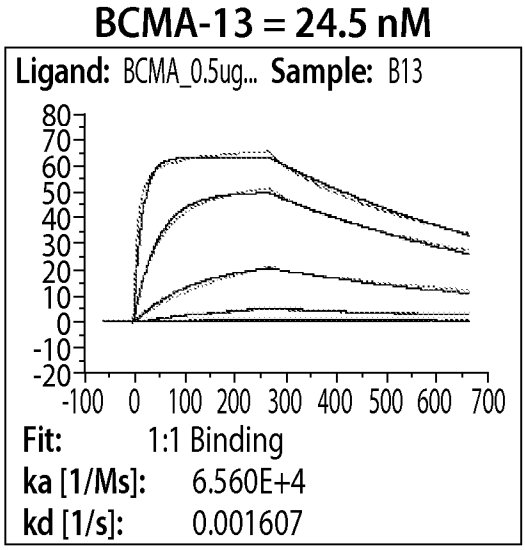


FIG. 30B

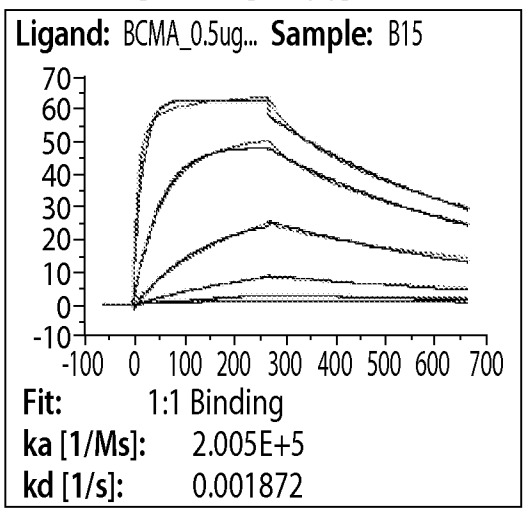


FIG. 30C

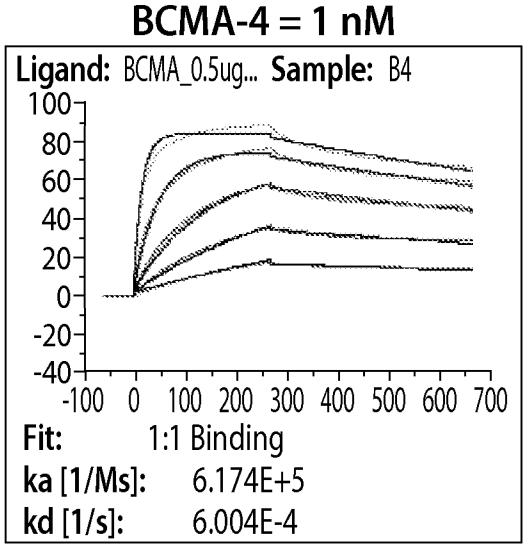


FIG. 30D

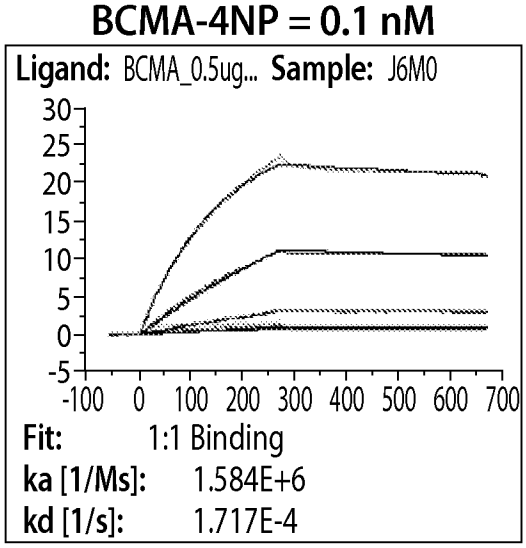


FIG. 30E

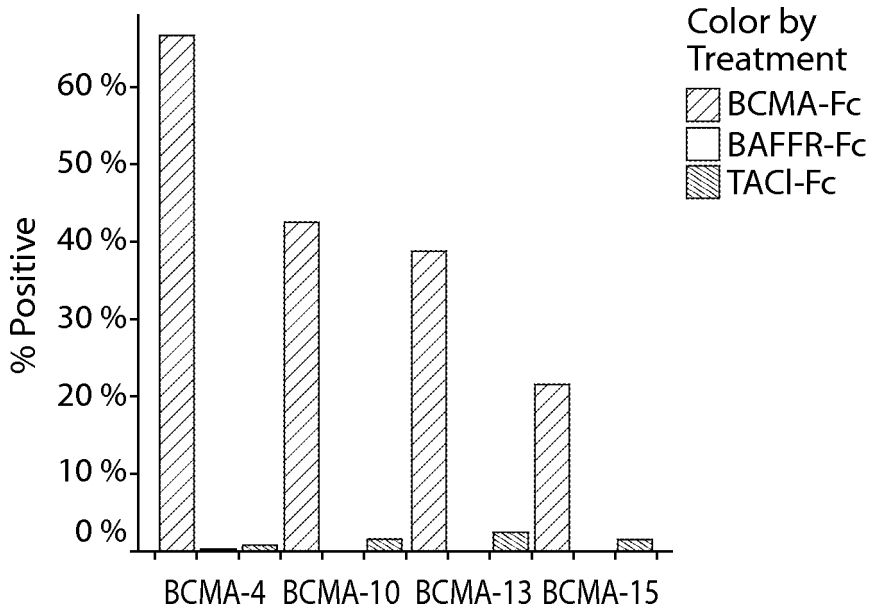

Color by Treatment
BCMA-Fc
BAFFR-Fc
TACI-Fc
% Positive
60 %
50 %
40 %
30 %
20 %
10 %
0 %
BCMA-4
BCMA-10
BCMA-13
BCMA-15

FIG. 31

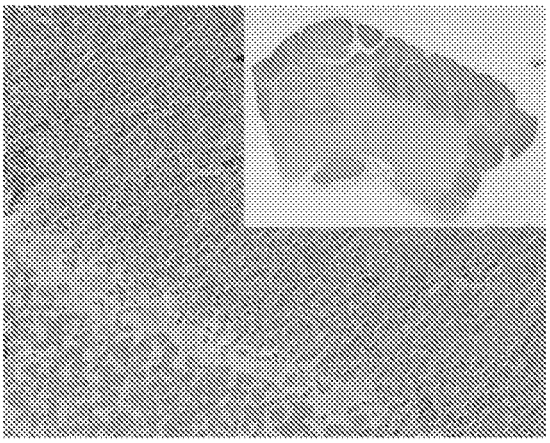


FIG. 32A

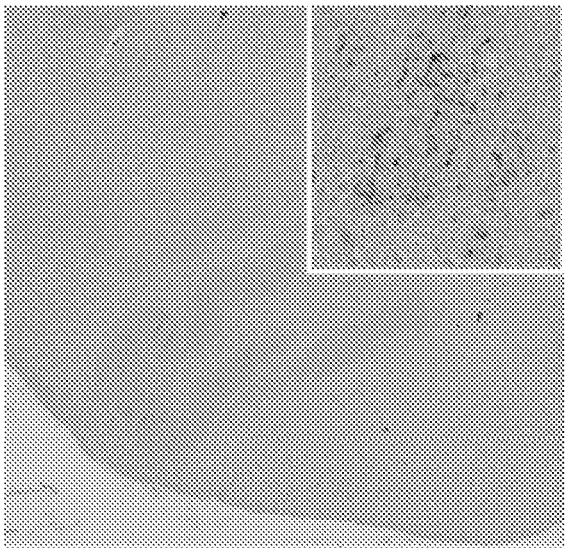


FIG. 32B

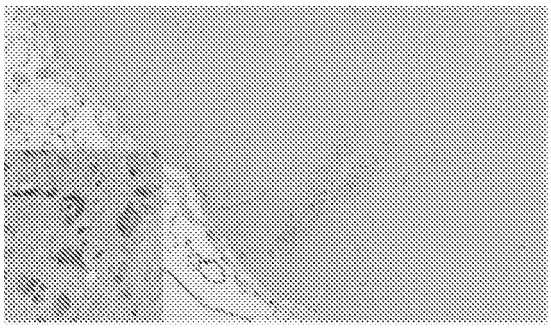


FIG. 32C

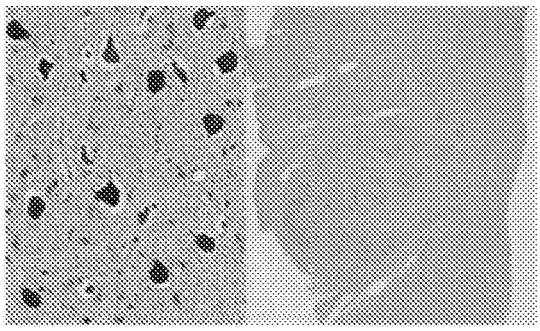


FIG. 32D

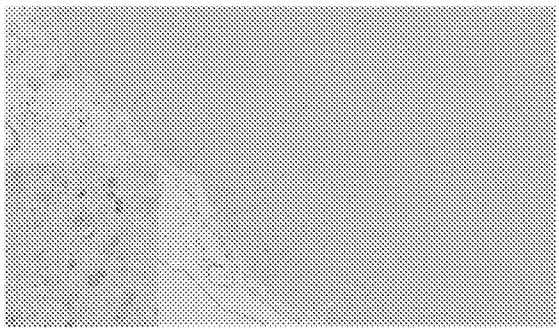


FIG. 32E

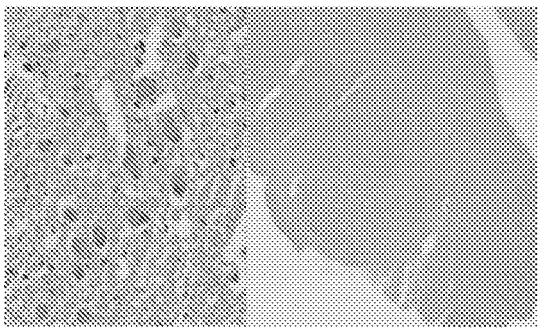


FIG. 32F

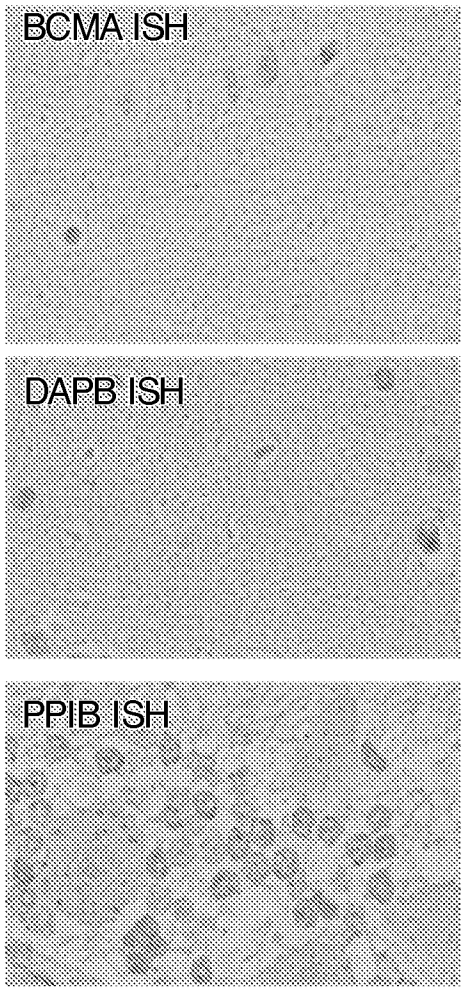


FIG. 33A

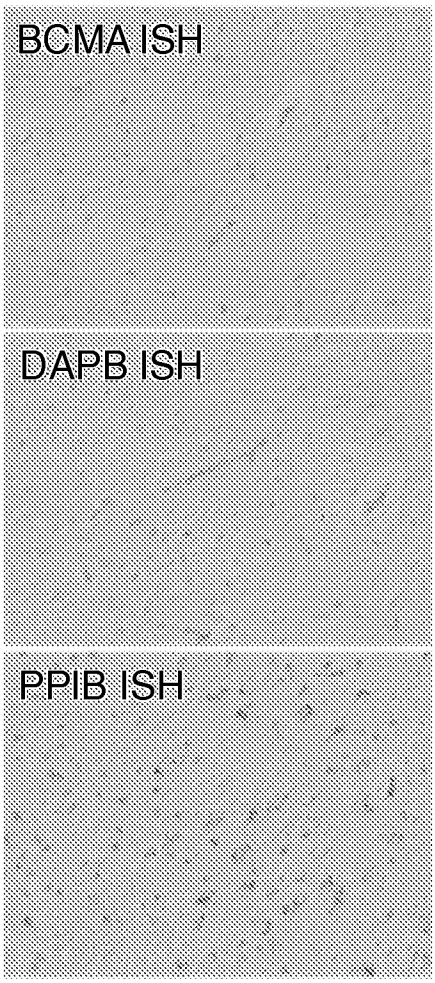


FIG. 33B

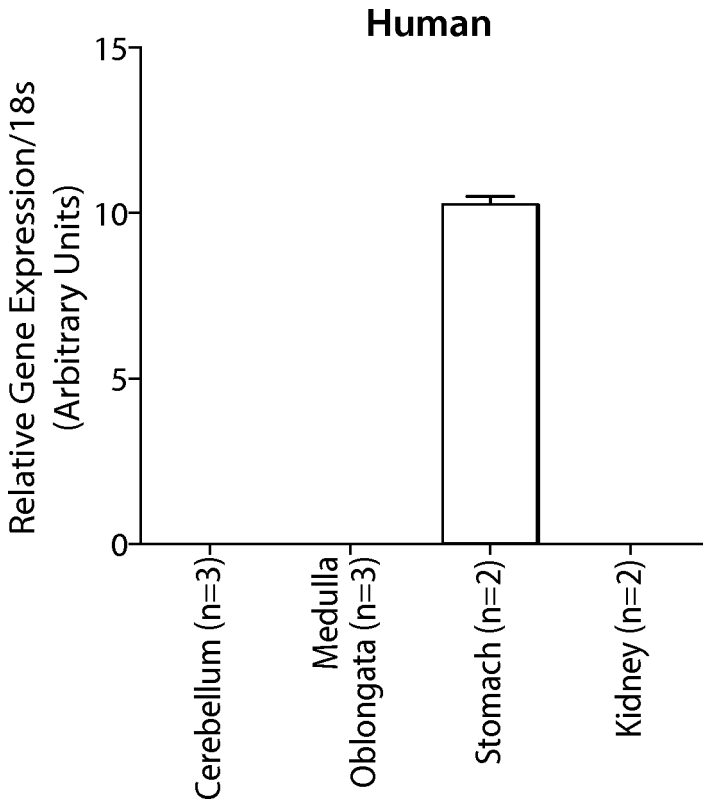


FIG. 33C

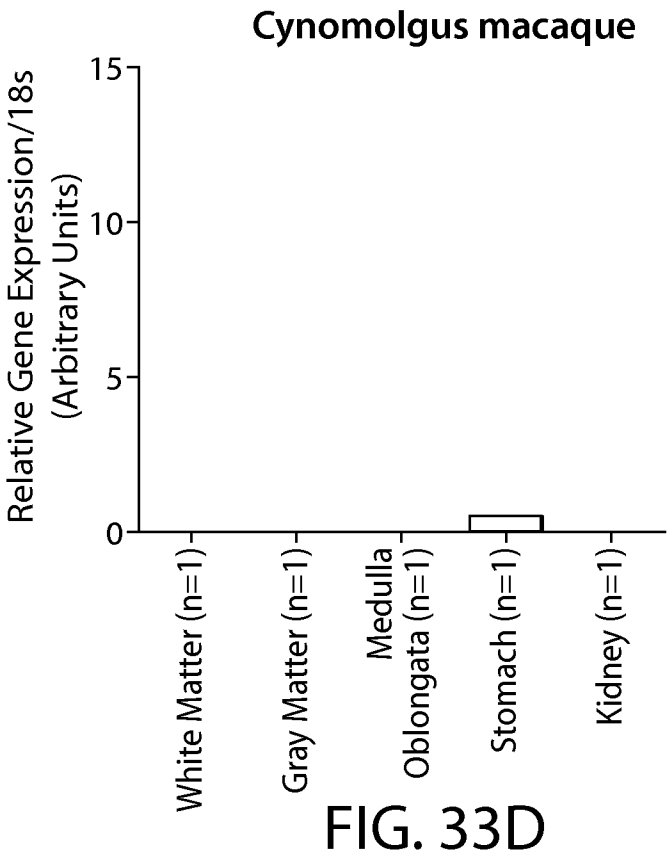


FIG. 33D

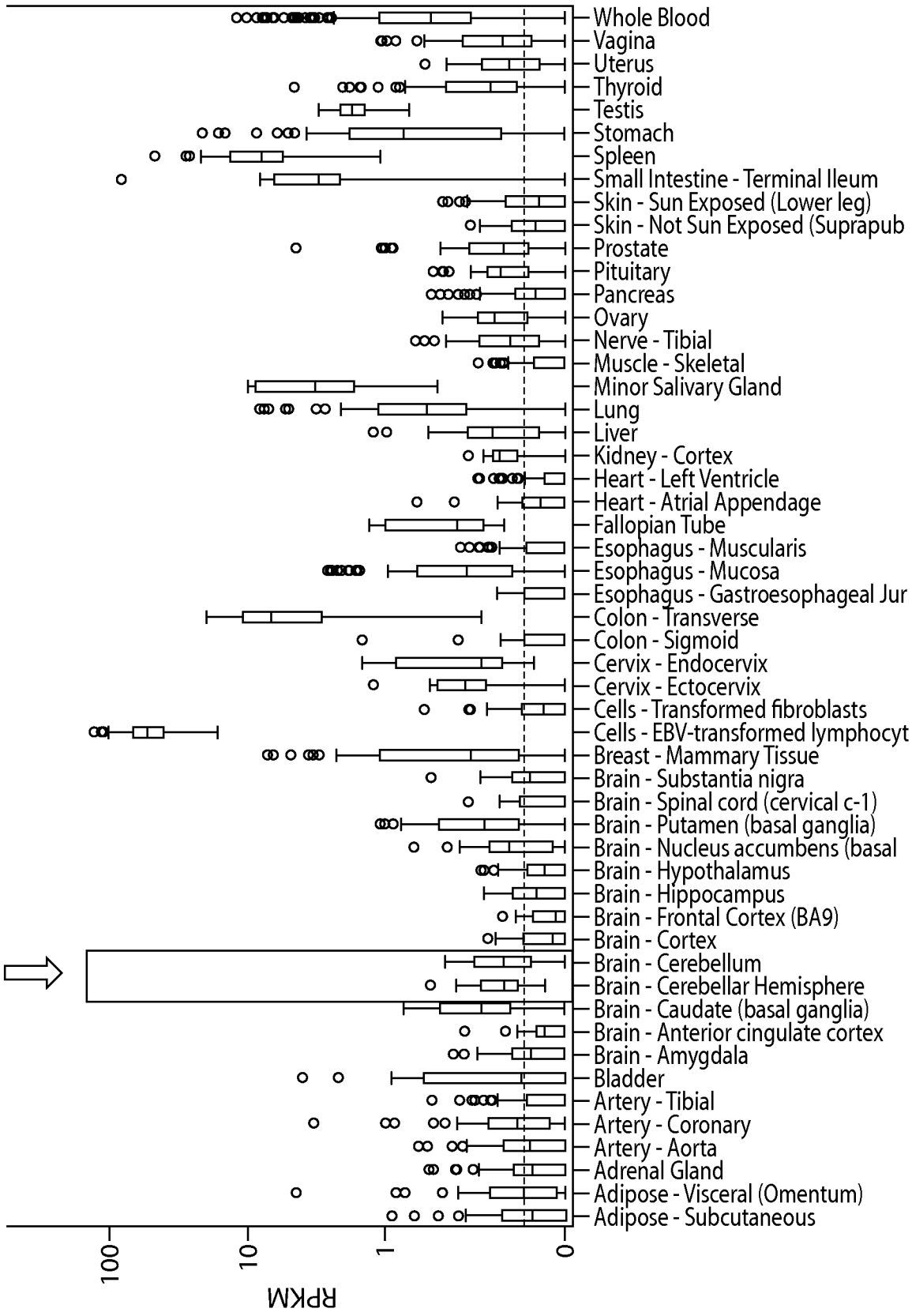

Whole Blood
Vagina
Uterus
Thyroid
Testis
Stomach
Spleen
Small Intestine - Terminal Ileum
Skin - Sun Exposed (Lower leg)
Skin - Not Sun Exposed (Suprapub
Prostate
Pituitary
Pancreas
Ovary
Nerve - Tibial
Muscle - Skeletal
Minor Salivary Gland
Lung
Liver
Kidney - Cortex
Heart - Left Ventricle
Heart - Atrial Appendage
Fallopian Tube
Esophagus - Muscularis
Esophagus - Mucosa
Esophagus - Gastroesophageal Jur
Colon - Transverse
Colon - Sigmoid
Cervix - Endocervix
Cervix - Ectocervix
Cells - Transformed fibroblasts
Cells - EBV-transformed lymphocyt
Breast - Mammary Tissue
Brain - Substantia nigra
Brain - Spinal cord (cervical c-1)
Brain - Putamen (basal ganglia)
Brain - Nucleus accumbens (basal
Brain - Hypothalamus
Brain - Hippocampus
Brain - Frontal Cortex (BA9)
Brain - Cortex
Brain - Cerebellum
Brain - Cerebellar Hemisphere
Brain - Caudate (basal ganglia)
Brain - Anterior cingulate cortex
Brain - Amygdala
Bladder
Artery - Tibial
Artery - Coronary
Artery - Aorta
Adrenal Gland
Adipose - Visceral (Omentum)
Adipose - Subcutaneous
100
10
1
0
RPKM

FIG. 33E

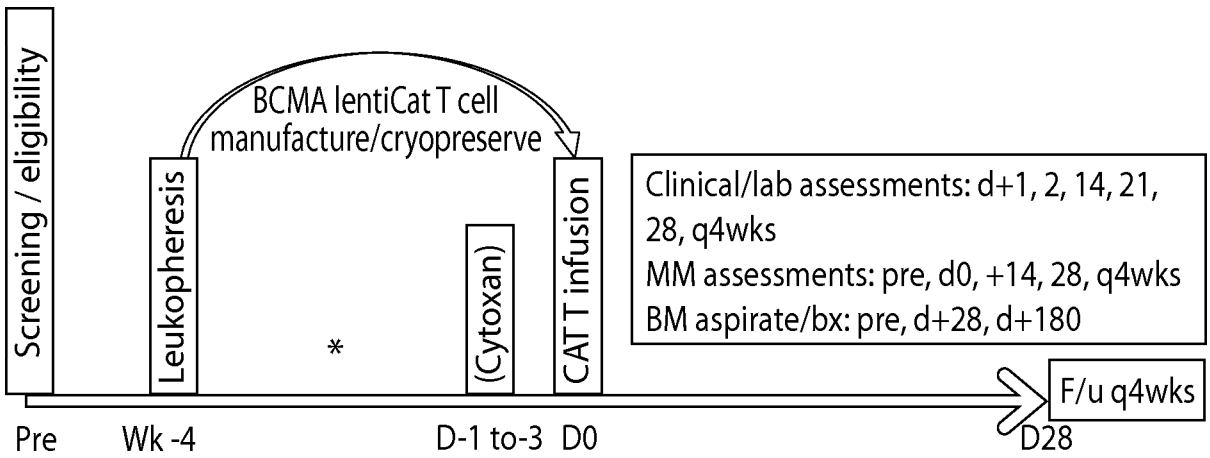

Screening / eligibility
BCMA lentiCat T cell manufacture/cryopreserve
Leukopheresis
*
(Cytoxan)
CAT T infusion
Clinical/lab assessments: d+1, 2, 14, 21, 28, q4wks
MM assessments: pre, d0, +14, 28, q4wks
BM aspirate/bx: pre, d+28, d+180
F/u q4wks
Pre
Wk -4
D-1 to-3
D0
D28
* Patients may receive therapy during manufacturing to maintain disease control

FIG. 34

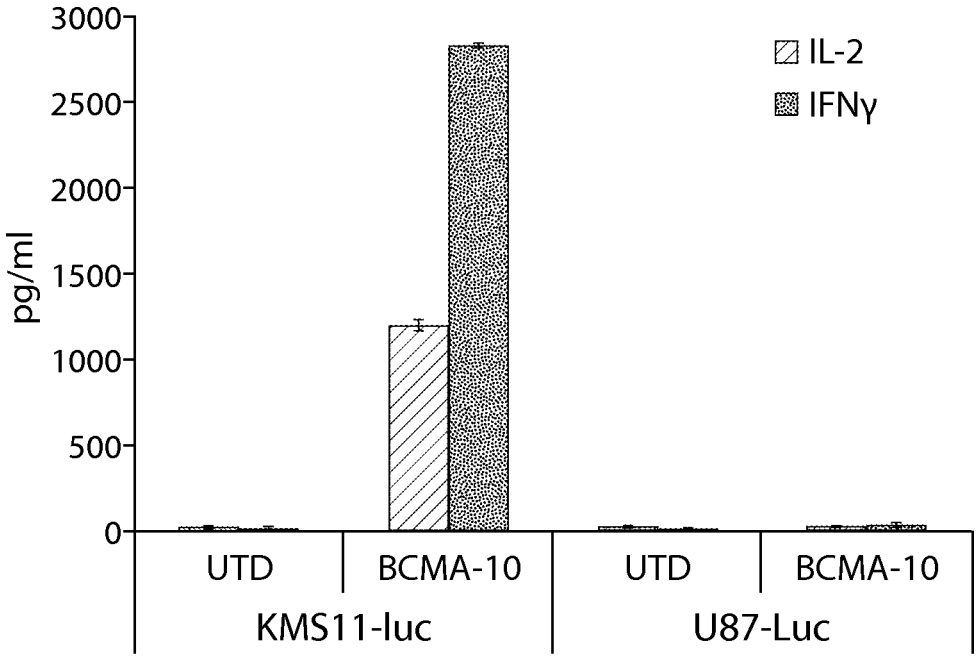


FIG. 35A

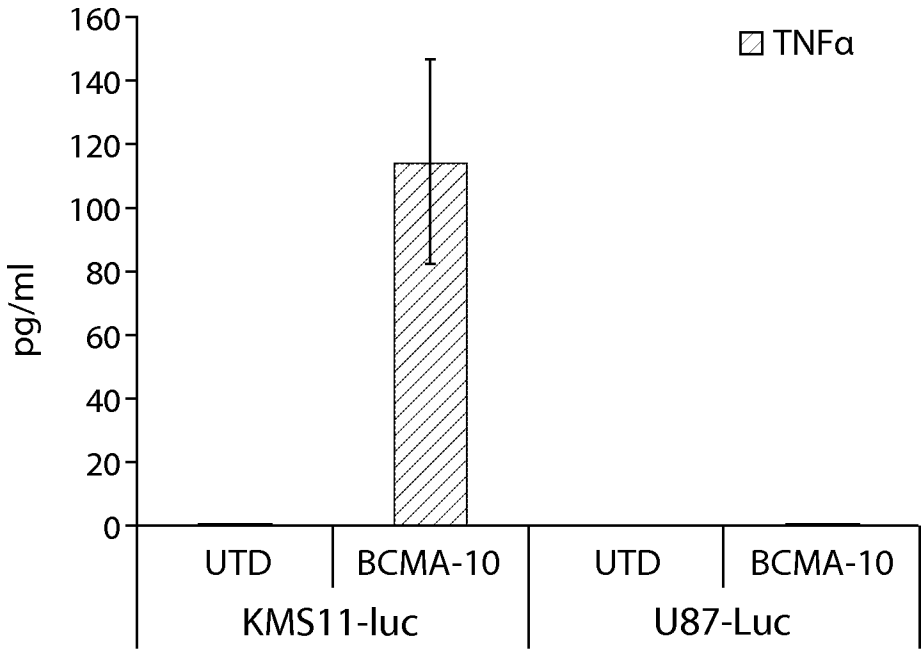


FIG. 35B

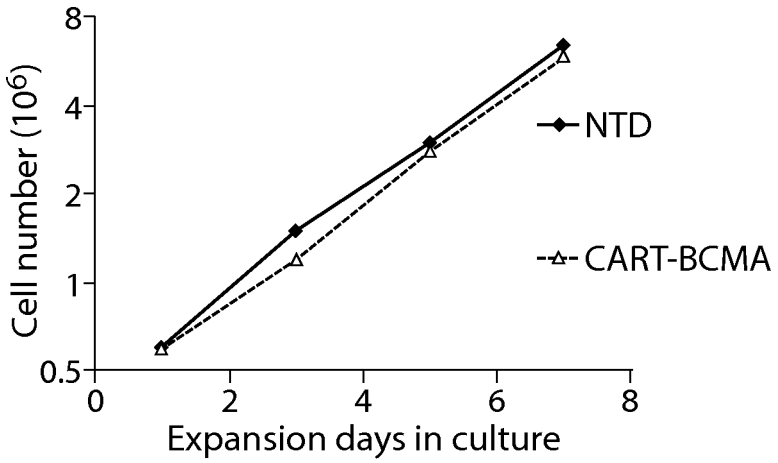


FIG. 36A

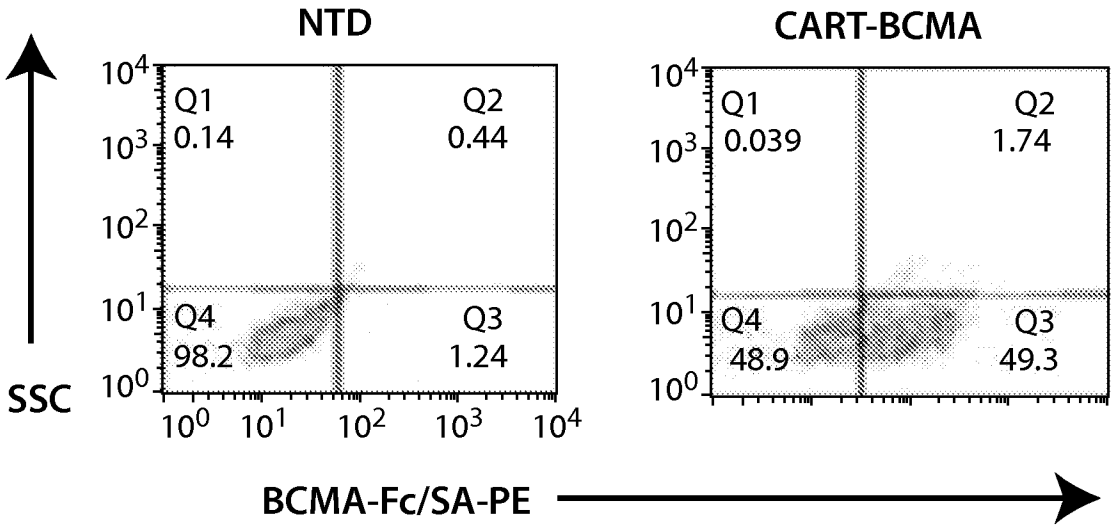


FIG. 36B

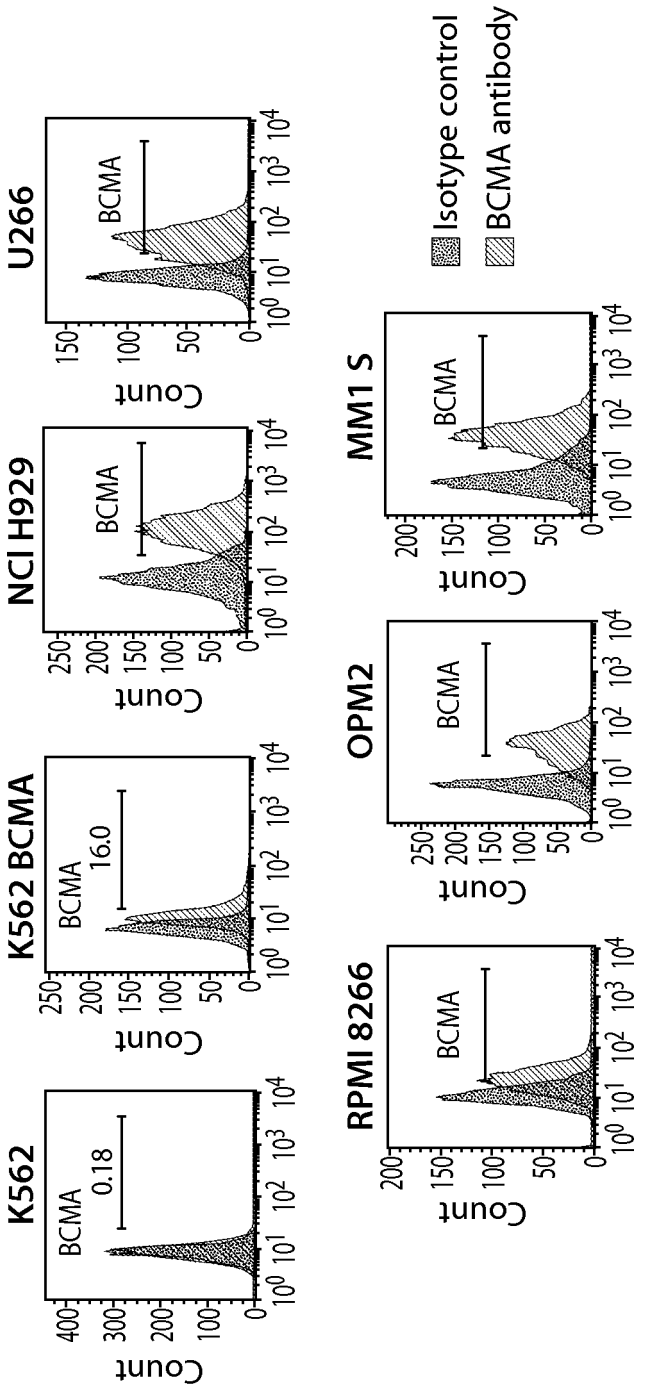

K562
BCMA
0.18
K562 BCMA
BCMA
16.0
NCI H929
BCMA
U266
BCMA
RPMI 8266
BCMA
OPM2
BCMA
MM1 S
BCMA
Count
Isotype control
BCMA antibody

FIG. 37

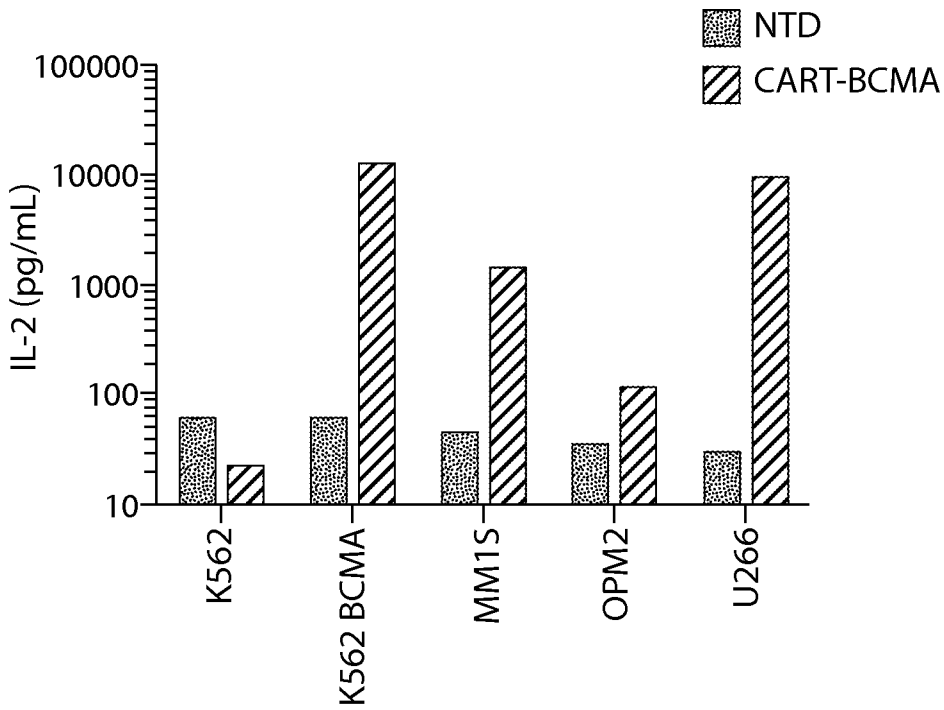


FIG. 38A

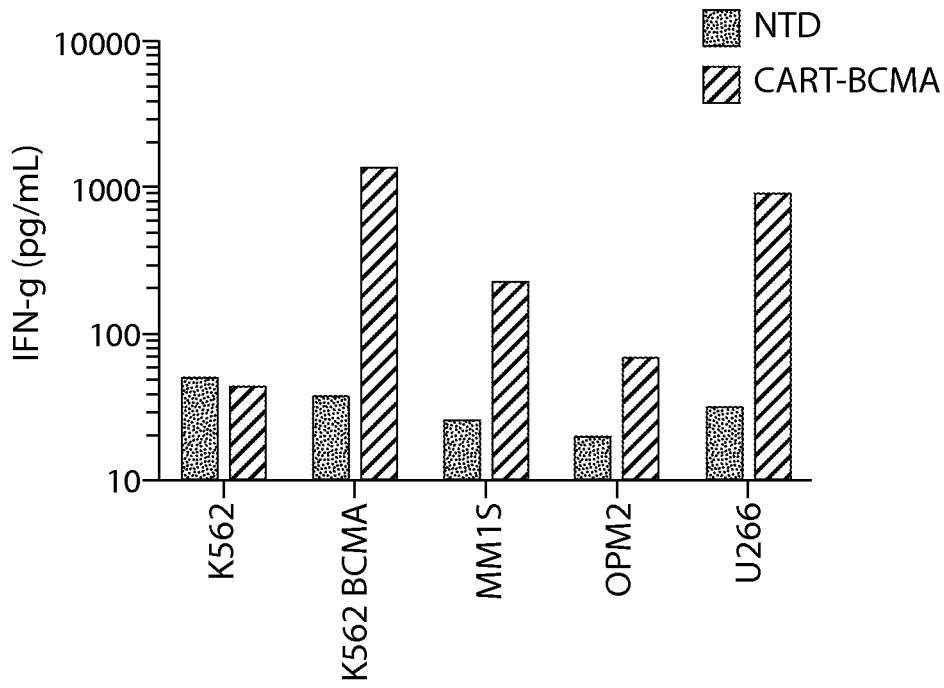


FIG. 38B

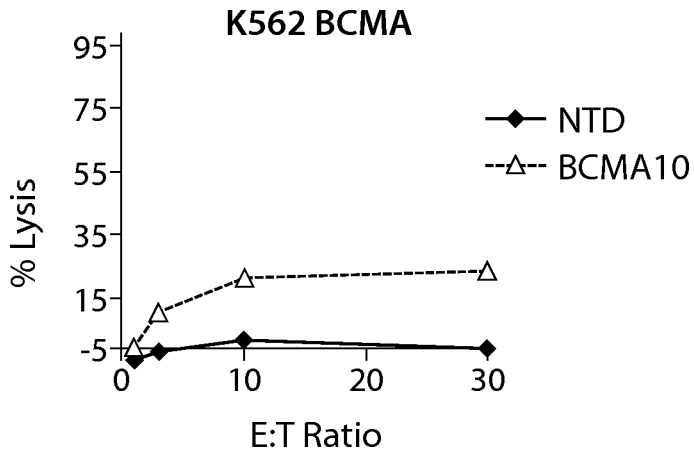


FIG. 39A

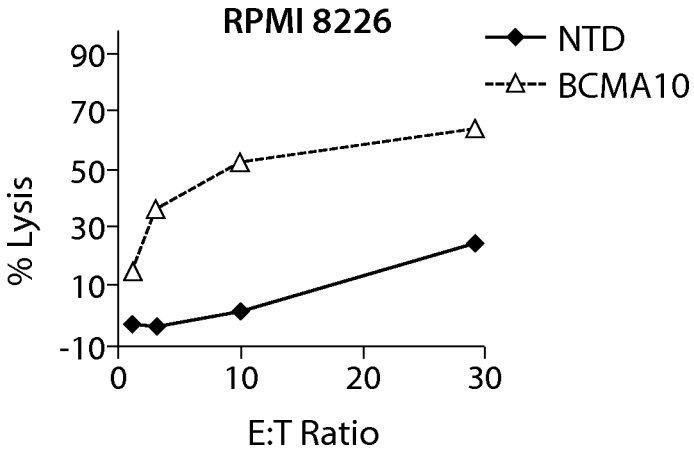


FIG. 39B

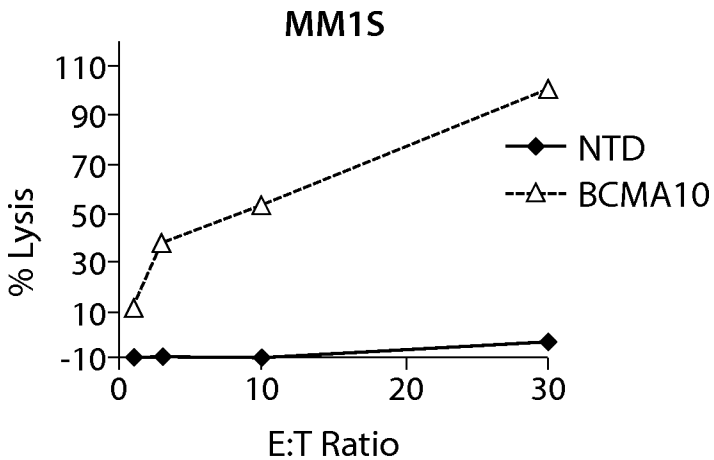


FIG. 39C

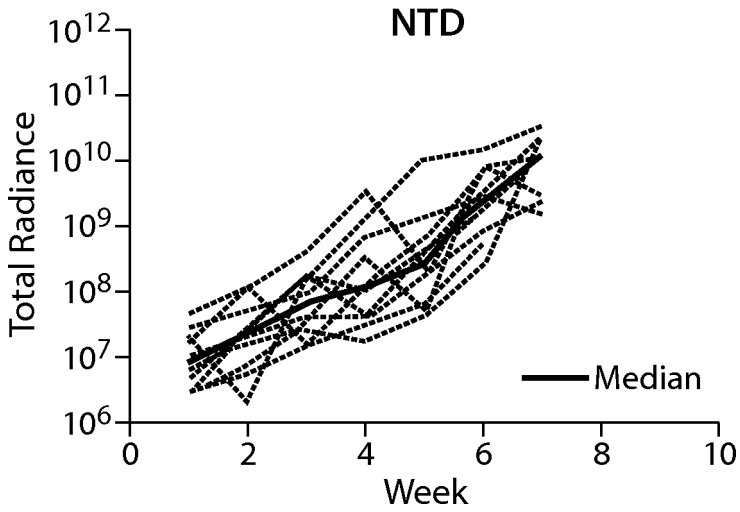


FIG. 40A

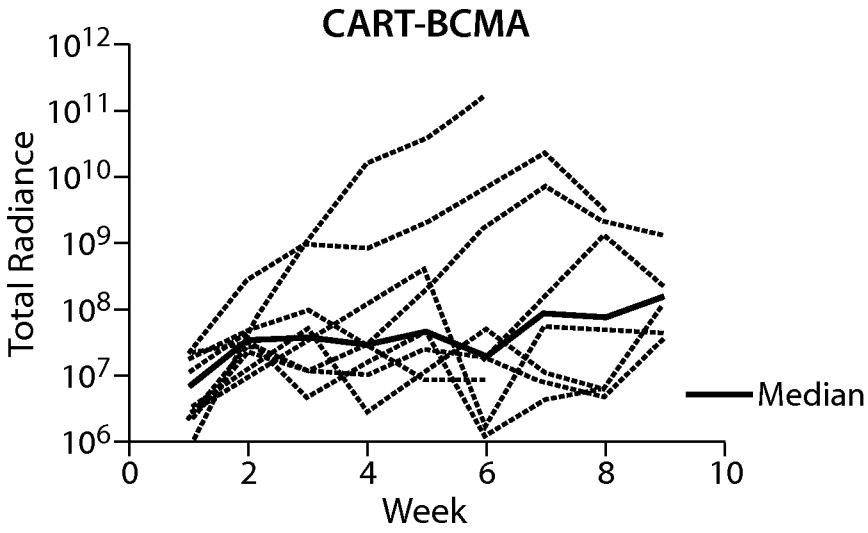


FIG. 40B

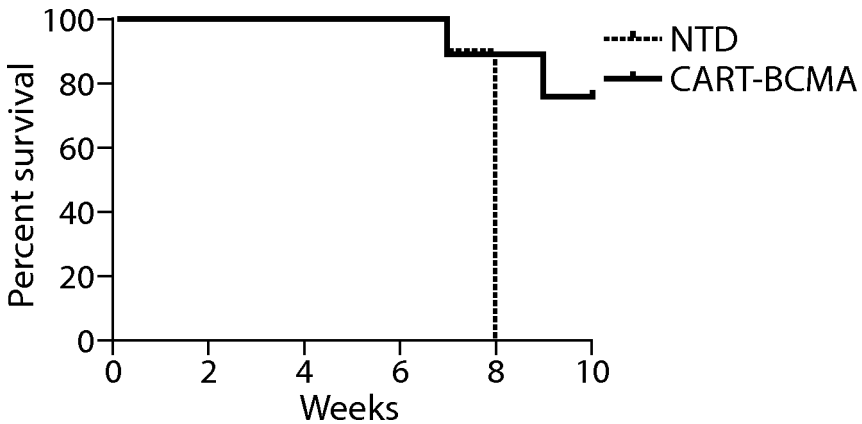


FIG. 40C

Vector constructs

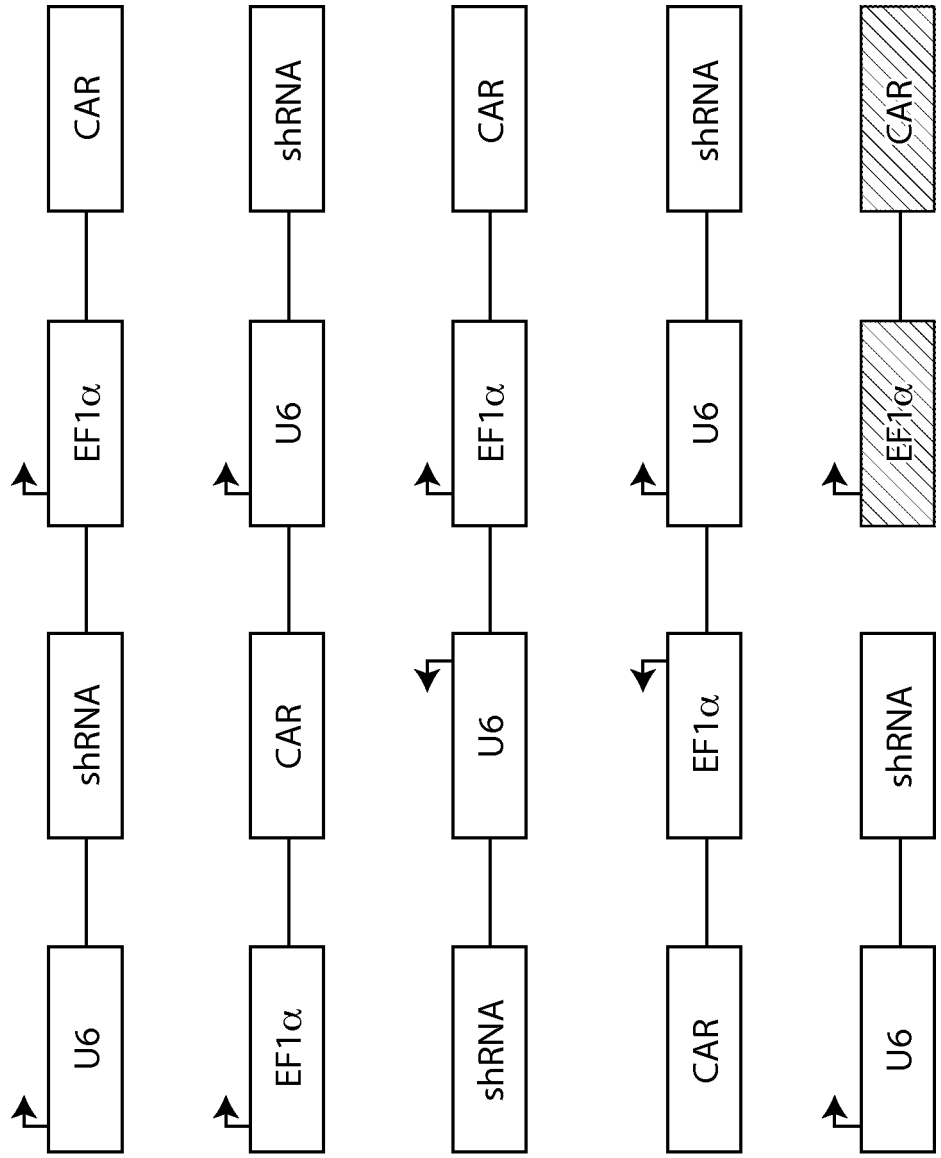


FIG. 41A FIG. 41B FIG. 41C FIG. 41D FIG. 41E

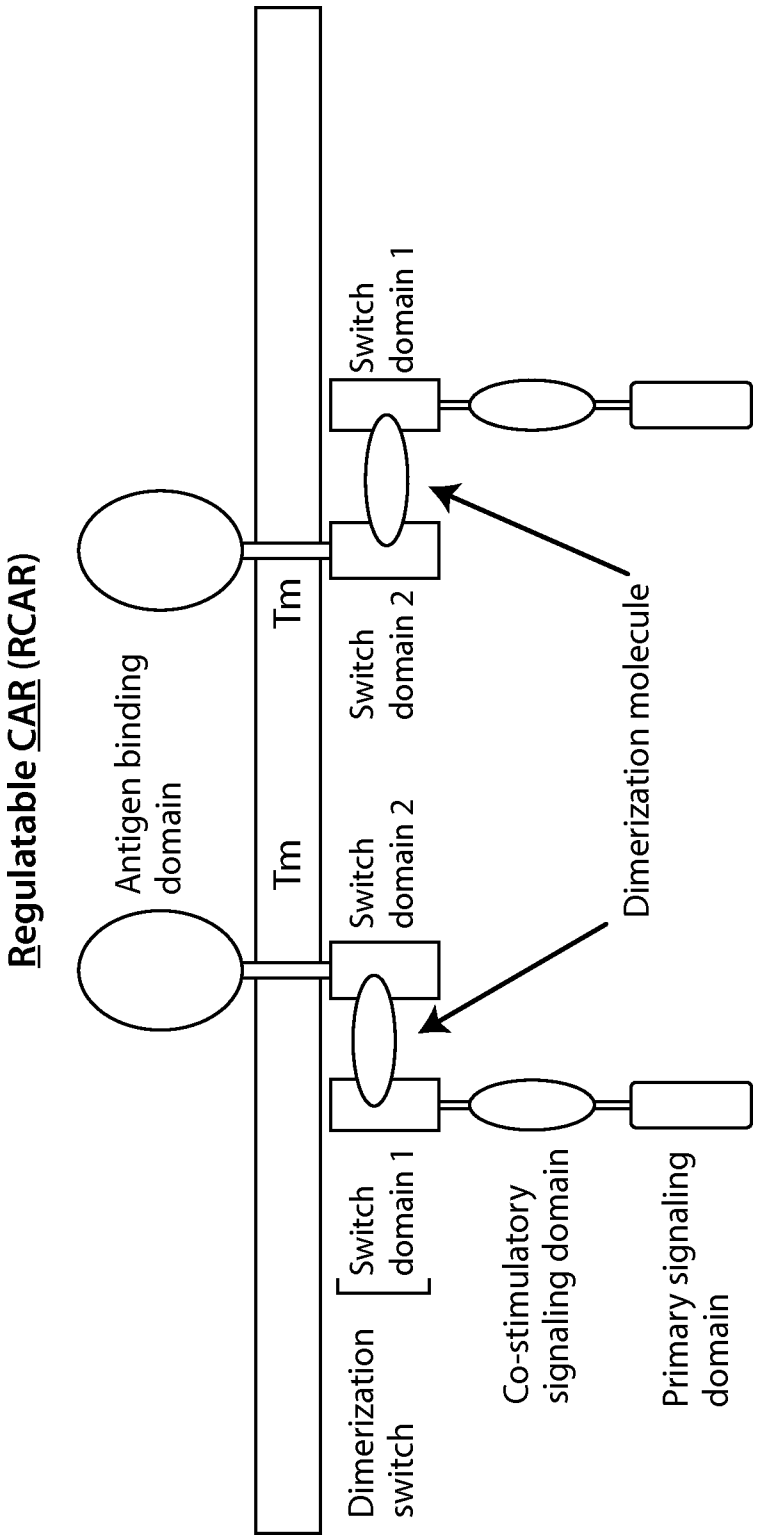

Regulatable CAR (RCAR)
Antigen binding domain
Tm
Tm
Switch domain 1
Switch domain 2
Switch domain 2
Dimerization molecule
Switch domain 1
Dimerization switch
Co-stimulatory signaling domain
Primary signaling domain

Fig. 42

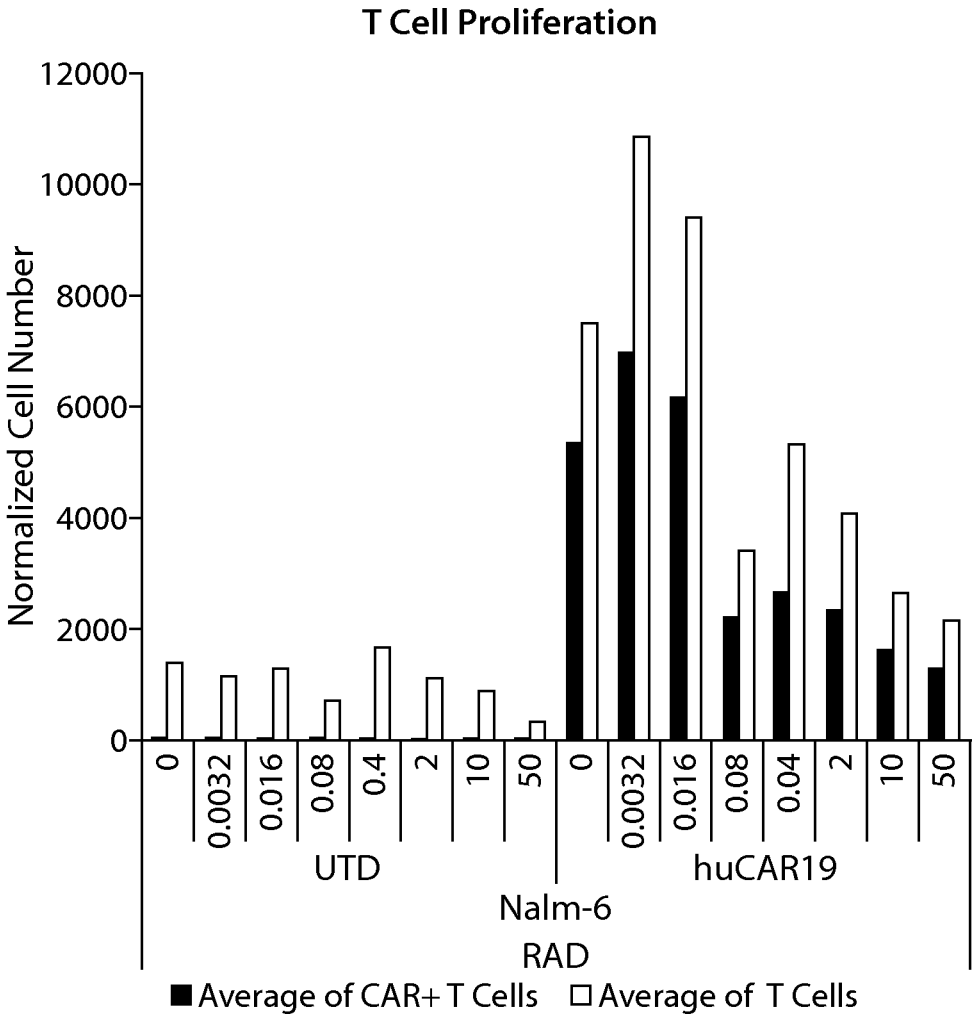

T Cell Proliferation
Normalized Cell Number
12000
10000
8000
6000
4000
2000
0
0
0.0032
0.016
0.08
0.4
2
10
50
0
0.0032
0.016
0.08
0.04
2
10
50
UTD
huCAR19
Nalm-6
RAD
Average of CAR+ T Cells
Average of T Cells

FIG. 43

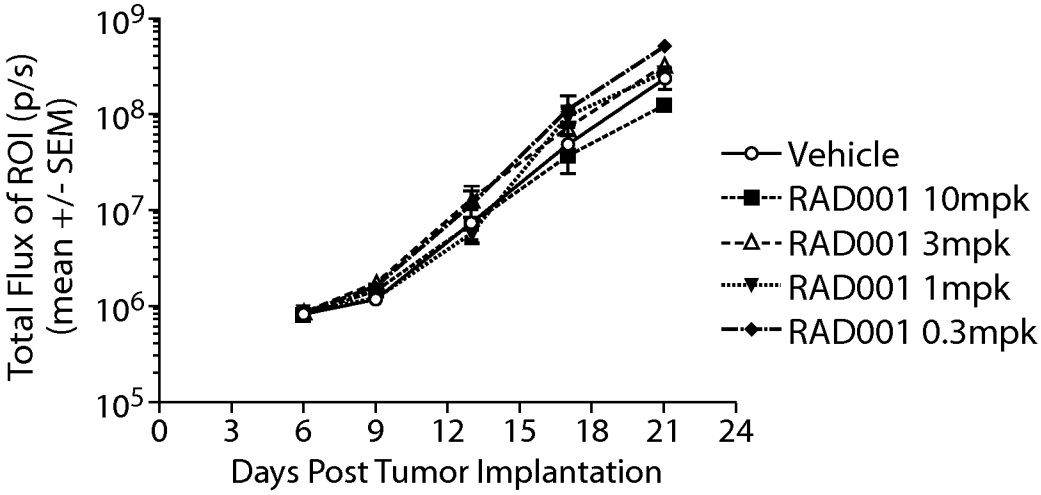

Total Flux of ROI (p/s)
(mean +/- SEM)
10^9
10^8
10^7
10^6
10^5
0
3
6
9
12
15
18
21
24
Days Post Tumor Implantation
Vehicle
RAD001 10mpk
RAD001 3mpk
RAD001 1mpk
RAD001 0.3mpk

FIG. 44

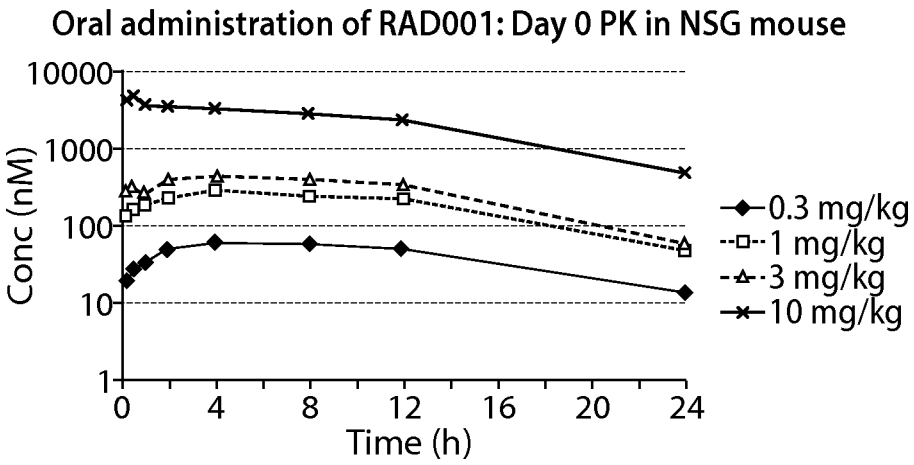


FIG. 45A

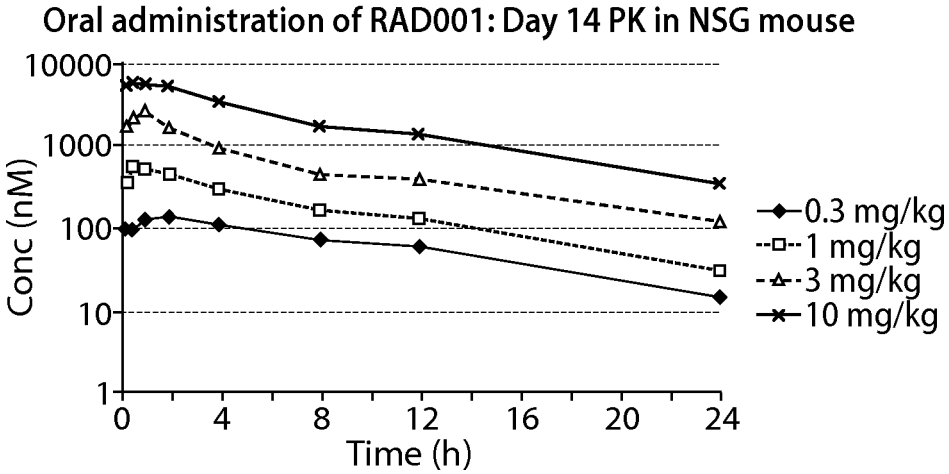


FIG. 45B

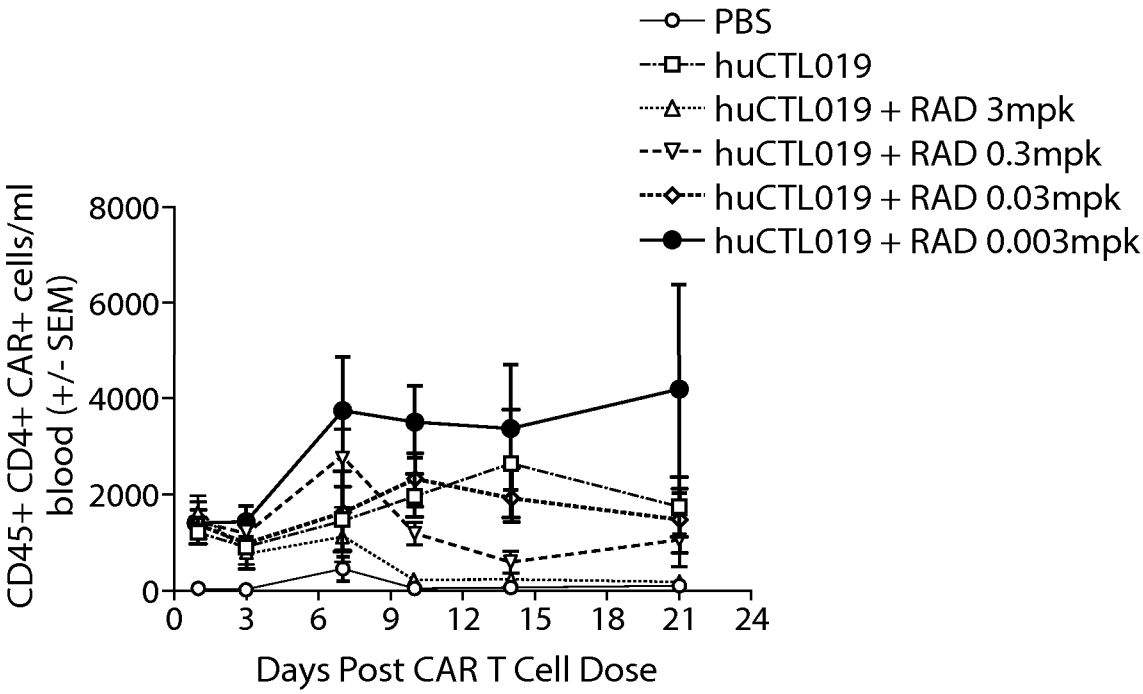


FIG. 46A

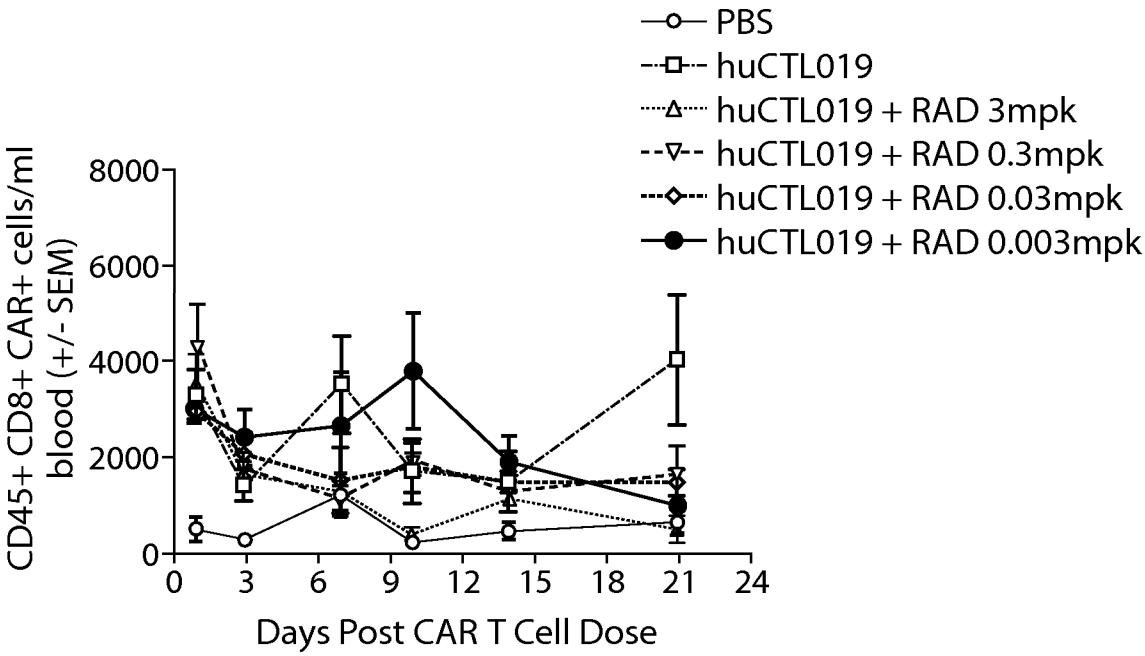
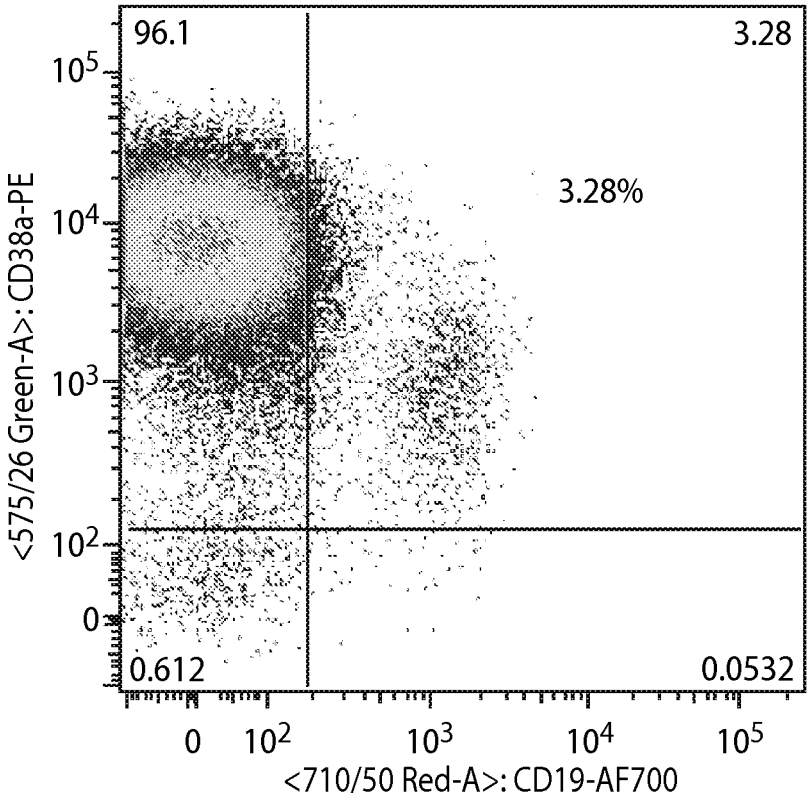


FIG. 46B



CD138+ CD45 dim tumor cells stained for CD19 (x-axis) and CD38 (y-axis)

FIG. 47

SEQUENCE LISTING

<110> NOVARTIS AG
THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA

<120> TREATMENT OF CANCER USING HUMANIZED ANTI BCMA CHIMERIC ANTIGEN RECEPTOR

<130> N2067-7045WO3

<140>
<141>

<150> PCT/CN2014/082586
<151> 2014-07-21

<150> PCT/CN2014/090501
<151> 2014-11-06

<160> 1103

<170> PatentIn version 3.5

<210> 1
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro
20

<210> 2
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 2
Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
1 5 10 15

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
20 25 30

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
35 40 45

<210> 3
<211> 230
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 3

```
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1               5                  10                  15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            20                  25                  30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        35                  40                  45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
    50                  55                  60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65                  70                  75                  80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                85                  90                  95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            100                 105                 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115                 120                 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
145                 150                 155                 160

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
                165                 170                 175

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220

Leu Ser Leu Gly Lys Met
225                 230
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<210> 4
<211> 282
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 4

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Arg Trp Pro Glu Ser Pro Lys Ala Gln Ala Ser Ser Val Pro Thr Ala
1               5                   10                  15

Gln Pro Gln Ala Glu Gly Ser Leu Ala Lys Ala Thr Thr Ala Pro Ala
            20                  25                  30

Thr Thr Arg Asn Thr Gly Arg Gly Gly Glu Glu Lys Lys Lys Glu Lys
        35                  40                  45

Glu Lys Glu Glu Gln Glu Glu Arg Glu Thr Lys Thr Pro Glu Cys Pro
    50                  55                  60

Ser His Thr Gln Pro Leu Gly Val Tyr Leu Leu Thr Pro Ala Val Gln
65                  70                  75                  80

Asp Leu Trp Leu Arg Asp Lys Ala Thr Phe Thr Cys Phe Val Val Gly
                85                  90                  95

Ser Asp Leu Lys Asp Ala His Leu Thr Trp Glu Val Ala Gly Lys Val
            100                 105                 110

Pro Thr Gly Gly Val Glu Glu Gly Leu Leu Glu Arg His Ser Asn Gly
        115                 120                 125

Ser Gln Ser Gln His Ser Arg Leu Thr Leu Pro Arg Ser Leu Trp Asn
    130                 135                 140

Ala Gly Thr Ser Val Thr Cys Thr Leu Asn His Pro Ser Leu Pro Pro
145                 150                 155                 160

Gln Arg Leu Met Ala Leu Arg Glu Pro Ala Ala Gln Ala Pro Val Lys
                165                 170                 175

Leu Ser Leu Asn Leu Leu Ala Ser Ser Asp Pro Pro Glu Ala Ala Ser
            180                 185                 190

Trp Leu Leu Cys Glu Val Ser Gly Phe Ser Pro Pro Asn Ile Leu Leu
        195                 200                 205

Met Trp Leu Glu Asp Gln Arg Glu Val Asn Thr Ser Gly Phe Ala Pro
    210                 215                 220

Ala Arg Pro Pro Pro Gln Pro Gly Ser Thr Thr Phe Trp Ala Trp Ser
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225 230 235 240

Val Leu Arg Val Pro Ala Pro Pro Ser Pro Gln Pro Ala Thr Tyr Thr
245 250 255

Cys Val Val Ser His Glu Asp Ser Arg Thr Leu Leu Asn Ala Ser Arg
260 265 270

Ser Leu Glu Val Ser Tyr Val Thr Asp His
275 280

<210> 5
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 5
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10

<210> 6
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 6
Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
1 5 10 15

Ser Leu Val Ile Thr Leu Tyr Cys
20

<210> 7
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 7
Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
1 5 10 15

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
20 25 30

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
35 40

<210> 8
<211> 48
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 8
Gln Arg Arg Lys Tyr Arg Ser Asn Lys Gly Glu Ser Pro Val Glu Pro
1 5 10 15

Ala Glu Pro Cys Arg Tyr Ser Cys Pro Arg Glu Glu Glu Gly Ser Thr
20 25 30

Ile Pro Ile Gln Glu Asp Tyr Arg Lys Pro Glu Pro Ala Cys Ser Pro
35 40 45

<210> 9
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 9
Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly
1 5 10 15

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
20 25 30

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
35 40 45

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
50 55 60

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
65 70 75 80

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
85 90 95

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
100 105 110

<210> 10
<211> 112

<212> PRT
<213> Homo sapiens

<400> 10
Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly
1 5 10 15

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
20 25 30

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
35 40 45

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
50 55 60

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
65 70 75 80

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
85 90 95

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
100 105 110

<210> 11
<211> 1184
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 11
cgtgaggctc cggtgcccgt cagtgggcag agcgcacatc gcccacagtc cccgagaagt 60

tgggggggagg ggtcggcaat tgaaccggtg cctagagaag gtggcgcggg gtaaactggg 120

aaagtgatgt cgtgtactgg ctccgccttt ttcccgaggg tgggggagaa ccgtatataa 180

gtgcagtagt cgccgtgaac gttcttttttc gcaacgggtt tgccgccaga acacaggtaa 240

gtgccgtgtg tggttcccgc gggcctggcc tctttacggg ttatggccct tgcgtgcctt 300

gaattacttc cacctggctg cagtacgtga ttcttgatcc cgagcttcgg gttggaagtg 360

ggtgggagag ttcgaggcct tgcgcttaag gagccccttc gcctcgtgct tgagttgagg 420

cctggcctgg gcgctggggc cgccgcgtgc gaatctggtg gcaccttcgc gcctgtctcg 480

ctgctttcga taagtctcta gccatttaaa atttttgatg acctgctgcg acgcttttt 540

tctggcaaga tagtcttgta aatgcgggcc aagatctgca cactggtatt tcggtttttg 600

gggccgcggg cggcgacggg gcccgtgcgt cccagcgcac atgttcggcg aggcggggcc 660

tgcgagcgcg gccaccgaga atcggacggg ggtagtctca agctggccgg cctgctctgg 720

tgcctggcct cgcgccgccg tgtatcgccc cgccctgggc ggcaaggctg gcccggtcgg 780

caccagttgc gtgagcggaa agatggccgc ttcccggccc tgctgcaggg agctcaaaat 840

ggaggacgcg gcgctcggga gagcgggcgg gtgagtcacc cacacaaagg aaaagggcct 900

ttccgtcctc agccgtcgct tcatgtgact ccacggagta ccgggcgccg tccaggcacc 960

tcgattagtt ctcgagcttt tggagtacgt cgtctttagg ttgggggggag gggttttatg 1020

cgatggagtt tccccacact gagtgggtgg agactgaagt taggccagct tggcacttga 1080

tgtaattctc cttggaattt gccctttttg agtttggatc ttggttcatt ctcaagcctc 1140

agacagtggt tcaaagtttt tttcttccat ttcaggtgtc gtga 1184

<210> 12
<211> 63
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 12
atggccctgc ctgtgacagc cctgctgctg cctctggctc tgctgctgca tgccgctaga 60

ccc 63

<210> 13
<211> 135
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 13
accacgacgc cagcgccgcg accaccaaca ccggcgccca ccatcgcgtc gcagcccctg 60

tccctgcgcc cagaggcgtg ccggccagcg gcgggggggcg cagtgcacac gaggggctg 120

gacttcgcct gtgat 135

<210> 14
<211> 690
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 14
gagagcaagt acggccctcc ctgcccccct tgccctgccc ccgagttcct gggcggaccc 60

agcgtgttcc tgttcccccc caagcccaag gacaccctga tgatcagccg gacccccgag 120

gtgacctgtg tggtggtgga cgtgtcccag gaggaccccg aggtccagtt caactggtac 180

gtggacggcg tggaggtgca caacgccaag accaagcccc gggaggagca gttcaatagc 240

acctaccggg tggtgtccgt gctgaccgtg ctgcaccagg actggctgaa cggcaaggaa 300

tacaagtgta aggtgtccaa caagggcctg cccagcagca tcgagaaaac catcagcaag 360

gccaagggcc agcctcggga gccccaggtg tacaccctgc cccctagcca agaggagatg 420

accaagaacc aggtgtccct gacctgcctg gtgaagggct tctaccccag cgacatcgcc 480

gtggagtggg agagcaacgg ccagcccgag aacaactaca agaccacccc ccctgtgctg 540

gacagcgacg gcagcttctt cctgtacagc cggctgaccg tggacaagag ccggtggcag 600

gagggcaacg tctttagctg ctccgtgatg cacgaggccc tgcacaacca ctacacccag 660

aagagcctga gcctgtccct gggcaagatg 690

<210> 15
<211> 847
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 15
aggtggcccg aaagtcccaa ggcccaggca tctagtgttc ctactgcaca gccccaggca 60

gaaggcagcc tagccaaagc tactactgca cctgccacta cgcgcaatac tggccgtggc 120

ggggaggaga agaaaaagga gaaagagaaa gaagaacagg aagagaggga gaccaagacc 180

cctgaatgtc catcccatac ccagccgctg ggcgtctatc tcttgactcc cgcagtacag 240

gacttgtggc ttagagataa ggccaccttt acatgtttcg tcgtgggctc tgacctgaag 300

gatgcccatt tgacttggga ggttgccgga aaggtaccca cagggggggt tgaggaaggg 360

ttgctggagc gccattccaa tggctctcag agccagcact caagactcac ccttccgaga 420

tccctgtgga acgccgggac ctctgtcaca tgtactctaa atcatcctag cctgccccca 480

cagcgtctga tggcccttag agagccagcc gcccaggcac cagttaagct tagcctgaat 540

ctgctcgcca gtagtgatcc cccagaggcc gccagctggc tcttatgcga agtgtccggc 600

tttagcccgc ccaacatctt gctcatgtgg ctggaggacc agcgagaagt gaacaccagc 660

ggcttcgctc cagcccggcc cccaccccag ccgggttcta ccacattctg ggcctggagt 720

gtcttaaggg tcccagcacc acctagcccc cagccagcca catacacctg tgttgtgtcc 780

catgaagata gcaggaccct gctaaatgct tctaggagtc tggaggtttc ctacgtgact 840

gaccatt 847

<210> 16
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

oligonucleotide"

<400> 16
ggtggcggag gttctggagg tggaggttcc 30

<210> 17
<211> 72
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 17
atctacatct gggcgcccttggccgggact tgtggggtcc ttctcctgtc actggttatc 60

acccttttact gc 72

<210> 18
<211> 126
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 18
aaacggggca gaaagaaact cctgtatata ttcaaacaac catttatgag accagtacaa 60

actactcaag aggaagatgg ctgtagctgc cgatttccag aagaagaaga aggaggatgt 120

gaactg 126

<210> 19
<211> 123
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 19
aggagtaaga ggagcaggct cctgcacagt gactacatga acatgactcc ccgccgcccc 60

gggcccaccc gcaagcatta ccagccctat gccccaccac gcgacttcgc agcctatcgc 120

tcc 123

<210> 20
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 20
agagtgaagt tcagcaggag cgcagacgcc cccgcgtaca agcagggcca gaaccagctc 60

tataacgagc tcaatctagg acgaagagag gagtacgatg ttttggacaa gagacgtggc 120

cgggaccctg agatgggggg aaagccgaga aggaagaacc ctcaggaagg cctgtacaat 180

gaactgcaga aagataagat ggcggaggcc tacagtgaga ttgggatgaa aggcgagcgc 240

cggaggggca aggggcacga tggcctttac cagggtctca gtacagccac caaggacacc 300

tacgacgccc ttcacatgca ggccctgccc cctcgc 336

<210> 21
<211> 336
<212> DNA
<213> Homo sapiens

<400> 21
agagtgaagt tcagcaggag cgcagacgcc cccgcgtacc agcagggcca gaaccagctc 60

tataacgagc tcaatctagg acgaagagag gagtacgatg ttttggacaa gagacgtggc 120

cgggaccctg agatgggggg aaagccgaga aggaagaacc ctcaggaagg cctgtacaat 180

gaactgcaga aagataagat ggcggaggcc tacagtgaga ttgggatgaa aggcgagcgc 240

cggaggggca aggggcacga tggcctttac cagggtctca gtacagccac caaggacacc 300

tacgacgccc ttcacatgca ggccctgccc cctcgc 336

<210> 22
<211> 373
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 22
Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp Asn Pro Pro Thr
1 5 10 15

Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp Asn Ala Thr Phe
20 25 30

Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val Leu Asn Trp Tyr
35 40 45

Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala Ala Phe Pro Glu
50 55 60

Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg Val Thr Gln Leu
65 70 75 80

Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg Ala Arg Arg Asn
85 90 95

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Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu Ala Pro Lys Ala
            100                 105                 110

Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val Thr Glu Arg Arg
        115                 120                 125

Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro Arg Pro Ala Gly
    130                 135                 140

Gln Phe Gln Thr Leu Val Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr
145                 150                 155                 160

Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala
                165                 170                 175

Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe
            180                 185                 190

Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
        195                 200                 205

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys
    210                 215                 220

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
225                 230                 235                 240

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
                245                 250                 255

Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
            260                 265                 270

Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
        275                 280                 285

Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
    290                 295                 300

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
305                 310                 315                 320

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
                325                 330                 335

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
            340                 345                 350

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
        355                 360                 365
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Ala Leu Pro Pro Arg
370

<210> 23
<211> 1182
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 23
atggccctcc ctgtcactgc cctgcttctc cccctcgcac tcctgctcca cgccgctaga 60

ccacccggat ggtttctgga ctctccggat cgcccgtgga atcccccaac cttctcaccg 120

gcactcttgg ttgtgactga gggcgataat gcgaccttca cgtgctcgtt ctccaacacc 180

tccgaatcat tcgtgctgaa ctggtaccgc atgagcccgt caaaccagac cgacaagctc 240

gccgcgtttc cggaagatcg gtcgcaaccg ggacaggatt gtcggttccg cgtgactcaa 300

ctgccgaatg gcagagactt ccacatgagc gtggtccgcg ctaggcgaaa cgactccggg 360

acctacctgt gcggagccat ctcgctggcg cctaaggccc aaatcaaaga gagcttgagg 420

gccgaactga gagtgaccga gcgcagagct gaggtgccaa ctgcacatcc atccccatcg 480

cctcggcctg cggggcagtt tcagaccctg gtcacgacca ctccggcgcc gcgcccaccg 540

actccggccc caactatcgc gagccagccc ctgtcgctga ggccggaagc atgccgccct 600

gccgccggag gtgctgtgca tacccgggga ttggacttcg catgcgacat ctacatttgg 660

gctcctctcg ccggaacttg tggcgtgctc cttctgtccc tggtcatcac cctgtactgc 720

aagcggggtc ggaaaaagct tctgtacatt ttcaagcagc ccttcatgag gcccgtgcaa 780

accacccagg aggaggacgg ttgctcctgc cggttccccg aagaggaaga aggaggttgc 840

gagctgcgcg tgaagttctc ccggagcgcc gacgcccccg cctataagca gggccagaac 900

cagctgtaca acgaactgaa cctgggacgg cgggaagagt acgatgtgct ggacaagcgg 960

cgcggccggg accccgaaat gggcgggaag cctagaagaa agaaccctca ggaaggcctg 1020

tataacgagc tgcagaagga caagatggcc gaggcctact ccgaaattgg gatgaaggga 1080

gagcggcgga ggggaaaggg gcacgacggc ctgtaccaag gactgtccac cgccaccaag 1140

gacacatacg atgccctgca catgcaggcc cttccccctc gc 1182

<210> 24
<211> 394
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 24
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu

1 5 10 15

His Ala Ala Arg Pro Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro
20 25 30

Trp Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly
35 40 45

Asp Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe
50 55 60

Val Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu
65 70 75 80

Ala Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe
85 90 95

Arg Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val
100 105 110

Arg Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser
115 120 125

Leu Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg
130 135 140

Val Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser
145 150 155 160

Pro Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Thr Thr Thr Pro Ala
165 170 175

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
180 185 190

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
195 200 205

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
210 215 220

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
225 230 235 240

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
245 250 255

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
260 265 270

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg

275 280 285

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
290 295 300

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
305 310 315 320

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
325 330 335

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
340 345 350

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
355 360 365

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
370 375 380

Ala Leu His Met Gln Ala Leu Pro Pro Arg
385 390

<210> 25
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 25
Gly Gly Gly Gly Ser
1 5

<210> 26
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<220>
<221> misc_feature
<222> (1)..(30)
<223> /note="This sequence may encompass 1-6 'Gly Gly Gly Gly Ser' repeating units, wherein some positions may be absent"

<220>
<221> source
<223> /note="See specification as filed for detailed description of substitutions and preferred embodiments"

<400> 26
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25 30

<210> 27
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 27
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser
20

<210> 28
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 28
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 29
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 29
Gly Gly Gly Ser
1

<210> 30
<211> 5000
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<220>
<221> misc_feature
<222> (1)..(5000)
<223> /note="This sequence may encompass 50-5,000 nucleotides,
wherein some positions may be absent"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 30
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 60

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 120

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 180

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 240

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 300

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 360

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 420

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 480

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 540

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 600

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 660

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 720

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 780

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 840

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 900

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 960

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1020

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1080

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1140

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1200

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1260

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1320

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1380

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1440

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1500

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1560

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1620

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1680

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aaaaaaaaaa aaaaaaaaaa 5000

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<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 31
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<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<220>
<221> misc_feature
<222> (1)..(5000)
<223> /note="This sequence may encompass 50-5,000 nucleotides, wherein some positions may be absent"

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ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 180

ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 240

ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 300

ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 360

ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 420

ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 480

ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 540

ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt ttttttttt 600

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tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 3420
tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 3480
tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 3540
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<210> 33
<211> 5000
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (1)..(5000)
<223> /note="This sequence may encompass 100-5,000 nucleotides,
wherein some positions may be absent"

<400> 33
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 60

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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 180

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 240

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 300

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 360

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 420

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 480

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 540

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 600

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 660

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 720

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 780

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 840

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 900

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 960

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1020

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1080

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1140

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1200

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aaaaaaaaaa aaaaaaaaaa 5000

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<211> 400
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<220>
<221> misc_feature
<222> (1)..(400)
<223> /note="This sequence may encompass 100-400 nucleotides, wherein some positions may be absent"

<220>
<221> source
<223> /note="See specification as filed for detailed description of substitutions and preferred embodiments"

<400> 34
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 240

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 300

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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 400

<210> 35
<211> 2000

<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<220>
<221> misc_feature
<222> (1)..(2000)
<223> /note="This sequence may encompass 50-2,000 nucleotides, wherein some positions may be absent"

<400> 35
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 240

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 300

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 360

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 420

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 480

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 540

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 600

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 660

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 720

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 780

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 840

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 900

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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1140

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aaaaaaaaaa aaaaaaaaaa 2000

<210> 36
<211> 230
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 36
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1 5 10 15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
20 25 30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
35 40 45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
50 55 60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65 70 75 80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
85 90 95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
100 105 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
115 120 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
130 135 140

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
145 150 155 160

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
165 170 175

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
180 185 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
195 200 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
210 215 220

Leu Ser Leu Gly Lys Met
225 230

<210> 37
<211> 690
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

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gtgacctgtg tggtggtgga cgtgtcccag gaggaccccg aggtccagtt caactggtac 180

gtggacggcg tggaggtgca caacgccaag accaagcccc gggaggagca gttcaatagc 240

acctaccggg tggtgtccgt gctgaccgtg ctgcaccagg actggctgaa cggcaaggaa 300

tacaagtgta aggtgtccaa caagggcctg cccagcagca tcgagaaaac catcagcaag 360

gccaagggcc agcctcggga gccccaggtg tacaccctgc cccctagcca agaggagatg 420

accaagaacc aggtgtccct gacctgcctg gtgaagggct tctaccccag cgacatcgcc 480

gtggagtggg agagcaacgg ccagcccgag aacaactaca agaccacccc ccctgtgctg 540

gacagcgacg gcagcttctt cctgtacagc cggctgaccg tggacaagag ccggtggcag 600

gagggcaacg tctttagctg ctccgtgatg cacgaggccc tgcacaacca ctacacccag 660

aagagcctga gcctgtccct gggcaagatg 690

<210> 38
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<220>

<221> misc_feature
<222> (1)..(40)
<223> /note="This sequence may encompass 1-10 'Gly Gly Gly Ser' repeating units, wherein some positions may be absent"

<220>
<221> source
<223> /note="See specification as filed for detailed description of substitutions and preferred embodiments"

<400> 38
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
20 25 30

Gly Gly Gly Ser Gly Gly Gly Ser
35 40

<210> 39
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 39
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Gly Trp Val
35 40 45

Ser Gly Ile Ser Arg Ser Gly Glu Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Pro Ala His Tyr Tyr Gly Gly Met Asp Val Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Arg Ala Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Thr Gln Ser
130 135 140

```
Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
145                 150                 155                 160

Arg Ala Ser Gln Ser Ile Ser Ser Ser Phe Leu Ala Trp Tyr Gln Gln
                165                 170                 175

Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Arg Arg
            180                 185                 190

Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
        195                 200                 205

Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Ser Ala Val Tyr
    210                 215                 220

Tyr Cys Gln Gln Tyr His Ser Ser Pro Ser Trp Thr Phe Gly Gln Gly
225                 230                 235                 240

Thr Lys Leu Glu Ile Lys
                245
```

<210> 40
<211> 244
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 40

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Ser Val His Ser Phe Leu Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110
```

```
Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly Gly Arg Ala Ser Gly
        115                 120                 125

Gly Gly Gly Ser Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro
    130                 135                 140

Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser
145                 150                 155                 160

Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys
                165                 170                 175

Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala
            180                 185                 190

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
        195                 200                 205

Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr
    210                 215                 220

Cys Met Gln Ala Leu Gln Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys
225                 230                 235                 240

Val Glu Ile Lys
```

<210> 41
<211> 243
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 41

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ala Leu Ser Asn His
            20                  25                  30

Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr Leu
65                  70                  75                  80
```

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Ile Tyr Tyr Cys Ser
85 90 95

Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly Gly Arg Ala Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Ser
130 135 140

Val Thr Pro Gly Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser
145 150 155 160

Leu Leu Arg Asn Asp Gly Lys Thr Pro Leu Tyr Trp Tyr Leu Gln Lys
165 170 175

Ala Gly Gln Pro Pro Gln Leu Leu Ile Tyr Glu Val Ser Asn Arg Phe
180 185 190

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
195 200 205

Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Ala Tyr Tyr
210 215 220

Cys Met Gln Asn Ile Gln Phe Pro Ser Phe Gly Gly Gly Thr Lys Leu
225 230 235 240

Glu Ile Lys

<210> 42
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 42
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Arg Lys Thr Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Asp Asn Phe
20 25 30

Gly Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Pro Lys Asn Asn Asn Thr Asn Tyr Ala Gln Lys Phe

50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Asn Thr Ala Tyr
65 70 75 80

Met Glu Val Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Pro Tyr Tyr Tyr Gln Ser Tyr Met Asp Val Trp Gly Gln
100 105 110

Gly Thr Met Val Thr Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Arg Ala Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Thr
130 135 140

Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys
145 150 155 160

Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu Asn
165 170 175

Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu
180 185 190

Gly Ser Lys Arg Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly
195 200 205

Ser Gly Thr Asp Phe Thr Leu His Ile Thr Arg Val Gly Ala Glu Asp
210 215 220

Val Gly Val Tyr Tyr Cys Met Gln Ala Leu Gln Thr Pro Tyr Thr Phe
225 230 235 240

Gly Gln Gly Thr Lys Leu Glu Ile Lys
245

<210> 43
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 43
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Asp
20 25 30

```
Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Val Ile Ser Gly Ser Gly Gly Thr Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Leu Asp Ser Ser Gly Tyr Tyr Tyr Ala Arg Gly Pro Arg Tyr
            100                 105                 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Arg Ala Ser Gly Gly Gly Gly Ser Asp Ile Gln Leu
    130                 135                 140

Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr
145                 150                 155                 160

Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr
                165                 170                 175

Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Gly Ala Ser
            180                 185                 190

Thr Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205

Thr His Phe Thr Leu Thr Ile Asn Ser Leu Gln Ser Glu Asp Ser Ala
    210                 215                 220

Thr Tyr Tyr Cys Gln Gln Ser Tyr Lys Arg Ala Ser Phe Gly Gln Gly
225                 230                 235                 240

Thr Lys Val Glu Ile Lys
                245
```

<210> 44
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 44

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Asn Tyr
            20                  25                  30

Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asn Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Pro Tyr Tyr Tyr Tyr Met Asp Val Trp Gly Lys Gly Thr
            100                 105                 110

Met Val Thr Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly Gly Arg
        115                 120                 125

Ala Ser Gly Gly Gly Gly Ser Glu Ile Val Met Thr Gln Ser Pro Leu
    130                 135                 140

Ser Leu Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser
145                 150                 155                 160

Ser Gln Ser Leu Leu Tyr Ser Asn Gly Tyr Asn Tyr Val Asp Trp Tyr
                165                 170                 175

Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu Gly Ser
            180                 185                 190

Asn Arg Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205

Thr Asp Phe Lys Leu Gln Ile Ser Arg Val Glu Ala Glu Asp Val Gly
    210                 215                 220

Ile Tyr Tyr Cys Met Gln Gly Arg Gln Phe Pro Tyr Ser Phe Gly Gln
225                 230                 235                 240

Gly Thr Lys Val Glu Ile Lys
                245
```

<210> 45
<211> 238
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 45

```
Glu Val Gln Leu Leu Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ala Leu Ser Asn His
            20                  25                  30

Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Ile Tyr Tyr Cys Ser
                85                  90                  95

Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110

Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly Gly Arg Ala Ser Gly
        115                 120                 125

Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
    130                 135                 140

Val Ser Pro Gly Glu Ser Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
145                 150                 155                 160

Val Ser Ser Asn Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
                165                 170                 175

Arg Leu Leu Ile Tyr Gly Ala Ser Thr Arg Ala Ser Gly Ile Pro Asp
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Tyr Gly
    210                 215                 220

Ser Ser Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
225                 230                 235
```

<210> 46
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 46

```
Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ala Leu Ser Asn His
            20                  25                  30

Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Ile Tyr Tyr Cys Ser
                85                  90                  95

Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110

Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly Gly Arg Ala Ser Gly
        115                 120                 125

Gly Gly Gly Ser Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser
    130                 135                 140

Val Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
145                 150                 155                 160

Val Ser Ser Lys Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
                165                 170                 175

Arg Leu Leu Met Tyr Gly Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly
    210                 215                 220

Ser Ser Ser Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
```

225 230 235

<210> 47
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 47
Glu Val Gln Leu Val Glu Thr Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ala Leu Ser Asn His
20 25 30

Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Ile Tyr Tyr Cys Ser
85 90 95

Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly Gly Arg Ala Ser Gly
115 120 125

Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
130 135 140

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
145 150 155 160

Val Gly Ser Thr Asn Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
165 170 175

Pro Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro
180 185 190

Asp Arg Phe Ser Gly Gly Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
195 200 205

Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr
210 215 220

Gly Ser Ser Pro Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
225 230 235 240

Lys

<210> 48
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 48
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Ser Gly Asp Gly Met Asp Val Trp Gly Gln Gly Thr Thr
100 105 110

Val Thr Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly Gly Arg Ala
115 120 125

Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
130 135 140

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
145 150 155 160

Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
165 170 175

Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
180 185 190

```
Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
        195                 200                 205


Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
    210                 215                 220


Ser Tyr Thr Leu Ala Phe Gly Gln Gly Thr Lys Val Asp Ile Lys
225                 230                 235


<210> 49
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 49
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ala Leu Ser Asn His
            20                  25                  30


Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Ile Tyr Tyr Cys Ser
                85                  90                  95


Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110


Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly Gly Arg Ala Ser Gly
        115                 120                 125


Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser
    130                 135                 140


Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser
145                 150                 155                 160


Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175
```

Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser
180 185 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
195 200 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr
210 215 220

Ser Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
225 230 235

<210> 50
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 50
Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Ser Gly Asn Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Thr Met Val Arg Glu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly Gly Arg Ala
115 120 125

Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Thr Gln Ser Pro Leu Ser
130 135 140

Leu Pro Val Thr Leu Gly Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser
145 150 155 160

Glu Ser Leu Val His Asn Ser Gly Lys Thr Tyr Leu Asn Trp Phe His

165 170 175

Gln Arg Pro Gly Gln Ser Pro Arg Arg Leu Ile Tyr Glu Val Ser Asn
180 185 190

Arg Asp Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr
195 200 205

Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val
210 215 220

Tyr Tyr Cys Met Gln Gly Thr His Trp Pro Gly Thr Phe Gly Gln Gly
225 230 235 240

Thr Lys Leu Glu Ile Lys
245

<210> 51
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 51
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ala Leu Ser Asn His
20 25 30

Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Ile Tyr Tyr Cys Ser
85 90 95

Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly Gly Arg Ala Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Arg Leu Thr Gln Ser Pro Ser Pro Leu Ser
130 135 140

```
Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Glu Asp
145                 150                 155                 160


Ile Asn Lys Phe Leu Asn Trp Tyr His Gln Thr Pro Gly Lys Ala Pro
                165                 170                 175


Lys Leu Leu Ile Tyr Asp Ala Ser Thr Leu Gln Thr Gly Val Pro Ser
            180                 185                 190


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn
        195                 200                 205


Ser Leu Gln Pro Glu Asp Ile Gly Thr Tyr Tyr Cys Gln Gln Tyr Glu
    210                 215                 220


Ser Leu Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
225                 230                 235


<210> 52
<211> 240
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 52
Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ala Leu Ser Asn His
            20                  25                  30


Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Ile Tyr Tyr Cys Ser
                85                  90                  95


Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110


Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly Gly Arg Ala Ser Gly
        115                 120                 125
```

```
Gly Gly Gly Ser Glu Thr Thr Leu Thr Gln Ser Pro Ala Thr Leu Ser
    130                 135                 140

Val Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
145                 150                 155                 160

Val Gly Ser Asn Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Gly Pro
                165                 170                 175

Arg Leu Leu Ile Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn
    210                 215                 220

Asp Trp Leu Pro Val Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
225                 230                 235                 240


<210> 53
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 53
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ala Leu Ser Asn His
            20                  25                  30

Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Ile Tyr Tyr Cys Ser
                85                  90                  95

Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110
```

```
Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly Gly Arg Ala Ser Gly
        115                 120                 125

Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
    130                 135                 140

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
145                 150                 155                 160

Ile Gly Ser Ser Ser Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
                165                 170                 175

Pro Arg Leu Leu Met Tyr Gly Ala Ser Ser Arg Ala Ser Gly Ile Pro
            180                 185                 190

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
        195                 200                 205

Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr
    210                 215                 220

Ala Gly Ser Pro Pro Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
225                 230                 235                 240

Lys
```

<210> 54
<211> 738
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 54

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caagtgcaac tcgtggaatc tggtggagga ctcgtgcaac ccggaagatc gcttagactg       60

tcgtgtgccg ccagcgggtt cactttctcg aactacgcga tgtcctgggt ccgccaggca      120

cccggaaagg gactcggttg ggtgtccggc atttcccggt ccggcgaaaa tacctactac      180

gccgactccg tgaagggccg cttcaccatc tcaagggaca acagcaaaaa caccctgtac      240

ttgcaaatga actccctgcg ggatgaagat acagccgtgt actattgcgc ccggtcgcct      300

gcccattact acggcggaat ggacgtctgg ggacagggaa ccactgtgac tgtcagcagc      360

gcgtcgggtg gcggcggctc aggggtcgg gcctccgggg ggggagggtc cgacatcgtg      420

ctgacccagt ccccgggaac cctgagcctg agcccgggag agcgcgcgac cctgtcatgc      480

cgggcatccc agagcattag ctcctccttt ctcgcctggt atcagcagaa gcccggacag      540

gccccgaggc tgctgatcta cggcgctagc agaagggcta ccggaatccc agaccggttc      600

tccggctccg gttccgggac cgatttcacc cttactatct cgcgcctgga acctgaggac      660
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tccgccgtct actactgcca gcagtaccac tcatccccgt cgtggacgtt cggacagggc 720

accaagctgg agattaag 738

<210> 55
<211> 732
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 55
caagtgcaac tcgtcgaatc cggtggaggt ctggtccaac ctggtagaag cctgagactg 60

tcgtgtgcgg ccagcggatt cacctttgat gactatgcta tgcactgggt gcggcaggcc 120

ccaggaaagg gcctggaatg ggtgtcggga attagctgga actccgggtc cattggctac 180

gccgactccg tgaagggccg cttcaccatc tcccgcgaca acgcaaagaa ctccctgtac 240

ttgcaaatga actcgctcag ggctgaggat accgcgctgt actactgctc cgtgcattcc 300

ttcctggcct actggggaca gggaactctg gtcaccgtgt cgagcgcctc cggcggcggg 360

ggctcgggtg gacgggcctc gggcggaggg gggtccgaca tcgtgatgac ccagaccccg 420

ctgagcttgc ccgtgactcc cggagagcct gcatccatct cctgccggtc atcccagtcc 480

cttctccact ccaacggata caactacctc gactggtacc tccagaagcc gggacagagc 540

cctcagcttc tgatctacct ggggtcaaat agagcctcag gagtgccgga tcggttcagc 600

ggatctggtt cgggaactga tttcactctg aagatttccc gcgtggaagc cgaggacgtg 660

ggcgtctact actgtatgca ggcgctgcag acccccctata ccttcggcca agggacgaaa 720

gtggagatca ag 732

<210> 56
<211> 729
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 56
gaagtgcaat tgttggaatc tggaggagga cttgtgcagc ctggaggatc actgagactt 60

tcgtgtgcgg tgtcaggctt cgccctgagc aaccacggca tgagctgggt gcggagagcc 120

ccggggaagg gtctggaatg ggtgtccggg atcgtctact ccggttcaac ttactacgcc 180

gcaagcgtga agggtcgctt caccatttcc cgcgataact cccggaacac cctgtacctc 240

caaatgaact ccctgcggcc cgaggacacc gccatctact actgttccgc gcatggagga 300

gagtccgatg tctggggaca gggcactacc gtgaccgtgt cgagcgcctc gggggggaga 360

ggctccggcg gtcgcgcctc cgggggggt ggcagcgaca ttgtgatgac gcagactcca 420

ctctcgctgt ccgtgacccc gggacagccc gcgtccatct cgtgcaagag ctcccagagc 480

ctgctgagga acgacggaaa gactcctctg tattggtacc tccagaaggc tggacagccc 540

ccgcaactgc tcatctacga agtgtcaaat cgcttctccg gggtgccgga tcggttttcc 600

ggctcgggat cgggcaccga cttcaccctg aaaatctcca gggtcgaggc cgaggacgtg 660

ggagcctact actgcatgca aaacatccag ttcccttcct tcggcggcgg cacaaagctg 720

gagattaag 729

<210> 57
<211> 747
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 57
caagtccaac tcgtccagtc cggcgcagaa gtcagaaaaa ccggtgctag cgtgaaagtg 60

tcctgcaagg cctccggcta cattttcgat aacttcggaa tcaactgggt cagacaggcc 120

ccgggccagg ggctggaatg gatgggatgg atcaacccca agaacaacaa caccaactac 180

gcacagaagt tccagggccg cgtgactatc accgccgatg aatcgaccaa taccgcctac 240

atggaggtgt cctccctgcg gtcggaggac actgccgtgt attactgcgc gaggggccca 300

tactactacc aaagctacat ggacgtctgg ggacagggaa ccatggtgac cgtgtcatcc 360

gcctccggtg gtggaggctc ggggggcgg gcttcaggag gcggaggaag cgatattgtg 420

atgacccaga ctccgcttag cctgcccgtg actcctggag aaccggcctc catttcctgc 480

cggtcctcgc aatcactcct gcattccaac ggttacaact acctgaattg gtacctccag 540

aagcctggcc agtcgcccca gttgctgatc tatctgggct cgaagcgcgc ctccggggtg 600

cctgaccggt ttagcggatc tgggagcggc acggacttca ctctccacat cacccgcgtg 660

ggagcggagg acgtgggagt gtactactgt atgcaggcgc tgcagactcc gtacacattc 720

ggacagggca ccaagctgga gatcaag 747

<210> 58
<211> 738
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 58
caagtgcaac ttcaagaatc aggcggagga ctcgtgcagc ccggaggatc attgcggctc 60

tcgtgcgccg cctcgggctt caccttctcg agcgacgcca tgacctgggt ccgccaggcc 120

ccggggaagg ggctggaatg ggtgtctgtg atttccggct ccgggggaac tacgtactac 180

gccgattccg tgaaaggtcg cttcactatc tcccgggaca acagcaagaa cacccttttat 240

ctgcaaatga attccctccg cgccgaggac accgccgtgt actactgcgc caagctggac 300

tcctcgggct actactatgc ccggggtccg agatactggg gacagggaac cctcgtgacc 360

gtgtcctccg cgtccggcgg aggagggtcg ggagggcggg cctccggcgg cggcggttcg 420

gacatccagc tgacccagtc cccatcctca ctgagcgcaa gcgtgggcga cagagtcacc 480

attacatgca gggcgtccca gagcatcagc tcctacctga actggtacca acagaagcct 540

ggaaaggctc ctaagctgtt gatctacggg gcttcgaccc tggcatccgg ggtgcccgcg 600

aggtttagcg gaagcggtag cggcactcac ttcactctga ccattaacag cctccagtcc 660

gaggattcag ccacttacta ctgtcagcag tcctacaagc gggccagctt cggacagggc 720

actaaggtcg agatcaag 738

<210> 59
<211> 741
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 59
caagtccaac tggtccagag cggtgcagaa gtgaagaagc ccggagcgag cgtgaaagtg 60

tcctgcaagg cttccgggta caccttctcc aactacggca tcacttgggt gcgccaggcc 120

ccgggacagg gcctggaatg gatggggtgg atttccgcgt acaacggcaa tacgaactac 180

gctcagaagt tccagggtag agtgaccatg actaggaaca cctccatttc caccgcctac 240

atggaactgt cctccctgcg gagcgaggac accgccgtgt actattgcgc ccggggacca 300

tactactact acatggatgt ctgggggaag gggactatgg tcaccgtgtc atccgcctcg 360

ggaggcggcg gatcaggagg acgcgcctct ggtggtggag gatcggagat cgtgatgacc 420

cagagccctc tctccttgcc cgtgactcct ggggagcccg catccatttc atgccggagc 480

tcccagtcac ttctctactc caacggctat aactacgtgg attggtacct ccaaaagccg 540

ggccagagcc cgcagctgct gatctacctg ggctcgaaca gggccagcgg agtgcctgac 600

cggttctccg ggtcgggaag cgggaccgac ttcaagctgc aaatctcgag agtggaggcc 660

gaggacgtgg gaatctacta ctgtatgcag ggccgccagt ttccgtactc gttcggacag 720

ggcaccaaag tggaaatcaa g 741

<210> 60
<211> 714
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polynucleotide"

<400> 60
gaagtgcaat tgctcgaaac tggaggaggt ctggtgcaac ctggaggatc acttcgcctg 60

tcctgcgccg tgtcgggctt tgccctgtcc aaccatggaa tgagctgggt ccgccgcgcg 120

ccggggaagg gcctcgaatg ggtgtccggc atcgtctact ccggctccac ctactacgcc 180

gcgtccgtga agggccggtt cacgatttca cgggacaact cgcggaacac cctgtacctc 240

caaatgaatt cccttcggcc ggaggatact gccatctact actgctccgc ccacggtggc 300

gaatccgacg tctggggcca gggaaccacc gtgaccgtgt ccagcgcgtc cgggggagga 360

ggaagcgggg gtagagcatc gggtggaggc ggatcagaga tcgtgctgac ccagtccccc 420

gccaccttga gcgtgtcacc aggagagtcc gccaccctgt catgccgcgc cagccagtcc 480

gtgtcctcca acctggcttg gtaccagcag aagccggggc aggcccctag actcctgatc 540

tatggggcgt cgacccgggc atctggaatt cccgataggt tcagcggatc gggctcgggc 600

actgacttca ctctgaccat ctcctcgctg caagccgagg acgtggctgt gtactactgt 660

cagcagtacg gaagctccct gactttcggt ggcgggacca aagtcgagat taag 714

<210> 61
<211> 717
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 61
gaagtgcaat tggtggaaac tggaggagga cttgtgcaac ctggaggatc attgagactg 60

agctgcgcag tgtcgggatt cgccctgagc aaccatggaa tgtcctgggt cagaagggcc 120

cctggaaaag gcctcgaatg ggtgtcaggg atcgtgtact ccggttccac ttactacgcc 180

gcctccgtga aggggcgctt cactatctca cgggataact cccgcaatac cctgtacctc 240

caaatgaaca gcctgcggcc ggaggatacc gccatctact actgttccgc ccacggtgga 300

gagtctgacg tctggggcca gggaactacc gtgaccgtgt cctccgcgtc cggcggtgga 360

gggagcggcg gccgcgccag cggcggcgga ggctccgaga tcgtgatgac ccagagcccc 420

gctactctgt cggtgtcgcc cggagaaagg gcgaccctgt cctgccgggc gtcgcagtcc 480

gtgagcagca agctggcttg gtaccagcag aagccgggcc aggcaccacg cctgcttatg 540

tacggtgcct ccattcgggc caccggaatc ccggaccggt tctcggggtc ggggtccggt 600

accgagttca cactgaccat ttcctcgctc gagcccgagg actttgccgt ctattactgc 660

cagcagtacg gctcctcctc atggacgttc ggccagggga ccaaggtcga aatcaag 717

<210> 62
<211> 723
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 62
gaagtgcaat tggtggagac tggaggagga gtggtgcaac ctggaggaag cctgagactg 60

tcatgcgcgg tgtcgggctt cgccctctcc aaccacggaa tgtcctgggt ccgccgggcc 120

cctgggaaag gacttgaatg ggtgtccggc atcgtgtact cgggttccac ctactacgcg 180

gcctcagtga agggccggtt tactattagc cgcgacaact ccagaaacac actgtacctc 240

caaatgaact cgctgcggcc ggaagatacc gctatctact actgctccgc ccatggggga 300

gagtcggacg tctggggaca gggcaccact gtcactgtgt ccagcgcttc cggcggtggt 360

ggaagcgggg gacgggcctc aggaggcggt ggcagcgaga ttgtgctgac ccagtccccc 420

gggaccctga gcctgtcccc gggagaaagg gccaccctct cctgtcgggc atcccagtcc 480

gtggggtcta ctaaccttgc atggtaccag cagaagcccg gccaggcccc tcgcctgctg 540

atctacgacg cgtccaatag agccaccggc atcccggatc gcttcagcgg aggcggatcg 600

ggcaccgact tcaccctcac catttcaagg ctggaaccgg aggacttcgc cgtgtactac 660

tgccagcagt atggttcgtc cccaccctgg acgttcggcc aggggactaa ggtcgagatc 720

aag 723

<210> 63
<211> 717
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 63
caagtgcaac tcgtggaatc tggtggagga ctcgtgaaac ctggaggatc attgagactg 60

tcatgcgcgg cctcgggatt cacgttctcc gattactaca tgagctggat tcgccaggct 120

ccggggaagg gactggaatg ggtgtcctac atttcctcat ccggctccac catctactac 180

gcggactccg tgaaggggag attcaccatt agccgcgata acgccaagaa cagcctgtac 240

cttcagatga actccctgcg ggctgaagat actgccgtct actactgcgc aagggagagc 300

ggagatggga tggacgtctg gggacagggt accactgtga ccgtgtcgtc ggcctccggc 360

ggaggggttt cgggtggaag ggccagcggc ggcggaggca gcgacatcca gatgacccag 420

tccccctcat cgctgtccgc ctccgtgggc gaccgcgtca ccatcacatg ccgggcctca 480

cagtcgatct cctcctacct caattggtat cagcagaagc ccggaaaggc ccctaagctt 540

ctgatctacg cagcgtcctc cctgcaatcc ggggtcccat ctcggttctc cggctcgggc 600

agcggtaccg acttcactct gaccatctcg agcctgcagc cggaggactt cgccacttac 660

tactgtcagc aaagctacac cctcgcgttt ggccagggca ccaaagtgga catcaag 717

<210> 64
<211> 717
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 64
gaagtgcaat tggtggaatc agggggagga cttgtgcagc ctggaggatc gctgagactg 60

tcatgtgccg tgtccggctt tgccctgtcc aaccacggga tgtcctgggt ccgccgcgcg 120

cctggaaagg gcctcgaatg ggtgtcgggt attgtgtaca gcggtagcac ctactatgcc 180

gcatccgtga aggggagatt caccatcagc cgggacaact ccaggaacac tctgtacctc 240

caaatgaatt cgctgaggcc agaggacact gccatctact actgctccgc gcatggcgga 300

gagtccgacg tctggggaca ggggaccacc gtgaccgtgt ctagcgcgtc cggcggaggc 360

ggcagcgggg gtcgggcatc agggggcggc ggatcggaca tccagctcac ccagtccccg 420

agctcgctgt ccgcctccgt gggagatcgg gtcaccatca cgtgccgcgc cagccagtcg 480

atttcctcct acctgaactg gtaccaacag aagcccggaa aagccccgaa gcttctcatc 540

tacgccgcct cgagcctgca gtcaggagtg ccctcacggt tctccggctc cggttccggt 600

actgatttca ccctgaccat ttcctccctg caaccggagg acttcgctac ttactactgc 660

cagcagtcgt actccacccc ctacactttc ggacaaggca ccaaggtcga aatcaag 717

<210> 65
<211> 738
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 65
caagtgcaac tggtgcaaag cggaggagga ttggtcaaac ccggaggaag cctgagactg 60

tcatgcgcgg cctctggatt caccttctcc gattactaca tgtcatggat cagacaggcc 120

ccggggaagg gcctcgaatg ggtgtcctac atctcgtcct ccgggaacac catctactac 180

gccgacagcg tgaagggccg ctttaccatt tcccgcgaca acgcaaagaa ctcgctgtac 240

cttcagatga attccctgcg ggctgaagat accgcggtgt actattgcgc ccggtccact 300

atggtccggg aggactactg gggacagggc acactcgtga ccgtgtccag cgcgagcggg 360

ggtggaggca gcggtggacg cgcctccggc ggcggcggtt cagacatcgt gctgactcag 420

tcgcccctgt cgctgccggt caccctgggc caaccggcct caattagctg caagtcctcg 480

gagagcctgg tgcacaactc aggaaagact tacctgaact ggttccatca gcggcctgga 540

cagtccccac ggaggctcat ctatgaagtg tccaacaggg attcgggggt gcccgaccgc 600

ttcactggct ccgggtccgg caccgacttc accttgaaaa tctccagagt ggaagccgag 660

gacgtgggcg tgtactactg tatgcagggt acccactggc ctggaacctt tggacaagga 720

actaagctcg agattaag 738

<210> 66
<211> 717
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 66
caagtgcaac tcgtggaatc tggtggagga ctcgtgcaac ccggtggaag ccttaggctg 60

tcgtgcgccg tcagcgggtt tgctctgagc aaccatggaa tgtcctgggt ccgccgggca 120

ccgggaaaag ggctggaatg ggtgtccggc atcgtgtaca gcgggtcaac ctattacgcc 180

gcgtccgtga agggcagatt cactatctca agagacaaca gccggaacac cctgtacttg 240

caaatgaatt ccctgcgccc cgaggacacc gccatctact actgctccgc ccacggagga 300

gagtcggacg tgtggggcca gggaacgact gtgactgtgt ccagcgcatc aggaggggt 360

ggttcgggcg gccgggcctc gggggggagga ggttccgaca ttcggctgac ccagtccccg 420

tccccactgt cggcctccgt cggcgaccgc gtgaccatca cttgtcaggc gtccgaggac 480

attaacaagt tcctgaactg gtaccaccag acccctggaa aggcccccaa gctgctgatc 540

tacgatgcct cgacccttca aactggagtg cctagccggt tctccgggtc cggctccggc 600

actgatttca ctctgaccat caactcattg cagccggaag atatcgggac ctactattgc 660

cagcagtacg aatccctccc gctcacattc ggcgggggaa ccaaggtcga gattaag 717

<210> 67
<211> 720
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 67
gaagtgcaat tggtggaaac tggaggagga cttgtgcaac ctggaggatc attgcggctc 60

tcatgcgctg tctccggctt cgccctgtca aatcacggga tgtcgtgggt cagacgggcc 120

ccgggaaagg gtctggaatg ggtgtcgggg attgtgtaca gcggctccac ctactacgcc 180

gcttcggtca agggccgctt cactatttca cgggacaaca gccgcaacac cctctatctg 240

caaatgaact ctctccgccc ggaggatacc gccatctact actgctccgc acacggcggc 300

gaatccgacg tgtggggaca gggaaccact gtcaccgtgt cgtccgcatc cggtggcgga 360

ggatcgggtg gccgggcctc cgggggcggc ggcagcgaga ctaccctgac ccagtcccct 420

gccactctgt ccgtgagccc gggagagaga gccaccctta gctgccgggc cagccagagc 480

gtgggctcca acctggcctg gtaccagcag aagccaggac agggtcccag gctgctgatc 540

tacggagcct ccactcgcgc gaccggcatc cccgcgaggt tctccgggtc gggttccggg 600

accgagttca ccctgaccat ctcctccctc caaccggagg acttcgcggt gtactactgt 660

cagcagtaca acgattggct gcccgtgaca tttggacagg ggacgaaggt ggaaatcaaa 720

<210> 68
<211> 723
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 68
gaagtgcaat tggtggaatc tggtggagga cttgtgcaac ctggaggatc actgagactg 60

tcatgcgcgg tgtccggttt tgccctgagc aatcatggga tgtcgtgggt ccggcgcgcc 120

cccggaaagg gtctggaatg ggtgtcgggt atcgtctact ccgggagcac ttactacgcc 180

gcgagcgtga agggccgctt caccatttcc cgcgataact cccgcaacac cctgtacttg 240

caaatgaact cgctccggcc tgaggacact gccatctact actgctccgc acacggagga 300

gaatccgacg tgtggggcca gggaactacc gtgaccgtca gcagcgcctc cggcggcggg 360

ggctcaggcg gacgggctag cggcggcggt ggctccgaga tcgtgctgac ccagtcgcct 420

ggcactctct cgctgagccc cggggaaagg gcaaccctgt cctgtcgggc cagccagtcc 480

attggatcat cctccctcgc ctggtatcag cagaaaccgg gacaggctcc gcggctgctt 540

atgtatgggg ccagctcaag agcctccggc attcccgacc ggttctccgg gtccggttcc 600

ggcaccgatt tcaccctgac tatctcgagg ctggagccag aggacttcgc cgtgtactac 660

tgccagcagt acgcggggtc cccgccgttc acgttcggac agggaaccaa ggtcgagatc 720

aag 723

<210> 69
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 69
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

```
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Gly Trp Val
        35                  40                  45


Ser Gly Ile Ser Arg Ser Gly Glu Asn Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Ser Pro Ala His Tyr Tyr Gly Gly Met Asp Val Trp Gly Gln
            100                 105                 110


Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> 70
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 70
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30


Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95


Ser Val His Ser Phe Leu Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser
        115
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<210> 71
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 71
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ala Leu Ser Asn His
20 25 30

Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Ile Tyr Tyr Cys Ser
85 90 95

Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser
115

<210> 72
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 72
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Arg Lys Thr Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Asp Asn Phe
20 25 30

Gly Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Pro Lys Asn Asn Asn Thr Asn Tyr Ala Gln Lys Phe
50 55 60

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Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Asn Thr Ala Tyr
65                  70                  75                  80


Met Glu Val Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Pro Tyr Tyr Tyr Gln Ser Tyr Met Asp Val Trp Gly Gln
            100                 105                 110


Gly Thr Met Val Thr Val Ser Ser
        115                 120


<210> 73
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 73
Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Asp
            20                  25                  30


Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Val Ile Ser Gly Ser Gly Gly Thr Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Lys Leu Asp Ser Ser Gly Tyr Tyr Tyr Ala Arg Gly Pro Arg Tyr
            100                 105                 110


Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> 74
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
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<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 74
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Asn Tyr
20 25 30

Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asn Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Pro Tyr Tyr Tyr Tyr Met Asp Val Trp Gly Lys Gly Thr
100 105 110

Met Val Thr Val Ser Ser
115

<210> 75
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 75
Glu Val Gln Leu Leu Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ala Leu Ser Asn His
20 25 30

Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Ile Tyr Tyr Cys Ser

85 90 95

Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser
115

<210> 76
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 76
Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ala Leu Ser Asn His
20 25 30

Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Ile Tyr Tyr Cys Ser
85 90 95

Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser
115

<210> 77
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 77
Glu Val Gln Leu Val Glu Thr Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

```
Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ala Leu Ser Asn His
            20                  25                  30

Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Ile Tyr Tyr Cys Ser
                85                  90                  95

Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110

Val Ser Ser
        115


<210> 78
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 78
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Ser Gly Asp Gly Met Asp Val Trp Gly Gln Gly Thr Thr
            100                 105                 110
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Val Thr Val Ser Ser
        115

<210> 79
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 79
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ala Leu Ser Asn His
            20   25   30

Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys
    50   55   60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr Leu
65   70   75   80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Ile Tyr Tyr Cys Ser
                85   90   95

Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln Gly Thr Thr Val Thr
            100   105   110

Val Ser Ser
        115

<210> 80
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 80
Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20   25   30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Tyr Ile Ser Ser Ser Gly Asn Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Thr Met Val Arg Glu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 81
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 81
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ala Leu Ser Asn His
20 25 30

Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Ile Tyr Tyr Cys Ser
85 90 95

Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser
115

<210> 82
<211> 115
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 82
Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ala Leu Ser Asn His
            20   25   30

Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys
    50   55   60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr Leu
65   70   75   80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Ile Tyr Tyr Cys Ser
                85   90   95

Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln Gly Thr Thr Val Thr
            100   105   110

Val Ser Ser
        115

<210> 83
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 83
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Ala Leu Ser Asn His
            20   25   30

Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys
    50   55   60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr Leu

65 70 75 80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Ile Tyr Tyr Cys Ser
85 90 95

Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser
115

<210> 84
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 84
Asp Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Ser
20 25 30

Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Arg Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Ser Ala Val Tyr Tyr Cys Gln Gln Tyr His Ser Ser Pro
85 90 95

Ser Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 85
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 85
Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Leu Gln Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 86
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 86
Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Ser Val Thr Pro Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Arg Asn
20 25 30

Asp Gly Lys Thr Pro Leu Tyr Trp Tyr Leu Gln Lys Ala Gly Gln Pro
35 40 45

Pro Gln Leu Leu Ile Tyr Glu Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Ala Tyr Tyr Cys Met Gln Asn
85 90 95

Ile Gln Phe Pro Ser Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 87
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 87
Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asn Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Lys Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu His Ile
65 70 75 80

Thr Arg Val Gly Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Leu Gln Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 88
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 88
Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr His Phe Thr Leu Thr Ile Asn Ser Leu Gln Ser
65 70 75 80

Glu Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Lys Arg Ala Ser
85 90 95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 89
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 89
Glu Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Tyr Ser
20 25 30

Asn Gly Tyr Asn Tyr Val Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Lys Leu Gln Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Ile Tyr Tyr Cys Met Gln Gly
85 90 95

Arg Gln Phe Pro Tyr Ser Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 90
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 90
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Ser Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Ser Gly Ile Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65 70 75 80

Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Leu Thr
85 90 95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 91
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 91
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Lys
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Met
35 40 45

Tyr Gly Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Ser Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 92
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 92
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Gly Ser Thr
20 25 30

Asn Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Gly Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
85 90 95

Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 93
<211> 105
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 93
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Thr Leu Ala Phe
85 90 95

Gly Gln Gly Thr Lys Val Asp Ile Lys
100 105

<210> 94
<211> 107
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 94
Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
            20   25   30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 95
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 95
Asp Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1   5   10   15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Glu Ser Leu Val His Asn
            20   25   30

Ser Gly Lys Thr Tyr Leu Asn Trp Phe His Gln Arg Pro Gly Gln Ser
        35   40   45

Pro Arg Arg Leu Ile Tyr Glu Val Ser Asn Arg Asp Ser Gly Val Pro
    50   55   60

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65   70   75   80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly

85 90 95

Thr His Trp Pro Gly Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 96
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 96
Asp Ile Arg Leu Thr Gln Ser Pro Ser Pro Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Glu Asp Ile Asn Lys Phe
20 25 30

Leu Asn Trp Tyr His Gln Thr Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Thr Leu Gln Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Gly Thr Tyr Tyr Cys Gln Gln Tyr Glu Ser Leu Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 97
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 97
Glu Thr Thr Leu Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Gly Ser Asn
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Gly Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asp Trp Leu Pro
85 90 95

Val Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 98
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 98
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Gly Ser Ser
20 25 30

Ser Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Gly Ala Ser Ser Arg Ala Ser Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ala Gly Ser Pro
85 90 95

Pro Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 99
<211> 490
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 99
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu

1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Thr Phe Ser Asn Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys
50 55 60

Gly Leu Gly Trp Val Ser Gly Ile Ser Arg Ser Gly Glu Asn Thr Tyr
65 70 75 80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
85 90 95

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Ser Pro Ala His Tyr Tyr Gly Gly Met
115 120 125

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Arg Ala Ser Gly Gly Gly Gly Ser Asp Ile
145 150 155 160

Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg
165 170 175

Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Ser Phe Leu
180 185 190

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
195 200 205

Gly Ala Ser Arg Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser
210 215 220

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu
225 230 235 240

Asp Ser Ala Val Tyr Tyr Cys Gln Gln Tyr His Ser Ser Pro Ser Trp
245 250 255

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro Ala
260 265 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser

275 280 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
290 295 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305 310 315 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
325 330 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
340 345 350

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
355 360 365

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
370 375 380

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
385 390 395 400

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
405 410 415

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
420 425 430

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
435 440 445

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
450 455 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465 470 475 480

Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 100
<211> 488
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 100
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

```
His Ala Ala Arg Pro Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu
            20                  25                  30

Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
        35                  40                  45

Thr Phe Asp Asp Tyr Ala Met His Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Val Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly
65                  70                  75                  80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
                85                  90                  95

Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110

Ala Leu Tyr Tyr Cys Ser Val His Ser Phe Leu Ala Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Arg Ala Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Thr
145                 150                 155                 160

Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys
                165                 170                 175

Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu Asp
            180                 185                 190

Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu
        195                 200                 205

Gly Ser Asn Arg Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly
    210                 215                 220

Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp
225                 230                 235                 240

Val Gly Val Tyr Tyr Cys Met Gln Ala Leu Gln Thr Pro Tyr Thr Phe
                245                 250                 255

Gly Gln Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg
            260                 265                 270

Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
        275                 280                 285
```

```
Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
    290                 295                 300

Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
305                 310                 315                 320

Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg
                325                 330                 335

Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro
            340                 345                 350

Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu
        355                 360                 365

Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala
    370                 375                 380

Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
385                 390                 395                 400

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
                405                 410                 415

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
            420                 425                 430

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
        435                 440                 445

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
    450                 455                 460

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
465                 470                 475                 480

His Met Gln Ala Leu Pro Pro Arg
                485
```

<210> 101
<211> 487
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 101

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15
```

```
His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
            20                  25                  30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe
        35                  40                  45

Ala Leu Ser Asn His Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Val Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr
65                  70                  75                  80

Ala Ala Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg
                85                  90                  95

Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala
            100                 105                 110

Ile Tyr Tyr Cys Ser Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Arg Ala Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Thr
145                 150                 155                 160

Pro Leu Ser Leu Ser Val Thr Pro Gly Gln Pro Ala Ser Ile Ser Cys
                165                 170                 175

Lys Ser Ser Gln Ser Leu Leu Arg Asn Asp Gly Lys Thr Pro Leu Tyr
            180                 185                 190

Trp Tyr Leu Gln Lys Ala Gly Gln Pro Pro Gln Leu Leu Ile Tyr Glu
        195                 200                 205

Val Ser Asn Arg Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly
    210                 215                 220

Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp
225                 230                 235                 240

Val Gly Ala Tyr Tyr Cys Met Gln Asn Ile Gln Phe Pro Ser Phe Gly
                245                 250                 255

Gly Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro
            260                 265                 270

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
        275                 280                 285
```

```
Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
    290                 295                 300

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
305                 310                 315                 320

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
                325                 330                 335

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
            340                 345                 350

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
        355                 360                 365

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
    370                 375                 380

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
385                 390                 395                 400

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
                405                 410                 415

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
            420                 425                 430

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
        435                 440                 445

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
    450                 455                 460

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
465                 470                 475                 480

Met Gln Ala Leu Pro Pro Arg
                485

<210> 102
<211> 493
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 102
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15
```

```
His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30

Arg Lys Thr Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Ile Phe Asp Asn Phe Gly Ile Asn Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Trp Ile Asn Pro Lys Asn Asn Asn Thr Asn
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser
                85                  90                  95

Thr Asn Thr Ala Tyr Met Glu Val Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Pro Tyr Tyr Tyr Gln Ser Tyr Met
        115                 120                 125

Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Arg Ala Ser Gly Gly Gly Gly Ser Asp Ile
145                 150                 155                 160

Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro
                165                 170                 175

Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly
            180                 185                 190

Tyr Asn Tyr Leu Asn Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln
        195                 200                 205

Leu Leu Ile Tyr Leu Gly Ser Lys Arg Ala Ser Gly Val Pro Asp Arg
    210                 215                 220

Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu His Ile Thr Arg
225                 230                 235                 240

Val Gly Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala Leu Gln
                245                 250                 255

Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Thr Thr
            260                 265                 270

Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln
        275                 280                 285
```

```
Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala
    290                 295                 300

Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala
305                 310                 315                 320

Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr
                325                 330                 335

Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln
            340                 345                 350

Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser
        355                 360                 365

Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys
    370                 375                 380

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln
385                 390                 395                 400

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
                405                 410                 415

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg
            420                 425                 430

Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
        435                 440                 445

Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly
    450                 455                 460

Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp
465                 470                 475                 480

Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490


<210> 103
<211> 490
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 103
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu
```

```
            20                  25                  30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
        35                  40                  45

Thr Phe Ser Ser Asp Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Val Ser Val Ile Ser Gly Ser Gly Gly Thr Thr Tyr
65                  70                  75                  80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
                85                  90                  95

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Lys Leu Asp Ser Ser Gly Tyr Tyr Tyr Ala
        115                 120                 125

Arg Gly Pro Arg Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    130                 135                 140

Ala Ser Gly Gly Gly Gly Ser Gly Gly Arg Ala Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
                165                 170                 175

Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser
            180                 185                 190

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
        195                 200                 205

Ile Tyr Gly Ala Ser Thr Leu Ala Ser Gly Val Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr His Phe Thr Leu Thr Ile Asn Ser Leu Gln
225                 230                 235                 240

Ser Glu Asp Ser Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Lys Arg Ala
                245                 250                 255

Ser Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
```

290 295 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305 310 315 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
325 330 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
340 345 350

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
355 360 365

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
370 375 380

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
385 390 395 400

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
405 410 415

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
420 425 430

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
435 440 445

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
450 455 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465 470 475 480

Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 104
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 104
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

```
Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Ser Asn Tyr Gly Ile Thr Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asn Thr Ser
                85                  90                  95

Ile Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Pro Tyr Tyr Tyr Tyr Met Asp Val
        115                 120                 125

Trp Gly Lys Gly Thr Met Val Thr Val Ser Ser Ala Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Arg Ala Ser Gly Gly Gly Gly Ser Glu Ile Val Met
145                 150                 155                 160

Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro Ala Ser
                165                 170                 175

Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Tyr Ser Asn Gly Tyr Asn
            180                 185                 190

Tyr Val Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu
        195                 200                 205

Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro Asp Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Phe Lys Leu Gln Ile Ser Arg Val Glu
225                 230                 235                 240

Ala Glu Asp Val Gly Ile Tyr Tyr Cys Met Gln Gly Arg Gln Phe Pro
                245                 250                 255

Tyr Ser Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300
```

```
Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
            420                 425                 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450                 455                 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465                 470                 475                 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490


<210> 105
<211> 482
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 105
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Thr Gly Gly Gly Leu
            20                  25                  30
```

```
Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe
        35                  40                  45

Ala Leu Ser Asn His Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Val Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr
65                  70                  75                  80

Ala Ala Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg
                85                  90                  95

Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala
            100                 105                 110

Ile Tyr Tyr Cys Ser Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Arg Ala Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser
145                 150                 155                 160

Pro Ala Thr Leu Ser Val Ser Pro Gly Glu Ser Ala Thr Leu Ser Cys
                165                 170                 175

Arg Ala Ser Gln Ser Val Ser Ser Asn Leu Ala Trp Tyr Gln Gln Lys
            180                 185                 190

Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Thr Arg Ala
        195                 200                 205

Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
    210                 215                 220

Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr
225                 230                 235                 240

Cys Gln Gln Tyr Gly Ser Ser Leu Thr Phe Gly Gly Gly Thr Lys Val
                245                 250                 255

Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
            260                 265                 270

Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
        275                 280                 285

Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
    290                 295                 300
```

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
305 310 315 320

Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu
325 330 335

Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
340 345 350

Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys
355 360 365

Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys
370 375 380

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
385 390 395 400

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
405 410 415

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
420 425 430

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
435 440 445

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
450 455 460

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
465 470 475 480

Pro Arg

<210> 106
<211> 483
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 106
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu
20 25 30

```
Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe
        35                  40                  45

Ala Leu Ser Asn His Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Val Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr
65                  70                  75                  80

Ala Ala Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg
                85                  90                  95

Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala
            100                 105                 110

Ile Tyr Tyr Cys Ser Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Arg Ala Ser Gly Gly Gly Gly Ser Glu Ile Val Met Thr Gln Ser
145                 150                 155                 160

Pro Ala Thr Leu Ser Val Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
                165                 170                 175

Arg Ala Ser Gln Ser Val Ser Ser Lys Leu Ala Trp Tyr Gln Gln Lys
            180                 185                 190

Pro Gly Gln Ala Pro Arg Leu Leu Met Tyr Gly Ala Ser Ile Arg Ala
        195                 200                 205

Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe
    210                 215                 220

Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr
225                 230                 235                 240

Cys Gln Gln Tyr Gly Ser Ser Ser Trp Thr Phe Gly Gln Gly Thr Lys
                245                 250                 255

Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
            260                 265                 270

Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
        275                 280                 285

Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
    290                 295                 300
```

```
Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu
305                 310                 315                 320

Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu
                325                 330                 335

Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln
            340                 345                 350

Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly
        355                 360                 365

Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
    370                 375                 380

Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
385                 390                 395                 400

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
                405                 410                 415

Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
            420                 425                 430

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
        435                 440                 445

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
    450                 455                 460

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu
465                 470                 475                 480

Pro Pro Arg
```

<210> 107
<211> 485
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 107

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Thr Gly Gly Gly Val
            20                  25                  30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe
```

```
        35                  40                  45

Ala Leu Ser Asn His Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Val Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr
65                  70                  75                  80

Ala Ala Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg
                85                  90                  95

Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala
            100                 105                 110

Ile Tyr Tyr Cys Ser Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Arg Ala Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser
145                 150                 155                 160

Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
                165                 170                 175

Arg Ala Ser Gln Ser Val Gly Ser Thr Asn Leu Ala Trp Tyr Gln Gln
            180                 185                 190

Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg
        195                 200                 205

Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Gly Gly Ser Gly Thr Asp
    210                 215                 220

Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr
225                 230                 235                 240

Tyr Cys Gln Gln Tyr Gly Ser Ser Pro Pro Trp Thr Phe Gly Gln Gly
                245                 250                 255

Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr
            260                 265                 270

Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala
        275                 280                 285

Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe
    290                 295                 300

Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
```

305 310 315 320

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys
325 330 335

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
340 345 350

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
355 360 365

Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
370 375 380

Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
385 390 395 400

Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
405 410 415

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
420 425 430

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
435 440 445

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
450 455 460

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
465 470 475 480

Ala Leu Pro Pro Arg
485

<210> 108
<211> 483
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 108
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu
20 25 30

Val Lys Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

```
Thr Phe Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr
65                  70                  75                  80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
                85                  90                  95

Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Glu Ser Gly Asp Gly Met Asp Val Trp
        115                 120                 125

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Gly Gly Gly Gly
    130                 135                 140

Ser Gly Gly Arg Ala Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr
145                 150                 155                 160

Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
                165                 170                 175

Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln
            180                 185                 190

Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser
        195                 200                 205

Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
    210                 215                 220

Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
225                 230                 235                 240

Tyr Tyr Cys Gln Gln Ser Tyr Thr Leu Ala Phe Gly Gln Gly Thr Lys
                245                 250                 255

Val Asp Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
            260                 265                 270

Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
        275                 280                 285

Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
    290                 295                 300

Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu
305                 310                 315                 320
```

```
Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu
                325                 330                 335

Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln
            340                 345                 350

Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly
        355                 360                 365

Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
    370                 375                 380

Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
385                 390                 395                 400

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
                405                 410                 415

Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
            420                 425                 430

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
        435                 440                 445

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
    450                 455                 460

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu
465                 470                 475                 480

Pro Pro Arg
```

<210> 109
<211> 483
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 109

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
            20                  25                  30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe
        35                  40                  45
```

```
Ala Leu Ser Asn His Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Val Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr
65                  70                  75                  80

Ala Ala Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg
                85                  90                  95

Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala
            100                 105                 110

Ile Tyr Tyr Cys Ser Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Arg Ala Ser Gly Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser
145                 150                 155                 160

Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
                165                 170                 175

Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys
            180                 185                 190

Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln
        195                 200                 205

Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
    210                 215                 220

Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
225                 230                 235                 240

Cys Gln Gln Ser Tyr Ser Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys
                245                 250                 255

Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
            260                 265                 270

Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
        275                 280                 285

Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
    290                 295                 300

Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu
305                 310                 315                 320
```

```
Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu
                325                 330                 335

Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln
            340                 345                 350

Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly
        355                 360                 365

Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
    370                 375                 380

Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
385                 390                 395                 400

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
                405                 410                 415

Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
            420                 425                 430

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
        435                 440                 445

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
    450                 455                 460

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu
465                 470                 475                 480

Pro Pro Arg
```

<210> 110
<211> 490
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 110

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu
            20                  25                  30

Val Lys Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
        35                  40                  45
```

```
Thr Phe Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Asn Thr Ile Tyr
65                  70                  75                  80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
                85                  90                  95

Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Ser Thr Met Val Arg Glu Asp Tyr Trp
        115                 120                 125

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Gly Gly Gly Gly
    130                 135                 140

Ser Gly Gly Arg Ala Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Thr
145                 150                 155                 160

Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly Gln Pro Ala Ser Ile
                165                 170                 175

Ser Cys Lys Ser Ser Glu Ser Leu Val His Asn Ser Gly Lys Thr Tyr
            180                 185                 190

Leu Asn Trp Phe His Gln Arg Pro Gly Gln Ser Pro Arg Arg Leu Ile
        195                 200                 205

Tyr Glu Val Ser Asn Arg Asp Ser Gly Val Pro Asp Arg Phe Thr Gly
    210                 215                 220

Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala
225                 230                 235                 240

Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly Thr His Trp Pro Gly
                245                 250                 255

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320
```

```
Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
            340                 345                 350

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
        355                 360                 365

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
    370                 375                 380

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
385                 390                 395                 400

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                405                 410                 415

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
            420                 425                 430

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
        435                 440                 445

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
    450                 455                 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465                 470                 475                 480

Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490
```

<210> 111
<211> 483
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 111

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu
            20                  25                  30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe
        35                  40                  45

Ala Leu Ser Asn His Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys
```

```
    50                  55                  60

Gly Leu Glu Trp Val Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr
65                  70                  75                  80

Ala Ala Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg
                85                  90                  95

Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala
            100                 105                 110

Ile Tyr Tyr Cys Ser Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Arg Ala Ser Gly Gly Gly Gly Ser Asp Ile Arg Leu Thr Gln Ser
145                 150                 155                 160

Pro Ser Pro Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
                165                 170                 175

Gln Ala Ser Glu Asp Ile Asn Lys Phe Leu Asn Trp Tyr His Gln Thr
            180                 185                 190

Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser Thr Leu Gln
        195                 200                 205

Thr Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
    210                 215                 220

Thr Leu Thr Ile Asn Ser Leu Gln Pro Glu Asp Ile Gly Thr Tyr Tyr
225                 230                 235                 240

Cys Gln Gln Tyr Glu Ser Leu Pro Leu Thr Phe Gly Gly Gly Thr Lys
                245                 250                 255

Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
            260                 265                 270

Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
        275                 280                 285

Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
    290                 295                 300

Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu
305                 310                 315                 320

Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu
```

325 330 335

Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln
340 345 350

Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly
355 360 365

Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
370 375 380

Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
385 390 395 400

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
405 410 415

Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
420 425 430

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
435 440 445

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
450 455 460

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu
465 470 475 480

Pro Pro Arg

<210> 112
<211> 484
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 112
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe
35 40 45

Ala Leu Ser Asn His Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys
50 55 60

```
Gly Leu Glu Trp Val Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr
65                  70                  75                  80

Ala Ala Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg
                85                  90                  95

Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala
            100                 105                 110

Ile Tyr Tyr Cys Ser Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Arg Ala Ser Gly Gly Gly Gly Ser Glu Thr Thr Leu Thr Gln Ser
145                 150                 155                 160

Pro Ala Thr Leu Ser Val Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
                165                 170                 175

Arg Ala Ser Gln Ser Val Gly Ser Asn Leu Ala Trp Tyr Gln Gln Lys
            180                 185                 190

Pro Gly Gln Gly Pro Arg Leu Leu Ile Tyr Gly Ala Ser Thr Arg Ala
        195                 200                 205

Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe
    210                 215                 220

Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Tyr
225                 230                 235                 240

Cys Gln Gln Tyr Asn Asp Trp Leu Pro Val Thr Phe Gly Gln Gly Thr
                245                 250                 255

Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro
            260                 265                 270

Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys
        275                 280                 285

Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
    290                 295                 300

Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu
305                 310                 315                 320

Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys
                325                 330                 335
```

```
Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr
            340                 345                 350

Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly
        355                 360                 365

Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
    370                 375                 380

Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
385                 390                 395                 400

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
                405                 410                 415

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
            420                 425                 430

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
        435                 440                 445

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
    450                 455                 460

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
465                 470                 475                 480

Leu Pro Pro Arg
```

<210> 113
<211> 485
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 113

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
            20                  25                  30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe
        35                  40                  45

Ala Leu Ser Asn His Gly Met Ser Trp Val Arg Arg Ala Pro Gly Lys
    50                  55                  60
```

```
Gly Leu Glu Trp Val Ser Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr
65                  70                  75                  80

Ala Ala Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg
                85                  90                  95

Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala
            100                 105                 110

Ile Tyr Tyr Cys Ser Ala His Gly Gly Glu Ser Asp Val Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Arg Ala Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser
145                 150                 155                 160

Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
                165                 170                 175

Arg Ala Ser Gln Ser Ile Gly Ser Ser Ser Leu Ala Trp Tyr Gln Gln
            180                 185                 190

Lys Pro Gly Gln Ala Pro Arg Leu Leu Met Tyr Gly Ala Ser Ser Arg
        195                 200                 205

Ala Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
    210                 215                 220

Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr
225                 230                 235                 240

Tyr Cys Gln Gln Tyr Ala Gly Ser Pro Pro Phe Thr Phe Gly Gln Gly
                245                 250                 255

Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr
            260                 265                 270

Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala
        275                 280                 285

Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe
    290                 295                 300

Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
305                 310                 315                 320

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys
                325                 330                 335
```

```
Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
            340                 345                 350

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
        355                 360                 365

Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
    370                 375                 380

Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
385                 390                 395                 400

Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
                405                 410                 415

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
            420                 425                 430

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
        435                 440                 445

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
    450                 455                 460

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
465                 470                 475                 480

Ala Leu Pro Pro Arg
                485
```

<210> 114
<211> 1470
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 114

```
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg       60

ccccaagtgc aactcgtgga atctggtgga ggactcgtgc aacccggaag atcgcttaga      120

ctgtcgtgtg ccgccagcgg gttcactttc tcgaactacg cgatgtcctg ggtccgccag      180

gcacccggaa agggactcgg ttgggtgtcc ggcatttccc ggtccggcga aaatacctac      240

tacgccgact ccgtgaaggg ccgcttcacc atctcaaggg acaacagcaa aaacaccctg      300

tacttgcaaa tgaactccct gcgggatgaa gatacagccg tgtactattg cgcccggtcg      360

cctgcccatt actacggcgg aatggacgtc tggggacagg gaaccactgt gactgtcagc      420

agcgcgtcgg gtggcggcgg ctcaggggggt cgggcctccg ggggggggagg gtccgacatc      480
```

gtgctgaccc agtccccggg aaccctgagc ctgagcccgg gagagcgcgc gaccctgtca 540

tgccgggcat cccagagcat tagctcctcc tttctcgcct ggtatcagca gaagcccgga 600

caggccccga ggctgctgat ctacggcgct agcagaaggg ctaccggaat cccagaccgg 660

ttctccggct ccggttccgg gaccgatttc acccttacta tctcgcgcct ggaacctgag 720

gactccgccg tctactactg ccagcagtac cactcatccc cgtcgtggac gttcggacag 780

ggcaccaagc tggagattaa gaccactacc ccagcaccga ggccacccac cccggctcct 840

accatcgcct cccagcctct gtccctgcgt ccggaggcat gtagacccgc agctggtggg 900

gccgtgcata cccggggtct tgacttcgcc tgcgatatct acatttgggc ccctctggct 960

ggtacttgcg gggtcctgct gctttcactc gtgatcactc tttactgtaa gcgcggtcgg 1020

aagaagctgc tgtacatctt taagcaaccc ttcatgaggc ctgtgcagac tactcaagag 1080

gaggacggct gttcatgccg gttcccagag gaggaggaag gcggctgcga actgcgcgtg 1140

aaattcagcc gcagcgcaga tgctccagcc tacaagcagg ggcagaacca gctctacaac 1200

gaactcaatc ttggtcggag agaggagtac gacgtgctgg acaagcggag aggacgggac 1260

ccagaaatgg gcgggaagcc gcgcagaaag aatccccaag agggcctgta caacgagctc 1320

caaaaggata agatggcaga agcctatagc gagattggta tgaaagggga acgcagaaga 1380

ggcaaaggcc acgacggact gtaccaggga ctcagcaccg ccaccaagga cacctatgac 1440

gctcttcaca tgcaggccct gccgcctcgg 1470

<210> 115
<211> 1464
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 115
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc aactcgtcga atccggtgga ggtctggtcc aacctggtag aagcctgaga 120

ctgtcgtgtg cggccagcgg attcaccttt gatgactatg ctatgcactg ggtgcggcag 180

gccccaggaa agggcctgga atgggtgtcg ggaattagct ggaactccgg gtccattggc 240

tacgccgact ccgtgaaggg ccgcttcacc atctcccgcg acaacgcaaa gaactccctg 300

tacttgcaaa tgaactcgct cagggctgag gataccgcgc tgtactactg ctccgtgcat 360

tccttcctgg cctactgggg acagggaact ctggtcaccg tgtcgagcgc ctccggcggc 420

gggggctcgg gtggacgggc ctcgggcgga ggggggtccg acatcgtgat gacccagacc 480

ccgctgagct tgcccgtgac tcccggagag cctgcatcca tctcctgccg gtcatcccag 540

tcccttctcc actccaacgg atacaactac ctcgactggt acctccagaa gccgggacag 600

agccctcagc ttctgatcta cctggggtca aatagagcct caggagtgcc ggatcggttc 660

agcggatctg gttcgggaac tgatttcact ctgaagattt cccgcgtgga agccgaggac 720

gtgggcgtct actactgtat gcaggcgctg cagacccccc ataccttcgg ccaagggacg 780

aaagtggaga tcaagaccac taccccagca ccgaggccac ccaccccggc tcctaccatc 840

gcctcccagc ctctgtccct gcgtccggag gcatgtagac ccgcagctgg tggggccgtg 900

catacccggg gtcttgactt cgcctgcgat atctacattt gggcccctct ggctggtact 960

tgcggggtcc tgctgctttc actcgtgatc actctttact gtaagcgcgg tcggaagaag 1020

ctgctgtaca tctttaagca acccttcatg aggcctgtgc agactactca agaggaggac 1080

ggctgttcat gccggttccc agaggaggag gaaggcggct gcgaactgcg cgtgaaattc 1140

agccgcagcg cagatgctcc agcctacaag caggggcaga accagctcta caacgaactc 1200

aatcttggtc ggagagagga gtacgacgtg ctggacaagc ggagaggacg ggacccagaa 1260

atgggcggga agccgcgcag aaagaatccc caagagggcc tgtacaacga gctccaaaag 1320

gataagatgg cagaagccta tagcgagatt ggtatgaaag gggaacgcag aagaggcaaa 1380

ggccacgacg gactgtacca gggactcagc accgccacca aggacaccta tgacgctctt 1440

cacatgcagg ccctgccgcc tcgg 1464

<210> 116
<211> 1461
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 116
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aattgttgga atctggagga ggacttgtgc agcctggagg atcactgaga 120

ctttcgtgtg cggtgtcagg cttcgccctg agcaaccacg gcatgagctg ggtgcggaga 180

gccccgggga agggtctgga atgggtgtcc gggatcgtct actccggttc aacttactac 240

gccgcaagcg tgaagggtcg cttcaccatt tcccgcgata actcccggaa caccctgtac 300

ctccaaatga actccctgcg gcccgaggac accgccatct actactgttc cgcgcatgga 360

ggagagtccg atgtctgggg acagggcact accgtgaccg tgtcgagcgc ctcgggggga 420

ggaggctccg gcggtcgcgc ctccgggggg ggtggcagcg acattgtgat gacgcagact 480

ccactctcgc tgtccgtgac cccgggacag cccgcgtcca tctcgtgcaa gagctcccag 540

agcctgctga ggaacgacgg aaagactcct ctgtattggt acctccagaa ggctggacag 600

cccccgcaac tgctcatcta cgaagtgtca aatcgcttct ccggggtgcc ggatcggttt 660

tccggctcgg gatcgggcac cgacttcacc ctgaaaatct ccagggtcga ggccgaggac 720

gtgggagcct actactgcat gcaaaacatc cagttccctt ccttcggcgg cggcacaaag 780

ctggagatta agaccactac cccagcaccg aggccaccca ccccggctcc taccatcgcc 840

tcccagcctc tgtccctgcg tccggaggca tgtagacccg cagctggtgg ggccgtgcat 900

acccggggtc ttgacttcgc ctgcgatatc tacatttggg cccctctggc tggtacttgc 960

ggggtcctgc tgctttcact cgtgatcact ctttactgta agcgcggtcg gaagaagctg 1020

ctgtacatct ttaagcaacc cttcatgagg cctgtgcaga ctactcaaga ggaggacggc 1080

tgttcatgcc ggttcccaga ggaggaggaa ggcggctgcg aactgcgcgt gaaattcagc 1140

cgcagcgcag atgctccagc ctacaagcag gggcagaacc agctctacaa cgaactcaat 1200

cttggtcgga gagaggagta cgacgtgctg gacaagcgga gaggacggga cccagaaatg 1260

ggcgggaagc cgcgcagaaa gaatccccaa gagggcctgt acaacgagct ccaaaaggat 1320

aagatggcag aagcctatag cgagattggt atgaaagggg aacgcagaag aggcaaaggc 1380

cacgacggac tgtaccaggg actcagcacc gccaccaagg acacctatga cgctcttcac 1440

atgcaggccc tgccgcctcg g 1461

<210> 117
<211> 1479
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 117
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcc aactcgtcca gtccggcgca gaagtcagaa aaaccggtgc tagcgtgaaa 120

gtgtcctgca aggcctccgg ctacattttc gataacttcg gaatcaactg ggtcagacag 180

gccccgggcc aggggctgga atggatggga tggatcaacc ccaagaacaa caacaccaac 240

tacgcacaga agttccaggg ccgcgtgact atcaccgccg atgaatcgac caataccgcc 300

tacatggagg tgtcctccct gcggtcggag gacactgccg tgtattactg cgcgaggggc 360

ccatactact accaaagcta catggacgtc tggggacagg gaaccatggt gaccgtgtca 420

tccgcctccg gtggtggagg ctccgggggg cgggcttcag gaggcggagg aagcgatatt 480

gtgatgaccc agactccgct tagcctgccc gtgactcctg gagaaccggc ctccatttcc 540

tgccggtcct cgcaatcact cctgcattcc aacggttaca actacctgaa ttggtacctc 600

cagaagcctg gccagtcgcc ccagttgctg atctatctgg gctcgaagcg cgcctccggg 660

gtgcctgacc ggtttagcgg atctgggagc ggcacggact tcactctcca catcacccgc 720

gtgggagcgg aggacgtggg agtgtactac tgtatgcagg cgctgcagac tccgtacaca 780

ttcggacagg gcaccaagct ggagatcaag accactaccc cagcaccgag gccacccacc 840

ccggctccta ccatcgcctc ccagcctctg tccctgcgtc cggaggcatg tagacccgca 900

gctggtgggg ccgtgcatac ccggggtctt gacttcgcct gcgatatcta catttgggcc 960

cctctggctg gtacttgcgg ggtcctgctg ctttcactcg tgatcactct ttactgtaag 1020

cgcggtcgga agaagctgct gtacatcttt aagcaaccct tcatgaggcc tgtgcagact 1080

actcaagagg aggacggctg ttcatgccgg ttcccagagg aggaggaagg cggctgcgaa 1140

ctgcgcgtga aattcagccg cagcgcagat gctccagcct acaagcaggg gcagaaccag 1200

ctctacaacg aactcaatct tggtcggaga gaggagtacg acgtgctgga caagcggaga 1260

ggacgggacc cagaaatggg cgggaagccg cgcagaaaga atccccaaga gggcctgtac 1320

aacgagctcc aaaaggataa gatggcagaa gcctatagcg agattggtat gaaaggggaa 1380

cgcagaagag gcaaaggcca cgacggactg taccagggac tcagcaccgc caccaaggac 1440

acctatgacg ctcttcacat gcaggccctg ccgcctcgg 1479

<210> 118
<211> 1470
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 118
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc aacttcaaga atcaggcgga ggactcgtgc agcccggagg atcattgcgg 120

ctctcgtgcg ccgcctcggg cttcaccttc tcgagcgacg ccatgacctg ggtccgccag 180

gccccgggga aggggctgga atgggtgtct gtgatttccg gctccggggg aactacgtac 240

tacgccgatt ccgtgaaagg tcgcttcact atctcccggg acaacagcaa gaacaccctt 300

tatctgcaaa tgaattccct ccgcgccgag gacaccgccg tgtactactg cgccaagctg 360

gactcctcgg gctactacta tgcccggggt ccgagatact ggggacaggg aaccctcgtg 420

accgtgtcct ccgcgtccgg cggaggaggg tcgggagggc gggcctccgg cggcggcggt 480

tcggacatcc agctgaccca gtccccatcc tcactgagcg caagcgtggg cgacagagtc 540

accattacat gcagggcgtc ccagagcatc agctcctacc tgaactggta ccaacagaag 600

cctggaaagg ctcctaagct gttgatctac ggggcttcga ccctggcatc cggggtgccc 660

gcgaggttta gcggaagcgg tagcggcact cacttcactc tgaccattaa cagcctccag 720

tccgaggatt cagccactta ctactgtcag cagtcctaca agcgggccag cttcggacag 780

ggcactaagg tcgagatcaa gaccactacc ccagcaccga ggccacccac cccggctcct 840

accatcgcct cccagcctct gtccctgcgt ccggaggcat gtagacccgc agctggtggg 900

gccgtgcata cccggggtct tgacttcgcc tgcgatatct acatttgggc ccctctggct 960

ggtacttgcg gggtcctgct gctttcactc gtgatcactc tttactgtaa gcgcggtcgg 1020

aagaagctgc tgtacatctt taagcaaccc ttcatgaggc ctgtgcagac tactcaagag 1080

gaggacggct gttcatgccg gttcccagag gaggaggaag gcggctgcga actgcgcgtg 1140

aaattcagcc gcagcgcaga tgctccagcc tacaagcagg ggcagaacca gctctacaac 1200

gaactcaatc ttggtcggag agaggagtac gacgtgctgg acaagcggag aggacgggac 1260

ccagaaatgg gcgggaagcc gcgcagaaag aatccccaag agggcctgta caacgagctc 1320

caaaaggata agatggcaga agcctatagc gagattggta tgaaagggga acgcagaaga 1380

ggcaaaggcc acgacggact gtaccaggga ctcagcaccg ccaccaagga cacctatgac 1440

gctcttcaca tgcaggccct gccgcctcgg 1470

<210> 119
<211> 1473
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 119
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcc aactggtcca gagcggtgca gaagtgaaga agcccggagc gagcgtgaaa 120

gtgtcctgca aggcttccgg gtacaccttc tccaactacg gcatcacttg ggtgcgccag 180

gccccgggac agggcctgga atggatgggg tggatttccg cgtacaacgg caatacgaac 240

tacgctcaga agttccaggg tagagtgacc atgactagga acacctccat ttccaccgcc 300

tacatggaac tgtcctccct gcggagcgag gacaccgccg tgtactattg cgcccgggga 360

ccatactact actacatgga tgtctggggg aaggggacta tggtcaccgt gtcatccgcc 420

tcgggaggcg gcggatcagg aggacgcgcc tctggtggtg gaggatcgga gatcgtgatg 480

acccagagcc ctctctcctt gcccgtgact cctggggagc ccgcatccat ttcatgccgg 540

agctcccagt cacttctcta ctccaacggc tataactacg tggattggta cctccaaaag 600

ccgggccaga gcccgcagct gctgatctac ctgggctcga acagggccag cggagtgcct 660

gaccggttct ccgggtcggg aagcgggacc gacttcaagc tgcaaatctc gagagtggag 720

gccgaggacg tgggaatcta ctactgtatg cagggccgcc agtttccgta ctcgttcgga 780

cagggcacca aagtggaaat caagaccact accccagcac cgaggccacc caccccggct 840

cctaccatcg cctcccagcc tctgtccctg cgtccggagg catgtagacc cgcagctggt 900

ggggccgtgc atacccgggg tcttgacttc gcctgcgata tctacatttg ggcccctctg 960

gctggtactt gcggggtcct gctgctttca ctcgtgatca ctctttactg taagcgcggt 1020

cggaagaagc tgctgtacat ctttaagcaa cccttcatga ggcctgtgca gactactcaa 1080

gaggaggacg gctgttcatg ccggttccca gaggaggagg aaggcggctg cgaactgcgc 1140

gtgaaattca gccgcagcgc agatgctcca gcctacaagc aggggcagaa ccagctctac 1200

aacgaactca atcttggtcg gagagaggag tacgacgtgc tggacaagcg gagaggacgg 1260

gacccagaaa tgggcgggaa gccgcgcaga aagaatcccc aagagggcct gtacaacgag 1320

ctccaaaagg ataagatggc agaagcctat agcgagattg gtatgaaagg ggaacgcaga 1380

agaggcaaag gccacgacgg actgtaccag ggactcagca ccgccaccaa ggacacctat 1440

gacgctcttc acatgcaggc cctgccgcct cgg 1473

<210> 120
<211> 1446
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 120
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aattgctcga aactggagga ggtctggtgc aacctggagg atcacttcgc 120

ctgtcctgcg ccgtgtcggg ctttgccctg tccaaccatg gaatgagctg ggtccgccgc 180

gcgccgggga agggcctcga atgggtgtcc ggcatcgtct actccggctc cacctactac 240

gccgcgtccg tgaagggccg gttcacgatt tcacgggaca actcgcggaa caccctgtac 300

ctccaaatga attcccttcg gccggaggat actgccatct actactgctc cgcccacggt 360

ggcgaatccg acgtctgggg ccagggaacc accgtgaccg tgtccagcgc gtccggggga 420

ggaggaagcg ggggtagagc atcgggtgga ggcggatcag agatcgtgct gacccagtcc 480

cccgccacct tgagcgtgtc accaggagag tccgccaccc tgtcatgccg cgccagccag 540

tccgtgtcct ccaacctggc ttggtaccag cagaagccgg ggcaggcccc tagactcctg 600

atctatgggg cgtcgacccg ggcatctgga attcccgata ggttcagcgg atcgggctcg 660

ggcactgact tcactctgac catctcctcg ctgcaagccg aggacgtggc tgtgtactac 720

tgtcagcagt acggaagctc cctgactttc ggtggcggga ccaaagtcga gattaagacc 780

actaccccag caccgaggcc acccaccccg gctcctacca tcgcctccca gcctctgtcc 840

ctgcgtccgg aggcatgtag acccgcagct ggtggggccg tgcatacccg gggtcttgac 900

ttcgcctgcg atatctacat ttgggccccc ctggctggta cttgcggggt cctgctgctt 960

tcactcgtga tcactcttta ctgtaagcgc ggtcggaaga agctgctgta catctttaag 1020

caacccttca tgaggcctgt gcagactact caagaggagg acggctgttc atgccggttc 1080

ccagaggagg aggaaggcgg ctgcgaactg cgcgtgaaat tcagccgcag cgcagatgct 1140

ccagcctaca agcaggggca gaaccagctc tacaacgaac tcaatcttgg tcggagagag 1200

gagtacgacg tgctggacaa gcggagagga cgggacccag aaatgggcgg gaagccgcgc 1260

agaaagaatc cccaagaggg cctgtacaac gagctccaaa aggataagat ggcagaagcc 1320

tatagcgaga ttggtatgaa aggggaacgc agaagaggca aaggccacga cggactgtac 1380

cagggactca gcaccgccac caaggacacc tatgacgctc ttcacatgca ggccctgccg 1440

cctcgg 1446

<210> 121

<211> 1449
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 121
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aattggtgga aactggagga ggacttgtgc aacctggagg atcattgaga 120

ctgagctgcg cagtgtcggg attcgccctg agcaaccatg gaatgtcctg ggtcagaagg 180

gcccctggaa aaggcctcga atgggtgtca gggatcgtgt actccggttc cacttactac 240

gccgcctccg tgaaggggcg cttcactatc tcacgggata actcccgcaa taccctgtac 300

ctccaaatga acagcctgcg gccggaggat accgccatct actactgttc cgcccacggt 360

ggagagtctg acgtctgggg ccagggaact accgtgaccg tgtcctccgc gtccggcggt 420

ggagggagcg gcggccgcgc cagcggcggc ggaggctccg agatcgtgat gacccagagc 480

cccgctactc tgtcggtgtc gcccggagaa agggcgaccc tgtcctgccg ggcgtcgcag 540

tccgtgagca gcaagctggc ttggtaccag cagaagccgg gccaggcacc acgcctgctt 600

atgtacggtg cctccattcg ggccaccgga atcccggacc ggttctcggg gtcggggtcc 660

ggtaccgagt tcacactgac catttcctcg ctcgagcccg aggactttgc cgtctattac 720

tgccagcagt acggctcctc ctcatggacg ttcggccagg ggaccaaggt cgaaatcaag 780

accactaccc cagcaccgag gccacccacc ccggctccta ccatcgcctc ccagcctctg 840

tccctgcgtc cggaggcatg tagacccgca gctggtgggg ccgtgcatac ccggggtctt 900

gacttcgcct gcgatatcta catttgggcc cctctggctg gtacttgcgg ggtcctgctg 960

ctttcactcg tgatcactct ttactgtaag cgcggtcgga agaagctgct gtacatcttt 1020

aagcaaccct tcatgaggcc tgtgcagact actcaagagg aggacggctg ttcatgccgg 1080

ttcccagagg aggaggaagg cggctgcgaa ctgcgcgtga aattcagccg cagcgcagat 1140

gctccagcct acaagcaggg gcagaaccag ctctacaacg aactcaatct tggtcggaga 1200

gaggagtacg acgtgctgga caagcggaga ggacgggacc cagaaatggg cgggaagccg 1260

cgcagaaaga atccccaaga gggcctgtac aacgagctcc aaaaggataa gatggcagaa 1320

gcctatagcg agattggtat gaaaggggaa cgcagaagag gcaaaggcca cgacggactg 1380

taccagggac tcagcaccgc caccaaggac acctatgacg ctcttcacat gcaggccctg 1440

ccgcctcgg 1449

<210> 122
<211> 1455
<212> DNA
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 122
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aattggtgga gactggagga ggagtggtgc aacctggagg aagcctgaga 120

ctgtcatgcg cggtgtcggg cttcgccctc tccaaccacg gaatgtcctg ggtccgccgg 180

gcccctggga aaggacttga atgggtgtcc ggcatcgtgt actcgggttc cacctactac 240

gcggcctcag tgaagggccg gtttactatt agccgcgaca actccagaaa cacactgtac 300

ctccaaatga actcgctgcg gccggaagat accgctatct actactgctc cgcccatggg 360

ggagagtcgg acgtctgggg acagggcacc actgtcactg tgtccagcgc ttccggcggt 420

ggtggaagcg ggggacgggc ctcaggaggc ggtggcagcg agattgtgct gacccagtcc 480

cccgggaccc tgagcctgtc cccgggagaa agggccaccc tctcctgtcg ggcatcccag 540

tccgtggggt ctactaacct tgcatggtac cagcagaagc ccggccaggc ccctcgcctg 600

ctgatctacg acgcgtccaa tagagccacc ggcatcccgg atcgcttcag cggaggcgga 660

tcgggcaccg acttcaccct caccatttca aggctggaac cggaggactt cgccgtgtac 720

tactgccagc agtatggttc gtccccaccc tggacgttcg gccaggggac taaggtcgag 780

atcaagacca ctaccccagc accgaggcca cccaccccgg ctcctaccat cgcctcccag 840

cctctgtccc tgcgtccgga ggcatgtaga cccgcagctg gtggggccgt gcatacccgg 900

ggtcttgact tcgcctgcga tatctacatt tgggcccctc tggctggtac ttgcggggtc 960

ctgctgcttt cactcgtgat cactctttac tgtaagcgcg gtcggaagaa gctgctgtac 1020

atctttaagc aacccttcat gaggcctgtg cagactactc aagaggagga cggctgttca 1080

tgccggttcc cagaggagga ggaaggcggc tgcgaactgc gcgtgaaatt cagccgcagc 1140

gcagatgctc cagcctacaa gcaggggcag aaccagctct acaacgaact caatcttggt 1200

cggagagagg agtacgacgt gctggacaag cggagaggac gggacccaga aatgggcggg 1260

aagccgcgca gaaagaatcc ccaagagggc ctgtacaacg agctccaaaa ggataagatg 1320

gcagaagcct atagcgagat tggtatgaaa ggggaacgca gaagaggcaa aggccacgac 1380

ggactgtacc agggactcag caccgccacc aaggacacct atgacgctct tcacatgcag 1440

gccctgccgc ctcgg 1455

<210> 123
<211> 1449
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 123
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc aactcgtgga atctggtgga ggactcgtga aacctggagg atcattgaga 120

ctgtcatgcg cggcctcggg attcacgttc tccgattact acatgagctg gattcgccag 180

gctccgggga agggactgga atgggtgtcc tacatttcct catccggctc caccatctac 240

tacgcggact ccgtgaaggg gagattcacc attagccgcg ataacgccaa gaacagcctg 300

taccttcaga tgaactccct gcgggctgaa gatactgccg tctactactg cgcaagggag 360

agcggagatg ggatggacgt ctggggacag ggtaccactg tgaccgtgtc gtcggcctcc 420

ggcggagggg gttcgggtgg aagggccagc ggcggcggag gcagcgacat ccagatgacc 480

cagtcccccc catcgctgtc cgcctccgtg ggcgaccgcg tcaccatcac atgccgggcc 540

tcacagtcga tctcctccta cctcaattgg tatcagcaga agcccggaaa ggcccctaag 600

cttctgatct acgcagcgtc ctccctgcaa tccggggtcc catctcggtt ctccggctcg 660

ggcagcggta ccgacttcac tctgaccatc tcgagcctgc agccggagga cttcgccact 720

tactactgtc agcaaagcta caccctcgcg tttggccagg gcaccaaagt ggacatcaag 780

accactaccc cagcaccgag gccacccacc ccggctccta ccatcgcctc ccagcctctg 840

tccctgcgtc cggaggcatg tagacccgca gctggtgggg ccgtgcatac ccggggtctt 900

gacttcgcct gcgatatcta catttgggcc cctctggctg gtacttgcgg ggtcctgctg 960

ctttcactcg tgatcactct ttactgtaag cgcggtcgga agaagctgct gtacatcttt 1020

aagcaaccct tcatgaggcc tgtgcagact actcaagagg aggacggctg ttcatgccgg 1080

ttcccagagg aggaggaagg cggctgcgaa ctgcgcgtga aattcagccg cagcgcagat 1140

gctccagcct acaagcaggg gcagaaccag ctctacaacg aactcaatct tggtcggaga 1200

gaggagtacg acgtgctgga caagcggaga ggacgggacc cagaaatggg cgggaagccg 1260

cgcagaaaga atccccaaga gggcctgtac aacgagctcc aaaaggataa gatggcagaa 1320

gcctatagcg agattggtat gaaaggggaa cgcagaagag gcaaaggcca cgacggactg 1380

taccagggac tcagcaccgc caccaaggac acctatgacg ctcttcacat gcaggccctg 1440

ccgcctcgg 1449

<210> 124
<211> 1449
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 124
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aattggtgga atcaggggga ggacttgtgc agcctggagg atcgctgaga 120

ctgtcatgtg ccgtgtccgg ctttgccctg tccaaccacg ggatgtcctg ggtccgccgc 180

gcgcctggaa agggcctcga atgggtgtcg ggtattgtgt acagcggtag cacctactat 240

gccgcatccg tgaaggggag attcaccatc agccgggaca actccaggaa cactctgtac 300

ctccaaatga attcgctgag gccagaggac actgccatct actactgctc cgcgcatggc 360

ggagagtccg acgtctgggg acaggggacc accgtgaccg tgtctagcgc gtccggcgga 420

ggcggcagcg ggggtcgggc atcaggggc ggcggatcgg acatccagct cacccagtcc 480

ccgagctcgc tgtccgcctc cgtgggagat cgggtcacca tcacgtgccg cgccagccag 540

tcgatttcct cctacctgaa ctggtaccaa cagaagcccg gaaaagcccc gaagcttctc 600

atctacgccg cctcgagcct gcagtcagga gtgccctcac ggttctccgg ctccggttcc 660

ggtactgatt tcaccctgac catttcctcc ctgcaaccgg aggacttcgc tacttactac 720

tgccagcagt cgtactccac cccctacact ttcggacaag gcaccaaggt cgaaatcaag 780

accactaccc cagcaccgag gccacccacc ccggctccta ccatcgcctc ccagcctctg 840

tccctgcgtc cggaggcatg tagacccgca gctggtgggg ccgtgcatac ccggggtctt 900

gacttcgcct gcgatatcta catttgggcc cctctggctg gtacttgcgg ggtcctgctg 960

ctttcactcg tgatcactct ttactgtaag cgcggtcgga agaagctgct gtacatcttt 1020

aagcaaccct tcatgaggcc tgtgcagact actcaagagg aggacggctg ttcatgccgg 1080

ttcccagagg aggaggaagg cggctgcgaa ctgcgcgtga aattcagccg cagcgcagat 1140

gctccagcct acaagcaggg gcagaaccag ctctacaacg aactcaatct tggtcggaga 1200

gaggagtacg acgtgctgga caagcggaga ggacgggacc cagaaatggg cgggaagccg 1260

cgcagaaaga atccccaaga gggcctgtac aacgagctcc aaaaggataa gatggcagaa 1320

gcctatagcg agattggtat gaaaggggaa cgcagaagag gcaaaggcca cgacggactg 1380

taccagggac tcagcaccgc caccaaggac acctatgacg ctcttcacat gcaggccctg 1440

ccgcctcgg 1449

<210> 125
<211> 1470
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 125
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc aactggtgca aagcggagga ggattggtca aacccggagg aagcctgaga 120

ctgtcatgcg cggcctctgg attcaccttc tccgattact acatgtcatg gatcagacag 180

gccccgggga agggcctcga atgggtgtcc tacatctcgt cctccgggaa caccatctac 240

tacgccgaca gcgtgaaggg ccgctttacc atttcccgcg acaacgcaaa gaactcgctg 300

taccttcaga tgaattccct gcgggctgaa gataccgcgg tgtactattg cgcccggtcc 360

actatggtcc gggaggacta ctggggacag ggcacactcg tgaccgtgtc cagcgcgagc 420

gggggtggag gcagcggtgg acgcgcctcc ggcggcggcg gttcagacat cgtgctgact 480

cagtcgcccc tgtcgctgcc ggtcaccctg ggccaaccgg cctcaattag ctgcaagtcc 540

tcggagagcc tggtgcacaa ctcaggaaag acttacctga actggttcca tcagcggcct 600

ggacagtccc cacggaggct catctatgaa gtgtccaaca gggattcggg ggtgcccgac 660

cgcttcactg gctccgggtc cggcaccgac ttcaccttga aaatctccag agtggaagcc 720

gaggacgtgg gcgtgtacta ctgtatgcag ggtacccact ggcctggaac ctttggacaa 780

ggaactaagc tcgagattaa gaccactacc ccagcaccga ggccacccac cccggctcct 840

accatcgcct cccagcctct gtccctgcgt ccggaggcat gtagacccgc agctggtggg 900

gccgtgcata cccggggtct tgacttcgcc tgcgatatct acatttgggc ccctctggct 960

ggtacttgcg gggtcctgct gctttcactc gtgatcactc tttactgtaa gcgcggtcgg 1020

aagaagctgc tgtacatctt taagcaaccc ttcatgaggc ctgtgcagac tactcaagag 1080

gaggacggct gttcatgccg gttcccagag gaggaggaag gcggctgcga actgcgcgtg 1140

aaattcagcc gcagcgcaga tgctccagcc tacaagcagg ggcagaacca gctctacaac 1200

gaactcaatc ttggtcggag agaggagtac gacgtgctgg acaagcggag aggacgggac 1260

ccagaaatgg gcgggaagcc gcgcagaaag aatccccaag agggcctgta caacgagctc 1320

caaaaggata agatggcaga agcctatagc gagattggta tgaaagggga acgcagaaga 1380

ggcaaaggcc acgacggact gtaccaggga ctcagcaccg ccaccaagga cacctatgac 1440

gctcttcaca tgcaggccct gccgcctcgg 1470

<210> 126
<211> 1449
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 126
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc aactcgtgga atctggtgga ggactcgtgc aacccggtgg aagccttagg 120

ctgtcgtgcg ccgtcagcgg gtttgctctg agcaaccatg gaatgtcctg ggtccgccgg 180

gcaccgggaa aagggctgga atgggtgtcc ggcatcgtgt acagcgggtc aacctattac 240

gccgcgtccg tgaagggcag attcactatc tcaagagaca acagccggaa caccctgtac 300

ttgcaaatga attccctgcg ccccgaggac accgccatct actactgctc cgcccacgga 360

ggagagtcgg acgtgtgggg ccagggaacg actgtgactg tgtccagcgc atcaggaggg 420

ggtggttcgg gcggccgggc ctcgggggga ggaggttccg acattcggct gacccagtcc 480

ccgtccccac tgtcggcctc cgtcggcgac cgcgtgacca tcacttgtca ggcgtccgag 540

gacattaaca agttcctgaa ctggtaccac cagacccctg gaaaggcccc caagctgctg 600

atctacgatg cctcgaccct tcaaactgga gtgcctagcc ggttctccgg gtccggctcc 660

ggcactgatt tcactctgac catcaactca ttgcagccgg aagatatcgg gacctactat 720

tgccagcagt acgaatccct cccgctcaca ttcggcgggg gaaccaaggt cgagattaag 780

accactaccc cagcaccgag gccacccacc ccggctccta ccatcgcctc ccagcctctg 840

tccctgcgtc cggaggcatg tagacccgca gctggtgggg ccgtgcatac ccggggtctt 900

gacttcgcct gcgatatcta catttgggcc cctctggctg gtacttgcgg ggtcctgctg 960

ctttcactcg tgatcactct ttactgtaag cgcggtcgga agaagctgct gtacatcttt 1020

aagcaaccct tcatgaggcc tgtgcagact actcaagagg aggacggctg ttcatgccgg 1080

ttcccagagg aggaggaagg cggctgcgaa ctgcgcgtga aattcagccg cagcgcagat 1140

gctccagcct acaagcaggg gcagaaccag ctctacaacg aactcaatct tggtcggaga 1200

gaggagtacg acgtgctgga caagcggaga ggacgggacc cagaaatggg cgggaagccg 1260

cgcagaaaga atccccaaga gggcctgtac aacgagctcc aaaaggataa gatggcagaa 1320

gcctatagcg agattggtat gaaaggggaa cgcagaagag gcaaaggcca cgacggactg 1380

taccagggac tcagcaccgc caccaaggac acctatgacg ctcttcacat gcaggccctg 1440

ccgcctcgg 1449

<210> 127
<211> 1452
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 127
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aattggtgga aactggagga ggacttgtgc aacctggagg atcattgcgg 120

ctctcatgcg ctgtctccgg cttcgccctg tcaaatcacg ggatgtcgtg ggtcagacgg 180

gccccgggaa agggtctgga atgggtgtcg gggattgtgt acagcggctc cacctactac 240

gccgcttcgg tcaagggccg cttcactatt tcacgggaca acagccgcaa caccctctat 300

ctgcaaatga actctctccg cccggaggat accgccatct actactgctc cgcacacggc 360

ggcgaatccg acgtgtgggg acagggaacc actgtcaccg tgtcgtccgc atccggtggc 420

ggaggatcgg gtggccgggc ctccgggggc ggcggcagcg agactaccct gacccagtcc 480

cctgccactc tgtccgtgag cccgggagag agagccaccc ttagctgccg ggccagccag 540

agcgtgggct ccaacctggc ctggtaccag cagaagccag gacagggtcc caggctgctg 600

atctacggag cctccactcg cgcgaccggc atccccgcga ggttctccgg gtcgggttcc 660

gggaccgagt tcaccctgac catctcctcc ctccaaccgg aggacttcgc ggtgtactac 720

tgtcagcagt acaacgattg gctgcccgtg acatttggac aggggacgaa ggtggaaatc 780

aaaaccacta ccccagcacc gaggccaccc accccggctc ctaccatcgc ctcccagcct 840

ctgtccctgc gtccggaggc atgtagaccc gcagctggtg gggccgtgca tacccggggt 900

cttgacttcg cctgcgatat ctacatttgg gcccctctgg ctggtacttg cggggtcctg 960

ctgctttcac tcgtgatcac tctttactgt aagcgcggtc ggaagaagct gctgtacatc 1020

tttaagcaac ccttcatgag gcctgtgcag actactcaag aggaggacgg ctgttcatgc 1080

cggttcccag aggaggagga aggcggctgc gaactgcgcg tgaaattcag ccgcagcgca 1140

gatgctccag cctacaagca ggggcagaac cagctctaca acgaactcaa tcttggtcgg 1200

agagaggagt acgacgtgct ggacaagcgg agaggacggg acccagaaat gggcgggaag 1260

ccgcgcagaa agaatcccca agagggcctg tacaacgagc tccaaaagga taagatggca 1320

gaagcctata gcgagattgg tatgaaaggg gaacgcagaa gaggcaaagg ccacgacgga 1380

ctgtaccagg gactcagcac cgccaccaag gacacctatg acgctcttca catgcaggcc 1440

ctgccgcctc gg 1452

<210> 128
<211> 1455
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 128
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aattggtgga atctggtgga ggacttgtgc aacctggagg atcactgaga 120

ctgtcatgcg cggtgtccgg ttttgccctg agcaatcatg ggatgtcgtg ggtccggcgc 180

gcccccggaa agggtctgga atgggtgtcg ggtatcgtct actccgggag cacttactac 240

gccgcgagcg tgaagggccg cttcaccatt tcccgcgata actcccgcaa caccctgtac 300

ttgcaaatga actcgctccg gcctgaggac actgccatct actactgctc cgcacacgga 360

ggagaatccg acgtgtgggg ccagggaact accgtgaccg tcagcagcgc ctccggcggc 420

gggggctcag gcggacgggc tagcggcggc ggtggctccg agatcgtgct gacccagtcg 480

cctggcactc tctcgctgag ccccggggaa agggcaaccc tgtcctgtcg ggccagccag 540

tccattggat catcctccct cgcctggtat cagcagaaac cgggacaggc tccgcggctg 600

cttatgtatg gggccagctc aagagcctcc ggcattcccg accggttctc cgggtccggt 660

tccggcaccg atttcaccct gactatctcg aggctggagc cagaggactt cgccgtgtac 720

tactgccagc agtacgcggg gtccccgccg ttcacgttcg gacagggaac caaggtcgag 780

atcaagacca ctaccccagc accgaggcca cccaccccgg ctcctaccat cgcctcccag 840

cctctgtccc tgcgtccgga ggcatgtaga cccgcagctg gtggggccgt gcatacccgg 900

ggtcttgact tcgcctgcga tatctacatt tgggcccctc tggctggtac ttgcggggtc 960

ctgctgcttt cactcgtgat cactctttac tgtaagcgcg gtcggaagaa gctgctgtac 1020

atctttaagc aacccttcat gaggcctgtg cagactactc aagaggagga cggctgttca 1080

tgccggttcc cagaggagga ggaaggcggc tgcgaactgc gcgtgaaatt cagccgcagc 1140

gcagatgctc cagcctacaa gcaggggcag aaccagctct acaacgaact caatcttggt 1200

cggagagagg agtacgacgt gctggacaag cggagaggac gggacccaga aatgggcggg 1260

aagccgcgca gaaagaatcc ccaagagggc ctgtacaacg agctccaaaa ggataagatg 1320

gcagaagcct atagcgagat tggtatgaaa ggggaacgca gaagaggcaa aggccacgac 1380

ggactgtacc agggactcag caccgccacc aaggacacct atgacgctct tcacatgcag 1440

gccctgccgc ctcgg 1455

<210> 129
<211> 243
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 129

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
20 25 30

Tyr Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ser Ala Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg His Trp Gln Glu Trp Pro Asp Ala Phe Asp Ile Trp Gly
100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Glu Thr Thr Leu Thr Gln Ser Pro
130 135 140

Ala Phe Met Ser Ala Thr Pro Gly Asp Lys Val Ile Ile Ser Cys Lys
145 150 155 160

```
Ala Ser Gln Asp Ile Asp Asp Ala Met Asn Trp Tyr Gln Gln Lys Pro
                165                 170                 175

Gly Glu Ala Pro Leu Phe Ile Ile Gln Ser Ala Thr Ser Pro Val Pro
            180                 185                 190

Gly Ile Pro Pro Arg Phe Ser Gly Ser Gly Phe Gly Thr Asp Phe Ser
        195                 200                 205

Leu Thr Ile Asn Asn Ile Glu Ser Glu Asp Ala Ala Tyr Tyr Phe Cys
    210                 215                 220

Leu Gln His Asp Asn Phe Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu
225                 230                 235                 240

Glu Ile Lys
```

<210> 130
<211> 244
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 130

```
Val Asn Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln Thr
1               5                   10                  15

Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Arg Thr Ser Gly
            20                  25                  30

Met Cys Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu Trp
        35                  40                  45

Leu Ala Arg Ile Asp Trp Asp Glu Asp Lys Phe Tyr Ser Thr Ser Leu
    50                  55                  60

Lys Thr Arg Leu Thr Ile Ser Lys Asp Thr Ser Asp Asn Gln Val Val
65                  70                  75                  80

Leu Arg Met Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr Cys
                85                  90                  95

Ala Arg Ser Gly Ala Gly Gly Thr Ser Ala Thr Ala Phe Asp Ile Trp
            100                 105                 110

Gly Pro Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125
```

```
Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser
    130                 135                 140

Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
145                 150                 155                 160

Arg Ala Ser Gln Asp Ile Tyr Asn Asn Leu Ala Trp Phe Gln Leu Lys
                165                 170                 175

Pro Gly Ser Ala Pro Arg Ser Leu Met Tyr Ala Ala Asn Lys Ser Gln
            180                 185                 190

Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Ala Ser Gly Thr Asp Phe
        195                 200                 205

Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
    210                 215                 220

Cys Gln His Tyr Tyr Arg Phe Pro Tyr Ser Phe Gly Gln Gly Thr Lys
225                 230                 235                 240

Leu Glu Ile Lys
```

<210> 131
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 131

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ala Lys Thr Ile Ala Ala Val Tyr Ala Phe Asp Ile Trp Gly Gln Gly
            100                 105                 110

Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Leu Ser
    130                 135                 140

Leu Pro Val Thr Pro Glu Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser
145                 150                 155                 160

Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu
                165                 170                 175

Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn
            180                 185                 190

Arg Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
        195                 200                 205

Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val
    210                 215                 220

Tyr Tyr Cys Met Gln Ala Leu Gln Thr Pro Tyr Thr Phe Gly Gln Gly
225                 230                 235                 240

Thr Lys Leu Glu Ile Lys
                245
```

<210> 132
<211> 240
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 132

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
```

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Leu Arg Gly Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Ala
130 135 140

Ala Pro Gly Tyr Thr Ala Thr Ile Ser Cys Gly Gly Asn Asn Ile Gly
145 150 155 160

Thr Lys Ser Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu
165 170 175

Leu Val Ile Arg Asp Asp Ser Val Arg Pro Ser Lys Ile Pro Gly Arg
180 185 190

Phe Ser Gly Ser Asn Ser Gly Asn Met Ala Thr Leu Thr Ile Ser Gly
195 200 205

Val Gln Ala Gly Asp Glu Ala Asp Phe Tyr Cys Gln Val Trp Asp Ser
210 215 220

Asp Ser Glu His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
225 230 235 240

<210> 133
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 133
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Pro Ser Gly Tyr Thr Val Thr Ser His
20 25 30

Tyr Ile His Trp Val Arg Arg Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Met Ile Asn Pro Ser Gly Gly Val Thr Ala Tyr Ser Gln Thr Leu
50 55 60

```
Gln Gly Arg Val Thr Met Thr Ser Asp Thr Ser Ser Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Gly Ser Gly Ser Gly Trp Tyr Phe Asp Phe Trp Gly Arg
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Ser Tyr Val Leu Thr Gln Pro Pro Ser
    130                 135                 140

Val Ser Val Ser Pro Gly Gln Thr Ala Ser Ile Thr Cys Ser Gly Asp
145                 150                 155                 160

Gly Leu Ser Lys Lys Tyr Val Ser Trp Tyr Gln Gln Lys Ala Gly Gln
                165                 170                 175

Ser Pro Val Val Leu Ile Ser Arg Asp Lys Glu Arg Pro Ser Gly Ile
            180                 185                 190

Pro Asp Arg Phe Ser Gly Ser Asn Ser Ala Asp Thr Ala Thr Leu Thr
        195                 200                 205

Ile Ser Gly Thr Gln Ala Met Asp Glu Ala Asp Tyr Tyr Cys Gln Ala
    210                 215                 220

Trp Asp Asp Thr Thr Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val
225                 230                 235                 240

Leu
```

<210> 134
<211> 245
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 134

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
            20                  25                  30
```

```
Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
        35                  40                  45

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65                  70                  75                  80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Arg Ala Gly Ile Ala Ala Arg Leu Arg Gly Ala Phe Asp Ile
            100                 105                 110

Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln
    130                 135                 140

Ser Pro Ser Ser Val Ser Ala Ser Val Gly Asp Arg Val Ile Ile Thr
145                 150                 155                 160

Cys Arg Ala Ser Gln Gly Ile Arg Asn Trp Leu Ala Trp Tyr Gln Gln
                165                 170                 175

Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile Tyr Ala Ala Ser Asn Leu
            180                 185                 190

Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Ala Asp
        195                 200                 205

Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Val Ala Thr Tyr
    210                 215                 220

Tyr Cys Gln Lys Tyr Asn Ser Ala Pro Phe Thr Phe Gly Pro Gly Thr
225                 230                 235                 240

Lys Val Asp Ile Lys
                245
```

<210> 135
<211> 253
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 135

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
            20                  25                  30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Gly Gly Tyr Gln Leu Leu Arg Trp Asp Val Gly Leu Leu
            100                 105                 110

Arg Ser Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser
        115                 120                 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
    130                 135                 140

Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
145                 150                 155                 160

Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Gly Ser Lys Ser Val
                165                 170                 175

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Leu Tyr
            180                 185                 190

Gly Lys Asn Asn Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser
        195                 200                 205

Arg Ser Gly Thr Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
    210                 215                 220

Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Arg Asp Ser Ser Gly Asp His
225                 230                 235                 240

Leu Arg Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
                245                 250
```

<210> 136
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 136
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Ser Phe Tyr Ala
50 55 60

Ile Ser Leu Lys Ser Arg Ile Ile Ile Asn Pro Asp Thr Ser Lys Asn
65 70 75 80

Gln Phe Ser Leu Gln Leu Lys Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Ser Ser Pro Glu Gly Leu Phe Leu Tyr Trp Phe
100 105 110

Asp Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Asp
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Ser Glu Leu
130 135 140

Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr Ile Arg Ile
145 150 155 160

Thr Cys Gln Gly Asp Ser Leu Gly Asn Tyr Tyr Ala Thr Trp Tyr Gln
165 170 175

Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr Gly Thr Asn Asn
180 185 190

Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Ala Ser Ser Ser Gly Asn
195 200 205

Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp
210 215 220

Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly His His Leu Leu Phe Gly
225 230 235 240

Thr Gly Thr Lys Val Thr Val Leu

245

<210> 137
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 137
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Val Glu Gly Ser Gly Ser Leu Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
115 120 125

Gly Gly Gly Gly Ser Glu Ile Val Met Thr Gln Ser Pro Gly Thr Leu
130 135 140

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
145 150 155 160

Ser Val Ser Ser Ala Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
165 170 175

Pro Pro Arg Leu Leu Ile Ser Gly Ala Ser Thr Arg Ala Thr Gly Ile
180 185 190

Pro Asp Arg Phe Gly Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
195 200 205

Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His
210 215 220

Tyr Gly Ser Ser Phe Asn Gly Ser Ser Leu Phe Thr Phe Gly Gln Gly
225 230 235 240

Thr Arg Leu Glu Ile Lys
245

<210> 138
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 138
Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ile Thr Phe Ser Arg Tyr
20 25 30

Pro Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Asp Ser Gly Val Ser Thr Tyr Tyr Ala Asp Ser Ala
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Ser Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Val Thr Arg Ala Gly Ser Glu Ala Ser Asp Ile Trp Gly Gln Gly Thr
100 105 110

Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
115 120 125

Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu
130 135 140

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
145 150 155 160

Ser Val Ser Asn Ser Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
165 170 175

Pro Arg Leu Leu Ile Tyr Asp Ala Ser Ser Arg Ala Thr Gly Ile Pro
180 185 190

```
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
        195                 200                 205

Ser Arg Leu Glu Pro Glu Asp Phe Ala Ile Tyr Tyr Cys Gln Gln Phe
    210                 215                 220

Gly Thr Ser Ser Gly Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
225                 230                 235                 240

Lys
```

<210> 139
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 139

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
                85                  90                  95

Ala Arg Ala Thr Tyr Lys Arg Glu Leu Arg Tyr Tyr Tyr Gly Met Asp
            100                 105                 110

Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met Thr
    130                 135                 140

Gln Ser Pro Gly Thr Val Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu
145                 150                 155                 160
```

```
Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser Phe Leu Ala Trp Tyr
                165                 170                 175

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser
            180                 185                 190

Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205

Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Ser Ala
    210                 215                 220

Val Tyr Tyr Cys Gln Gln Tyr His Ser Ser Pro Ser Trp Thr Phe Gly
225                 230                 235                 240

Gln Gly Thr Arg Leu Glu Ile Lys
                245
```

<210> 140
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 140

```
Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Thr Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Ala Thr Tyr Lys Arg Glu Leu Arg Tyr Tyr Tyr Gly Met Asp
            100                 105                 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr
```

130 135 140

Gln Ser Pro Ser Thr Leu Ser Leu Ser Pro Gly Glu Ser Ala Thr Leu
145 150 155 160

Ser Cys Arg Ala Ser Gln Ser Val Ser Thr Thr Phe Leu Ala Trp Tyr
165 170 175

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Gly Ser Ser
180 185 190

Asn Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
195 200 205

Thr Asp Phe Thr Leu Thr Ile Arg Arg Leu Glu Pro Glu Asp Phe Ala
210 215 220

Val Tyr Tyr Cys Gln Gln Tyr His Ser Ser Pro Ser Trp Thr Phe Gly
225 230 235 240

Gln Gly Thr Lys Val Glu Ile Lys
245

<210> 141
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 141
Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val Gly Lys Ala Val Pro Asp Val Trp Gly Gln Gly Thr Thr
100 105 110

```
Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Asp Ile Val Met Thr Gln Thr Pro Ser Ser Leu Ser
    130                 135                 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser
145                 150                 155                 160

Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr
    210                 215                 220

Ser Thr Pro Tyr Ser Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
225                 230                 235
```

<210> 142
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 142

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30

Ala Met His Trp Val Arg Gln Arg Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Ser Ile Asn Trp Lys Gly Asn Ser Leu Ala Tyr Gly Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Ala Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Phe
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ala Ser His Gln Gly Val Ala Tyr Tyr Asn Tyr Ala Met Asp Val Trp
            100                 105                 110

Gly Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser
    130                 135                 140

Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
145                 150                 155                 160

Arg Ala Thr Gln Ser Ile Gly Ser Ser Phe Leu Ala Trp Tyr Gln Gln
                165                 170                 175

Arg Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Gln Arg
            180                 185                 190

Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Arg Gly Ser Gly Thr Asp
        195                 200                 205

Phe Thr Leu Thr Ile Ser Arg Val Glu Pro Glu Asp Ser Ala Val Tyr
    210                 215                 220

Tyr Cys Gln His Tyr Glu Ser Ser Pro Ser Trp Thr Phe Gly Gln Gly
225                 230                 235                 240

Thr Lys Val Glu Ile Lys
                245
```

<210> 143
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 143

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60
```

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Val Val Arg Asp Gly Met Asp Val Trp Gly Gln Gly Thr Thr
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
130 135 140

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
145 150 155 160

Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
165 170 175

Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro
180 185 190

Asp Arg Phe Ser Gly Asn Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
195 200 205

Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr
210 215 220

Gly Ser Pro Pro Arg Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile
225 230 235 240

Lys

<210> 144
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 144
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Ile Pro Gln Thr Gly Thr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
115 120 125

Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu
130 135 140

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
145 150 155 160

Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln
165 170 175

Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile
180 185 190

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
195 200 205

Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His
210 215 220

Tyr Gly Ser Ser Pro Ser Trp Thr Phe Gly Gln Gly Thr Arg Leu Glu
225 230 235 240

Ile Lys

<210> 145
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 145
Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Met Ser Arg Glu Asn Asp Lys Asn Ser Val Phe
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Gly Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Ala Asn Tyr Lys Arg Glu Leu Arg Tyr Tyr Tyr Gly Met Asp
            100                 105                 110

Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met Thr
    130                 135                 140

Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Ser Ala Thr Leu
145                 150                 155                 160

Ser Cys Arg Ala Ser Gln Arg Val Ala Ser Asn Tyr Leu Ala Trp Tyr
                165                 170                 175

Gln His Lys Pro Gly Gln Ala Pro Ser Leu Leu Ile Ser Gly Ala Ser
            180                 185                 190

Ser Arg Ala Thr Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205

Thr Asp Phe Thr Leu Ala Ile Ser Arg Leu Glu Pro Glu Asp Ser Ala
    210                 215                 220

Val Tyr Tyr Cys Gln His Tyr Asp Ser Ser Pro Ser Trp Thr Phe Gly
225                 230                 235                 240

Gln Gly Thr Lys Val Glu Ile Lys
                245
```

<210> 146
<211> 244
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 146

```
Glu Val Gln Leu Leu Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Ser Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Ala Leu Val Gly Ala Thr Gly Ala Phe Asp Ile Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly
    130                 135                 140

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
145                 150                 155                 160

Ser Gln Ser Leu Ser Ser Asn Phe Leu Ala Trp Tyr Gln Gln Lys Pro
                165                 170                 175

Gly Gln Ala Pro Gly Leu Leu Ile Tyr Gly Ala Ser Asn Trp Ala Thr
            180                 185                 190

Gly Thr Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
        195                 200                 205

Leu Thr Ile Thr Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
    210                 215                 220

Gln Tyr Tyr Gly Thr Ser Pro Met Tyr Thr Phe Gly Gln Gly Thr Lys
225                 230                 235                 240

Val Glu Ile Lys
```

<210> 147
<211> 244
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 147
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Val Leu Trp Phe Gly Glu Gly Phe Asp Pro Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro
130 135 140

Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser
145 150 155 160

Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys
165 170 175

Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala
180 185 190

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
195 200 205

Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr
210 215 220

Cys Met Gln Ala Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys
225 230 235 240

Val Asp Ile Lys

<210> 148
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 148
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Val Gly Tyr Asp Ser Ser Gly Tyr Tyr Arg Asp Tyr Tyr Gly
100 105 110

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly
115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val
130 135 140

Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala
145 150 155 160

Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala
165 170 175

Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Gly
180 185 190

Thr Ser Ser Arg Ala Thr Gly Ile Ser Asp Arg Phe Ser Gly Ser Gly

195 200 205

Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp
210 215 220

Phe Ala Val Tyr Tyr Cys Gln His Tyr Gly Asn Ser Pro Pro Lys Phe
225 230 235 240

Thr Phe Gly Pro Gly Thr Lys Leu Glu Ile Lys
245 250

<210> 149
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 149
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Met Gly Trp Ser Ser Gly Tyr Leu Gly Ala Phe Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser
130 135 140

Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
145 150 155 160

Arg Ala Ser Gln Ser Val Ala Ser Ser Phe Leu Ala Trp Tyr Gln Gln
165 170 175

Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Gly Arg
180 185 190

Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
195 200 205

Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr
210 215 220

Tyr Cys Gln His Tyr Gly Gly Ser Pro Arg Leu Thr Phe Gly Gly Gly
225 230 235 240

Thr Lys Val Asp Ile Lys
245

<210> 150
<211> 729
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 150
caagtgcagc ttcaggaaag cggaccgggc ctggtcaagc catccgaaac tctctccctg 60

acttgcactg tgtctggcgg ttccatctca tcgtcgtact actactgggg ctggattagg 120

cagccgcccg gaaagggact ggagtggatc ggaagcatct actattccgg ctcggcgtac 180

tacaacccta gcctcaagtc gagagtgacc atctccgtgg atacctccaa gaaccagttt 240

tccctgcgcc tgagctccgt gaccgccgct gacaccgccg tgtactactg tgctcggcat 300

tggcaggaat ggcccgatgc cttcgacatt tggggccagg gcactatggt cactgtgtca 360

tccgggggtg gaggcagcgg gggaggaggg tccggggggg gaggttcaga gacaaccttg 420

acccagtcac ccgcattcat gtccgccact ccgggagaca aggtcatcat ctcgtgcaaa 480

gcgtcccagg atatcgacga tgccatgaat tggtaccagc agaagcctgg cgaagcgccg 540

ctgttcatta tccaatccgc aacctcgccc gtgcctggaa tcccaccgcg gttcagcggc 600

agcggtttcg gaaccgactt ttccctgacc attaacaaca ttgagtccga ggacgccgcc 660

tactacttct gcctgcaaca cgacaacttc cctctcacgt tcggccaggg aaccaagctg 720

gaaatcaag 729

<210> 151
<211> 735
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polynucleotide"

<400> 151
caagtcaatc tgcgcgaatc cggccccgcc ttggtcaagc ctacccagac cctcactctg 60

acctgtactt tctccggctt ctccctgcgg acttccggga tgtgcgtgtc ctggatcaga 120

cagcctccgg gaaaggccct ggagtggctc gctcgcattg actgggatga ggacaagttc 180

tactccacct cactcaagac caggctgacc atcagcaaag atacctctga caaccaagtg 240

gtgctccgca tgaccaacat ggacccagcc gacactgcca cttactactg cgcgaggagc 300

ggagcgggcg gaacctccgc caccgccttc gatatttggg gcccgggtac catggtcacc 360

gtgtcaagcg gaggaggggg gtccgggggc ggcggttccg ggggaggcgg atcggacatt 420

cagatgactc agtcaccatc gtccctgagc gctagcgtgg gcgacagagt gacaatcact 480

tgccgggcat cccaggacat ctataacaac cttgcgtggt tccagctgaa gcctggttcc 540

gcaccgcggt cacttatgta cgccgccaac aagagccagt cgggagtgcc gtcccggttt 600

tccggttcgg cctcgggaac tgacttcacc ctgacgatct ccagcctgca acccgaggat 660

ttcgccacct actactgcca gcactactac cgctttccct actcgttcgg acagggaacc 720

aagctggaaa tcaag 735

<210> 152
<211> 738
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 152
gaagtgcagc ttgtcgaatc cgggggggga ctggtcaagc cgggcggatc actgagactg 60

tcctgcgccg cgagcggctt cacgttctcc tcctactcca tgaactgggt ccgccaagcc 120

cccgggaagg gactggaatg ggtgtcctct atctcctcgt cgtcgtccta catctactac 180

gccgactccg tgaagggaag attcaccatt tcccgcgaca acgcaaagaa ctcactgtac 240

ttgcaaatga actcactccg ggccgaagat actgctgtgt actattgcgc caagactatt 300

gccgccgtct acgctttcga catctggggc cagggaacca ccgtgactgt gtcgtccggt 360

ggtggtggct cgggcggagg aggaagcggc ggcggggggt ccgagattgt gctgacccag 420

tcgccactga gcctccctgt gacccccgag gaacccgcca gcatcagctg ccggtccagc 480

cagtccctgc tccactccaa cggatacaat tacctcgatt ggtaccttca gaagcctgga 540

caaagcccgc agctgctcat ctacttggga tcaaaccgcg cgtcaggagt gcctgaccgg 600

ttctccggct cgggcagcgg taccgatttc accctgaaaa tctccagggt ggaggcagag 660

gacgtgggag tgtattactg tatgcaggcg ctgcagactc cgtacacatt tgggcagggc 720

accaagctgg agatcaag 738

<210> 153
<211> 720
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 153
gaagtccagc tcgtggagtc cggcggaggc cttgtgaagc ctggaggttc gctgagactg 60

tcctgcgccg cctccggctt caccttctcc gactactaca tgtcctggat cagacaggcc 120

ccgggaaagg gcctggaatg ggtgtcctac atctcgtcat cgggcagcac tatctactac 180

gcggactcag tgaaggggcg gttcaccatt tcccgggata acgcgaagaa ctcgctgtat 240

ctgcaaatga actcactgag ggccgaggac accgccgtgt actactgcgc ccgcgatctc 300

cgcggggcat ttgacatctg gggacaggga accatggtca cagtgtccag cggaggggga 360

ggatcgggtg gcggaggttc cgggggtgga ggctcctcct acgtgctgac tcagagccca 420

agcgtcagcg ctgcgcccgg ttacacggca accatctcct gtggcggaaa caacattggg 480

accaagtctg tgcactggta tcagcagaag ccgggccaag ctcccctgtt ggtgatccgc 540

gatgactccg tgcggcctag caaaattccg ggacggttct ccggctccaa cagcggcaat 600

atggccactc tcaccatctc gggagtgcag gccggagatg aagccgactt ctactgccaa 660

gtctgggact cagactccga gcatgtggtg ttcgggggcg gaaccaagct gactgtgctc 720

<210> 154
<211> 723
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 154
caagtgcagc tggtgcagag cggggccgaa gtcaagaagc cgggagcctc cgtgaaagtg 60

tcctgcaagc cttcgggata caccgtgacc tcccactaca ttcattgggt ccgccgcgcc 120

cccggccaag gactcgagtg gatgggcatg atcaacccta gcggcggagt gaccgcgtac 180

agccagacgc tgcagggacg cgtgactatg acctcggata cctcctcctc caccgtctat 240

atggaactgt ccagcctgcg gtccgaggat accgccatgt actactgcgc ccgggaagga 300

tcaggctccg ggtggtattt cgacttctgg ggaagaggca ccctcgtgac tgtgtcatct 360

gggggagggg gttccggtgg tggcggatcg ggaggaggcg gttcatccta cgtgctgacc 420

cagccaccct ccgtgtccgt gagccccggc cagactgcat cgattacatg tagcggcgac 480

ggcctctcca agaaatacgt gtcgtggtac cagcagaagg ccggacagag cccggtggtg 540

ctgatctcaa gagataagga gcggcctagc ggaatcccgg acaggttctc gggttccaac 600

tccgcggaca ctgctactct gaccatctcg gggacccagg ctatggacga agccgattac 660

tactgccaag cctgggacga cactactgtc gtgtttggag ggggcaccaa gttgaccgtc 720

ctt 723

<210> 155
<211> 735
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 155
caagtgcagc ttcaggagag cggcccggga ctcgtgaagc cgtcccagac cctgtccctg 60

acttgcaccg tgtcgggagg aagcatctcg agcggaggct actattggtc gtggattcgg 120

cagcaccctg gaaagggcct ggaatggatc ggctacatct actactccgg ctcgacctac 180

tacaacccat cgctgaagtc cagagtgaca atctcagtgg acacgtccaa gaatcagttc 240

agcctgaagc tctcttccgt gactgcggcc gacaccgccg tgtactactg cgcacgcgct 300

ggaattgccg cccggctgag gggtgccttc gacatttggg gacagggcac catggtcacc 360

gtgtcctccg gcggcggagg ttccgggggt ggaggctcag gaggaggggg gtccgacatc 420

gtcatgactc agtcgccctc aagcgtcagc gcgtccgtcg gggacagagt gatcatcacc 480

tgtcgggcgt cccagggaat tcgcaactgg ctggcctggt atcagcagaa gcccggaaag 540

gcccccaacc tgttgatcta cgccgcctca aacctccaat ccggggtgcc gagccgcttc 600

agcggctccg gttcgggtgc cgatttcact ctgaccatct cctccctgca acctgaagat 660

gtggctacct actactgcca aaagtacaac tccgcacctt ttactttcgg accggggacc 720

aaagtggaca ttaag 735

<210> 156
<211> 759
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 156
caagtgcagc tggtccagtc gggcgccgag gtcaagaagc ccgggagctc tgtgaaagtg 60

tcctgcaagg cctccggggg cacctttagc tcctacgcca tctcctgggt ccgccaagca 120

ccgggtcaag gcctggagtg gatgggggga attatcccta tcttcggcac tgccaactac 180

gcccagaagt tccagggacg cgtgaccatt accgcggacg aatccacctc caccgcttat 240

atggagctgt ccagcttgcg ctcggaagat accgccgtgt actactgcgc ccggaggggt 300

ggataccagc tgctgagatg ggacgtgggc ctcctgcggt cggcgttcga catctggggc 360

cagggcacta tggtcactgt gtccagcgga ggaggcggat cgggaggcgg cggatcaggg 420

ggaggcggtt ccagctacgt gcttactcaa ccccttcgg tgtccgtggc cccgggacag 480

accgccagaa tcacttgcgg aggaaacaac attgggtcca agagcgtgca ttggtaccag 540

cagaagccag gacaggcccc tgtgctggtg ctctacggga agaacaatcg gcccagcgga 600

gtgccggaca ggttctcggg ttcacgctcc ggtacaaccg cttcactgac tatcaccggg 660

gcccaggcag aggatgaagc ggactactac tgttcctccc gggattcatc cggcgaccac 720

ctccgggtgt tcggaaccgg aacgaaggtc accgtgctg 759

<210> 157
<211> 744
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 157
gaagtgcagc tccaacagtc aggaccgggg ctcgtgaagc catcccagac cctgtccctg 60

acttgtgcca tctcgggaga tagcgtgtca tcgaactccg ccgcctggaa ctggattcgg 120

cagagcccgt cccgcggact ggagtggctt ggaaggacct actaccggtc caagtggtac 180

tctttctacg cgatctcgct gaagtcccgc attatcatta accctgatac ctccaagaat 240

cagttctccc tccaactgaa atccgtcacc cccgaggaca cagcagtgta ttactgcgca 300

cggagcagcc ccgaaggact gttcctgtat tggtttgacc cctggggcca ggggactctt 360

gtgaccgtgt cgagcggcgg agatgggtcc ggtggcggtg gttcgggggg cggcggatca 420

tcatccgaac tgacccagga cccggctgtg tccgtggcgc tgggacaaac catccgcatt 480

acgtgccagg gagactccct gggcaactac tacgccactt ggtaccagca gaagccgggc 540

caagcccctg tgttggtcat ctacgggacc aacaacagac cttccggcat ccccgaccgg 600

ttcagcgctt cgtcctccgg caacactgcc agcctgacca tcactggagc gcaggccgaa 660

gatgaggccg actactactg caacagcaga gactcctcgg gtcatcacct cttgttcgga 720

actggaacca aggtcaccgt gctg 744

<210> 158
<211> 738
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 158
gaagtgcagc tcgtggagtc aggaggcggc ctggtccagc cgggagggtc ccttagactg 60

tcatgcgccg caagcggatt cactttctcc tcctatgcca tgagctgggt ccgccaagcc 120

cccggaaagg gactggaatg ggtgtccgcc atctcggggt ctggaggctc aacttactac 180

gctgactccg tgaagggacg gttcaccatt agccgcgaca actccaagaa caccctctac 240

ctccaaatga actccctgcg ggccgaggat accgccgtct actactgcgc caaagtggaa 300

ggttcaggat cgctggacta ctggggacag ggtactctcg tgaccgtgtc atcgggcgga 360

ggaggttccg gcggtggcgg ctccggcggc ggagggtcgg agatcgtgat gacccagagc 420

cctggtactc tgagcctttc gccgggagaa agggccaccc tgtcctgccg cgcttcccaa 480

tccgtgtcct ccgcgtactt ggcgtggtac cagcagaagc cgggacagcc ccctcggctg 540

ctgatcagcg gggccagcac ccgggcaacc ggaatcccag acagattcgg gggttccggc 600

agcggcacag atttcaccct gactatttcg aggttggagc ccgaggactt tgcggtgtat 660

tactgtcagc actacgggtc gtcctttaat ggctccagcc tgttcacgtt cggacagggg 720

acccgcctgg aaatcaag 738

<210> 159
<211> 723
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 159
gaagtgcaac tggtggaaac cggtggcggc ctggtgcagc ctggaggatc attgaggctg 60

tcatgcgcgg ccagcggtat taccttctcc cggtacccca tgtcctgggt cagacaggcc 120

ccggggaaag ggcttgaatg ggtgtccggg atctcggact ccggtgtcag cacttactac 180

gccgactccg ccaagggacg cttcaccatt tcccgggaca actcgaagaa caccctgttc 240

ctccaaatga gctccctccg ggacgaggat actgcagtgt actactgcgt gacccgcgcc 300

gggtccgagg cgtctgacat ttggggacag ggcactatgg tcaccgtgtc gtccggcgga 360

gggggctcgg gaggcggtgg cagcggagga ggagggtccg agatcgtgct gacccaatcc 420

ccggccaccc tctcgctgag ccctggagaa agggcaacct tgtcctgtcg cgcgagccag 480

tccgtgagca actccctggc ctggtaccag cagaagcccg gacaggctcc gagacttctg 540

atctacgacg cttcgagccg ggccactgga atccccgacc gcttttcggg gtccggctca 600

ggaaccgatt tcaccctgac aatctcacgg ctggagccag aggatttcgc catctattac 660

tgccagcagt tcggtacttc ctccggcctg actttcggag gcggcacgaa gctcgaaatc 720

aag 723

<210> 160
<211> 744
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polynucleotide"

<400> 160
caagtgcagc tcgtggaatc gggtggcgga ctggtgcagc cgggggctc acttagactg 60

tcctgcgcgg ccagcggatt cactttctcc tcctacgcca tgtcctgggt cagacaggcc 120

cctggaaagg gcctggaatg ggtgtccgca atcagcggca gcggcggctc gacctattac 180

gcggattcag tgaagggcag attcaccatt tcccgggaca acgccaagaa ctccttgtac 240

cttcaaatga actccctccg cgcggaagat accgcaatct actactgcgc tcgggccact 300

tacaagaggg aactgcgcta ctactacggg atggacgtct ggggccaggg aaccatggtc 360

accgtgtcca gcggaggagg aggatcggga ggaggcggta gcgggggtgg agggtcggag 420

atcgtgatga cccagtcccc cggcactgtg tcgctgtccc ccggcgaacg ggccaccctg 480

tcatgtcggg ccagccagtc agtgtcgtca agcttcctcg cctggtacca gcagaaaccg 540

ggacaagctc cccgcctgct gatctacgga gccagcagcc gggccaccgg tattcctgac 600

cggttctccg gttcggggtc cgggaccgac tttactctga ctatctctcg cctcgagcca 660

gaggactccg ccgtgtatta ctgccagcag taccactcct ccccgtcctg gacgttcgga 720

cagggcacaa ggctggagat taag 744

<210> 161
<211> 744
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 161
gaggtgcagc ttgtggaaac cggtggcgga ctggtgcagc ccggaggaag cctcaggctg 60

tcctgcgccg cgtccggctt caccttctcc tcgtacgcca tgtcctgggt ccgccaggcc 120

cccggaaagg gcctggaatg ggtgtccgcc atctctggaa gcggaggttc cacgtactac 180

gcggacagcg tcaagggaag gttcacaatc tcccgcgata attcgaagaa cactctgtac 240

cttcaaatga acaccctgaa ggccgaggac actgctgtgt actactgcgc acgggccacc 300

tacaagagag agctccggta ctactacgga atggacgtct ggggccaggg aactactgtg 360

accgtgtcct cgggaggggg tggctccggg gggggcggct ccggcggagg cggttccgag 420

attgtgctga cccagtcacc ttcaactctg tcgctgtccc cgggagagag cgctactctg 480

agctgccggg ccagccagtc cgtgtccacc accttcctcg cctggtatca gcagaagccg 540

gggcaggcac cacggctctt gatctacggg tcaagcaaca gagcgaccgg aattcctgac 600

cgcttctcgg ggagcggttc aggcaccgac ttcaccctga ctatccggcg cctggaaccc 660

gaagatttcg ccgtgtatta ctgtcaacag taccactcct cgccgtcctg gacctttggc 720

caaggaacca aagtggaaat caag 744

<210> 162
<211> 717
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 162
gaagtgcagc tcgtggaaac tggaggtgga ctcgtgcagc ctggacggtc gctgcggctg 60

agctgcgctg catccggctt caccttcgac gattatgcca tgcactgggt cagacaggcg 120

ccagggaagg gacttgagtg ggtgtccggt atcagctgga atagcggctc aatcggatac 180

gcggactccg tgaagggaag gttcaccatt tcccgcgaca acgccaagaa ctccctgtac 240

ttgcaaatga acagcctccg ggatgaggac actgccgtgt actactgcgc ccgcgtcgga 300

aaagctgtgc ccgacgtctg gggccaggga accactgtga ccgtgtccag cggcgggggt 360

ggatcgggcg gtggagggtc cggtggaggg ggctcagata ttgtgatgac ccagaccccc 420

tcgtccctgt ccgcctcggt cggcgaccgc gtgactatca catgtagagc ctcgcagagc 480

atctccagct acctgaactg gtatcagcag aagccgggga aggccccgaa gctcctgatc 540

tacgcggcat catcactgca atcgggagtg ccgagccggt tttccgggtc cggctccggc 600

accgacttca cgctgaccat ttcttccctg caacccgagg acttcgccac ttactactgc 660

cagcagtcct actccacccc ttactccttc ggccaaggaa ccaggctgga aatcaag 717

<210> 163
<211> 738
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 163
gaagtgcagc tcgtggagag cgggggagga ttggtgcagc ccggaaggtc cctgcggctc 60

tcctgcactg cgtctggctt caccttcgac gactacgcga tgcactgggt cagacagcgc 120

ccgggaaagg gcctggaatg ggtcgcctca atcaactgga agggaaactc cctggcctat 180

ggcgacagcg tgaagggccg cttcgccatt tcgcgcgaca acgccaagaa caccgtgttt 240

ctgcaaatga attccctgcg gaccgaggat accgctgtgt actactgcgc cagccaccag 300

ggcgtggcat actataacta cgccatggac gtgtggggaa gagggacgct cgtcaccgtg 360

tcctccgggg gcggtggatc gggtggagga ggaagcggtg gcgggggcag cgaaatcgtg 420

ctgactcaga gcccgggaac tctttcactg tccccgggag aacgggccac tctctcgtgc 480

cgggccaccc agtccatcgg ctcctccttc cttgcctggt accagcagag gccaggacag 540

gcgccccgcc tgctgatcta cggtgcttcc caacgcgcca ctggcattcc tgaccggttc 600

agcggcagag ggtcgggaac cgatttcaca ctgaccattt cccgggtgga gcccgaagat 660

tcggcagtct actactgtca gcattacgag tcctcccctt catggacctt cggtcaaggg 720

accaaagtgg agatcaag 738

<210> 164
<211> 723
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 164
gaggtgcagt tggtcgaaag cgggggcggg cttgtgcagc ctggcggatc actgcggctg 60

tcctgcgcgg catcaggctt cacgttttct tcctacgcca tgtcctgggt gcgccaggcc 120

cctggaaagg gactggaatg ggtgtccgcg atttcggggt ccggcgggag cacctactac 180

gccgattccg tgaagggccg cttcactatc tcgcgggaca actccaagaa caccctctac 240

ctccaaatga atagcctgcg ggccgaggat accgccgtct actattgcgc taaggtcgtg 300

cgcgacggaa tggacgtgtg gggacagggt accaccgtga cagtgtcctc ggggggaggc 360

ggtagcggcg gaggaggaag cggtggtgga ggttccgaga ttgtgctgac tcaatcaccc 420

gcgaccctga gcctgtcccc cggcgaaagg gccactctgt cctgtcgggc cagccaatca 480

gtctcctcct cgtacctggc ctggtaccag cagaagccag gacaggctcc gagactcctt 540

atctatggcg catcctcccg cgccaccgga atcccggata ggttctcggg aaacggatcg 600

gggaccgact tcactctcac catctcccgg ctggaaccgg aggacttcgc cgtgtactac 660

tgccagcagt acggcagccc gcctagattc actttcggcc ccggcaccaa agtggacatc 720

aag 723

<210> 165
<211> 726
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 165
gaagtgcagc tgctggagtc cggcggtgga ttggtgcaac cgggggggatc gctcagactg 60

tcctgtgcgg cgtcaggctt caccttctcg agctacgcca tgtcatgggt cagacaggcc 120

cctggaaagg gtctggaatg ggtgtccgcc atttccggga gcgggggatc tacatactac 180

gccgatagcg tgaagggccg cttcaccatt tcccgggaca actccaagaa cactctctat 240

ctgcaaatga actccctccg cgctgaggac actgccgtgt actactgcgc caaaatccct 300

cagaccggca ccttcgacta ctggggacag gggactctgg tcaccgtcag cagcggtggc 360

ggaggttcgg ggggaggagg aagcggcggc ggagggtccg agattgtgct gacccagtca 420

cccggcactt tgtccctgtc gcctggagaa agggccaccc tttcctgccg ggcatcccaa 480

tccgtgtcct cctcgtacct ggcctggtac cagcagaggc ccggacaggc cccacggctt 540

ctgatctacg gagcaagcag ccgcgcgacc ggtatcccgg accggttttc gggctcgggc 600

tcaggaactg acttcaccct caccatctcc cgcctggaac ccgaagattt cgctgtgtat 660

tactgccagc actacggcag ctccccgtcc tggacgttcg gccagggaac tcggctggag 720

atcaag 726

<210> 166
<211> 744
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 166
gaagtgcaac tggtggaaac cggtggagga ctcgtgcagc ctggcggcag cctccggctg 60

agctgcgccg cttcgggatt cacctttcc tcctacgcga tgtcttgggt cagacaggcc 120

cccggaaagg ggctggaatg ggtgtcagcc atctccggct ccggcggatc aacgtactac 180

gccgactccg tgaaaggccg gttcaccatg tcgcgcgaga atgacaagaa ctccgtgttc 240

ctgcaaatga actccctgag ggtggaggac accggagtgt actattgtgc gcgcgccaac 300

tacaagagag agctgcggta ctactacgga atggacgtct ggggacaggg aactatggtg 360

accgtgtcat ccggtggagg gggaagcggc ggtggaggca gcgggggcgg gggttcagaa 420

attgtcatga cccagtcccc gggaactctt tccctctccc ccggggaatc cgcgactttg 480

tcctgccggg ccagccagcg cgtggcctcg aactacctcg catggtacca gcataagcca 540

ggccaagccc cttccctgct gatttccggg gctagcagcc gcgccactgg cgtgccggat 600

aggttctcgg gaagcggctc gggtaccgat ttcaccctgg caatctcgcg gctggaaccg 660

gaggattcgg ccgtgtacta ctgccagcac tatgactcat ccccctcctg gacattcgga 720

cagggcacca aggtcgagat caag 744

<210> 167
<211> 732
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 167
gaagtgcagc tgctcgaaac cggtggaggg ctggtgcagc caggggctc cctgaggctt 60

tcatgcgccg ctagcggatt ctccttctcc tcttacgcca tgtcgtgggt ccgccaagcc 120

cctggaaaag gcctggaatg ggtgtccgcg atttccggga gcggaggttc gacctattac 180

gccgactccg tgaagggccg ctttaccatc tcccgggata actccaagaa cactctgtac 240

ctccaaatga actcgctgag agccgaggac accgccgtgt attactgcgc gaaggcgctg 300

gtcggcgcga ctggggcatt cgacatctgg ggacagggaa ctcttgtgac cgtgtcgagc 360

ggaggcggcg gctccggcgg aggagggagc gggggcggtg gttccgaaat cgtgttgact 420

cagtccccgg gaaccctgag cttgtcaccc ggggagcggg ccactctctc ctgtcgcgcc 480

tcccaatcgc tctcatccaa tttcctggcc tggtaccagc agaagcccgg acaggccccg 540

ggcctgctca tctacggcgc ttcaaactgg gcaacgggaa cccctgatcg gttcagcgga 600

agcggatcgg gtactgactt taccctgacc atcaccagac tggaaccgga ggacttcgcc 660

gtgtactact gccagtacta cggcacctcc cccatgtaca cattcggaca gggtaccaag 720

gtcgagatta ag 732

<210> 168
<211> 733
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 168
gaagtgcagc tgcttgagag cggtggaggt ctggtgcagc ccgggggatc actgcgcctg 60

tcctgtgccg cgtccggttt cactttctcc tcgtacgcca tgtcgtgggt cagacaggca 120

ccgggaaagg gactggaatg ggtgtcagcc atttcgggtt cgggggcag cacctactac 180

gctgactccg tgaagggccg gttcaccatt tcccgcgaca actccaagaa caccttgtac 240

ctccaaatga actccctgcg ggccgaagat accgccgtgt attactgcgt gctgtggttc 300

ggagagggat tcgacccgtg gggacaagga acactcgtga ctgtgtcatc cggcggaggc 360

ggcagcggtg gcggcggttc cggcggcggc ggatctgaca tcgtgttgac ccagtcccct 420

ctgagcctgc cggtcactcc tggcgaacca gccagcatct cctgccggtc gagccagtcc 480

ctcctgcact ccaatgggta caactacctc gattggtatc tgcaaaagcc gggccagagc 540

ccccagctgc tgatctacct tgggtcaaac cgcgcttccg gggtgcctga tagattctcc 600

gggtccggga gcggaaccga ctttaccctg aaaatctcga gggtggaggc cgaggacgtc 660

ggagtgtact actgcatgca ggcgctccag actcccctga ccttcggagg aggaacgaag 720

gtcgacatca aga 733

<210> 169
<211> 753
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polynucleotide"

<400> 169
caagtgcagc tcgtggagtc aggcggagga ctggtgcagc ccgggggctc cctgagactt 60

tcctgcgcgg catcgggttt taccttctcc tcctatgcta tgtcctgggt gcgccaggcc 120

ccgggaaagg gactggaatg ggtgtccgca atcagcggta gcgggggctc aacatactac 180

gccgactccg tcaagggtcg cttcactatt tcccgggaca actccaagaa taccctgtac 240

ctccaaatga acagcctcag ggccgaggat actgccgtgt actactgcgc caaagtcgga 300

tacgatagct ccggttacta ccgggactac tacggaatgg acgtgtgggg acagggcacc 360

accgtgaccg tgtcaagcgg cggaggcggt tcaggagggg gaggctccgg cggtggaggg 420

tccgaaatcg tcctgactca gtcgcctggc actctgtcgt tgtccccggg ggagcgcgct 480

accctgtcgt gtcgggcgtc gcagtccgtg tcgagctcct acctcgcgtg gtaccagcag 540

aagcccggac aggcccctag acttctgatc tacggcactt cttcacgcgc caccgggatc 600

agcgacaggt tcagcggctc cggctccggg accgacttca ccctgaccat tagccggctg 660

gagcctgaag atttcgccgt gtattactgc caacactacg gaaactcgcc gccaaagttc 720

acgttcggac ccggaaccaa gctggaaatc aag 753

<210> 170
<211> 739
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 170
gaagtccaac tggtggagtc cgggggaggg ctcgtgcagc ccggaggcag ccttcggctg 60

tcgtgcgccg cctccgggtt cacgttctca tcctacgcga tgtcgtgggt cagacaggca 120

ccaggaaagg gactggaatg ggtgtccgcc attagcggct ccggcggtag cacctactat 180

gccgactcag tgaagggaag gttcactatc tcccgcgaca acagcaagaa caccctgtac 240

ctccaaatga actctctgcg ggccgaggat accgcggtgt actattgcgc caagatgggt 300

tggtccagcg gatacttggg agccttcgac atttggggac agggcactac tgtgaccgtg 360

tcctccgggg gtggcggatc gggaggcggc ggctcgggtg gaggggttc cgaaatcgtg 420

ttgacccagt caccgggaac cctctcgctg tccccgggag aacgggctac actgtcatgt 480

agagcgtccc agtccgtggc ttcctcgttc ctggcctggt accagcagaa gccgggacag 540

gcaccccgcc tgctcatcta cggagccagc ggccgggcga ccggcatccc tgaccgcttc 600

tccggttccg gctcgggcac cgactttact ctgaccatta gcaggcttga gcccgaggat 660

tttgccgtgt actactgcca acactacggg gggagccctc gcctgacctt cggaggcgga 720

actaaggtcg atatcaaaa 739

<210> 171
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 171
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
20 25 30

Tyr Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ser Ala Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg His Trp Gln Glu Trp Pro Asp Ala Phe Asp Ile Trp Gly
100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 172
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 172
Gln Val Asn Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Arg Thr Ser
20 25 30

Gly Met Cys Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
35 40 45

Trp Leu Ala Arg Ile Asp Trp Asp Glu Asp Lys Phe Tyr Ser Thr Ser
50 55 60

```
Leu Lys Thr Arg Leu Thr Ile Ser Lys Asp Thr Ser Asp Asn Gln Val
65                  70                  75                  80


Val Leu Arg Met Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
                85                  90                  95


Cys Ala Arg Ser Gly Ala Gly Gly Thr Ser Ala Thr Ala Phe Asp Ile
            100                 105                 110


Trp Gly Pro Gly Thr Met Val Thr Val Ser Ser
        115                 120


<210> 173
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 173
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30


Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Lys Thr Ile Ala Ala Val Tyr Ala Phe Asp Ile Trp Gly Gln Gly
            100                 105                 110


Thr Thr Val Thr Val Ser Ser
        115


<210> 174
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
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<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 174
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Leu Arg Gly Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
100 105 110

Val Thr Val Ser Ser
115

<210> 175
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 175
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Pro Ser Gly Tyr Thr Val Thr Ser His
20 25 30

Tyr Ile His Trp Val Arg Arg Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Met Ile Asn Pro Ser Gly Gly Val Thr Ala Tyr Ser Gln Thr Leu
50 55 60

Gln Gly Arg Val Thr Met Thr Ser Asp Thr Ser Ser Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys

85 90 95

Ala Arg Glu Gly Ser Gly Ser Gly Trp Tyr Phe Asp Phe Trp Gly Arg
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 176
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 176
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
20 25 30

Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Ala Gly Ile Ala Ala Arg Leu Arg Gly Ala Phe Asp Ile
100 105 110

Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 177
<211> 129
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 177
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

```
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
            20                  25                  30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Gly Gly Tyr Gln Leu Leu Arg Trp Asp Val Gly Leu Leu
            100                 105                 110

Arg Ser Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser
        115                 120                 125

Ser
```

<210> 178
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 178

```
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
            20                  25                  30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35                  40                  45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Ser Phe Tyr Ala
    50                  55                  60

Ile Ser Leu Lys Ser Arg Ile Ile Ile Asn Pro Asp Thr Ser Lys Asn
65                  70                  75                  80

Gln Phe Ser Leu Gln Leu Lys Ser Val Thr Pro Glu Asp Thr Ala Val
                85                  90                  95
```

Tyr Tyr Cys Ala Arg Ser Ser Pro Glu Gly Leu Phe Leu Tyr Trp Phe
100 105 110

Asp Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 179
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 179
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Val Glu Gly Ser Gly Ser Leu Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 180
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 180
Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ile Thr Phe Ser Arg Tyr
20 25 30

Pro Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Asp Ser Gly Val Ser Thr Tyr Tyr Ala Asp Ser Ala
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Ser Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Val Thr Arg Ala Gly Ser Glu Ala Ser Asp Ile Trp Gly Gln Gly Thr
100 105 110

Met Val Thr Val Ser Ser
115

<210> 181
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 181
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Arg Ala Thr Tyr Lys Arg Glu Leu Arg Tyr Tyr Tyr Gly Met Asp
100 105 110

Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 182
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 182
Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Thr Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ala Thr Tyr Lys Arg Glu Leu Arg Tyr Tyr Tyr Gly Met Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 183
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 183
Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val Gly Lys Ala Val Pro Asp Val Trp Gly Gln Gly Thr Thr
100 105 110

Val Thr Val Ser Ser
115

<210> 184
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 184
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ala Met His Trp Val Arg Gln Arg Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Ser Ile Asn Trp Lys Gly Asn Ser Leu Ala Tyr Gly Asp Ser Val
50 55 60

Lys Gly Arg Phe Ala Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ser His Gln Gly Val Ala Tyr Tyr Asn Tyr Ala Met Asp Val Trp
100 105 110

Gly Arg Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 185
<211> 117
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 185
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Val Val Arg Asp Gly Met Asp Val Trp Gly Gln Gly Thr Thr
100 105 110

Val Thr Val Ser Ser
115

<210> 186
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 186
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Ile Pro Gln Thr Gly Thr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 187
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 187
Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Met Ser Arg Glu Asn Asp Lys Asn Ser Val Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Gly Val Tyr Tyr Cys
85 90 95

Ala Arg Ala Asn Tyr Lys Arg Glu Leu Arg Tyr Tyr Tyr Gly Met Asp
100 105 110

Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 188
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 188
Glu Val Gln Leu Leu Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Ser Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Ala Leu Val Gly Ala Thr Gly Ala Phe Asp Ile Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> 189
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 189
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Val Leu Trp Phe Gly Glu Gly Phe Asp Pro Trp Gly Gln Gly Thr Leu
            100                 105                 110
```

Val Thr Val Ser Ser
        115

<210> 190
<211> 126
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 190
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Lys Val Gly Tyr Asp Ser Ser Gly Tyr Tyr Arg Asp Tyr Tyr Gly
            100   105   110

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115   120   125

<210> 191
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 191
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Met Gly Trp Ser Ser Gly Tyr Leu Gly Ala Phe Asp Ile Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 192
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 192
Glu Thr Thr Leu Thr Gln Ser Pro Ala Phe Met Ser Ala Thr Pro Gly
1 5 10 15

Asp Lys Val Ile Ile Ser Cys Lys Ala Ser Gln Asp Ile Asp Asp Ala
20 25 30

Met Asn Trp Tyr Gln Gln Lys Pro Gly Glu Ala Pro Leu Phe Ile Ile
35 40 45

Gln Ser Ala Thr Ser Pro Val Pro Gly Ile Pro Pro Arg Phe Ser Gly
50 55 60

Ser Gly Phe Gly Thr Asp Phe Ser Leu Thr Ile Asn Asn Ile Glu Ser
65 70 75 80

Glu Asp Ala Ala Tyr Tyr Phe Cys Leu Gln His Asp Asn Phe Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 193
<211> 107
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 193
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Tyr Asn Asn
20 25 30

Leu Ala Trp Phe Gln Leu Lys Pro Gly Ser Ala Pro Arg Ser Leu Met
35 40 45

Tyr Ala Ala Asn Lys Ser Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Ala Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Tyr Tyr Arg Phe Pro Tyr
85 90 95

Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 194
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 194
Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Glu
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Leu Gln Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 195
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 195
Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Ala Ala Pro Gly Tyr
1 5 10 15

Thr Ala Thr Ile Ser Cys Gly Gly Asn Asn Ile Gly Thr Lys Ser Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu Val Ile Arg
35 40 45

Asp Asp Ser Val Arg Pro Ser Lys Ile Pro Gly Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Met Ala Thr Leu Thr Ile Ser Gly Val Gln Ala Gly
65 70 75 80

Asp Glu Ala Asp Phe Tyr Cys Gln Val Trp Asp Ser Asp Ser Glu His
85 90 95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 196
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 196
Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Gly Leu Ser Lys Lys Tyr Val
20 25 30

Ser Trp Tyr Gln Gln Lys Ala Gly Gln Ser Pro Val Val Leu Ile Ser
35 40 45

Arg Asp Lys Glu Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60

```
Asn Ser Ala Asp Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65                  70                  75                  80


Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Asp Thr Thr Val Val
                85                  90                  95


Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105


<210> 197
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 197
Asp Ile Val Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Ile Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Trp
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Ala Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Val Ala Thr Tyr Tyr Cys Gln Lys Tyr Asn Ser Ala Pro Phe
                85                  90                  95


Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105


<210> 198
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 198
Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1               5                   10                  15
```

Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Gly Ser Lys Ser Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Leu Tyr
35 40 45

Gly Lys Asn Asn Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser
50 55 60

Arg Ser Gly Thr Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Arg Asp Ser Ser Gly Asp His
85 90 95

Leu Arg Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105

<210> 199
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 199
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15

Thr Ile Arg Ile Thr Cys Gln Gly Asp Ser Leu Gly Asn Tyr Tyr Ala
20 25 30

Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Gly Thr Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Ala Ser
50 55 60

Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly His His
85 90 95

Leu Leu Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105

<210> 200
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 200
Glu Ile Val Met Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ala
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Arg Leu Leu
35 40 45

Ile Ser Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Asp Arg Phe Gly
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Gly Ser Ser Phe
85 90 95

Asn Gly Ser Ser Leu Phe Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile
100 105 110

Lys

<210> 201
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 201
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Asn Ser
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Ile Tyr Tyr Cys Gln Gln Phe Gly Thr Ser Ser Gly
85 90 95

Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 202
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 202
Glu Ile Val Met Thr Gln Ser Pro Gly Thr Val Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Ser Ala Val Tyr Tyr Cys Gln Gln Tyr His Ser Ser Pro
85 90 95

Ser Trp Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 203
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 203
Glu Ile Val Leu Thr Gln Ser Pro Ser Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Ser Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Thr Thr
20 25 30

Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu

35 40 45

Ile Tyr Gly Ser Ser Asn Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Arg Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr His Ser Ser Pro
85 90 95

Ser Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 204
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 204
Asp Ile Val Met Thr Gln Thr Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr
85 90 95

Ser Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 205
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 205
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Thr Gln Ser Ile Gly Ser Ser
20 25 30

Phe Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Gln Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Arg Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Val Glu
65 70 75 80

Pro Glu Asp Ser Ala Val Tyr Tyr Cys Gln His Tyr Glu Ser Ser Pro
85 90 95

Ser Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 206
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 206
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Asn Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Pro Pro
85 90 95

Arg Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 207
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 207
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Gly Ser Ser Pro
85 90 95

Ser Trp Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 208
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 208
Glu Ile Val Met Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Ser Ala Thr Leu Ser Cys Arg Ala Ser Gln Arg Val Ala Ser Asn
20 25 30

Tyr Leu Ala Trp Tyr Gln His Lys Pro Gly Gln Ala Pro Ser Leu Leu
35 40 45

Ile Ser Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Ala Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Ser Ala Val Tyr Tyr Cys Gln His Tyr Asp Ser Ser Pro
85 90 95

Ser Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 209
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 209
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Leu Ser Ser Asn
20 25 30

Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Gly Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Asn Trp Ala Thr Gly Thr Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Tyr Tyr Gly Thr Ser Pro
85 90 95

Met Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 210
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 210
Asp Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Asp Ile Lys
100 105 110

<210> 211
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 211
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Thr Ser Ser Arg Ala Thr Gly Ile Ser Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Gly Asn Ser Pro
85 90 95

Pro Lys Phe Thr Phe Gly Pro Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 212
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 212
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ala Ser Ser
20 25 30

Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Gly Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Gly Gly Ser Pro
85 90 95

Arg Leu Thr Phe Gly Gly Gly Thr Lys Val Asp Ile Lys
100 105

<210> 213
<211> 487
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 213
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly
35 40 45

Ser Ile Ser Ser Ser Tyr Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro
50 55 60

Gly Lys Gly Leu Glu Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ser Ala
65 70 75 80

Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr
85 90 95

Ser Lys Asn Gln Phe Ser Leu Arg Leu Ser Ser Val Thr Ala Ala Asp
100 105 110

```
Thr Ala Val Tyr Tyr Cys Ala Arg His Trp Gln Glu Trp Pro Asp Ala
        115                 120                 125

Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Thr Thr
145                 150                 155                 160

Leu Thr Gln Ser Pro Ala Phe Met Ser Ala Thr Pro Gly Asp Lys Val
                165                 170                 175

Ile Ile Ser Cys Lys Ala Ser Gln Asp Ile Asp Asp Ala Met Asn Trp
            180                 185                 190

Tyr Gln Gln Lys Pro Gly Glu Ala Pro Leu Phe Ile Ile Gln Ser Ala
        195                 200                 205

Thr Ser Pro Val Pro Gly Ile Pro Pro Arg Phe Ser Gly Ser Gly Phe
    210                 215                 220

Gly Thr Asp Phe Ser Leu Thr Ile Asn Asn Ile Glu Ser Glu Asp Ala
225                 230                 235                 240

Ala Tyr Tyr Phe Cys Leu Gln His Asp Asn Phe Pro Leu Thr Phe Gly
                245                 250                 255

Gln Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro
            260                 265                 270

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
        275                 280                 285

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
    290                 295                 300

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
305                 310                 315                 320

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
                325                 330                 335

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
            340                 345                 350

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
        355                 360                 365

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
    370                 375                 380
```

```
Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
385                 390                 395                 400

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
                405                 410                 415

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
            420                 425                 430

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
        435                 440                 445

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
    450                 455                 460

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
465                 470                 475                 480

Met Gln Ala Leu Pro Pro Arg
                485
```

<210> 214
<211> 489
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 214

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Gln Val Asn Leu Arg Glu Ser Gly Pro Ala Leu
            20                  25                  30

Val Lys Pro Thr Gln Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe
        35                  40                  45

Ser Leu Arg Thr Ser Gly Met Cys Val Ser Trp Ile Arg Gln Pro Pro
    50                  55                  60

Gly Lys Ala Leu Glu Trp Leu Ala Arg Ile Asp Trp Asp Glu Asp Lys
65                  70                  75                  80

Phe Tyr Ser Thr Ser Leu Lys Thr Arg Leu Thr Ile Ser Lys Asp Thr
                85                  90                  95

Ser Asp Asn Gln Val Val Leu Arg Met Thr Asn Met Asp Pro Ala Asp
            100                 105                 110
```

```
Thr Ala Thr Tyr Tyr Cys Ala Arg Ser Gly Ala Gly Gly Thr Ser Ala
        115                 120                 125

Thr Ala Phe Asp Ile Trp Gly Pro Gly Thr Met Val Thr Val Ser Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp
145                 150                 155                 160

Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
                165                 170                 175

Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Tyr Asn Asn Leu
            180                 185                 190

Ala Trp Phe Gln Leu Lys Pro Gly Ser Ala Pro Arg Ser Leu Met Tyr
        195                 200                 205

Ala Ala Asn Lys Ser Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    210                 215                 220

Ala Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
225                 230                 235                 240

Asp Phe Ala Thr Tyr Tyr Cys Gln His Tyr Tyr Arg Phe Pro Tyr Ser
                245                 250                 255

Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro Ala Pro
            260                 265                 270

Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
        275                 280                 285

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
    290                 295                 300

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
305                 310                 315                 320

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys
                325                 330                 335

Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg
            340                 345                 350

Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro
        355                 360                 365

Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser
    370                 375                 380
```

Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu
385 390 395 400

Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg
405 410 415

Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln
420 425 430

Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
435 440 445

Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp
450 455 460

Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
465 470 475 480

Leu His Met Gln Ala Leu Pro Pro Arg
485

<210> 215
<211> 490
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 215
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
20 25 30

Val Lys Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Thr Phe Ser Ser Tyr Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys
50 55 60

Gly Leu Glu Trp Val Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr
65 70 75 80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
85 90 95

Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Lys Thr Ile Ala Ala Val Tyr Ala Phe Asp

```
        115                 120                 125

Ile Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly
    130                 135                 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr
145                 150                 155                 160

Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Glu Glu Pro Ala Ser Ile
                165                 170                 175

Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr
            180                 185                 190

Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile
        195                 200                 205

Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro Asp Arg Phe Ser Gly
    210                 215                 220

Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala
225                 230                 235                 240

Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala Leu Gln Thr Pro Tyr
                245                 250                 255

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
            340                 345                 350

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
        355                 360                 365

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
    370                 375                 380

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
```

385 390 395 400

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
405 410 415

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
420 425 430

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
435 440 445

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
450 455 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465 470 475 480

Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 216
<211> 484
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 216
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
20 25 30

Val Lys Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Thr Phe Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys
50 55 60

Gly Leu Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr
65 70 75 80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
85 90 95

Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Asp Leu Arg Gly Ala Phe Asp Ile Trp
115 120 125

```
Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Tyr Val Leu Thr Gln Ser
145                 150                 155                 160

Pro Ser Val Ser Ala Ala Pro Gly Tyr Thr Ala Thr Ile Ser Cys Gly
                165                 170                 175

Gly Asn Asn Ile Gly Thr Lys Ser Val His Trp Tyr Gln Gln Lys Pro
            180                 185                 190

Gly Gln Ala Pro Leu Leu Val Ile Arg Asp Asp Ser Val Arg Pro Ser
        195                 200                 205

Lys Ile Pro Gly Arg Phe Ser Gly Ser Asn Ser Gly Asn Met Ala Thr
    210                 215                 220

Leu Thr Ile Ser Gly Val Gln Ala Gly Asp Glu Ala Asp Phe Tyr Cys
225                 230                 235                 240

Gln Val Trp Asp Ser Asp Ser Glu His Val Val Phe Gly Gly Gly Thr
                245                 250                 255

Lys Leu Thr Val Leu Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro
            260                 265                 270

Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys
        275                 280                 285

Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala
    290                 295                 300

Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu
305                 310                 315                 320

Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys
                325                 330                 335

Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr
            340                 345                 350

Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly
        355                 360                 365

Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
    370                 375                 380

Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
385                 390                 395                 400
```

```
Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
                405                 410                 415

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
            420                 425                 430

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
        435                 440                 445

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
    450                 455                 460

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
465                 470                 475                 480

Leu Pro Pro Arg
```

<210> 217
<211> 485
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 217

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Pro Ser Gly Tyr
        35                  40                  45

Thr Val Thr Ser His Tyr Ile His Trp Val Arg Arg Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Met Ile Asn Pro Ser Gly Gly Val Thr Ala
65                  70                  75                  80

Tyr Ser Gln Thr Leu Gln Gly Arg Val Thr Met Thr Ser Asp Thr Ser
                85                  90                  95

Ser Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Met Tyr Tyr Cys Ala Arg Glu Gly Ser Gly Ser Gly Trp Tyr Phe
        115                 120                 125
```

```
Asp Phe Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Tyr Val Leu
145                 150                 155                 160

Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln Thr Ala Ser Ile
                165                 170                 175

Thr Cys Ser Gly Asp Gly Leu Ser Lys Lys Tyr Val Ser Trp Tyr Gln
            180                 185                 190

Gln Lys Ala Gly Gln Ser Pro Val Val Leu Ile Ser Arg Asp Lys Glu
        195                 200                 205

Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Asn Ser Ala Asp
    210                 215                 220

Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met Asp Glu Ala Asp
225                 230                 235                 240

Tyr Tyr Cys Gln Ala Trp Asp Asp Thr Thr Val Val Phe Gly Gly Gly
                245                 250                 255

Thr Lys Leu Thr Val Leu Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr
            260                 265                 270

Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala
        275                 280                 285

Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe
    290                 295                 300

Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
305                 310                 315                 320

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys
                325                 330                 335

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
            340                 345                 350

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
        355                 360                 365

Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
    370                 375                 380

Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
385                 390                 395                 400
```

```
Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
                405                 410                 415

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
            420                 425                 430

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
        435                 440                 445

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
    450                 455                 460

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
465                 470                 475                 480

Ala Leu Pro Pro Arg
                485


<210> 218
<211> 489
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 218
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu
            20                  25                  30

Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly
        35                  40                  45

Ser Ile Ser Ser Gly Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro
    50                  55                  60

Gly Lys Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr
65                  70                  75                  80

Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr
                85                  90                  95

Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp
            100                 105                 110

Thr Ala Val Tyr Tyr Cys Ala Arg Ala Gly Ile Ala Ala Arg Leu Arg
        115                 120                 125
```

```
Gly Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp
145                 150                 155                 160

Ile Val Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly Asp
                165                 170                 175

Arg Val Ile Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Trp Leu
            180                 185                 190

Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile Tyr
        195                 200                 205

Ala Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    210                 215                 220

Gly Ser Gly Ala Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
225                 230                 235                 240

Asp Val Ala Thr Tyr Tyr Cys Gln Lys Tyr Asn Ser Ala Pro Phe Thr
                245                 250                 255

Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Thr Thr Thr Pro Ala Pro
            260                 265                 270

Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
        275                 280                 285

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
    290                 295                 300

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
305                 310                 315                 320

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys
                325                 330                 335

Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg
            340                 345                 350

Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro
        355                 360                 365

Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser
    370                 375                 380

Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu
385                 390                 395                 400
```

Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg
405 410 415

Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln
420 425 430

Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
435 440 445

Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp
450 455 460

Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
465 470 475 480

Leu His Met Gln Ala Leu Pro Pro Arg
485

<210> 219
<211> 497
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 219
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly
35 40 45

Thr Phe Ser Ser Tyr Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn
65 70 75 80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser
85 90 95

Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Arg Gly Gly Tyr Gln Leu Leu Arg Trp
115 120 125

Asp Val Gly Leu Leu Arg Ser Ala Phe Asp Ile Trp Gly Gln Gly Thr

130 135 140

Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145 150 155 160

Gly Gly Gly Gly Ser Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser
165 170 175

Val Ala Pro Gly Gln Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile
180 185 190

Gly Ser Lys Ser Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
195 200 205

Val Leu Val Leu Tyr Gly Lys Asn Asn Arg Pro Ser Gly Val Pro Asp
210 215 220

Arg Phe Ser Gly Ser Arg Ser Gly Thr Thr Ala Ser Leu Thr Ile Thr
225 230 235 240

Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Arg Asp
245 250 255

Ser Ser Gly Asp His Leu Arg Val Phe Gly Thr Gly Thr Lys Val Thr
260 265 270

Val Leu Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr
275 280 285

Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala
290 295 300

Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile
305 310 315 320

Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser
325 330 335

Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr
340 345 350

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
355 360 365

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
370 375 380

Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln
385 390 395 400

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu

405 410 415

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
420 425 430

Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
435 440 445

Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu
450 455 460

Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr
465 470 475 480

Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro
485 490 495

Arg

<210> 220
<211> 492
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 220
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp
35 40 45

Ser Val Ser Ser Asn Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro
50 55 60

Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp
65 70 75 80

Tyr Ser Phe Tyr Ala Ile Ser Leu Lys Ser Arg Ile Ile Ile Asn Pro
85 90 95

Asp Thr Ser Lys Asn Gln Phe Ser Leu Gln Leu Lys Ser Val Thr Pro
100 105 110

Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Ser Ser Pro Glu Gly Leu
115 120 125

```
Phe Leu Tyr Trp Phe Asp Pro Trp Gly Gln Gly Thr Leu Val Thr Val
    130                 135                 140

Ser Ser Gly Gly Asp Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly
                165                 170                 175

Gln Thr Ile Arg Ile Thr Cys Gln Gly Asp Ser Leu Gly Asn Tyr Tyr
            180                 185                 190

Ala Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile
        195                 200                 205

Tyr Gly Thr Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Ala
    210                 215                 220

Ser Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala
225                 230                 235                 240

Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly His
                245                 250                 255

His Leu Leu Phe Gly Thr Gly Thr Lys Val Thr Val Leu Thr Thr Thr
            260                 265                 270

Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro
        275                 280                 285

Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val
    290                 295                 300

His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro
305                 310                 315                 320

Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu
                325                 330                 335

Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
            340                 345                 350

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
        355                 360                 365

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
    370                 375                 380

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu
385                 390                 395                 400
```

```
Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
                405                 410                 415

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
            420                 425                 430

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
        435                 440                 445

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
    450                 455                 460

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
465                 470                 475                 480

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490


<210> 221
<211> 490
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 221
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
            20                  25                  30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
        35                  40                  45

Thr Phe Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr
65                  70                  75                  80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
                85                  90                  95

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Lys Val Glu Gly Ser Gly Ser Leu Asp Tyr
        115                 120                 125
```

```
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met Thr Gln
145                 150                 155                 160

Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser
                165                 170                 175

Cys Arg Ala Ser Gln Ser Val Ser Ser Ala Tyr Leu Ala Trp Tyr Gln
            180                 185                 190

Gln Lys Pro Gly Gln Pro Pro Arg Leu Leu Ile Ser Gly Ala Ser Thr
        195                 200                 205

Arg Ala Thr Gly Ile Pro Asp Arg Phe Gly Gly Ser Gly Ser Gly Thr
    210                 215                 220

Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val
225                 230                 235                 240

Tyr Tyr Cys Gln His Tyr Gly Ser Ser Phe Asn Gly Ser Ser Leu Phe
                245                 250                 255

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
            340                 345                 350

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
        355                 360                 365

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
    370                 375                 380

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
385                 390                 395                 400
```

```
Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                405                 410                 415

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
            420                 425                 430

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
        435                 440                 445

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
    450                 455                 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465                 470                 475                 480

Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490


<210> 222
<211> 485
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 222
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu
            20                  25                  30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ile
        35                  40                  45

Thr Phe Ser Arg Tyr Pro Met Ser Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Val Ser Gly Ile Ser Asp Ser Gly Val Ser Thr Tyr
65                  70                  75                  80

Tyr Ala Asp Ser Ala Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
                85                  90                  95

Lys Asn Thr Leu Phe Leu Gln Met Ser Ser Leu Arg Asp Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Val Thr Arg Ala Gly Ser Glu Ala Ser Asp Ile
        115                 120                 125
```

```
Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln
145                 150                 155                 160

Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser
                165                 170                 175

Cys Arg Ala Ser Gln Ser Val Ser Asn Ser Leu Ala Trp Tyr Gln Gln
            180                 185                 190

Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser Ser Arg
        195                 200                 205

Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
    210                 215                 220

Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Ile Tyr
225                 230                 235                 240

Tyr Cys Gln Gln Phe Gly Thr Ser Ser Gly Leu Thr Phe Gly Gly Gly
                245                 250                 255

Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr
            260                 265                 270

Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala
        275                 280                 285

Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe
    290                 295                 300

Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
305                 310                 315                 320

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys
                325                 330                 335

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
            340                 345                 350

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
        355                 360                 365

Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
    370                 375                 380

Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
385                 390                 395                 400
```

```
Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
                405                 410                 415

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
            420                 425                 430

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
        435                 440                 445

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
    450                 455                 460

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
465                 470                 475                 480

Ala Leu Pro Pro Arg
                485

<210> 223
<211> 492
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 223
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu
            20                  25                  30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
        35                  40                  45

Thr Phe Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr
65                  70                  75                  80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
                85                  90                  95

Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110

Ala Ile Tyr Tyr Cys Ala Arg Ala Thr Tyr Lys Arg Glu Leu Arg Tyr
        115                 120                 125

Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser
```

130 135 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145 150 155 160

Glu Ile Val Met Thr Gln Ser Pro Gly Thr Val Ser Leu Ser Pro Gly
165 170 175

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
180 185 190

Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
195 200 205

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
210 215 220

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
225 230 235 240

Pro Glu Asp Ser Ala Val Tyr Tyr Cys Gln Gln Tyr His Ser Ser Pro
245 250 255

Ser Trp Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Thr Thr Thr
260 265 270

Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro
275 280 285

Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val
290 295 300

His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro
305 310 315 320

Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu
325 330 335

Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
340 345 350

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
355 360 365

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
370 375 380

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu
385 390 395 400

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp

405 410 415

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
420 425 430

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
435 440 445

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
450 455 460

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
465 470 475 480

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 224
<211> 492
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 224
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Thr Phe Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys
50 55 60

Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr
65 70 75 80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
85 90 95

Lys Asn Thr Leu Tyr Leu Gln Met Asn Thr Leu Lys Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Ala Thr Tyr Lys Arg Glu Leu Arg Tyr
115 120 125

Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
130 135 140

```
Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145                 150                 155                 160

Glu Ile Val Leu Thr Gln Ser Pro Ser Thr Leu Ser Leu Ser Pro Gly
                165                 170                 175

Glu Ser Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Thr Thr
            180                 185                 190

Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        195                 200                 205

Ile Tyr Gly Ser Ser Asn Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Arg Arg Leu Glu
225                 230                 235                 240

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr His Ser Ser Pro
                245                 250                 255

Ser Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Thr Thr Thr
            260                 265                 270

Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro
        275                 280                 285

Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val
    290                 295                 300

His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro
305                 310                 315                 320

Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu
                325                 330                 335

Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
            340                 345                 350

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
        355                 360                 365

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
    370                 375                 380

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu
385                 390                 395                 400

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
                405                 410                 415
```

```
Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
            420                 425                 430

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
        435                 440                 445

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
    450                 455                 460

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
465                 470                 475                 480

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490


<210> 225
<211> 483
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 225
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu
            20                  25                  30

Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
        35                  40                  45

Thr Phe Asp Asp Tyr Ala Met His Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Val Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly
65                  70                  75                  80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
                85                  90                  95

Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Val Gly Lys Ala Val Pro Asp Val Trp
        115                 120                 125

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140
```

```
Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Thr
145                 150                 155                 160

Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
                165                 170                 175

Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys
            180                 185                 190

Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln
        195                 200                 205

Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
    210                 215                 220

Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
225                 230                 235                 240

Cys Gln Gln Ser Tyr Ser Thr Pro Tyr Ser Phe Gly Gln Gly Thr Arg
                245                 250                 255

Leu Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
            260                 265                 270

Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
        275                 280                 285

Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
    290                 295                 300

Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu
305                 310                 315                 320

Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu
                325                 330                 335

Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln
            340                 345                 350

Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly
        355                 360                 365

Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
    370                 375                 380

Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
385                 390                 395                 400

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
                405                 410                 415
```

```
Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
            420                 425                 430

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
        435                 440                 445

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
    450                 455                 460

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu
465                 470                 475                 480

Pro Pro Arg
```

<210> 226
<211> 490
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 226

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
            20                  25                  30

Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe
        35                  40                  45

Thr Phe Asp Asp Tyr Ala Met His Trp Val Arg Gln Arg Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Val Ala Ser Ile Asn Trp Lys Gly Asn Ser Leu Ala
65                  70                  75                  80

Tyr Gly Asp Ser Val Lys Gly Arg Phe Ala Ile Ser Arg Asp Asn Ala
                85                  90                  95

Lys Asn Thr Val Phe Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Ser His Gln Gly Val Ala Tyr Tyr Asn Tyr
        115                 120                 125

Ala Met Asp Val Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Gly
    130                 135                 140
```

```
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile
145                 150                 155                 160

Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg
                165                 170                 175

Ala Thr Leu Ser Cys Arg Ala Thr Gln Ser Ile Gly Ser Ser Phe Leu
            180                 185                 190

Ala Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
        195                 200                 205

Gly Ala Ser Gln Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Arg
    210                 215                 220

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Val Glu Pro Glu
225                 230                 235                 240

Asp Ser Ala Val Tyr Tyr Cys Gln His Tyr Glu Ser Ser Pro Ser Trp
                245                 250                 255

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
            340                 345                 350

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
        355                 360                 365

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
    370                 375                 380

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
385                 390                 395                 400

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                405                 410                 415
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Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
            420                 425                 430

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
        435                 440                 445

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
    450                 455                 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465                 470                 475                 480

Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490


<210> 227
<211> 485
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 227
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
            20                  25                  30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
        35                  40                  45

Thr Phe Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr
65                  70                  75                  80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
                85                  90                  95

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Lys Val Val Arg Asp Gly Met Asp Val Trp
        115                 120                 125

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser
```

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145                 150                 155                 160

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
                165                 170                 175

Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln
            180                 185                 190

Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg
        195                 200                 205

Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Asn Gly Ser Gly Thr Asp
    210                 215                 220

Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr
225                 230                 235                 240

Tyr Cys Gln Gln Tyr Gly Ser Pro Pro Arg Phe Thr Phe Gly Pro Gly
                245                 250                 255

Thr Lys Val Asp Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr
            260                 265                 270

Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala
        275                 280                 285

Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe
    290                 295                 300

Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
305                 310                 315                 320

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys
                325                 330                 335

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
            340                 345                 350

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
        355                 360                 365

Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
    370                 375                 380

Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
385                 390                 395                 400

Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
                405                 410                 415

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
```

420 425 430

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
435 440 445

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
450 455 460

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
465 470 475 480

Ala Leu Pro Pro Arg
485

<210> 228
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 228
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Thr Phe Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys
50 55 60

Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr
65 70 75 80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
85 90 95

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Lys Ile Pro Gln Thr Gly Thr Phe Asp Tyr
115 120 125

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser
130 135 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln
145 150 155 160

```
Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser
                165                 170                 175

Cys Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln
            180                 185                 190

Gln Arg Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser
        195                 200                 205

Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
    210                 215                 220

Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val
225                 230                 235                 240

Tyr Tyr Cys Gln His Tyr Gly Ser Ser Pro Ser Trp Thr Phe Gly Gln
                245                 250                 255

Gly Thr Arg Leu Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430
```

```
Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480

Gln Ala Leu Pro Pro Arg
                485
```

<210> 229
<211> 492
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 229

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu
            20                  25                  30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
        35                  40                  45

Thr Phe Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr
65                  70                  75                  80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Met Ser Arg Glu Asn Asp
                85                  90                  95

Lys Asn Ser Val Phe Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr
            100                 105                 110

Gly Val Tyr Tyr Cys Ala Arg Ala Asn Tyr Lys Arg Glu Leu Arg Tyr
        115                 120                 125

Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser
    130                 135                 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145                 150                 155                 160
```

```
Glu Ile Val Met Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
                165                 170                 175

Glu Ser Ala Thr Leu Ser Cys Arg Ala Ser Gln Arg Val Ala Ser Asn
            180                 185                 190

Tyr Leu Ala Trp Tyr Gln His Lys Pro Gly Gln Ala Pro Ser Leu Leu
        195                 200                 205

Ile Ser Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Asp Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Ala Ile Ser Arg Leu Glu
225                 230                 235                 240

Pro Glu Asp Ser Ala Val Tyr Tyr Cys Gln His Tyr Asp Ser Ser Pro
                245                 250                 255

Ser Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Thr Thr Thr
            260                 265                 270

Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro
        275                 280                 285

Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val
    290                 295                 300

His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro
305                 310                 315                 320

Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu
                325                 330                 335

Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
            340                 345                 350

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
        355                 360                 365

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
    370                 375                 380

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu
385                 390                 395                 400

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
                405                 410                 415

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
            420                 425                 430
```

```
Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
        435                 440                 445


Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
    450                 455                 460


Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
465                 470                 475                 480


Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490


<210> 230
<211> 488
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 230
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Thr Gly Gly Gly Leu
            20                  25                  30


Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
        35                  40                  45


Ser Phe Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60


Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr
65                  70                  75                  80


Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
                85                  90                  95


Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110


Ala Val Tyr Tyr Cys Ala Lys Ala Leu Val Gly Ala Thr Gly Ala Phe
        115                 120                 125


Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu
145                 150                 155                 160
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```
Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
                165                 170                 175

Leu Ser Cys Arg Ala Ser Gln Ser Leu Ser Ser Asn Phe Leu Ala Trp
            180                 185                 190

Tyr Gln Gln Lys Pro Gly Gln Ala Pro Gly Leu Leu Ile Tyr Gly Ala
        195                 200                 205

Ser Asn Trp Ala Thr Gly Thr Pro Asp Arg Phe Ser Gly Ser Gly Ser
    210                 215                 220

Gly Thr Asp Phe Thr Leu Thr Ile Thr Arg Leu Glu Pro Glu Asp Phe
225                 230                 235                 240

Ala Val Tyr Tyr Cys Gln Tyr Tyr Gly Thr Ser Pro Met Tyr Thr Phe
                245                 250                 255

Gly Gln Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg
            260                 265                 270

Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
        275                 280                 285

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
    290                 295                 300

Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
305                 310                 315                 320

Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg
                325                 330                 335

Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro
            340                 345                 350

Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu
        355                 360                 365

Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala
    370                 375                 380

Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
385                 390                 395                 400

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
                405                 410                 415

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
            420                 425                 430
```

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
435 440 445

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
450 455 460

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
465 470 475 480

His Met Gln Ala Leu Pro Pro Arg
485

<210> 231
<211> 488
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 231
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Thr Phe Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys
50 55 60

Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr
65 70 75 80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
85 90 95

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Val Leu Trp Phe Gly Glu Gly Phe Asp Pro Trp
115 120 125

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Thr Gln Ser
145 150 155 160

Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys

```
                165                 170                 175

Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu Asp
            180                 185                 190

Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu
        195                 200                 205

Gly Ser Asn Arg Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly
    210                 215                 220

Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp
225                 230                 235                 240

Val Gly Val Tyr Tyr Cys Met Gln Ala Leu Gln Thr Pro Leu Thr Phe
                245                 250                 255

Gly Gly Gly Thr Lys Val Asp Ile Lys Thr Thr Thr Pro Ala Pro Arg
            260                 265                 270

Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
        275                 280                 285

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
    290                 295                 300

Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
305                 310                 315                 320

Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg
                325                 330                 335

Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro
            340                 345                 350

Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu
        355                 360                 365

Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala
    370                 375                 380

Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
385                 390                 395                 400

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
                405                 410                 415

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
            420                 425                 430

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
```

435 440 445

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
450 455 460

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
465 470 475 480

His Met Gln Ala Leu Pro Pro Arg
485

<210> 232
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 232
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Thr Phe Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys
50 55 60

Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr
65 70 75 80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
85 90 95

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Lys Val Gly Tyr Asp Ser Ser Gly Tyr Tyr
115 120 125

Arg Asp Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr
130 135 140

Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
145 150 155 160

Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser
165 170 175

```
Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser
            180                 185                 190

Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg
        195                 200                 205

Leu Leu Ile Tyr Gly Thr Ser Ser Arg Ala Thr Gly Ile Ser Asp Arg
    210                 215                 220

Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg
225                 230                 235                 240

Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Gly Asn
                245                 250                 255

Ser Pro Pro Lys Phe Thr Phe Gly Pro Gly Thr Lys Leu Glu Ile Lys
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
    370                 375                 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln
385                 390                 395                 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
                405                 410                 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
            420                 425                 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
        435                 440                 445
```

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
450 455 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465 470 475 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490 495

<210> 233
<211> 490
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 233
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Thr Phe Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys
50 55 60

Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr
65 70 75 80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
85 90 95

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Lys Met Gly Trp Ser Ser Gly Tyr Leu Gly
115 120 125

Ala Phe Asp Ile Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile
145 150 155 160

Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg
165 170 175

```
Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ala Ser Ser Phe Leu
            180                 185                 190

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
        195                 200                 205

Gly Ala Ser Gly Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser
    210                 215                 220

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu
225                 230                 235                 240

Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Gly Gly Ser Pro Arg Leu
                245                 250                 255

Thr Phe Gly Gly Gly Thr Lys Val Asp Ile Lys Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
            340                 345                 350

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
        355                 360                 365

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
    370                 375                 380

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
385                 390                 395                 400

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                405                 410                 415

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
            420                 425                 430

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
        435                 440                 445
```

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
450 455 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465 470 475 480

Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 234
<211> 1461
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 234
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc agcttcagga aagcggaccg ggcctggtca agccatccga aactctctcc 120

ctgacttgca ctgtgtctgg cggttccatc tcatcgtcgt actactactg gggctggatt 180

aggcagccgc ccggaaaggg actggagtgg atcggaagca tctactattc cggctcggcg 240

tactacaacc ctagcctcaa gtcgagagtg accatctccg tggatacctc caagaaccag 300

ttttccctgc gcctgagctc cgtgaccgcc gctgacaccg ccgtgtacta ctgtgctcgg 360

cattggcagg aatggcccga tgccttcgac atttggggcc agggcactat ggtcactgtg 420

tcatccgggg gtggaggcag cgggggagga gggtccgggg ggggaggttc agagacaacc 480

ttgacccagt cacccgcatt catgtccgcc actccgggag acaaggtcat catctcgtgc 540

aaagcgtccc aggatatcga cgatgccatg aattggtacc agcagaagcc tggcgaagcg 600

ccgctgttca ttatccaatc cgcaacctcg cccgtgcctg gaatcccacc gcggttcagc 660

ggcagcggtt tcggaaccga cttttccctg accattaaca acattgagtc cgaggacgcc 720

gcctactact tctgcctgca acacgacaac ttccctctca cgttcggcca gggaaccaag 780

ctggaaatca agaccactac cccagcaccg aggccaccca ccccggctcc taccatcgcc 840

tcccagcctc tgtccctgcg tccggaggca tgtagacccg cagctggtgg ggccgtgcat 900

acccggggtc ttgacttcgc ctgcgatatc tacatttggg cccctctggc tggtacttgc 960

ggggtcctgc tgctttcact cgtgatcact ctttactgta agcgcggtcg gaagaagctg 1020

ctgtacatct ttaagcaacc cttcatgagg cctgtgcaga ctactcaaga ggaggacggc 1080

tgttcatgcc ggttcccaga ggaggaggaa ggcggctgcg aactgcgcgt gaaattcagc 1140

cgcagcgcag atgctccagc ctacaagcag gggcagaacc agctctacaa cgaactcaat 1200

cttggtcgga gagaggagta cgacgtgctg gacaagcgga gaggacggga cccagaaatg 1260

ggcgggaagc cgcgcagaaa gaatccccaa gagggcctgt acaacgagct ccaaaaggat 1320

aagatggcag aagcctatag cgagattggt atgaaagggg aacgcagaag aggcaaaggc 1380

cacgacggac tgtaccaggg actcagcacc gccaccaagg acacctatga cgctcttcac 1440

atgcaggccc tgccgcctcg g 1461

<210> 235
<211> 1467
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 235
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtca atctgcgcga atccggcccc gccttggtca agcctaccca gaccctcact 120

ctgacctgta ctttctccgg cttctccctg cggacttccg ggatgtgcgt gtcctggatc 180

agacagcctc cgggaaaggc cctggagtgg ctcgctcgca ttgactggga tgaggacaag 240

ttctactcca cctcactcaa gaccaggctg accatcagca aagatacctc tgacaaccaa 300

gtggtgctcc gcatgaccaa catggaccca gccgacactg ccacttacta ctgcgcgagg 360

agcggagcgg gcggaacctc cgccaccgcc ttcgatattt ggggcccggg taccatggtc 420

accgtgtcaa gcggaggagg ggggtccggg ggcggcggtt ccgggggagg cggatcggac 480

attcagatga ctcagtcacc atcgtccctg agcgctagcg tgggcgacag agtgacaatc 540

acttgccggg catcccagga catctataac aaccttgcgt ggttccagct gaagcctggt 600

tccgcaccgc ggtcacttat gtacgccgcc aacaagagcc agtcgggagt gccgtcccgg 660

ttttccggtt cggcctcggg aactgacttc accctgacga tctccagcct gcaacccgag 720

gatttcgcca cctactactg ccagcactac taccgctttc cctactcgtt cggacaggga 780

accaagctgg aaatcaagac cactacccca gcaccgaggc cacccacccc ggctcctacc 840

atcgcctccc agcctctgtc cctgcgtccg gaggcatgta gacccgcagc tggtggggcc 900

gtgcataccc ggggtcttga cttcgcctgc gatatctaca tttgggcccc tctggctggt 960

acttgcgggg tcctgctgct ttcactcgtg atcactcttt actgtaagcg cggtcggaag 1020

aagctgctgt acatctttaa gcaacccttc atgaggcctg tgcagactac tcaagaggag 1080

gacggctgtt catgccggtt cccagaggag gaggaaggcg gctgcgaact gcgcgtgaaa 1140

ttcagccgca gcgcagatgc tccagcctac aagcaggggc agaaccagct ctacaacgaa 1200

ctcaatcttg gtcggagaga ggagtacgac gtgctggaca agcggagagg acgggaccca 1260

gaaatgggcg ggaagccgcg cagaaagaat ccccaagagg gcctgtacaa cgagctccaa 1320

aaggataaga tggcagaagc ctatagcgag attggtatga aaggggaacg cagaagaggc 1380

aaaggccacg acggactgta ccagggactc agcaccgcca ccaaggacac ctatgacgct 1440

cttcacatgc aggccctgcc gcctcgg 1467

<210> 236
<211> 1470
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 236
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agcttgtcga atccgggggg ggactggtca agccgggcgg atcactgaga 120

ctgtcctgcg ccgcgagcgg cttcacgttc tcctcctact ccatgaactg ggtccgccaa 180

gcccccggga agggactgga atgggtgtcc tctatctcct cgtcgtcgtc ctacatctac 240

tacgccgact ccgtgaaggg aagattcacc atttcccgcg acaacgcaaa gaactcactg 300

tacttgcaaa tgaactcact ccgggccgaa gatactgctg tgtactattg cgccaagact 360

attgccgccg tctacgcttt cgacatctgg ggccagggaa ccaccgtgac tgtgtcgtcc 420

ggtggtggtg gctcgggcgg aggaggaagc ggcggcgggg ggtccgagat tgtgctgacc 480

cagtcgccac tgagcctccc tgtgaccccc gaggaacccg ccagcatcag ctgccggtcc 540

agccagtccc tgctccactc caacggatac aattacctcg attggtacct tcagaagcct 600

ggacaaagcc cgcagctgct catctacttg ggatcaaacc gcgcgtcagg agtgcctgac 660

cggttctccg gctcgggcag cggtaccgat ttcaccctga aaatctccag ggtggaggca 720

gaggacgtgg gagtgtatta ctgtatgcag gcgctgcaga ctccgtacac atttgggcag 780

ggcaccaagc tggagatcaa gaccactacc ccagcaccga ggccacccac cccggctcct 840

accatcgcct cccagcctct gtccctgcgt ccggaggcat gtagacccgc agctggtggg 900

gccgtgcata cccggggtct tgacttcgcc tgcgatatct acatttgggc ccctctggct 960

ggtacttgcg gggtcctgct gctttcactc gtgatcactc tttactgtaa gcgcggtcgg 1020

aagaagctgc tgtacatctt taagcaaccc ttcatgaggc ctgtgcagac tactcaagag 1080

gaggacggct gttcatgccg gttcccagag gaggaggaag gcggctgcga actgcgcgtg 1140

aaattcagcc gcagcgcaga tgctccagcc tacaagcagg ggcagaacca gctctacaac 1200

gaactcaatc ttggtcggag agaggagtac gacgtgctgg acaagcggag aggacgggac 1260

ccagaaatgg gcgggaagcc gcgcagaaag aatccccaag agggcctgta caacgagctc 1320

caaaaggata agatggcaga agcctatagc gagattggta tgaaagggga acgcagaaga 1380

ggcaaaggcc acgacggact gtaccaggga ctcagcaccg ccaccaagga cacctatgac 1440

gctcttcaca tgcaggccct gccgcctcgg 1470

<210> 237
<211> 1452
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 237
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtcc agctcgtgga gtccggcgga ggccttgtga agcctggagg ttcgctgaga 120

ctgtcctgcg ccgcctccgg cttcaccttc tccgactact acatgtcctg gatcagacag 180

gccccgggaa agggcctgga atgggtgtcc tacatctcgt catcgggcag cactatctac 240

tacgcggact cagtgaaggg gcggttcacc atttcccggg ataacgcgaa gaactcgctg 300

tatctgcaaa tgaactcact gagggccgag gacaccgccg tgtactactg cgcccgcgat 360

ctccgcgggg catttgacat ctggggacag ggaaccatgg tcacagtgtc cagcggaggg 420

ggaggatcgg gtggcggagg ttccgggggt ggaggctcct cctacgtgct gactcagagc 480

ccaagcgtca gcgctgcgcc cggttacacg gcaaccatct cctgtggcgg aaacaacatt 540

gggaccaagt ctgtgcactg gtatcagcag aagccgggcc aagctcccct gttggtgatc 600

cgcgatgact ccgtgcggcc tagcaaaatt ccgggacggt tctccggctc caacagcggc 660

aatatggcca ctctcaccat ctcgggagtg caggccggag atgaagccga cttctactgc 720

caagtctggg actcagactc cgagcatgtg gtgttcgggg gcggaaccaa gctgactgtg 780

ctcaccacta ccccagcacc gaggccaccc accccggctc ctaccatcgc ctcccagcct 840

ctgtccctgc gtccggaggc atgtagaccc gcagctggtg gggccgtgca tacccggggt 900

cttgacttcg cctgcgatat ctacatttgg gcccctctgg ctggtacttg cggggtcctg 960

ctgctttcac tcgtgatcac tctttactgt aagcgcggtc ggaagaagct gctgtacatc 1020

tttaagcaac ccttcatgag gcctgtgcag actactcaag aggaggacgg ctgttcatgc 1080

cggttcccag aggaggagga aggcggctgc gaactgcgcg tgaaattcag ccgcagcgca 1140

gatgctccag cctacaagca ggggcagaac cagctctaca acgaactcaa tcttggtcgg 1200

agagaggagt acgacgtgct ggacaagcgg agaggacggg acccagaaat gggcgggaag 1260

ccgcgcagaa agaatcccca agagggcctg tacaacgagc tccaaaagga taagatggca 1320

gaagcctata gcgagattgg tatgaaaggg gaacgcagaa gaggcaaagg ccacgacgga 1380

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ctgccgcctc gg 1452

<210> 238
<211> 1455
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 238

atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc agctggtgca gagcggggcc gaagtcaaga agccgggagc ctccgtgaaa 120

gtgtcctgca agccttcggg atacaccgtg acctcccact acattcattg ggtccgccgc 180

gcccccggcc aaggactcga gtggatgggc atgatcaacc ctagcggcgg agtgaccgcg 240

tacagccaga cgctgcaggg acgcgtgact atgacctcgg atacctcctc ctccaccgtc 300

tatatggaac tgtccagcct gcggtccgag gataccgcca tgtactactg cgcccgggaa 360

ggatcaggct ccgggtggta tttcgacttc tggggaagag gcaccctcgt gactgtgtca 420

tctgggggag ggggttccgg tggtggcgga tcgggaggag gcggttcatc ctacgtgctg 480

acccagccac cctccgtgtc cgtgagcccc ggccagactg catcgattac atgtagcggc 540

gacggcctct ccaagaaata cgtgtcgtgg taccagcaga aggccggaca gagcccggtg 600

gtgctgatct caagagataa ggagcggcct agcggaatcc cggacaggtt ctcgggttcc 660

aactccgcgg acactgctac tctgaccatc tcggggaccc aggctatgga cgaagccgat 720

tactactgcc aagcctggga cgacactact gtcgtgtttg gaggggcac caagttgacc 780

gtccttacca ctaccccagc accgaggcca cccaccccgg ctcctaccat cgcctcccag 840

cctctgtccc tgcgtccgga ggcatgtaga cccgcagctg gtggggccgt gcatacccgg 900

ggtcttgact tcgcctgcga tatctacatt tgggcccctc tggctggtac ttgcggggtc 960

ctgctgcttt cactcgtgat cactctttac tgtaagcgcg gtcggaagaa gctgctgtac 1020

atctttaagc aacccttcat gaggcctgtg cagactactc aagaggagga cggctgttca 1080

tgccggttcc cagaggagga ggaaggcggc tgcgaactgc gcgtgaaatt cagccgcagc 1140

gcagatgctc cagcctacaa gcaggggcag aaccagctct acaacgaact caatcttggt 1200

cggagagagg agtacgacgt gctggacaag cggagaggac gggacccaga aatgggcggg 1260

aagccgcgca gaaagaatcc ccaagagggc ctgtacaacg agctccaaaa ggataagatg 1320

gcagaagcct atagcgagat tggtatgaaa ggggaacgca gaagaggcaa aggccacgac 1380

ggactgtacc agggactcag caccgccacc aaggacacct atgacgctct tcacatgcag 1440

gccctgccgc ctcgg 1455

<210> 239
<211> 1467
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 239
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc agcttcagga gagcggcccg ggactcgtga agccgtccca gaccctgtcc 120

ctgacttgca ccgtgtcggg aggaagcatc tcgagcggag gctactattg gtcgtggatt 180

cggcagcacc ctggaaaggg cctggaatgg atcggctaca tctactactc cggctcgacc 240

tactacaacc catcgctgaa gtccagagtg acaatctcag tggacacgtc caagaatcag 300

ttcagcctga agctctcttc cgtgactgcg gccgacaccg ccgtgtacta ctgcgcacgc 360

gctggaattg ccgcccggct gaggggtgcc ttcgacattt ggggacaggg caccatggtc 420

accgtgtcct ccggcggcgg aggttccggg ggtggaggct caggaggagg ggggtccgac 480

atcgtcatga ctcagtcgcc ctcaagcgtc agcgcgtccg tcggggacag agtgatcatc 540

acctgtcggg cgtcccaggg aattcgcaac tggctggcct ggtatcagca gaagcccgga 600

aaggccccca acctgttgat ctacgccgcc tcaaacctcc aatccggggt gccgagccgc 660

ttcagcggct ccggttcggg tgccgatttc actctgacca tctcctccct gcaacctgaa 720

gatgtggcta cctactactg ccaaaagtac aactccgcac cttttacttt cggaccgggg 780

accaaagtgg acattaagac cactacccca gcaccgaggc cacccacccc ggctcctacc 840

atcgcctccc agcctctgtc cctgcgtccg gaggcatgta gacccgcagc tggtggggcc 900

gtgcataccc ggggtcttga cttcgcctgc gatatctaca tttgggcccc tctggctggt 960

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aagctgctgt acatctttaa gcaacccttc atgaggcctg tgcagactac tcaagaggag 1080

gacggctgtt catgccggtt cccagaggag gaggaaggcg gctgcgaact gcgcgtgaaa 1140

ttcagccgca gcgcagatgc tccagcctac aagcaggggc agaaccagct ctacaacgaa 1200

ctcaatcttg gtcggagaga ggagtacgac gtgctggaca agcggagagg acgggaccca 1260

gaaatgggcg ggaagccgcg cagaaagaat ccccaagagg gcctgtacaa cgagctccaa 1320

aaggataaga tggcagaagc ctatagcgag attggtatga aaggggaacg cagaagaggc 1380

aaaggccacg acggactgta ccagggactc agcaccgcca ccaaggacac ctatgacgct 1440

cttcacatgc aggccctgcc gcctcgg 1467

<210> 240
<211> 1491
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 240
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc agctggtcca gtcgggcgcc gaggtcaaga agcccgggag ctctgtgaaa 120

gtgtcctgca aggcctccgg gggcaccttt agctcctacg ccatctcctg ggtccgccaa 180

gcaccgggtc aaggcctgga gtggatgggg ggaattatcc ctatcttcgg cactgccaac 240

tacgcccaga agttccaggg acgcgtgacc attaccgcgg acgaatccac ctccaccgct 300

tatatggagc tgtccagctt gcgctcggaa gataccgccg tgtactactg cgcccggagg 360

ggtggatacc agctgctgag atgggacgtg ggcctcctgc ggtcggcgtt cgacatctgg 420

ggccagggca ctatggtcac tgtgtccagc ggaggaggcg gatcgggagg cggcggatca 480

gggggaggcg gttccagcta cgtgcttact caacccccct cggtgtccgt ggccccggga 540

cagaccgcca gaatcacttg cggaggaaac aacattgggt ccaagagcgt gcattggtac 600

cagcagaagc caggacaggc ccctgtgctg gtgctctacg ggaagaacaa tcggcccagc 660

ggagtgccgg acaggttctc gggttcacgc tccggtacaa ccgcttcact gactatcacc 720

ggggcccagg cagaggatga agcggactac tactgttcct cccgggattc atccggcgac 780

cacctccggg tgttcggaac cggaacgaag gtcaccgtgc tgaccactac cccagcaccg 840

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tacatttggg cccctctggc tggtacttgc ggggtcctgc tgctttcact cgtgatcact 1020

ctttactgta agcgcggtcg gaagaagctg ctgtacatct ttaagcaacc cttcatgagg 1080

cctgtgcaga ctactcaaga ggaggacggc tgttcatgcc ggttcccaga ggaggaggaa 1140

ggcggctgcg aactgcgcgt gaaattcagc cgcagcgcag atgctccagc ctacaagcag 1200

gggcagaacc agctctacaa cgaactcaat cttggtcgga gagaggagta cgacgtgctg 1260

gacaagcgga gaggacggga cccagaaatg ggcgggaagc cgcgcagaaa gaatccccaa 1320

gagggcctgt acaacgagct ccaaaaggat aagatggcag aagcctatag cgagattggt 1380

atgaaagggg aacgcagaag aggcaaaggc cacgacggac tgtaccaggg actcagcacc 1440

gccaccaagg acacctatga cgctcttcac atgcaggccc tgccgcctcg g 1491

<210> 241
<211> 1476
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 241
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agctccaaca gtcaggaccg gggctcgtga agccatccca gaccctgtcc 120

ctgacttgtg ccatctcggg agatagcgtg tcatcgaact ccgccgcctg gaactggatt 180

cggcagagcc cgtcccgcgg actggagtgg cttggaagga cctactaccg gtccaagtgg 240

tactctttct acgcgatctc gctgaagtcc cgcattatca ttaaccctga tacctccaag 300

aatcagttct ccctccaact gaaatccgtc acccccgagg acacagcagt gtattactgc 360

gcacggagca gccccgaagg actgttcctg tattggtttg acccctgggg ccaggggact 420

cttgtgaccg tgtcgagcgg cggagatggg tccggtggcg gtggttcggg gggcggcgga 480

tcatcatccg aactgaccca ggacccggct gtgtccgtgg cgctgggaca aaccatccgc 540

attacgtgcc agggagactc cctgggcaac tactacgcca cttggtacca gcagaagccg 600

ggccaagccc ctgtgttggt catctacggg accaacaaca gaccttccgg catccccgac 660

cggttcagcg cttcgtcctc cggcaacact gccagcctga ccatcactgg agcgcaggcc 720

gaagatgagg ccgactacta ctgcaacagc agagactcct cgggtcatca cctcttgttc 780

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cgggacccag aaatgggcgg gaagccgcgc agaaagaatc cccaagaggg cctgtacaac 1320

gagctccaaa aggataagat ggcagaagcc tatagcgaga ttggtatgaa aggggaacgc 1380

agaagaggca aaggccacga cggactgtac cagggactca gcaccgccac caaggacacc 1440

tatgacgctc ttcacatgca ggccctgccg cctcgg 1476

<210> 242
<211> 1470
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 242
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agctcgtgga gtcaggaggc ggcctggtcc agccgggagg gtcccttaga 120

ctgtcatgcg ccgcaagcgg attcactttc tcctcctatg ccatgagctg ggtccgccaa 180

gcccccggaa agggactgga atgggtgtcc gccatctcgg ggtctggagg ctcaacttac 240

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agccctggta ctctgagcct ttcgccggga gaaagggcca ccctgtcctg ccgcgcttcc 540

caatccgtgt cctccgcgta cttggcgtgg taccagcaga agccgggaca gccccctcgg 600

ctgctgatca gcggggccag cacccgggca accggaatcc cagacagatt cgggggttcc 660

ggcagcggca cagatttcac cctgactatt tcgaggttgg agcccgagga ctttgcggtg 720

tattactgtc agcactacgg gtcgtccttt aatggctcca gcctgttcac gttcggacag 780

gggacccgcc tggaaatcaa gaccactacc ccagcaccga ggccacccac cccggctcct 840

accatcgcct cccagcctct gtccctgcgt ccggaggcat gtagacccgc agctggtggg 900

gccgtgcata cccggggtct tgacttcgcc tgcgatatct acatttgggc ccctctggct 960

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gaactcaatc ttggtcggag agaggagtac gacgtgctgg acaagcggag aggacgggac 1260

ccagaaatgg gcgggaagcc gcgcagaaag aatccccaag agggcctgta caacgagctc 1320

caaaaggata agatggcaga agcctatagc gagattggta tgaaagggga acgcagaaga 1380

ggcaaaggcc acgacggact gtaccaggga ctcagcaccg ccaccaagga cacctatgac 1440

gctcttcaca tgcaggccct gccgcctcgg 1470

<210> 243
<211> 1455
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 243
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aactggtgga aaccggtggc ggcctggtgc agcctggagg atcattgagg 120

ctgtcatgcg cggccagcgg tattaccttc tcccggtacc ccatgtcctg ggtcagacag 180

gccccgggga aagggcttga atgggtgtcc gggatctcgg actccggtgt cagcacttac 240

tacgccgact ccgccaaggg acgcttcacc atttcccggg acaactcgaa gaacaccctg 300

ttcctccaaa tgagctccct ccgggacgag gatactgcag tgtactactg cgtgacccgc 360

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tccccggcca ccctctcgct gagccctgga gaaagggcaa ccttgtcctg tcgcgcgagc 540

cagtccgtga gcaactccct ggcctggtac cagcagaagc ccggacaggc tccgagactt 600

ctgatctacg acgcttcgag ccgggccact ggaatccccg accgcttttc ggggtccggc 660

tcaggaaccg atttcaccct gacaatctca cggctggagc cagaggattt cgccatctat 720

tactgccagc agttcggtac ttcctccggc ctgactttcg gaggcggcac gaagctcgaa 780

atcaagacca ctaccccagc accgaggcca cccaccccgg ctcctaccat cgcctcccag 840

cctctgtccc tgcgtccgga ggcatgtaga cccgcagctg gtggggccgt gcatacccgg 900

ggtcttgact tcgcctgcga tatctacatt tgggcccctc tggctggtac ttgcggggtc 960

ctgctgcttt cactcgtgat cactctttac tgtaagcgcg gtcggaagaa gctgctgtac 1020

atctttaagc aacccttcat gaggcctgtg cagactactc aagaggagga cggctgttca 1080

tgccggttcc cagaggagga ggaaggcggc tgcgaactgc gcgtgaaatt cagccgcagc 1140

gcagatgctc cagcctacaa gcaggggcag aaccagctct acaacgaact caatcttggt 1200

cggagagagg agtacgacgt gctggacaag cggagaggac gggacccaga aatgggcggg 1260

aagccgcgca gaaagaatcc ccaagagggc ctgtacaacg agctccaaaa ggataagatg 1320

gcagaagcct atagcgagat tggtatgaaa ggggaacgca gaagaggcaa aggccacgac 1380

ggactgtacc agggactcag caccgccacc aaggacacct atgacgctct tcacatgcag 1440

gccctgccgc ctcgg 1455

<210> 244
<211> 1476
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 244
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ccccaagtgc agctcgtgga atcgggtggc ggactggtgc agccgggggg ctcacttaga 120

ctgtcctgcg cggccagcgg attcactttc tcctcctacg ccatgtcctg ggtcagacag 180

gcccctggaa agggcctgga atgggtgtcc gcaatcagcg gcagcggcgg ctcgacctat 240

tacgcggatt cagtgaaggg cagattcacc atttcccggg acaacgccaa gaactccttg 300

taccttcaaa tgaactccct ccgcgcggaa gataccgcaa tctactactg cgctcgggcc 360

acttacaaga gggaactgcg ctactactac gggatggacg tctggggcca gggaaccatg 420

gtcaccgtgt ccagcggagg aggaggatcg ggaggaggcg gtagcggggg tggagggtcg 480

gagatcgtga tgacccagtc ccccggcact gtgtcgctgt cccccggcga acgggccacc 540

ctgtcatgtc gggccagcca gtcagtgtcg tcaagcttcc tcgcctggta ccagcagaaa 600

ccgggacaag ctccccgcct gctgatctac ggagccagca gccgggccac cggtattcct 660

gaccggttct ccggttcggg gtccgggacc gactttactc tgactatctc tcgcctcgag 720

ccagaggact ccgccgtgta ttactgccag cagtaccact cctccccgtc ctggacgttc 780

ggacagggca caaggctgga gattaagacc actaccccag caccgaggcc acccaccccg 840

gctcctacca tcgcctccca gcctctgtcc ctgcgtccgg aggcatgtag acccgcagct 900

ggtggggccg tgcatacccg gggtcttgac ttcgcctgcg atatctacat ttgggccccc 960

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ggtcggaaga agctgctgta catctttaag caacccttca tgaggcctgt gcagactact 1080

caagaggagg acggctgttc atgccggttc ccagaggagg aggaaggcgg ctgcgaactg 1140

cgcgtgaaat tcagccgcag cgcagatgct ccagcctaca agcaggggca gaaccagctc 1200

tacaacgaac tcaatcttgg tcggagagag gagtacgacg tgctggacaa gcggagagga 1260

cgggacccag aaatgggcgg gaagccgcgc agaaagaatc cccaagaggg cctgtacaac 1320

gagctccaaa aggataagat ggcagaagcc tatagcgaga ttggtatgaa aggggaacgc 1380

agaagaggca aaggccacga cggactgtac cagggactca gcaccgccac caaggacacc 1440

tatgacgctc ttcacatgca ggccctgccg cctcgg 1476

<210> 245
<211> 1476
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 245
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cccgaggtgc agcttgtgga aaccggtggc ggactggtgc agcccggagg aagcctcagg 120

ctgtcctgcg ccgcgtccgg cttcaccttc tcctcgtacg ccatgtcctg ggtccgccag 180

gcccccggaa agggcctgga atgggtgtcc gccatctctg gaagcggagg ttccacgtac 240

tacgcggaca gcgtcaaggg aaggttcaca atctcccgcg ataattcgaa gaacactctg 300

taccttcaaa tgaacaccct gaaggccgag gacactgctg tgtactactg cgcacgggcc 360

acctacaaga gagagctccg gtactactac ggaatggacg tctggggcca gggaactact 420

gtgaccgtgt cctcgggagg gggtggctcc gggggggggcg gctccggcgg aggcggttcc 480

gagattgtgc tgacccagtc accttcaact ctgtcgctgt ccccgggaga gagcgctact 540

ctgagctgcc gggccagcca gtccgtgtcc accaccttcc tcgcctggta tcagcagaag 600

ccggggcagg caccacggct cttgatctac gggtcaagca acagagcgac cggaattcct 660

gaccgcttct cggggagcgg ttcaggcacc gacttcaccc tgactatccg gcgcctggaa 720

cccgaagatt tcgccgtgta ttactgtcaa cagtaccact cctcgccgtc ctggaccttt 780

ggccaaggaa ccaaagtgga aatcaagacc actaccccag caccgaggcc acccaccccg 840

gctcctacca tcgcctccca gcctctgtcc ctgcgtccgg aggcatgtag acccgcagct 900

ggtggggccg tgcatacccg gggtcttgac ttcgcctgcg atatctacat ttgggccccc 960

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ggtcggaaga agctgctgta catctttaag caacccttca tgaggcctgt gcagactact 1080

caagaggagg acggctgttc atgccggttc ccagaggagg aggaaggcgg ctgcgaactg 1140

cgcgtgaaat tcagccgcag cgcagatgct ccagcctaca agcaggggca gaaccagctc 1200

tacaacgaac tcaatcttgg tcggagagag gagtacgacg tgctggacaa gcggagagga 1260

cgggacccag aaatgggcgg gaagccgcgc agaaagaatc cccaagaggg cctgtacaac 1320

gagctccaaa aggataagat ggcagaagcc tatagcgaga ttggtatgaa aggggaacgc 1380

agaagaggca aaggccacga cggactgtac cagggactca gcaccgccac caaggacacc 1440

tatgacgctc ttcacatgca ggccctgccg cctcgg 1476

<210> 246
<211> 1449
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 246
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cccgaagtgc agctcgtgga aactggaggt ggactcgtgc agcctggacg gtcgctgcgg 120

ctgagctgcg ctgcatccgg cttcaccttc gacgattatg ccatgcactg ggtcagacag 180

gcgccaggga agggacttga gtgggtgtcc ggtatcagct ggaatagcgg ctcaatcgga 240

tacgcggact ccgtgaaggg aaggttcacc atttcccgcg acaacgccaa gaactccctg 300

tacttgcaaa tgaacagcct ccgggatgag gacactgccg tgtactactg cgcccgcgtc 360

ggaaaagctg tgcccgacgt ctggggccag ggaaccactg tgaccgtgtc cagcggcggg 420

ggtggatcgg gcggtggagg gtccggtgga gggggctcag atattgtgat gacccagacc 480

ccctcgtccc tgtccgcctc ggtcggcgac cgcgtgacta tcacatgtag agcctcgcag 540

agcatctcca gctacctgaa ctggtatcag cagaagccgg ggaaggcccc gaagctcctg 600

atctacgcgg catcatcact gcaatcggga gtgccgagcc ggttttccgg gtccggctcc 660

ggcaccgact tcacgctgac catttcttcc ctgcaacccg aggacttcgc cacttactac 720

tgccagcagt cctactccac cccttactcc ttcggccaag gaaccaggct ggaaatcaag 780

accactaccc cagcaccgag gccacccacc ccggctccta ccatcgcctc ccagcctctg 840

tccctgcgtc cggaggcatg tagacccgca gctggtgggg ccgtgcatac ccggggtctt 900

gacttcgcct gcgatatcta catttgggcc cctctggctg gtacttgcgg ggtcctgctg 960

ctttcactcg tgatcactct ttactgtaag cgcggtcgga agaagctgct gtacatcttt 1020

aagcaaccct tcatgaggcc tgtgcagact actcaagagg aggacggctg ttcatgccgg 1080

ttcccagagg aggaggaagg cggctgcgaa ctgcgcgtga aattcagccg cagcgcagat 1140

gctccagcct acaagcaggg gcagaaccag ctctacaacg aactcaatct tggtcggaga 1200

gaggagtacg acgtgctgga caagcggaga ggacgggacc cagaaatggg cgggaagccg 1260

cgcagaaaga atccccaaga gggcctgtac aacgagctcc aaaaggataa gatggcagaa 1320

gcctatagcg agattggtat gaaaggggaa cgcagaagag gcaaaggcca cgacggactg 1380

taccagggac tcagcaccgc caccaaggac acctatgacg ctcttcacat gcaggccctg 1440

ccgcctcgg 1449

<210> 247
<211> 1470
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 247
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cccgaagtgc agctcgtgga gagcggggga ggattggtgc agcccggaag gtccctgcgg 120

ctctcctgca ctgcgtctgg cttcaccttc gacgactacg cgatgcactg ggtcagacag 180

cgcccgggaa agggcctgga atgggtcgcc tcaatcaact ggaagggaaa ctccctggcc 240

tatggcgaca gcgtgaaggg ccgcttcgcc atttcgcgcg acaacgccaa gaacaccgtg 300

tttctgcaaa tgaattccct gcggaccgag gataccgctg tgtactactg cgccagccac 360

cagggcgtgg catactataa ctacgccatg gacgtgtggg gaagagggac gctcgtcacc 420

gtgtcctccg ggggcggtgg atcgggtgga ggaggaagcg gtggcggggg cagcgaaatc 480

gtgctgactc agagcccggg aactctttca ctgtccccgg gagaacgggc cactctctcg 540

tgccgggcca cccagtccat cggctcctcc ttccttgcct ggtaccagca gaggccagga 600

caggcgcccc gcctgctgat ctacggtgct tcccaacgcg ccactggcat tcctgaccgg 660

ttcagcggca gagggtcggg aaccgatttc acactgacca tttcccgggt ggagcccgaa 720

gattcggcag tctactactg tcagcattac gagtcctccc cttcatggac cttcggtcaa 780

gggaccaaag tggagatcaa gaccactacc ccagcaccga ggccacccac cccggctcct 840

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ggtacttgcg gggtcctgct gctttcactc gtgatcactc tttactgtaa gcgcggtcgg 1020

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gaggacggct gttcatgccg gttcccagag gaggaggaag gcggctgcga actgcgcgtg 1140

aaattcagcc gcagcgcaga tgctccagcc tacaagcagg ggcagaacca gctctacaac 1200

gaactcaatc ttggtcggag agaggagtac gacgtgctgg acaagcggag aggacgggac 1260

ccagaaatgg gcgggaagcc gcgcagaaag aatccccaag agggcctgta caacgagctc 1320

caaaaggata agatggcaga agcctatagc gagattggta tgaaagggga acgcagaaga 1380

ggcaaaggcc acgacggact gtaccaggga ctcagcaccg ccaccaagga cacctatgac 1440

gctcttcaca tgcaggccct gccgcctcgg 1470

<210> 248
<211> 1455
<212> DNA

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 248
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cccgaggtgc agttggtcga aagcgggggc gggcttgtgc agcctggcgg atcactgcgg 120

ctgtcctgcg cggcatcagg cttcacgttt tcttcctacg ccatgtcctg ggtgcgccag 180

gcccctggaa agggactgga atgggtgtcc gcgatttcgg ggtccggcgg gagcacctac 240

tacgccgatt ccgtgaaggg ccgcttcact atctcgcggg acaactccaa gaacaccctc 300

tacctccaaa tgaatagcct gcgggccgag gataccgccg tctactattg cgctaaggtc 360

gtgcgcgacg gaatggacgt gtggggacag ggtaccaccg tgacagtgtc ctcgggggga 420

ggcggtagcg gcggaggagg aagcggtggt ggaggttccg agattgtgct gactcaatca 480

cccgcgaccc tgagcctgtc ccccggcgaa agggccactc tgtcctgtcg ggccagccaa 540

tcagtctcct cctcgtacct ggcctggtac cagcagaagc caggacaggc tccgagactc 600

cttatctatg gcgcatcctc ccgcgccacc ggaatcccgg ataggttctc gggaaacgga 660

tcggggaccg acttcactct caccatctcc cggctggaac cggaggactt cgccgtgtac 720

tactgccagc agtacggcag cccgcctaga ttcactttcg gccccggcac caaagtggac 780

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ctgctgcttt cactcgtgat cactctttac tgtaagcgcg gtcggaagaa gctgctgtac 1020

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tgccggttcc cagaggagga ggaaggcggc tgcgaactgc gcgtgaaatt cagccgcagc 1140

gcagatgctc cagcctacaa gcaggggcag aaccagctct acaacgaact caatcttggt 1200

cggagagagg agtacgacgt gctggacaag cggagaggac gggacccaga aatgggcggg 1260

aagccgcgca gaaagaatcc ccaagagggc ctgtacaacg agctccaaaa ggataagatg 1320

gcagaagcct atagcgagat tggtatgaaa ggggaacgca gaagaggcaa aggccacgac 1380

ggactgtacc agggactcag caccgccacc aaggacacct atgacgctct tcacatgcag 1440

gccctgccgc ctcgg 1455

<210> 249
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 249
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cccgaagtgc agctgctgga gtccggcggt ggattggtgc aaccgggggg atcgctcaga 120

ctgtcctgtg cggcgtcagg cttcaccttc tcgagctacg ccatgtcatg ggtcagacag 180

gcccctggaa agggtctgga atgggtgtcc gccatttccg ggagcggggg atctacatac 240

tacgccgata gcgtgaaggg ccgcttcacc atttcccggg acaactccaa gaacactctc 300

tatctgcaaa tgaactccct ccgcgctgag gacactgccg tgtactactg cgccaaaatc 360

cctcagaccg gcaccttcga ctactgggga caggggactc tggtcaccgt cagcagcggt 420

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tcacccggca ctttgtccct gtcgcctgga gaaagggcca ccctttcctg ccgggcatcc 540

caatccgtgt cctcctcgta cctggcctgg taccagcaga ggcccggaca ggccccacgg 600

cttctgatct acggagcaag cagccgcgcg accggtatcc cggaccggtt ttcgggctcg 660

ggctcaggaa ctgacttcac cctcaccatc tcccgcctgg aacccgaaga tttcgctgtg 720

tattactgcc agcactacgg cagctccccg tcctggacgt tcggccaggg aactcggctg 780

gagatcaaga ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

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tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

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ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

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caggccctgc cgcctcgg 1458

<210> 250
<211> 1476
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 250
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aactggtgga aaccggtgga ggactcgtgc agcctggcgg cagcctccgg 120

ctgagctgcg ccgcttcggg attcaccttt tcctcctacg cgatgtcttg ggtcagacag 180

gcccccggaa aggggctgga atgggtgtca gccatctccg gctccggcgg atcaacgtac 240

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gagctccaaa aggataagat ggcagaagcc tatagcgaga ttggtatgaa aggggaacgc 1380

agaagaggca aaggccacga cggactgtac cagggactca gcaccgccac caaggacacc 1440

tatgacgctc ttcacatgca ggccctgccg cctcgg 1476

<210> 251
<211> 1464
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 251
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cccgaagtgc agctgctcga aaccggtgga gggctggtgc agccaggggg ctccctgagg 120

ctttcatgcg ccgctagcgg attctccttc tcctcttacg ccatgtcgtg ggtccgccaa 180

gcccctggaa aaggcctgga atgggtgtcc gcgatttccg ggagcggagg ttcgacctat 240

tacgccgact ccgtgaaggg ccgctttacc atctcccggg ataactccaa gaacactctg 300

tacctccaaa tgaactcgct gagagccgag gacaccgccg tgtattactg cgcgaaggcg 360

ctggtcggcg cgactggggc attcgacatc tggggacagg gaactcttgt gaccgtgtcg 420

agcggaggcg gcggctccgg cggaggaggg agcgggggcg gtggttccga aatcgtgttg 480

actcagtccc cgggaaccct gagcttgtca cccggggagc gggccactct ctcctgtcgc 540

gcctcccaat cgctctcatc caatttcctg gcctggtacc agcagaagcc cggacaggcc 600

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ggaagcggat cgggtactga ctttaccctg accatcacca gactggaacc ggaggacttc 720

gccgtgtact actgccagta ctacggcacc tcccccatgt acacattcgg acagggtacc 780

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atgggcggga agccgcgcag aaagaatccc caagagggcc tgtacaacga gctccaaaag 1320

gataagatgg cagaagccta tagcgagatt ggtatgaaag gggaacgcag aagaggcaaa 1380

ggccacgacg gactgtacca gggactcagc accgccacca aggacaccta tgacgctctt 1440

cacatgcagg ccctgccgcc tcgg 1464

<210> 252
<211> 1464
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 252
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agctgcttga gagcggtgga ggtctggtgc agcccggggg atcactgcgc 120

ctgtcctgtg ccgcgtccgg tttcactttc tcctcgtacg ccatgtcgtg ggtcagacag 180

gcaccgggaa agggactgga atgggtgtca gccatttcgg gttcgggggg cagcacctac 240

tacgctgact ccgtgaaggg ccggttcacc atttcccgcg acaactccaa gaacaccttg 300

tacctccaaa tgaactccct gcgggccgaa gataccgccg tgtattactg cgtgctgtgg 360

ttcggagagg gattcgaccc gtggggacaa ggaacactcg tgactgtgtc atccggcgga 420

ggcggcagcg gtggcggcgg ttccggcggc ggcggatctg acatcgtgtt gacccagtcc 480

cctctgagcc tgccggtcac tcctggcgaa ccagccagca tctcctgccg gtcgagccag 540

tccctcctgc actccaatgg gtacaactac ctcgattggt atctgcaaaa gccgggccag 600

agcccccagc tgctgatcta ccttgggtca aaccgcgctt ccggggtgcc tgatagattc 660

tccgggtccg ggagcggaac cgactttacc ctgaaaatct cgagggtgga ggccgaggac 720

gtcggagtgt actactgcat gcaggcgctc cagactcccc tgaccttcgg aggaggaacg 780

aaggtcgaca tcaagaccac taccccagca ccgaggccac ccaccccggc tcctaccatc 840

gcctcccagc ctctgtccct gcgtccggag gcatgtagac ccgcagctgg tggggccgtg 900

catacccggg gtcttgactt cgcctgcgat atctacattt gggcccctct ggctggtact 960

tgcggggtcc tgctgctttc actcgtgatc actctttact gtaagcgcgg tcggaagaag 1020

ctgctgtaca tctttaagca acccttcatg aggcctgtgc agactactca agaggaggac 1080

ggctgttcat gccggttccc agaggaggag gaaggcggct gcgaactgcg cgtgaaattc 1140

agccgcagcg cagatgctcc agcctacaag caggggcaga accagctcta caacgaactc 1200

aatcttggtc ggagagagga gtacgacgtg ctggacaagc ggagaggacg ggacccagaa 1260

atgggcggga agccgcgcag aaagaatccc caagagggcc tgtacaacga gctccaaaag 1320

gataagatgg cagaagccta tagcgagatt ggtatgaaag gggaacgcag aagaggcaaa 1380

ggccacgacg gactgtacca gggactcagc accgccacca aggacaccta tgacgctctt 1440

cacatgcagg ccctgccgcc tcgg 1464

<210> 253
<211> 1485
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 253
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc agctcgtgga gtcaggcgga ggactggtgc agcccggggg ctccctgaga 120

ctttcctgcg cggcatcggg ttttaccttc tcctcctatg ctatgtcctg ggtgcgccag 180

gccccgggaa agggactgga atgggtgtcc gcaatcagcg gtagcggggg ctcaacatac 240

tacgccgact ccgtcaaggg tcgcttcact atttcccggg acaactccaa gaataccctg 300

tacctccaaa tgaacagcct cagggccgag gatactgccg tgtactactg cgccaaagtc 360

ggatacgata gctccggtta ctaccgggac tactacggaa tggacgtgtg gggacagggc 420

accaccgtga ccgtgtcaag cggcggaggc ggttcaggag ggggaggctc cggcggtgga 480

gggtccgaaa tcgtcctgac tcagtcgcct ggcactctgt cgttgtcccc gggggagcgc 540

gctaccctgt cgtgtcgggc gtcgcagtcc gtgtcgagct cctacctcgc gtggtaccag 600

cagaagcccg gacaggcccc tagacttctg atctacggca cttcttcacg cgccaccggg 660

atcagcgaca ggttcagcgg ctccggctcc gggaccgact tcaccctgac cattagccgg 720

ctggagcctg aagatttcgc cgtgtattac tgccaacact acggaaactc gccgccaaag 780

ttcacgttcg gacccggaac caagctggaa atcaagacca ctaccccagc accgaggcca 840

cccaccccgg ctcctaccat cgcctcccag cctctgtccc tgcgtccgga ggcatgtaga 900

cccgcagctg gtggggccgt gcatacccgg ggtcttgact tcgcctgcga tatctacatt 960

tgggcccctc tggctggtac ttgcggggtc ctgctgcttt cactcgtgat cactctttac 1020

tgtaagcgcg gtcggaagaa gctgctgtac atctttaagc aacccttcat gaggcctgtg 1080

cagactactc aagaggagga cggctgttca tgccggttcc cagaggagga ggaaggcggc 1140

tgcgaactgc gcgtgaaatt cagccgcagc gcagatgctc agcctacaa gcaggggcag 1200

aaccagctct acaacgaact caatcttggt cggagagagg agtacgacgt gctggacaag 1260

cggagaggac gggacccaga aatgggcggg aagccgcgca gaaagaatcc ccaagagggc 1320

ctgtacaacg agctccaaaa ggataagatg gcagaagcct atagcgagat tggtatgaaa 1380

ggggaacgca gaagaggcaa aggccacgac ggactgtacc agggactcag caccgccacc 1440

aaggacacct atgacgctct tcacatgcag gccctgccgc ctcgg 1485

<210> 254
<211> 1470
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 254
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtcc aactggtgga gtccggggga gggctcgtgc agcccggagg cagccttcgg 120

ctgtcgtgcg ccgcctccgg gttcacgttc tcatcctacg cgatgtcgtg ggtcagacag 180

gcaccaggaa agggactgga atgggtgtcc gccattagcg gctccggcgg tagcacctac 240

tatgccgact cagtgaaggg aaggttcact atctcccgcg acaacagcaa gaacaccctg 300

tacctccaaa tgaactctct gcgggccgag gataccgcgg tgtactattg cgccaagatg 360

ggttggtcca gcggatactt gggagccttc gacatttggg gacagggcac tactgtgacc 420

gtgtcctccg ggggtggcgg atcgggaggc ggcggctcgg gtggaggggg ttccgaaatc 480

gtgttgaccc agtcaccggg aaccctctcg ctgtccccgg gagaacgggc tacactgtca 540

tgtagagcgt cccagtccgt ggcttcctcg ttcctggcct ggtaccagca gaagccggga 600

caggcacccc gcctgctcat ctacggagcc agcggccggg cgaccggcat ccctgaccgc 660

ttctccggtt ccggctcggg caccgacttt actctgacca ttagcaggct tgagcccgag 720

gattttgccg tgtactactg ccaacactac ggggggagcc ctcgcctgac cttcggaggc 780

ggaactaagg tcgatatcaa aaccactacc ccagcaccga ggccacccac cccggctcct 840

accatcgcct cccagcctct gtccctgcgt ccggaggcat gtagacccgc agctggtggg 900

gccgtgcata cccggggtct tgacttcgcc tgcgatatct acatttgggc ccctctggct 960

ggtacttgcg gggtcctgct gctttcactc gtgatcactc tttactgtaa gcgcggtcgg 1020

aagaagctgc tgtacatctt taagcaaccc ttcatgaggc ctgtgcagac tactcaagag 1080

gaggacggct gttcatgccg gttcccagag gaggaggaag gcggctgcga actgcgcgtg 1140

aaattcagcc gcagcgcaga tgctccagcc tacaagcagg ggcagaacca gctctacaac 1200

gaactcaatc ttggtcggag agaggagtac gacgtgctgg acaagcggag aggacgggac 1260

ccagaaatgg gcgggaagcc gcgcagaaag aatccccaag agggcctgta caacgagctc 1320

caaaaggata agatggcaga agcctatagc gagattggta tgaaagggga acgcagaaga 1380

ggcaaaggcc acgacggact gtaccaggga ctcagcaccg ccaccaagga cacctatgac 1440

gctcttcaca tgcaggccct gccgcctcgg 1470

<210> 255
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 255
Gln Ile Gln Leu Val Gln Ser Gly Pro Asp Leu Lys Lys Pro Gly Glu
1 5 10 15

Thr Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Phe
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Phe Lys Trp Met
35 40 45

Ala Trp Ile Asn Thr Tyr Thr Gly Glu Ser Tyr Phe Ala Asp Asp Phe
50 55 60

Lys Gly Arg Phe Ala Phe Ser Val Glu Thr Ser Ala Thr Thr Ala Tyr
65 70 75 80

Leu Gln Ile Asn Asn Leu Lys Thr Glu Asp Thr Ala Thr Tyr Phe Cys
85 90 95

Ala Arg Gly Glu Ile Tyr Tyr Gly Tyr Asp Gly Gly Phe Ala Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ala
115 120

<210> 256
<211> 117

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 256
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Ser Ile Asn Trp Val Lys Arg Ala Pro Gly Lys Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Glu Thr Arg Glu Pro Ala Tyr Ala Tyr Asp Phe
50 55 60

Arg Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Asn Asn Leu Lys Tyr Glu Asp Thr Ala Thr Tyr Phe Cys
85 90 95

Ala Leu Asp Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
100 105 110

Val Thr Val Ser Ser
115

<210> 257
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 257
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Arg His Tyr
20 25 30

Ser Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
35 40 45

Gly Arg Ile Asn Thr Glu Ser Gly Val Pro Ile Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Phe Ala Phe Ser Val Glu Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Leu Val Ile Asn Asn Leu Lys Asp Glu Asp Thr Ala Ser Tyr Phe Cys
85 90 95

Ser Asn Asp Tyr Leu Tyr Ser Leu Asp Phe Trp Gly Gln Gly Thr Ala
100 105 110

Leu Thr Val Ser Ser
115

<210> 258
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 258
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr His Tyr
20 25 30

Ser Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
35 40 45

Gly Arg Ile Asn Thr Glu Thr Gly Glu Pro Leu Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Leu Val Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Phe Phe Cys
85 90 95

Ser Asn Asp Tyr Leu Tyr Ser Cys Asp Tyr Trp Gly Gln Gly Thr Thr
100 105 110

Leu Thr Val Ser Ser
115

<210> 259
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 259
Asp Val Val Met Thr Gln Ser His Arg Phe Met Ser Thr Ser Val Gly
1   5   10   15

Asp Arg Val Ser Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
            20   25   30

Val Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
        35   40   45

Phe Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
    50   55   60

Ser Gly Ser Gly Ala Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
65   70   75   80

Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Trp
                85   90   95

Thr Phe Gly Gly Gly Thr Lys Leu Asp Ile Lys
            100   105

<210> 260
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 260
Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Met Ser Leu Gly
1   5   10   15

Lys Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Ser Val Ile
            20   25   30

Gly Ala His Leu Ile His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35   40   45

Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu Thr Gly Val Pro Ala
    50   55   60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp
65   70   75   80

Pro Val Glu Glu Asp Asp Val Ala Ile Tyr Ser Cys Leu Gln Ser Arg
                85   90   95

Ile Phe Pro Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100   105   110

<210> 261
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 261
Asp Ile Val Leu Thr Gln Ser Pro Pro Ser Leu Ala Met Ser Leu Gly
1 5 10 15

Lys Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Thr Ile Leu
20 25 30

Gly Ser His Leu Ile Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Thr Leu Leu Ile Gln Leu Ala Ser Asn Val Gln Thr Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asp
65 70 75 80

Pro Val Glu Glu Asp Asp Val Ala Val Tyr Tyr Cys Leu Gln Ser Arg
85 90 95

Thr Ile Pro Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 262
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 262
Asp Ile Val Leu Thr Gln Ser Pro Pro Ser Leu Ala Met Ser Leu Gly
1 5 10 15

Lys Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Thr Ile Leu
20 25 30

Gly Ser His Leu Ile Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Thr Leu Leu Ile Gln Leu Ala Ser Asn Val Gln Thr Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asp

65 70 75 80

Pro Val Glu Glu Asp Asp Val Ala Val Tyr Tyr Cys Leu Gln Ser Arg
85 90 95

Thr Ile Pro Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 263
<211> 244
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 263
Gln Ile Gln Leu Val Gln Ser Gly Pro Asp Leu Lys Lys Pro Gly Glu
1 5 10 15

Thr Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Phe
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Phe Lys Trp Met
35 40 45

Ala Trp Ile Asn Thr Tyr Thr Gly Glu Ser Tyr Phe Ala Asp Asp Phe
50 55 60

Lys Gly Arg Phe Ala Phe Ser Val Glu Thr Ser Ala Thr Thr Ala Tyr
65 70 75 80

Leu Gln Ile Asn Asn Leu Lys Thr Glu Asp Thr Ala Thr Tyr Phe Cys
85 90 95

Ala Arg Gly Glu Ile Tyr Tyr Gly Tyr Asp Gly Gly Phe Ala Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ala Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Val Met Thr Gln Ser
130 135 140

His Arg Phe Met Ser Thr Ser Val Gly Asp Arg Val Ser Ile Thr Cys
145 150 155 160

Arg Ala Ser Gln Asp Val Asn Thr Ala Val Ser Trp Tyr Gln Gln Lys
165 170 175

Pro Gly Gln Ser Pro Lys Leu Leu Ile Phe Ser Ala Ser Tyr Arg Tyr
180 185 190

```
Thr Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Ala Asp Phe
        195                 200                 205

Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr
    210                 215                 220

Cys Gln Gln His Tyr Ser Thr Pro Trp Thr Phe Gly Gly Gly Thr Lys
225                 230                 235                 240

Leu Asp Ile Lys
```

<210> 264
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 264

```
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1               5                   10                  15

Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30

Ser Ile Asn Trp Val Lys Arg Ala Pro Gly Lys Gly Leu Lys Trp Met
        35                  40                  45

Gly Trp Ile Asn Thr Glu Thr Arg Glu Pro Ala Tyr Ala Tyr Asp Phe
    50                  55                  60

Arg Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Ile Asn Asn Leu Lys Tyr Glu Asp Thr Ala Thr Tyr Phe Cys
                85                  90                  95

Ala Leu Asp Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys
    130                 135                 140

Lys Pro Gly Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr
145                 150                 155                 160
```

```
Phe Thr Asp Tyr Ser Ile Asn Trp Val Lys Arg Ala Pro Gly Lys Gly
                165                 170                 175

Leu Lys Trp Met Gly Trp Ile Asn Thr Glu Thr Arg Glu Pro Ala Tyr
            180                 185                 190

Ala Tyr Asp Phe Arg Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala
        195                 200                 205

Ser Thr Ala Tyr Leu Gln Ile Asn Asn Leu Lys Tyr Glu Asp Thr Ala
    210                 215                 220

Thr Tyr Phe Cys Ala Leu Asp Tyr Ser Tyr Ala Met Asp Tyr Trp Gly
225                 230                 235                 240

Gln Gly Thr Ser Val Thr Val Ser Ser
                245


<210> 265
<211> 243
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 265
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1               5                   10                  15

Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Arg His Tyr
            20                  25                  30

Ser Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
        35                  40                  45

Gly Arg Ile Asn Thr Glu Ser Gly Val Pro Ile Tyr Ala Asp Asp Phe
    50                  55                  60

Lys Gly Arg Phe Ala Phe Ser Val Glu Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Leu Val Ile Asn Asn Leu Lys Asp Glu Asp Thr Ala Ser Tyr Phe Cys
                85                  90                  95

Ser Asn Asp Tyr Leu Tyr Ser Leu Asp Phe Trp Gly Gln Gly Thr Ala
            100                 105                 110

Leu Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125
```

```
Gly Gly Gly Ser Asp Ile Val Leu Thr Gln Ser Pro Pro Ser Leu Ala
    130                 135                 140

Met Ser Leu Gly Lys Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser
145                 150                 155                 160

Val Thr Ile Leu Gly Ser His Leu Ile Tyr Trp Tyr Gln Gln Lys Pro
                165                 170                 175

Gly Gln Pro Pro Thr Leu Leu Ile Gln Leu Ala Ser Asn Val Gln Thr
            180                 185                 190

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr
        195                 200                 205

Leu Thr Ile Asp Pro Val Glu Glu Asp Asp Val Ala Val Tyr Tyr Cys
    210                 215                 220

Leu Gln Ser Arg Thr Ile Pro Arg Thr Phe Gly Gly Gly Thr Lys Leu
225                 230                 235                 240

Glu Ile Lys
```

<210> 266
<211> 243
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 266

```
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1               5                   10                  15

Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr His Tyr
            20                  25                  30

Ser Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
        35                  40                  45

Gly Arg Ile Asn Thr Glu Thr Gly Glu Pro Leu Tyr Ala Asp Asp Phe
    50                  55                  60

Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Leu Val Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Phe Phe Cys
                85                  90                  95

Ser Asn Asp Tyr Leu Tyr Ser Cys Asp Tyr Trp Gly Gln Gly Thr Thr
```

100 105 110

Leu Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Val Leu Thr Gln Ser Pro Pro Ser Leu Ala
130 135 140

Met Ser Leu Gly Lys Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser
145 150 155 160

Val Thr Ile Leu Gly Ser His Leu Ile Tyr Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Gln Pro Pro Thr Leu Leu Ile Gln Leu Ala Ser Asn Val Gln Thr
180 185 190

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr
195 200 205

Leu Thr Ile Asp Pro Val Glu Glu Asp Asp Val Ala Val Tyr Tyr Cys
210 215 220

Leu Gln Ser Arg Thr Ile Pro Arg Thr Phe Gly Gly Gly Thr Lys Leu
225 230 235 240

Glu Ile Lys

<210> 267
<211> 467
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 267
Gln Ile Gln Leu Val Gln Ser Gly Pro Asp Leu Lys Lys Pro Gly Glu
1 5 10 15

Thr Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Phe
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Phe Lys Trp Met
35 40 45

Ala Trp Ile Asn Thr Tyr Thr Gly Glu Ser Tyr Phe Ala Asp Asp Phe
50 55 60

Lys Gly Arg Phe Ala Phe Ser Val Glu Thr Ser Ala Thr Thr Ala Tyr
65 70 75 80

```
Leu Gln Ile Asn Asn Leu Lys Thr Glu Asp Thr Ala Thr Tyr Phe Cys
                85                  90                  95

Ala Arg Gly Glu Ile Tyr Tyr Gly Tyr Asp Gly Gly Phe Ala Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ala Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Val Met Thr Gln Ser
    130                 135                 140

His Arg Phe Met Ser Thr Ser Val Gly Asp Arg Val Ser Ile Thr Cys
145                 150                 155                 160

Arg Ala Ser Gln Asp Val Asn Thr Ala Val Ser Trp Tyr Gln Gln Lys
                165                 170                 175

Pro Gly Gln Ser Pro Lys Leu Leu Ile Phe Ser Ala Ser Tyr Arg Tyr
            180                 185                 190

Thr Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Ala Asp Phe
        195                 200                 205

Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr
    210                 215                 220

Cys Gln Gln His Tyr Ser Thr Pro Trp Thr Phe Gly Gly Gly Thr Lys
225                 230                 235                 240

Leu Asp Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
                245                 250                 255

Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
            260                 265                 270

Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
        275                 280                 285

Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu
    290                 295                 300

Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu
305                 310                 315                 320

Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln
                325                 330                 335

Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly
            340                 345                 350
```

```
Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
        355                 360                 365

Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
    370                 375                 380

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
385                 390                 395                 400

Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
                405                 410                 415

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
            420                 425                 430

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
        435                 440                 445

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu
    450                 455                 460

Pro Pro Arg
465
```

<210> 268
<211> 472
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 268

```
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1               5                   10                  15

Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30

Ser Ile Asn Trp Val Lys Arg Ala Pro Gly Lys Gly Leu Lys Trp Met
        35                  40                  45

Gly Trp Ile Asn Thr Glu Thr Arg Glu Pro Ala Tyr Ala Tyr Asp Phe
    50                  55                  60

Arg Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Ile Asn Asn Leu Lys Tyr Glu Asp Thr Ala Thr Tyr Phe Cys
                85                  90                  95
```

```
Ala Leu Asp Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys
    130                 135                 140

Lys Pro Gly Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr
145                 150                 155                 160

Phe Thr Asp Tyr Ser Ile Asn Trp Val Lys Arg Ala Pro Gly Lys Gly
                165                 170                 175

Leu Lys Trp Met Gly Trp Ile Asn Thr Glu Thr Arg Glu Pro Ala Tyr
            180                 185                 190

Ala Tyr Asp Phe Arg Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala
        195                 200                 205

Ser Thr Ala Tyr Leu Gln Ile Asn Asn Leu Lys Tyr Glu Asp Thr Ala
    210                 215                 220

Thr Tyr Phe Cys Ala Leu Asp Tyr Ser Tyr Ala Met Asp Tyr Trp Gly
225                 230                 235                 240

Gln Gly Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg
                245                 250                 255

Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
            260                 265                 270

Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
        275                 280                 285

Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
    290                 295                 300

Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg
305                 310                 315                 320

Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro
                325                 330                 335

Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu
            340                 345                 350

Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala
        355                 360                 365
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Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
    370                 375                 380

Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
385                 390                 395                 400

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
                405                 410                 415

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
            420                 425                 430

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
        435                 440                 445

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
    450                 455                 460

His Met Gln Ala Leu Pro Pro Arg
465                 470


<210> 269
<211> 466
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 269
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1               5                   10                  15

Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Arg His Tyr
            20                  25                  30

Ser Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
        35                  40                  45

Gly Arg Ile Asn Thr Glu Ser Gly Val Pro Ile Tyr Ala Asp Asp Phe
    50                  55                  60

Lys Gly Arg Phe Ala Phe Ser Val Glu Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

Leu Val Ile Asn Asn Leu Lys Asp Glu Asp Thr Ala Ser Tyr Phe Cys
                85                  90                  95

Ser Asn Asp Tyr Leu Tyr Ser Leu Asp Phe Trp Gly Gln Gly Thr Ala
            100                 105                 110
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Leu Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Asp Ile Val Leu Thr Gln Ser Pro Pro Ser Leu Ala
    130                 135                 140

Met Ser Leu Gly Lys Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser
145                 150                 155                 160

Val Thr Ile Leu Gly Ser His Leu Ile Tyr Trp Tyr Gln Gln Lys Pro
                165                 170                 175

Gly Gln Pro Pro Thr Leu Leu Ile Gln Leu Ala Ser Asn Val Gln Thr
            180                 185                 190

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr
        195                 200                 205

Leu Thr Ile Asp Pro Val Glu Glu Asp Asp Val Ala Val Tyr Tyr Cys
    210                 215                 220

Leu Gln Ser Arg Thr Ile Pro Arg Thr Phe Gly Gly Gly Thr Lys Leu
225                 230                 235                 240

Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
                245                 250                 255

Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
            260                 265                 270

Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
        275                 280                 285

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
    290                 295                 300

Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu
305                 310                 315                 320

Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
                325                 330                 335

Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys
            340                 345                 350

Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys
        355                 360                 365

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
    370                 375                 380
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Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
385 390 395 400

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
405 410 415

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
420 425 430

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
435 440 445

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
450 455 460

Pro Arg
465

<210> 270
<211> 466
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 270
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr His Tyr
20 25 30

Ser Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
35 40 45

Gly Arg Ile Asn Thr Glu Thr Gly Glu Pro Leu Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Leu Val Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Phe Phe Cys
85 90 95

Ser Asn Asp Tyr Leu Tyr Ser Cys Asp Tyr Trp Gly Gln Gly Thr Thr
100 105 110

Leu Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Val Leu Thr Gln Ser Pro Pro Ser Leu Ala

130 135 140

Met Ser Leu Gly Lys Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser
145 150 155 160

Val Thr Ile Leu Gly Ser His Leu Ile Tyr Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Gln Pro Pro Thr Leu Leu Ile Gln Leu Ala Ser Asn Val Gln Thr
180 185 190

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr
195 200 205

Leu Thr Ile Asp Pro Val Glu Glu Asp Asp Val Ala Val Tyr Tyr Cys
210 215 220

Leu Gln Ser Arg Thr Ile Pro Arg Thr Phe Gly Gly Gly Thr Lys Leu
225 230 235 240

Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
245 250 255

Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
260 265 270

Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
275 280 285

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
290 295 300

Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu
305 310 315 320

Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
325 330 335

Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys
340 345 350

Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys
355 360 365

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
370 375 380

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
385 390 395 400

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu

405 410 415

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
420 425 430

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
435 440 445

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
450 455 460

Pro Arg
465

<210> 271
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 271
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Asn Tyr
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ala Thr Tyr Arg Gly His Ser Asp Thr Tyr Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Ala Ile Tyr Asn Gly Tyr Asp Val Leu Asp Asn Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln
130 135 140

Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val
145 150 155 160

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Thr Ile Thr Cys Ser Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn Trp
                165                 170                 175

Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Tyr Thr
            180                 185                 190

Ser Asn Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe
    210                 215                 220

Ala Thr Tyr Tyr Cys Gln Gln Tyr Arg Lys Leu Pro Trp Thr Phe Gly
225                 230                 235                 240

Gln Gly Thr Lys Leu Glu Ile Lys Arg
                245
```

<210> 272
<211> 747
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 272
caggtgcagc tggtccagag cggcgccgaa gtgaagaagc ccggcagctc cgtgaaagtg 60

agctgcaagg ccagcggcgg caccttcagc aactactgga tgcactgggt gaggcaggcc 120

cccggacagg gcctggagtg gatgggcgcc acctacaggg gccacagcga cacctactac 180

aaccagaagt tcaagggccg ggtgaccatc accgccgaca agagcaccag caccgcctac 240

atggaactga gcagcctcag gagcgaggac accgctgtgt attactgcgc caggggcgcc 300

atctacaacg gctacgacgt gctggacaac tggggccagg gcacactagt gaccgtgtcc 360

agcggtggag gaggtagcgg aggaggcggg agcggtggag gtggctctgg aggtggcgga 420

agcgacatcc agatgaccca gagccctagc tcactgagcg ccagcgtggg cgacagggtg 480

accattacct gctccgccag ccaggacatc agcaactacc tgaactggta ccagcagaag 540

cccggcaagg cccccaagct gctgatctac tacacctcca acctgcactc cggcgtgccc 600

agcaggttca gcggaagcgg cagcggcacc gatttcaccc tgaccatctc cagcctgcag 660

cccgaggact tcgccaccta ctactgccag cagtacagga agctcccctg gactttcggc 720

cagggcacca aactggagat caagcgt 747

<210> 273
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 273
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Tyr Thr Ser Asn Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Arg Lys Leu Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Gly Gly Gly Gly
100 105 110

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
115 120 125

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
130 135 140

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Asn Tyr
145 150 155 160

Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
165 170 175

Gly Ala Thr Tyr Arg Gly His Ser Asp Thr Tyr Tyr Asn Gln Lys Phe
180 185 190

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
195 200 205

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
210 215 220

Ala Arg Gly Ala Ile Tyr Asn Gly Tyr Asp Val Leu Asp Asn Trp Gly
225 230 235 240

Gln Gly Thr Leu Val Thr Val Ser Ser

245

<210> 274
<211> 747
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 274
gacatccaga tgacccagag ccctagctca ctgagcgcca gcgtgggcga cagggtgacc 60

attacctgct ccgccagcca ggacatcagc aactacctga actggtacca gcagaagccc 120

ggcaaggccc ccaagctgct gatctactac acctccaacc tgcactccgg cgtgcccagc 180

aggttcagcg gaagcggcag cggcaccgat ttcaccctga ccatctccag cctgcagccc 240

gaggacttcg ccacctacta ctgccagcag tacaggaagc tcccctggac tttcggccag 300

ggcaccaaac tggagatcaa gcgtggtgga ggaggtagcg gaggaggcgg gagcggtgga 360

ggtggctctg gaggtggcgg aagccaggtg cagctggtcc agagcggcgc cgaagtgaag 420

aagcccggca gctccgtgaa agtgagctgc aaggccagcg gcggcacctt cagcaactac 480

tggatgcact gggtgaggca ggcccccgga cagggcctgg agtggatggg cgccacctac 540

aggggccaca gcgacaccta ctacaaccag aagttcaagg gccgggtgac catcaccgcc 600

gacaagagca ccagcaccgc ctacatggaa ctgagcagcc tcaggagcga ggacaccgct 660

gtgtattact gcgccagggg cgccatctac aacggctacg acgtgctgga caactggggc 720

cagggcacac tagtgaccgt gtccagc 747

<210> 275
<211> 132
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 275
Asp Val Pro Asp Tyr Ala Ser Leu Gly Gly Pro Ser Ser Pro Lys Lys
1 5 10 15

Lys Arg Lys Val Ser Arg Gly Val Gln Val Glu Thr Ile Ser Pro Gly
20 25 30

Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr
35 40 45

Thr Gly Met Leu Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg Asp Arg
50 55 60

Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly
65 70 75 80

Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala Lys Leu
85 90 95

Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile
100 105 110

Ile Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu Lys Leu
115 120 125

Glu Thr Ser Tyr
130

<210> 276
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 276
Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr Phe Pro Lys
1 5 10 15

Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu Glu Asp Gly
20 25 30

Lys Lys Phe Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe Lys Phe Met
35 40 45

Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly Val Ala Gln
50 55 60

Met Ser Val Gly Gln Arg Ala Lys Leu Thr Ile Ser Pro Asp Tyr Ala
65 70 75 80

Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His Ala Thr Leu
85 90 95

Val Phe Asp Val Glu Leu Leu Lys Leu Glu Thr Ser
100 105

<210> 277
<211> 93
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 277
Ile Leu Trp His Glu Met Trp His Glu Gly Leu Glu Glu Ala Ser Arg
1   5   10   15

Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu
            20   25   30

Pro Leu His Ala Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr
        35   40   45

Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp
    50   55   60

Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Thr Gln Ala
65   70   75   80

Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys
                85   90

<210> 278
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 278
Ile Leu Trp His Glu Met Trp His Glu Gly Leu Ile Glu Ala Ser Arg
1   5   10   15

Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu
            20   25   30

Pro Leu His Ala Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr
        35   40   45

Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp
    50   55   60

Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Thr Gln Ala
65   70   75   80

Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys Thr Ser
                85   90   95

<210> 279
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 279
Ile Leu Trp His Glu Met Trp His Glu Gly Leu Leu Glu Ala Ser Arg
1   5   10   15

Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu
            20   25   30

Pro Leu His Ala Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr
        35   40   45

Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp
    50   55   60

Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Thr Gln Ala
65   70   75   80

Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys Thr Ser
                85   90   95

<210> 280
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 280
Ile Leu Trp His Glu Met Trp His Glu Gly Leu Glu Glu Ala Ser Arg
1   5   10   15

Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu
            20   25   30

Pro Leu His Ala Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr
        35   40   45

Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp
    50   55   60

Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Leu Gln Ala
65   70   75   80

Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys Thr Ser
                85   90   95

<210> 281
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<220>
<221> MOD_RES
<222> (12)..(12)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (78)..(78)
<223> Any amino acid

<400> 281
Ile Leu Trp His Glu Met Trp His Glu Gly Leu Xaa Glu Ala Ser Arg
1 5 10 15

Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu
20 25 30

Pro Leu His Ala Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr
35 40 45

Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp
50 55 60

Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Xaa Gln Ala
65 70 75 80

Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys Thr Ser
85 90 95

<210> 282
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 282
Ile Leu Trp His Glu Met Trp His Glu Gly Leu Ile Glu Ala Ser Arg
1 5 10 15

Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu
20 25 30

Pro Leu His Ala Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr
35 40 45

Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp
50 55 60

Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Leu Gln Ala
65 70 75 80

Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys Thr Ser
85 90 95

<210> 283
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 283
Ile Leu Trp His Glu Met Trp His Glu Gly Leu Leu Glu Ala Ser Arg
1 5 10 15

Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu
20 25 30

Pro Leu His Ala Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr
35 40 45

Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp
50 55 60

Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Leu Gln Ala
65 70 75 80

Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys Thr Ser
85 90 95

<210> 284
<211> 1132
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 284
Met Pro Arg Ala Pro Arg Cys Arg Ala Val Arg Ser Leu Leu Arg Ser
1 5 10 15

His Tyr Arg Glu Val Leu Pro Leu Ala Thr Phe Val Arg Arg Leu Gly
20 25 30

Pro Gln Gly Trp Arg Leu Val Gln Arg Gly Asp Pro Ala Ala Phe Arg
35 40 45

Ala Leu Val Ala Gln Cys Leu Val Cys Val Pro Trp Asp Ala Arg Pro
50 55 60

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Pro Pro Ala Ala Pro Ser Phe Arg Gln Val Ser Cys Leu Lys Glu Leu
65                  70                  75                  80

Val Ala Arg Val Leu Gln Arg Leu Cys Glu Arg Gly Ala Lys Asn Val
                85                  90                  95

Leu Ala Phe Gly Phe Ala Leu Leu Asp Gly Ala Arg Gly Gly Pro Pro
            100                 105                 110

Glu Ala Phe Thr Thr Ser Val Arg Ser Tyr Leu Pro Asn Thr Val Thr
        115                 120                 125

Asp Ala Leu Arg Gly Ser Gly Ala Trp Gly Leu Leu Leu Arg Arg Val
    130                 135                 140

Gly Asp Asp Val Leu Val His Leu Leu Ala Arg Cys Ala Leu Phe Val
145                 150                 155                 160

Leu Val Ala Pro Ser Cys Ala Tyr Gln Val Cys Gly Pro Pro Leu Tyr
                165                 170                 175

Gln Leu Gly Ala Ala Thr Gln Ala Arg Pro Pro Pro His Ala Ser Gly
            180                 185                 190

Pro Arg Arg Arg Leu Gly Cys Glu Arg Ala Trp Asn His Ser Val Arg
        195                 200                 205

Glu Ala Gly Val Pro Leu Gly Leu Pro Ala Pro Gly Ala Arg Arg Arg
    210                 215                 220

Gly Gly Ser Ala Ser Arg Ser Leu Pro Leu Pro Lys Arg Pro Arg Arg
225                 230                 235                 240

Gly Ala Ala Pro Glu Pro Glu Arg Thr Pro Val Gly Gln Gly Ser Trp
                245                 250                 255

Ala His Pro Gly Arg Thr Arg Gly Pro Ser Asp Arg Gly Phe Cys Val
            260                 265                 270

Val Ser Pro Ala Arg Pro Ala Glu Glu Ala Thr Ser Leu Glu Gly Ala
        275                 280                 285

Leu Ser Gly Thr Arg His Ser His Pro Ser Val Gly Arg Gln His His
    290                 295                 300

Ala Gly Pro Pro Ser Thr Ser Arg Pro Pro Arg Pro Trp Asp Thr Pro
305                 310                 315                 320

Cys Pro Pro Val Tyr Ala Glu Thr Lys His Phe Leu Tyr Ser Ser Gly
                325                 330                 335
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Asp Lys Glu Gln Leu Arg Pro Ser Phe Leu Leu Ser Ser Leu Arg Pro
            340                 345                 350

Ser Leu Thr Gly Ala Arg Arg Leu Val Glu Thr Ile Phe Leu Gly Ser
        355                 360                 365

Arg Pro Trp Met Pro Gly Thr Pro Arg Arg Leu Pro Arg Leu Pro Gln
    370                 375                 380

Arg Tyr Trp Gln Met Arg Pro Leu Phe Leu Glu Leu Leu Gly Asn His
385                 390                 395                 400

Ala Gln Cys Pro Tyr Gly Val Leu Leu Lys Thr His Cys Pro Leu Arg
                405                 410                 415

Ala Ala Val Thr Pro Ala Ala Gly Val Cys Ala Arg Glu Lys Pro Gln
            420                 425                 430

Gly Ser Val Ala Ala Pro Glu Glu Glu Asp Thr Asp Pro Arg Arg Leu
        435                 440                 445

Val Gln Leu Leu Arg Gln His Ser Ser Pro Trp Gln Val Tyr Gly Phe
    450                 455                 460

Val Arg Ala Cys Leu Arg Arg Leu Val Pro Pro Gly Leu Trp Gly Ser
465                 470                 475                 480

Arg His Asn Glu Arg Arg Phe Leu Arg Asn Thr Lys Lys Phe Ile Ser
                485                 490                 495

Leu Gly Lys His Ala Lys Leu Ser Leu Gln Glu Leu Thr Trp Lys Met
            500                 505                 510

Ser Val Arg Gly Cys Ala Trp Leu Arg Arg Ser Pro Gly Val Gly Cys
        515                 520                 525

Val Pro Ala Ala Glu His Arg Leu Arg Glu Glu Ile Leu Ala Lys Phe
    530                 535                 540

Leu His Trp Leu Met Ser Val Tyr Val Val Glu Leu Leu Arg Ser Phe
545                 550                 555                 560

Phe Tyr Val Thr Glu Thr Thr Phe Gln Lys Asn Arg Leu Phe Phe Tyr
                565                 570                 575

Arg Lys Ser Val Trp Ser Lys Leu Gln Ser Ile Gly Ile Arg Gln His
            580                 585                 590

Leu Lys Arg Val Gln Leu Arg Glu Leu Ser Glu Ala Glu Val Arg Gln
        595                 600                 605
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His Arg Glu Ala Arg Pro Ala Leu Leu Thr Ser Arg Leu Arg Phe Ile
    610                 615                 620

Pro Lys Pro Asp Gly Leu Arg Pro Ile Val Asn Met Asp Tyr Val Val
625                 630                 635                 640

Gly Ala Arg Thr Phe Arg Arg Glu Lys Arg Ala Glu Arg Leu Thr Ser
                645                 650                 655

Arg Val Lys Ala Leu Phe Ser Val Leu Asn Tyr Glu Arg Ala Arg Arg
            660                 665                 670

Pro Gly Leu Leu Gly Ala Ser Val Leu Gly Leu Asp Asp Ile His Arg
        675                 680                 685

Ala Trp Arg Thr Phe Val Leu Arg Val Arg Ala Gln Asp Pro Pro Pro
    690                 695                 700

Glu Leu Tyr Phe Val Lys Val Asp Val Thr Gly Ala Tyr Asp Thr Ile
705                 710                 715                 720

Pro Gln Asp Arg Leu Thr Glu Val Ile Ala Ser Ile Ile Lys Pro Gln
                725                 730                 735

Asn Thr Tyr Cys Val Arg Arg Tyr Ala Val Val Gln Lys Ala Ala His
            740                 745                 750

Gly His Val Arg Lys Ala Phe Lys Ser His Val Ser Thr Leu Thr Asp
        755                 760                 765

Leu Gln Pro Tyr Met Arg Gln Phe Val Ala His Leu Gln Glu Thr Ser
    770                 775                 780

Pro Leu Arg Asp Ala Val Val Ile Glu Gln Ser Ser Ser Leu Asn Glu
785                 790                 795                 800

Ala Ser Ser Gly Leu Phe Asp Val Phe Leu Arg Phe Met Cys His His
                805                 810                 815

Ala Val Arg Ile Arg Gly Lys Ser Tyr Val Gln Cys Gln Gly Ile Pro
            820                 825                 830

Gln Gly Ser Ile Leu Ser Thr Leu Leu Cys Ser Leu Cys Tyr Gly Asp
        835                 840                 845

Met Glu Asn Lys Leu Phe Ala Gly Ile Arg Arg Asp Gly Leu Leu Leu
    850                 855                 860

Arg Leu Val Asp Asp Phe Leu Leu Val Thr Pro His Leu Thr His Ala
865                 870                 875                 880
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Lys Thr Phe Leu Arg Thr Leu Val Arg Gly Val Pro Glu Tyr Gly Cys
                885                 890                 895

Val Val Asn Leu Arg Lys Thr Val Val Asn Phe Pro Val Glu Asp Glu
            900                 905                 910

Ala Leu Gly Gly Thr Ala Phe Val Gln Met Pro Ala His Gly Leu Phe
        915                 920                 925

Pro Trp Cys Gly Leu Leu Leu Asp Thr Arg Thr Leu Glu Val Gln Ser
    930                 935                 940

Asp Tyr Ser Ser Tyr Ala Arg Thr Ser Ile Arg Ala Ser Leu Thr Phe
945                 950                 955                 960

Asn Arg Gly Phe Lys Ala Gly Arg Asn Met Arg Arg Lys Leu Phe Gly
                965                 970                 975

Val Leu Arg Leu Lys Cys His Ser Leu Phe Leu Asp Leu Gln Val Asn
            980                 985                 990

Ser Leu Gln Thr Val Cys Thr Asn  Ile Tyr Lys Ile Leu  Leu Leu Gln
        995                 1000                1005

Ala Tyr  Arg Phe His Ala Cys  Val Leu Gln Leu Pro  Phe His Gln
    1010                1015                1020

Gln Val  Trp Lys Asn Pro Thr  Phe Phe Leu Arg Val  Ile Ser Asp
    1025                1030                1035

Thr Ala  Ser Leu Cys Tyr Ser  Ile Leu Lys Ala Lys  Asn Ala Gly
    1040                1045                1050

Met Ser  Leu Gly Ala Lys Gly  Ala Ala Gly Pro Leu  Pro Ser Glu
    1055                1060                1065

Ala Val  Gln Trp Leu Cys His  Gln Ala Phe Leu Leu  Lys Leu Thr
    1070                1075                1080

Arg His  Arg Val Thr Tyr Val  Pro Leu Leu Gly Ser  Leu Arg Thr
    1085                1090                1095

Ala Gln  Thr Gln Leu Ser Arg  Lys Leu Pro Gly Thr  Thr Leu Thr
    1100                1105                1110

Ala Leu  Glu Ala Ala Ala Asn  Pro Ala Leu Pro Ser  Asp Phe Lys
    1115                1120                1125

Thr Ile  Leu Asp
    1130
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<210> 285
<211> 4027
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<220>
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cgcgcgctcc ccgctgccga gccgtgcgct ccctgctgcg cagccactac cgcgaggtgc 120

tgccgctggc cacgttcgtg cggcgcctgg ggccccaggg ctggcggctg gtgcagcgcg 180

gggacccggc ggctttccgc gcgctggtgg cccagtgcct ggtgtgcgtg ccctgggacg 240

cacggccgcc ccccgccgcc ccctccttcc gccaggtgtc ctgcctgaag gagctggtgg 300

cccgagtgct gcagaggctg tgcgagcgcg gcgcgaagaa cgtgctggcc ttcggcttcg 360

cgctgctgga cggggcccgc gggggccccc ccgaggcctt caccaccagc gtgcgcagct 420

acctgcccaa cacggtgacc gacgcactgc gggggagcgg ggcgtggggg ctgctgttgc 480

gccgcgtggg cgacgacgtg ctggttcacc tgctggcacg ctgcgcgctc tttgtgctgg 540

tggctcccag ctgcgcctac caggtgtgcg ggccgccgct gtaccagctc ggcgctgcca 600

ctcaggcccg gcccccgcca cacgctagtg gaccccgaag gcgtctggga tgcgaacggg 660

cctggaacca tagcgtcagg gaggccgggg tccccctggg cctgccagcc ccgggtgcga 720

ggaggcgcgg gggcagtgcc agccgaagtc tgccgttgcc caagaggccc aggcgtggcg 780

ctgcccctga gccggagcgg acgcccgttg ggcaggggtc ctgggcccac ccgggcagga 840

cgcgtggacc gagtgaccgt ggtttctgtg tggtgtcacc tgccagaccc gccgaagaag 900

ccacctcttt ggagggtgcg ctctctggca cgcgccactc ccacccatcc gtgggccgcc 960

agcaccacgc gggcccccca tccacatcgc ggccaccacg tccctgggac acgccttgtc 1020

ccccggtgta cgccgagacc aagcacttcc tctactcctc aggcgacaag gagcagctgc 1080

ggccctcctt cctactcagc tctctgaggc ccagcctgac tggcgctcgg aggctcgtgg 1140

agaccatctt tctgggttcc aggccctgga tgccagggac tccccgcagg ttgccccgcc 1200

tgccccagcg ctactggcaa atgcggcccc tgtttctgga gctgcttggg aaccacgcgc 1260

agtgccccta cggggtgctc ctcaagacgc actgcccgct gcgagctgcg gtcaccccag 1320

cagccggtgt ctgtgcccgg gagaagcccc agggctctgt ggcggccccc gaggaggagg 1380

acacagaccc ccgtcgcctg gtgcagctgc tccgccagca cagcagcccc tggcaggtgt 1440

acggcttcgt gcgggcctgc ctgcgccggc tggtgccccc aggcctctgg ggctccaggc 1500

acaacgaacg ccgcttcctc aggaacacca agaagttcat ctccctgggg aagcatgcca 1560

agctctcgct gcaggagctg acgtggaaga tgagcgtgcg gggctgcgct tggctgcgca 1620

ggagcccagg ggttggctgt gttccggccg cagagcaccg tctgcgtgag gagatcctgg 1680

ccaagttcct gcactggctg atgagtgtgt acgtcgtcga gctgctcagg tctttctttt 1740

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gcaagttgca aagcattgga atcagacagc acttgaagag ggtgcagctg cgggagctgt 1860

cggaagcaga ggtcaggcag catcgggaag ccaggcccgc cctgctgacg tccagactcc 1920

gcttcatccc caagcctgac gggctgcggc cgattgtgaa catggactac gtcgtgggag 1980

ccagaacgtt ccgcagagaa aagagggccg agcgtctcac ctcgagggtg aaggcactgt 2040

tcagcgtgct caactacgag cgggcgcggc gccccggcct cctgggcgcc tctgtgctgg 2100

gcctggacga tatccacagg gcctggcgca ccttcgtgct gcgtgtgcgg gcccaggacc 2160

cgccgcctga gctgtacttt gtcaaggtgg atgtgacggg cgcgtacgac accatccccc 2220

aggacaggct cacggaggtc atcgccagca tcatcaaacc ccagaacacg tactgcgtgc 2280

gtcggtatgc cgtggtccag aaggccgccc atgggcacgt ccgcaaggcc ttcaagagcc 2340

acgtctctac cttgacagac ctccagccgt acatgcgaca gttcgtggct cacctgcagg 2400

agaccagccc gctgagggat gccgtcgtca tcgagcagag ctcctccctg aatgaggcca 2460

gcagtggcct cttcgacgtc ttcctacgct tcatgtgcca ccacgccgtg cgcatcaggg 2520

gcaagtccta cgtccagtgc caggggatcc cgcagggctc catcctctcc acgctgctct 2580

gcagcctgtg ctacggcgac atggagaaca agctgtttgc ggggattcgg cgggacgggc 2640

tgctcctgcg tttggtggat gatttcttgt tggtgacacc tcacctcacc cacgcgaaaa 2700

ccttcctcag gaccctggtc cgaggtgtcc ctgagtatgg ctgcgtggtg aacttgcgga 2760

agacagtggt gaacttccct gtagaagacg aggccctggg tggcacggct tttgttcaga 2820

tgccggccca cggcctattc ccctggtgcg gcctgctgct ggatacccgg accctggagg 2880

tgcagagcga ctactccagc tatgcccgga cctccatcag agccagtctc accttcaacc 2940

gcggcttcaa ggctgggagg aacatgcgtc gcaaactctt tggggtcttg cggctgaagt 3000

gtcacagcct gtttctggat ttgcaggtga acagcctcca gacggtgtgc accaacatct 3060

acaagatcct cctgctgcag gcgtacaggt ttcacgcatg tgtgctgcag ctcccatttc 3120

atcagcaagt ttggaagaac cccacatttt tcctgcgcgt catctctgac acggcctccc 3180

tctgctactc catcctgaaa gccaagaacg cagggatgtc gctgggggcc aagggcgccg 3240

ccggccctct gccctccgag gccgtgcagt ggctgtgcca ccaagcattc ctgctcaagc 3300

tgactcgaca ccgtgtcacc tacgtgccac tcctggggtc actcaggaca gcccagacgc 3360

agctgagtcg gaagctcccg gggacgacgc tgactgccct ggaggccgca gccaacccgg 3420

cactgccctc agacttcaag accatcctgg actgatggcc acccgcccac agccaggccg 3480

agagcagaca ccagcagccc tgtcacgccg ggctctacgt cccagggagg gaggggcggc 3540

ccacacccag gcccgcaccg ctgggagtct gaggcctgag tgagtgtttg gccgaggcct 3600

gcatgtccgg ctgaaggctg agtgtccggc tgaggcctga gcgagtgtcc agccaagggc 3660

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cccagattcg ccattgttca cccctcgccc tgccctcctt tgccttccac ccccaccatc 3840

caggtggaga ccctgagaag gaccctggga gctctgggaa tttggagtga ccaaaggtgt 3900

gccctgtaca caggcgagga ccctgcacct ggatgggggt ccctgtgggt caaattgggg 3960

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aaaaaaa 4027

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<210> 287
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<210> 288
<211> 19
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<210> 289
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ggtcattggt atcatgagt 19

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<211> 19
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<220>
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<210> 295
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<400> 295
gcatgcaggc tacagttca 19

<210> 296
<211> 19
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<220>
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<400> 296
ccagcacatg cactgttga 19

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<220>
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<400> 297
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<220>
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<210> 301
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<210> 302
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<210> 304
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<220>
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<210> 309
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 319
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caggcctaga gaagtttca 19

<210> 338
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<220>

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<210> 339
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<220>
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oligonucleotide"

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ggaacccatt cctgaaatt 19

<210> 340
<211> 19
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic
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<210> 341
<211> 19
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<210> 342
<211> 19
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<210> 343
<211> 19
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<210> 344
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<211> 19
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<210> 348
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peptide"

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<223> /note="Description of Artificial Sequence: Synthetic peptide"

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1 5

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<400> 420
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<400> 422

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<220>
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<400> 423
His Tyr Ser Met Asn
1 5

<210> 424
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<220>
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Gly

<210> 425
<211> 17
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 425
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1 5 10 15

Gly

<210> 426
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<220>
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<400> 426

Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys Gly
1 5 10 15

<210> 427
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<220>
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<400> 427
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1 5 10 15

Gly

<210> 428
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<220>
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<400> 428
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1 5 10 15

Gly

<210> 429
<211> 17
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<220>
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<400> 429
Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 430
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1 5 10 15

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Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys Gly
1 5 10 15

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<400> 432
Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys Gly
1 5 10 15

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Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

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<220>
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<400> 434

Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys Gly
1 5 10 15

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1 5 10 15

Gly

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1 5 10 15

<210> 437
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1 5 10 15

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<210> 441
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Gly

<210> 442
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Gly

<210> 443
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Gly

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<400> 444
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1 5 10 15

<210> 445
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Gly

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Lys Ser

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1 5 10 15

Gly

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Gly

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Gly

<210> 450
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1 5 10 15

Gly

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Gly

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Gly

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Gly

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1   5   10

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1 5 10

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1 5 10

<210> 725
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Ala Phe Asp Ile
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<210> 726
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Val Glu Gly Ser Gly Ser Leu Asp Tyr
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<210> 728
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<400> 728
Arg Ala Gly Ser Glu Ala Ser Asp Ile
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<210> 729
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<210> 730
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1 5 10 15

<210> 731
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<400> 731
Val Gly Lys Ala Val Pro Asp Val
1 5

<210> 732
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1 5 10

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<210> 736

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1 5 10

<210> 737
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<400> 737
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<210> 738
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<400> 738
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1 5 10 15

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<210> 739
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1 5 10

<210> 740
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Asp Tyr Leu Tyr Ser Cys Asp Tyr
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<210> 744
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<400> 744
Ser Gln Ser Ile Ser Ser Ser Phe
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<210> 745
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<400> 745
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<400> 751
Ser Gln Ser Val Ser Ser Lys
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<400> 752
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1 5

<210> 753
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<210> 772

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<223> /note="Description of Artificial Sequence: Synthetic peptide"

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1 5

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1 5

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1 5

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1 5

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1 5

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Gly Thr His Trp Pro Gly
1 5

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Tyr Glu Ser Leu Pro Leu
1 5

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Tyr Asn Asp Trp Leu Pro Val
1 5

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1 5

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<210> 840

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1 5

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1 5

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Tyr His Ser Ser Pro Ser Trp
1 5

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1 5

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1 5

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1 5

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1   5

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1   5

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1   5

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1   5

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<400> 858
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1 5

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Ser Arg Ile Phe Pro Arg
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<210> 876
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<210> 878
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<210> 879
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<210> 880
<211> 12
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<210> 881
<211> 10
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<210> 882
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<210> 883
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<400> 883
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<210> 884
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<210> 887
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<210> 888
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1 5 10

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1 5 10

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<400> 896
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1 5 10

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1 5 10

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1 5 10

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<220>
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<400> 899
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<210> 900
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<210> 901
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Gly Tyr Thr Phe Thr Asp Tyr Ser Ile Asn
1 5 10

<210> 902
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1 5 10

<210> 903
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<400> 903
Gly Tyr Thr Phe Thr His Tyr Ser Met Asn
1 5 10

<210> 904
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<220>
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<400> 904
Gly Ile Ser Arg Ser Gly Glu Asn Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 905
<211> 17
<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 905
Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 906
<211> 16
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 906
Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys Gly
1 5 10 15

<210> 907
<211> 17
<212> PRT
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<220>
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<400> 907
Trp Ile Asn Pro Lys Asn Asn Asn Thr Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 908
<211> 17
<212> PRT
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<220>
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<400> 908
Val Ile Ser Gly Ser Gly Gly Thr Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 909
<211> 17
<212> PRT
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<220>
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1 5 10 15

Gly

<210> 910
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<220>
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<400> 910
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1 5 10 15

<210> 911
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<220>
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<400> 911
Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys Gly
1 5 10 15

<210> 912
<211> 16
<212> PRT
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<220>
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Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys Gly
1 5 10 15

<210> 913
<211> 17
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<220>
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<400> 913
Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 914
<211> 16
<212> PRT
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<220>
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<400> 914
Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys Gly
1 5 10 15

<210> 915
<211> 17
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<220>
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<400> 915
Tyr Ile Ser Ser Ser Gly Asn Thr Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 916
<211> 16
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<220>
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<400> 916
Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys Gly
1 5 10 15

<210> 917
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<220>
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Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys Gly
1 5 10 15

<210> 918
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<220>
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<400> 918
Gly Ile Val Tyr Ser Gly Ser Thr Tyr Tyr Ala Ala Ser Val Lys Gly
1 5 10 15

<210> 919
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<220>
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<400> 919
Ser Ile Tyr Tyr Ser Gly Ser Ala Tyr Tyr Asn Pro Ser Leu Lys Ser

1 5 10 15

<210> 920
<211> 16
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<220>
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<400> 920
Arg Ile Asp Trp Asp Glu Asp Lys Phe Tyr Ser Thr Ser Leu Lys Thr
1 5 10 15

<210> 921
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<220>
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<400> 921
Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 922
<211> 17
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<220>
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<400> 922
Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 923
<211> 17
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<220>
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1 5 10 15

Gly

<210> 924
<211> 16
<212> PRT
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<220>
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<400> 924
Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 925
<211> 17
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 925
Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 926
<211> 18
<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 926
Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Ser Phe Tyr Ala Ile Ser Leu
1 5 10 15

Lys Ser

<210> 927
<211> 17
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic

peptide"

<400> 927
Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 928
<211> 17
<212> PRT
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<220>
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<400> 928
Gly Ile Ser Asp Ser Gly Val Ser Thr Tyr Tyr Ala Asp Ser Ala Lys
1 5 10 15

Gly

<210> 929
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<400> 929
Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
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Gly

<210> 930
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<400> 930
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1 5 10 15

Gly

<210> 931
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<400> 931
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1 5 10 15

Gly

<210> 932
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<400> 932
Ser Ile Asn Trp Lys Gly Asn Ser Leu Ala Tyr Gly Asp Ser Val Lys
1 5 10 15

Gly

<210> 933
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<220>
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<400> 933
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1 5 10 15

Gly

<210> 934
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<400> 934

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1 5 10 15

Gly

<210> 935
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1 5 10 15

Gly

<210> 936
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1 5 10 15

Gly

<210> 937
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<400> 937
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1 5 10 15

Gly

<210> 938
<211> 17
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1 5 10 15

Gly

<210> 939
<211> 17
<212> PRT
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<400> 939
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1 5 10 15

Gly

<210> 940
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<400> 940
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1 5 10 15

Gly

<210> 941
<211> 17
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1 5 10 15

Gly

<210> 942
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<400> 942
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1 5 10 15

Gly

<210> 943
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<400> 943
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1 5 10 15

Gly

<210> 944
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<400> 944
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<210> 945
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1 5

<210> 946
<211> 7
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<400> 946
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1 5

<210> 947
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<400> 947
Gly Pro Tyr Tyr Tyr Gln Ser Tyr Met Asp Val
1 5 10

<210> 948
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<400> 948
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1 5 10

<210> 949
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<400> 949
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1 5

<210> 950
<211> 7
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<400> 950
His Gly Gly Glu Ser Asp Val
1 5

<210> 951
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<400> 951
His Gly Gly Glu Ser Asp Val
1 5

<210> 952
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<212> PRT
<213> Artificial Sequence

<220>
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peptide"

<400> 952
His Gly Gly Glu Ser Asp Val
1 5

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Ala Phe Asp Ile
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<210> 1002
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<210> 1003
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<211> 11
<212> PRT
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1   5   10   15

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1 5

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<400> 1090
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<210> 1092
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<400> 1092
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<400> 1093
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<400> 1094

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1 5 10

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