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(54) Titre: TRAITEMENT DE PATIENTS SOUFFRANT DE NSCLC REFRACTAIRES A UN ANTICORPS ANTI-PD-1 (54) Title: TREATMENT OF NSCLC PATIENTS REFRACTORY FOR ANTI-PD-1 ANTIBODY

(57) Abrégé/Abstract:

The present invention provides improved and/or shortened processes and methods for preparing TILs in order to prepare therapeutic populations of TILs with increased therapeutic efficacy for the treatment of non-small cell lung carcinoma (NSCLC), wherein the NSCLC is refractory to treatment with an anti-PD-1 antibody.





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(57) Abstract: The present invention provides improved and/or shortened processes and methods for preparing TILs in order to prepare therapeutic populations of TILs with increased therapeutic efficacy for the treatment of non-small cell lung carcinoma (NSCLC), wherein the NSCLC is refractory to treatment with an anti-PD-1 antibody.

DEMANDE OU BREVET VOLUMINEUX

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JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

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TREATMENT OF NSCLC PATIENTS REFRACTORY FOR ANTI-PD-1 ANTIBODY

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 62/756,025, filed on November 5, 2018, and U.S. Provisional Patent Application No. 62/903,627, filed on September 20, 2019, which are hereby incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

Treatment of bulky, refractory cancers using adoptive transfer of tumor infiltrating [0002]lymphocytes (TILs) represents a powerful approach to therapy for patients with poor prognoses. Gattinoni, et al., Nat. Rev. Immunol. 2006, 6, 383-393. A large number of TILs are required for successful immunotherapy, and a robust and reliable process is needed for commercialization. This has been a challenge to achieve because of technical, logistical, and regulatory issues with cell expansion. IL-2-based TIL expansion followed by a "rapid expansion process" (REP) has become a preferred method for TIL expansion because of its speed and efficiency. Dudley, et al., Science 2002, 298, 850-54; Dudley, et al., J. Clin. Oncol. 2005, 23, 2346-57; Dudley, et al., J. Clin. Oncol. 2008, 26, 5233-39; Riddell, et al., Science 1992, 257, 238-41; Dudley, et al., J. Immunother. 2003, 26, 332-42. REP can result in a 1,000-fold expansion of TILs over a 14-day period, although it requires a large excess (e.g., 200-fold) of irradiated allogeneic peripheral blood mononuclear cells (PBMCs, also known as mononuclear cells (MNCs)), often from multiple donors, as feeder cells, as well as anti-CD3 antibody (OKT3) and high doses of IL-2. Dudley, et al., J. Immunother. 2003, 26, 332-42. TILs that have undergone an REP procedure have produced successful adoptive cell therapy following host immunosuppression in patients with melanoma. Current infusion acceptance parameters rely on readouts of the composition of TILs (e.g., CD28, CD8, or CD4 positivity) and on fold expansion and viability of the REP product.

[0003] Current TIL manufacturing and treatment processes are limited by length, cost, sterility concerns, and other factors described herein such that the potential to treat patients which are refractory to anti-PD1 and as such have been severly limited. There is an urgent need to provide TIL manufacturing processes and therapies based on such processes that are

appropriate for use in treating patients for whom very few or no viable treatment options remain. The present invention meets this need by providing a shortened manufacturing process for use in generating TILs which can then be employed in the treatment of non-small cell lung carcinoma (NSCLC) patients whom are refractory to anti-PD-1 treatment.

BRIEF SUMMARY OF THE INVENTION

[0004] The present invention provides improved and/or shortened methods for expanding TILs and producing therapeutic populations of TILs for use in treatment of non-small cell lung carcinoma (NSCLC) patients whom are refractory to anti-PD-1 treatment.

[0005] The present invention provides a method of treating non-small cell lung carcinoma (NSCLC) with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

- (a) obtaining and/or receiving a first population of TILs from surgical resection, needle biopsy, core biopsy, small biopsy, or other means for obtaining a sample that contains a mixture of tumor and TIL cells from a NSCLC tumor in a patient;
- (c) contacting the tumor fragments with a first cell culture medium;
- (d) performing an initial expansion of the first population of TILs in the first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2;
- (e) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), and optionally irradiated allogeneic peripheral blood mononuclear cells (PBMCs); and wherein the rapid expansion is performed over a period of 14 days or less;
- (f) harvesting the third population of TILs; and
- (g) administering a therapeutically effective portion of the third population of TILs to a patient with the NSCLC;

wherein the NSCLC is refractory to treatment with an anti-PD-1 antibody.

[0006] In some embodiments, "obtaining" indicates the TILs employed in the method and/or process can be derived directly from the sample (including from a surgical resection, needle biopsy, core biopsy, small biopsy, or other sample) as part of the method and/or process steps. In some embodiments, "receiving" indicates the TILs employed in the method and/or process can be derived indirectly from the sample (including from a surgical resection, needle biopsy, core biopsy, small biopsy, or other sample) and then employed in the method and/or process, (for example, where step (a) begins will TILs that have already been derived from the sample by a separate process not included in part (a), such TILs could be refered to as "received").

[0007] In some embodiments, the first population of TILs comprises a multilesional sampling method.

[0008] In some embodiments, the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 and/or anti-PD-L2 antibody.

[0009] In some embodiments, the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

[0010] In some embodiments, the refractory NSCLC has been treated with a chemotherapeutic agent.

[0011] In some embodiments, the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has been previously treated a chemotherapeutic agent.

[0012] In some embodiments, the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has been previously treated a chemotherapeutic agent.

[0013] In some embodiments, the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.

[0014] In some embodiments, the refractory NSCLC has low expression of PD-L1.

[0015] In some embodiments, the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has low expression of PD-L1.

[0016] In some embodiments, the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has low expression of PD-L1.

- [0017] In some embodiments, the refractory NSCLC has been treated with a chemotherapeutic agent and has low expression of PD-L1.
- [0018] In some embodiments, the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent and has low expression of PD-L1
- [0019] In some embodiments, the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has bulky disease at baseline.
- [0020] In some embodiments, the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has bulky disease at baseline.
- [0021] In some embodiments, the refractory NSCLC has been treated with a chemotherapeutic agent and has bulky disease at baseline.
- [0022] In some embodiments, the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent and has bulky disease at baseline.
- [0023] In some embodiments, bulky disease is indicated where the maximal tumor diameter is greater than 7 cm measured in either the transverse or coronal plane or swollen lymph nodes with a short-axis diameter of 20 mm or greater.
- [0024] In some embodiments, the refractory NSCLC is refractory to at least two prior systemic treatment courses, not including neo-adjuvant or adjuvant therapies.
- **[0025]** In some embodiments, the refractory NSCLC is refractory to an anti-PD-1 antibody or an anti-PD-L1 selected from the group consisting of nivolumab, pembrolizumab, ipilimumab, JS001, TSR-042, pidilizumab, BGB-A317, SHR-1210, REGN2810, MDX-1106, PDR001, anti-PD-1 from clone: RMP1-14, an anti-PD-1 antibodies disclosed in U.S. Patent No. 8,008,449, durvalumab, atezolizumab, avelumab, and fragments, derivatives, variants, as well as biosimilars thereof.
- [0026] In some embodiments, the refractory NSCLC is refractory to pembrolizumab or a biosimilar thereof.
- [0027] In some embodiments, the refractory NSCLC is refractory to nivolumab or a biosimilar thereof.

[0028] In some embodiments, the refractory NSCLC is refractory to ipilimumab or a biosimilar thereof.

[0029] In some embodiments, the refractory NSCLC is refractory to ipilimumab or a biosimilar thereof and pembrolizumab or a biosimilar thereof.

[0030] In some embodiments, the refractory NSCLC is refractory to ipilimumab or a biosimilar thereof and nivolumab or a biosimilar thereof.

[0031] In some embodiments, the refractory NSCLC is refractory to durvalumab or a biosimilar thereof.

[0032] In some embodiments, the refractory NSCLC is refractory to atezolizumab or a biosimilar thereof.

[0033] In some embodiments, the refractory NSCLC is refractory to avelumab or a biosimilar thereof.

[0034] In some embodiments, the initial expansion is performed over a period of 21 days or less.

[0035] In some embodiments, the initial expansion is performed over a period of 14 days or less.

[0036] In some embodiments, the IL-2 is present at an initial concentration of between 1000 IU/mL and 6000 IU/mL in the first cell culture medium.

[0037] In some embodiments, the IL-2 is present at an initial concentration of between 1000 IU/mL and 6000 IU/mL and the OKT-3 antibody is present at an initial concentration of about 30 ng/mL in the second cell culture medium.

[0038] In some embodiments, the initial expansion is performed using a gas permeable container.

[0039] In some embodiments, the rapid expansion is performed using a gas permeable container.

[0040] In some embodiments, the first cell culture medium further comprises a cytokine selected from the group consisting of IL-4, IL-7, IL-15, IL-21, and combinations thereof.

[0041] In some embodiments, the second cell culture medium further comprises a cytokine selected from the group consisting of IL-4, IL-7, IL-15, IL-21, and combinations thereof.

[0042] In some embodiments, the method further comprises the step of treating the patient with a non-myeloablative lymphodepletion regimen prior to administering the third population of TILs to the patient.

[0043] In some embodiments, the non-myeloablative lymphodepletion regimen comprises the steps of administration of cyclophosphamide at a dose of 60 mg/m²/day for two days followed by administration of fludarabine at a dose of 25 mg/m²/day for five days.

[0044] In some embodiments, the method further comprises the step of treating the patient with an IL-2 regimen starting on the day after administration of the third population of TILs to the patient.

[0045] In some embodiments, the IL-2 regimen is a high-dose IL-2 regimen comprising 600,000 or 720,000 IU/kg of aldesleukin, or a biosimilar or variant thereof, administered as a 15-minute bolus intravenous infusion every eight hours until tolerance.

[0046] In some embodiments, the invention provides a method of treating non-small cell lung carcinoma (NSCLC) with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:

- (a) resecting a tumor from a patient, the tumor comprising a first population of TILs;
- (b) fragmenting the tumor into tumor fragments;
- (c) contacting the tumor fragments with a first cell culture medium;
- (d) performing an initial expansion of the first population of TILs in the first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2;
- (e) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), and optionally irradiated allogeneic peripheral blood mononuclear cells (PBMCs); and wherein the rapid expansion is performed over a period of 14 days or less;
- (f) harvesting the third population of TILs; and
- (g) administering a therapeutically effective portion of the third population of TILs to a

patient with the cancer;

wherein the cancer is refractory to treatment with an anti-PD-1 antibody.

[0047] In some embodiments, the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

[0048] In some embodiments, the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

[0049] In some embodiments, the refractory NSCLC has been treated with a chemotherapeutic agent.

[0050] In some embodiments, the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has been previously treated a chemotherapeutic agent.

[0051] In some embodiments, the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has been previously treated a chemotherapeutic agent.

[0052] In some embodiments, the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.

[0053] In some embodiments, the refractory NSCLC has low expression of PD-L1.

[0054] In some embodiments, the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has low expression of PD-L1.

[0055] In some embodiments, the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has low expression of PD-L1.

[0056] In some embodiments, the refractory NSCLC has been treated with a chemotherapeutic agent and has low expression of PD-L1.

[0057] In some embodiments, the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent and has low expression of PD-L1

[0058] In some embodiments, the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has bulky disease at baseline.

[0059] In some embodiments, the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has bulky disease at baseline.

[0060] In some embodiments, the refractory NSCLC has been treated with a chemotherapeutic agent and has bulky disease at baseline.

[0061] In some embodiments, the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent and has bulky disease at baseline.

[0062] In some embodiments, bulky disease is indicated where the maximal tumor diameter is greater than 7 cm measured in either the transverse or coronal plane or swollen lymph nodes with a short-axis diameter of 20 mm or greater.

[0063] In some embodiments, the refractory NSCLC is refractory to at least two prior systemic treatment courses, not including neo-adjuvant or adjuvant therapies.

[0064] In some embodiments, the refractory NSCLC is refractory to an anti-PD-1 or an anti-PD-L1 antibody is selected from the group consisting of nivolumab, pembrolizumab, JS001, TSR-042, pidilizumab, (BGB-A317, SHR-1210, REGN2810, MDX-1106, PDR001, anti-PD-1 from clone: RMP1-14, an anti-PD-1 antibodies disclosed in U.S. Patent No. 8,008,449, durvalumab, atezolizumab, avelumab, and fragments, derivatives, variants, as well as biosimilars thereof.

[0065] In some embodiments, the refractory NSCLC is refractory to pembrolizumab or a biosimilar thereof.

[0066] In some embodiments, the refractory NSCLC is refractory to nivolumab or a biosimilar thereof.

[0067] In some embodiments, the refractory NSCLC is refractory to an anti-CLTA-4 antibody, such as ipilimumab or a biosimilar thereof.

[0068] In some embodiments, the refractory NSCLC is refractory to an anti-CLTA-4 antibody, such as ipilimumab or a biosimilar thereof and pembrolizumab or a biosimilar thereof.

[0069] In some embodiments, the refractory NSCLC is refractory to an anti-CLTA-4 antibody, such as ipilimumab or a biosimilar thereof and nivolumab or a biosimilar thereof.

[0070] In some embodiments, the refractory NSCLC is refractory to durvalumab or a biosimilar thereof.

[0071] In some embodiments, the refractory NSCLC is refractory to atezolizumab or a biosimilar thereof.

[0072] In some embodiments, the refractory NSCLC is refractory to avelumab or a biosimilar thereof.

[0073] In some embodiments, the initial expansion is performed over a period of 21 days or less.

[0074] In some embodiments, the initial expansion is performed over a period of 14 days or less.

[0075] In some embodiments, the IL-2 is present at an initial concentration of between 1000 IU/mL and 6000 IU/mL in the first cell culture medium.

[0076] In some embodiments, the IL-2 is present at an initial concentration of between 1000 IU/mL and 6000 IU/mL and the OKT-3 antibody is present at an initial concentration of about 30 ng/mL in the second cell culture medium.

[0077] In some embodiments, the initial expansion is performed using a gas permeable container.

[0078] In some embodiments, the rapid expansion is performed using a gas permeable container.

[0079] In some embodiments, the first cell culture medium further comprises a cytokine selected from the group consisting of IL-4, IL-7, IL-15, IL-21, and combinations thereof.

[0080] In some embodiments, the second cell culture medium further comprises a cytokine selected from the group consisting of IL-4, IL-7, IL-15, IL-21, and combinations thereof.

[0081] In some embodiments, the method further comprises the step of treating the patient with a non-myeloablative lymphodepletion regimen prior to administering the third population of TILs to the patient.

[0082] In some embodiments, the non-myeloablative lymphodepletion regimen comprises the steps of administration of cyclophosphamide at a dose of 60 mg/m²/day for two days followed by administration of fludarabine at a dose of 25 mg/m²/day for five days.

[0083] In some embodiments, the method further comprises the step of treating the patient with an IL-2 regimen starting on the day after administration of the third population of TILs to the patient.

[0084] In some embodiments, the IL-2 regimen is a high-dose IL-2 regimen comprising 600,000 or 720,000 IU/kg of aldesleukin, or a biosimilar or variant thereof, administered as a 15-minute bolus intravenous infusion every eight hours until tolerance.

[0085] In some embodiments, the invention provides a method for treating a subject with non-small cell lung carcinoma (NSCLC), wherein the cancer is refractory to treatment with an anti-PD-1 antibody, the method comprising administering expanded tumor infiltrating lymphocytes (TILs) comprising:

- (a) obtaining and/or receiving a first population of TILs from a tumor resected from a subject by processing a tumor sample obtained from the subject into multiple tumor fragments;
- (b) adding the tumor fragments into a closed system;
- (c) performing a first expansion by culturing the first population of TILs in a cell culture medium comprising IL-2 to produce a second population of TILs, wherein the first expansion is performed in a closed container providing a first gaspermeable surface area, wherein the first expansion is performed for about 3-113-14 days to obtain the second population of TILs, wherein the second population of TILs is at least 50-fold greater in number than the first population of TILs, and wherein the transition from step (b) to step (c) occurs without opening the system;
- (d) performing a second expansion by supplementing the cell culture medium of the second population of TILs with additional IL-2, OKT-3, and antigen presenting cells (APCs), to produce a third population of TILs, wherein the second expansion is performed for about 7-117-14 days to obtain the third population of TILs, wherein the third population of TILs is a therapeutic population of TILs which comprises an increased subpopulation of effector T cells and/or central memory T cells relative to the second population of TILs, wherein the second expansion is performed in a closed container providing a second gas-permeable surface area, and wherein the transition from step (c) to step (d) occurs without opening the system;
- (e) harvesting therapeutic population of TILs obtained from step (d), wherein the transition from step (d) to step (e) occurs without opening the system; and

- (f) transferring the harvested TIL population from step (e) to an infusion bag, wherein the transfer from step (e) to (f) occurs without opening the system;
- (g) cryopreserving the infusion bag comprising the harvested TIL population from step (f) using a cryopreservation process; and
- (h) administering a therapeutically effective dosage of the third population of TILs from the infusion bag in step (g) to the subject.

[0086] In some embodiments, the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

[0087] In some embodiments, the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

[0088] In some embodiments, the refractory NSCLC has been treated with a chemotherapeutic agent.

[0089] In some embodiments, the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has been previously treated a chemotherapeutic agent.

[0090] In some embodiments, the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has been previously treated a chemotherapeutic agent.

[0091] In some embodiments, the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.

[0092] In some embodiments, the refractory NSCLC has low expression of PD-L1.

[0093] In some embodiments, the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has low expression of PD-L1.

[0094] In some embodiments, the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has low expression of PD-L1.

[0095] In some embodiments, the refractory NSCLC has been treated with a chemotherapeutic agent and has low expression of PD-L1.

[0096] In some embodiments, the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent and has low expression of PD-L1.

[0097] In some embodiments, the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has bulky disease at baseline.

[0098] In some embodiments, the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has bulky disease at baseline.

[0099] In some embodiments, the refractory NSCLC has been treated with a chemotherapeutic agent and has bulky disease at baseline.

[00100] In some embodiments, the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent and has bulky disease at baseline.

[00101] In some embodiments, bulky disease is indicated where the maximal tumor diameter is greater than 7 cm measured in either the transverse or coronal plane or swollen lymph nodes with a short-axis diameter of 20 mm or greater.

[00102] In some embodiments, the refractory NSCLC is refractory to at least two prior systemic treatment courses, not including neo-adjuvant or adjuvant therapies.

[00103] In some embodiments, the refractory NSCLC is refractory to an anti-PD-1 or an anti-PD-L1 antibody is selected from the group consisting of nivolumab, pembrolizumab, JS001, TSR-042, pidilizumab, BGB-A317, SHR-1210, REGN2810, MDX-1106, PDR001, anti-PD-1 from clone: RMP1-14, an anti-PD-1 antibodies disclosed in U.S. Patent No. 8,008,449, durvalumab, atezolizumab, avelumab, and fragments, derivatives, variants, as well as biosimilars thereof.

[00104] In some embodiments, the refractory NSCLC is refractory to pembrolizumab or a biosimilar thereof.

[00105] In some embodiments, the refractory NSCLC is refractory to nivolumab or a biosimilar thereof.

[00106] In some embodiments, the refractory NSCLC is refractory to an anti-CLTA-4 antibody, such as ipilimumab or a biosimilar thereof.

[00107] In some embodiments, the refractory NSCLC is refractory to an anti-CLTA-4 antibody, such as ipilimumab or a biosimilar thereof and pembrolizumab or a biosimilar thereof.

[00108] In some embodiments, the refractory NSCLC is refractory to an anti-CLTA-4 antibody, such as ipilimumab or a biosimilar thereof and nivolumab or a biosimilar thereof.

[00109] In some embodiments, the refractory NSCLC is refractory to durvalumab or a biosimilar thereof.

[00110] In some embodiments, the refractory NSCLC is refractory to atezolizumab or a biosimilar thereof.

[00111] In some embodiments, the refractory NSCLC is refractory to avelumab or a biosimilar thereof.

[00112] In some embodiments, the initial expansion is performed over a period of 21 days or less.

[00113] In some embodiments, the initial expansion is performed over a period of 14 days or less.

[00114] In some embodiments, the IL-2 is present at an initial concentration of between 1000 IU/mL and 6000 IU/mL in the first cell culture medium.

[00115] In some embodiments, the IL-2 is present at an initial concentration of between 1000 IU/mL and 6000 IU/mL and the OKT-3 antibody is present at an initial concentration of about 30 ng/mL in the second cell culture medium.

[00116] In some embodiments, the initial expansion is performed using a gas permeable container.

[00117] In some embodiments, the rapid expansion is performed using a gas permeable container.

[00118] In some embodiments, the first cell culture medium further comprises a cytokine selected from the group consisting of IL-4, IL-7, IL-15, IL-21, and combinations thereof.

[00119] In some embodiments, the second cell culture medium further comprises a cytokine selected from the group consisting of IL-4, IL-7, IL-15, IL-21, and combinations thereof.

[00120] In some embodiments, the method further comprises the step of treating the patient with a non-myeloablative lymphodepletion regimen prior to administering the third population of TILs to the patient.

[00121] In some embodiments, the non-myeloablative lymphodepletion regimen comprises the steps of administration of cyclophosphamide at a dose of 60 mg/m²/day for two days followed by administration of fludarabine at a dose of 25 mg/m²/day for five days.

- [00122] In some embodiments, the method further comprises the step of treating the patient with an IL-2 regimen starting on the day after administration of the third population of TILs to the patient.
- [00123] In some embodiments, the IL-2 regimen is a high-dose IL-2 regimen comprising 600,000 or 720,000 IU/kg of aldesleukin, or a biosimilar or variant thereof, administered as a 15-minute bolus intravenous infusion every eight hours until tolerance.
- [00124] In some embodiments, the NSCLC is refractory to a combination treatment comprising an anti-PD-1 and chemotherapeutic agent.
- [00125] In some embodiments, the anti-PD-1 or the anti-PD-L1 antibody is selected from the group consisting of nivolumab, pembrolizumab, JS001, TSR-042, pidilizumab, (BGB-A317, SHR-1210, REGN2810, MDX-1106, PDR001, anti-PD-1 from clone: RMP1-14, an anti-PD-1 antibodies disclosed in U.S. Patent No. 8,008,449, durvalumab, atezolizumab, avelumab, and fragments, derivatives, variants, as well as biosimilars thereof.
- [00126] In some embodiments, the antiPD-1 is pembrolizumab.
- [00127] In some embodiments, the chemotherapeutic agent(s) is a platinum doublet chemotherapeutic agent.
- [00128] In some embodiments, the platinum doublet therapy comprises:
 - i) a first chemotherapeutic agent selected from the group consisting of cisplatin and carboplatin,
 - ii) and a second chemotherapeutic agent selected from the group consisting of vinorelbine, gemcitabine and a taxane (including for example, paclitaxel, docetaxel or nab-paclitaxel).
- [00129] In some embodiments, the chemotherapeutic agent is in combination with pemetrexed.
- **[00130]** In some embodiments, the NSCLC is refractory to a combination therapy comprising carboplatin, paclitaxel, pemetrexed, and cisplatin.

[00131] In some embodiments, the NSCLC is refractory to a combination therapy comprising carboplatin, paclitaxel, pemetrexed, cisplatin, nivolumab, and ipilimumab.

BRIEF DESCRIPTION OF THE DRAWINGS

- [00132] Figure 1: Exemplary Process 2A chart providing an overview of Steps A through F.
- [00133] Figure 2: Process Flow Chart of Process 2A.
- [00134] Figure 3: Shows a diagram of an embodiment of a cryopreserved TIL exemplary manufacturing process (~22 days).
- [00135] Figure 4: Shows a diagram of an embodiment of process 2A, a 22-day process for TIL manufacturing.
- [00136] Figure 5: Comparison table of Steps A through F from exemplary embodiments of process 1C and process 2A.
- [00137] Figure 6: Detailed comparison of an embodiment of process 1C and an embodiment of process 2A.
- [00138] Figure 7: Exemplary GEN 3 type process for NSCLC tumors.
- **[00139] Figure 8A-8B: A)** Shows a comparison between the 2A process (approximately 22-day process) and an embodiment of the Gen 3 process for TIL manufacturing (approximately 14-days to 16-days process). **B)** Exemplary Process Gen3 chart providing an overview of Steps A through F (approximately 14-days to 16-days process). **C)** Chart providing three exemplary Gen 3 processes with an overview of Steps A through F (approximately 14-days to 16-days process) for each of the three process variations.
- [00140] Figure 9: Provides an experimental flow chart for comparability between GEN 2 (process 2A) versus GEN 3.
- [00141] Figure 10A-10C: A) L4054 Phenotypic characterization on TIL product on Gen 2 and Gen 3 process. B) L4055-Phenotypic characterization on TIL product on Gen 2 and Gen 3 process. C) M1085T-Phenotypic characterization on TIL product on Gen 2 and Gen 3 process.
- [00142] Figure 11A-11C: A) L4054 Memory markers analysis on TIL product from the Gen 2 and Gen 3 processes. B) L4055 Memory markers analysis on TIL product from the

Gen 2 and Gen 3 processes. C) M1085T- Memory markers analysis on TIL product from the Gen 2 and Gen 3 processes.

- [00143] Figure 12: L4054 Activation and exhaustion markers (A) Gated on CD4+, (B) Gated on CD8+.
- [00144] Figure 13: L4055 Activation and exhaustion markers (A) Gated on CD4+, (B) Gated on CD8+.
- **[00145] Figure 14:** IFNγ production (pg/mL): (A) L4054, (B) L4055, and (C) M1085T for the Gen 2 and Gen 3 processes: Each bar represented here is mean + SEM for IFNγ levels of stimulated, unstimulated, and media control. Optical density measured at 450 nm.
- [00146] Figure 15: ELISA analysis of IL-2 concentration in cell culture supernatant: (A) L4054 and (B) L4055. Each bar represented here is mean + SEM for IL-2 levels on spent media. Optical density measured at 450 nm.
- **[00147] Figure 16:** Quantification of glucose and lactate (g/L) in spent media: (A) Glucose and (B) Lactate: In the two tumor lines, and in both processes, a decrease in glucose was observed throughout the REP expansion. Conversely, as expected, an increase in lactate was observed. Both the decrease in glucose and the increase in lactate were comparable between the Gen 2 and Gen 3 processes.
- [00148] Figure 17: A) Quantification of L-glutamine in spent media for L4054 and L4055. B) Quantification of Glutamax in spent media for L4054 and L4055. C) Quantification of ammonia in spent media for L4054 and L4055.
- [00149] Figure 18: Telomere length analysis. The relative telomere length (RTL) value indicates that the average telomere fluorescence per chromosome/genome in Gen 2 and Gen 3 process of the telomere fluorescence per chromosome/genome in the control cells line (1301 Leukemia cell line) using DAKO kit.
- **[00150] Figure 19:** Unique CDR3 sequence analysis for TIL final product on L4054 and L4055 under Gen 2 and Gen 3 process. Columns show the number of unique TCR B clonotypes identified from 1×10^6 cells collected on Harvest Day Gen 2 (*e.g.*, day 22) and Gen 3 process (*e.g.*, day 14-16). Gen 3 shows higher clonal diversity compared to Gen 2 based on the number of unique peptide CDRs within the sample.
- [00151] Figure 20: Frequency of unique CDR3 sequences on L4054 IL harvested final cell product (Gen 2 (e.g., day 22) and Gen 3 process (e.g., day 14-16)).

- [00152] Figure 21: Frequency of unique CDR3 sequences on L4055 TIL harvested final cell product (Gen 2 (e.g., day 22) and Gen 3 process (e.g., day 14-16)).
- [00153] Figure 22: Diversity Index for TIL final product on L4054 and L4055 under Gen 2 and Gen 3 process. Shanon entropy diversity index is a more reliable and common metric for comparison. Gen 3 L4054 and L4055 showed a slightly higher diversity than Gen 2.
- [00154] Figure 23: Raw data for cell counts Day 7-Gen 3 REP initiation presented in Table 45 (see Example 8 below).
- [00155] Figure 24: Raw data for cell counts Day 11-Gen 2 REP initiation and Gen 3 Scale Up presented in Table 45 (see Example 8 below).
- [00156] Figure 25: Raw data for cell counts Day 16-Gen 2 Scale Up and Gen 3 Harvest (e.g., day 16) presented in Table 46 (see Example 8 below).
- [00157] Figure 26: Raw data for cell counts Day 22-Gen 2 Harvest (*e.g.*, day 22) presented in Table 46 (see Example 8 below). For L4054 Gen 2, post LOVO count was extrapolated to 4 flasks, because was the total number of the study. 1 flask was contaminated, and the extrapolation was done for total = 6.67E+10.
- [00158] Figure 27: Raw data for flow cytometry results depicted in Figs. 10A, 10A, and 10B.
- [00159] Figure 28: Raw data for flow cytometry results depicted in Figs. 10C and 10C.
- [00160] Figure 29: Raw data for flow cytometry results depicted in Figs. 12 and 13.
- **[00161] Figure 30:** Raw data for IFNγ production assay results for L4054 samples depicted in Fig. 14.
- **[00162] Figure 31:** Raw data for IFNγ production assay results for L4055 samples depicted in Fig. 14.
- [00163] Figure 32: Raw data for IFN γ production assay results for M1085T samples depicted in Fig. 14.
- [00164] Figure 33: Raw data for IL-2 ELISA assay results depicted in Fig. 15.
- [00165] Figure 34: Raw data for the metabolic substrate and metabolic analysis results presented in Figs. 16 and 17.

- [00166] Figure 35: Raw data for the relative telomere length analysis results presented in Fig. 18.
- [00167] Figure 36: Raw data for the unique CD3 sequence and clonal diversity analyses results presented in Figs. 19 and 22.
- [00168] Figure 37: Shows a comparison between various Gen 2 (2A process) and the Gen 3.1 process embodiment.
- [00169] Figure 38: Table describing various features of embodiments of the Gen 2, Gen 2.1 and Gen 3.0 process.
- [00170] Figure 39: Overview of the media conditions for an embodiment of the Gen 3 process, referred to as Gen 3.1.
- [00171] Figure 40: Table describing various features of embodiments of the Gen 2, Gen 2.1 and Gen 3.0 process.
- [00172] Figure 41: Table comparing various features of embodiments of the Gen 2 and Gen 3.0 processes.
- [00173] Figure 42: Table providing media uses in the various embodiments of the described expansion processes.
- **[00174] Figure 43:** Phenotype comparison: Gen 3.0 and Gen 3.1 embodiments of the process showed comparable CD28, CD27 and CD57 expression.
- **[00175] Figure 44:** Higher production of IFNγ on Gen 3 final product. IFNγ analysis (by ELISA) was assessed in the culture frozen supernatant to compared both processes. For each tumor overnight stimulation with coated anti -CD3 plate, using fresh TIL product on each Gen 2 (*e.g.*, day 22) and Gen 3 process (*e.g.*, day 16). Each bar represents here are IFNγlevels of stimulated, unstimulated and media control.
- **[00176] Figure 45:** Top: Unique CDR3 sequence analysis for TIL final product: Columns show the number of unique TCR B clonotypes identified from 1×10^6 cells collected on Gen 2 (*e.g.*, day 22) and Gen 3 process (*e.g.*, day 14-16). Gen 3 shows higher clonal diversity compared to Gen 2 based on the number of unique peptide CDRs within the sample. Bottom: Diversity Index for TIL final product: Shanon entropy diversity index is a more reliable a common metric for comparison. Gen 3 showed a slightly higher diversity than Gen 2.

[00177] Figure 46: 199 sequences are shared between Gen 3 and Gen 2 final product, corresponding to 97.07% of top 80% of unique CDR3 sequences from Gen 2 shared with Gen 3 final product.

[00178] Figure 47: 1833 sequences are shared between Gen 3 and Gen 2 final product, corresponding to 99.45% of top 80% of unique CDR3 sequences from Gen 2 shared with Gen 3 final product.

[00179] Figure 48: Schematic of an exemplary embodiment of the Gen 3 process (a 16-day process).

[00180] Figure 49: Schematic of an exemplary embodiment of a method for expanding T cells from hematopoietic malignancies using Gen 3 expansion platform.

[00181] Figure 50: Provides the structures I-A and I-B, the cylinders refer to individual polypeptide binding domains. Structures I-A and I-B comprise three linearly-linked TNFRSF binding domains derived from e.g., 4-1BBL or an antibody that binds 4-1BB, which fold to form a trivalent protein, which is then linked to a second trivalent protein through IgG1-Fc (including CH3 and CH2 domains) is then used to link two of the trivalent proteins together through disulfide bonds (small elongated ovals), stabilizing the structure and providing an agonists capable of bringing together the intracellular signaling domains of the six receptors and signaling proteins to form a signaling complex. The TNFRSF binding domains denoted as cylinders may be scFv domains comprising, e.g., a VH and a VL chain connected by a linker that may comprise hydrophilic residues and Gly and Ser sequences for flexibility, as well as Glu and Lys for solubility.

[00182] Figure 51: Schematic of an exemplary embodiment of the Gen 3 process (a 16-day process).

[00183] Figure 52: Provides a process overview for an exemplary embodiment (Gen 3.1 Test) of the Gen 3.1 process (a 16 day process).

[00184] Figure 53: Provides data from TIL proliferation, average total viable cell counts per tumor fragment, percent viability at Harvest Day and total viable cell counts (TVC) at Harvest Day for exemplary embodiments of the Gen 3 process (Gen 3.0, Gen 3.1 Control, Gen 3.1 Test). Gen 3.1 Test (which includes the addition of OKT-3 and feeders on Day 0) reached maximum capacity of the flask at harvest. If a maximum of 4 flasks are initiated on day 0, each TVC harvest should be multiplied by 4.

[00185] Figure 54: Bar graph depicting total viable cell count (TVC) and percent viability for exemplary embodiments of the Gen 3 process (Gen 3.0, Gen 3.1 Control, Gen 3.1 Test), a 16-day process.

[00186] Figure 55: Provides data showing that exemplary embodiments of the Gen 3 process (Gen 3.0, Gen 3.1 Control and Gen 3.1 Test) yielded cells that showed comparable CD28, CD27 and CD57 expression.

[00187] Figure 56: Provides data showing TIL memory statuses were comparable across cells yielded by exemplary embodiments of the Gen 3 process (Gen 3.0, Gen 3.1 Control, and Gen 3.1 Test). Memory statuses of REP TIL are depicted as follows: CD4+ or CD8+ TIL Memory subsets were divided into different memory subsets. Naïve (CD45RA+CD62L+), CM: Central memory (CD45RA-CD62L+), EM: Effector memory (CD45RA-CD62L-), TEMRA/TEFF: RA+ Effector memory/Effectors (CD45RA+CD62L+). Bar graph presented are percentage positive CD45+/-CD62L +/- when gated on CD4+ or CD8+.

[00188] Figure 57: Provides data showing TIL activation / exhaustion markers were comparable across cells yielded by exemplary embodiments of the Gen 3 process (Gen 3.0, Gen 3.1 Control, and Gen 3.1 Test) when gated on CD4+. Activation and exhaustion of REP TIL were determined by multicolor flow cytometry. Harvested TIL samples were stained with flow cytometry antibodies (CD3-BUV395, PD-1-BV421, 2B4/CD244-PB, CD8-BB515, CD25-BUV563, BTLA-PE, KLRG1-PE-Dazzle 594, TIM-3-BV650, CD194/CCR4-APC, CD4-VioGreen, TIGIT-PerCP-eFluor 710, CD183-BV711, CD69-APC-R700, CD95-BUV737, CD127-PE-Cy7, CD103-BV786, LAG-3-APC-eFluor 780). Bar graph presented are percentage of CD4+ or CD8+ TIL of REP TIL.

[00189] Figure 58: Provides data showing TIL activation / exhaustion markers were comparable across cells yielded by exemplary embodiments of the Gen 3 process (Gen 3.0, Gen 3.0, Gen 3.1 Control and Gen 3.1) when gated on CD8+. Activation and exhaustion of REP TIL were determined by multicolor flow cytometry. TIL Harvested samples were stained with flow cytometry antibodies (CD3-BUV395, PD-1-BV421, 2B4/CD244-PB, CD8-BB515, CD25-BUV563, BTLA-PE, KLRG1-PE-Dazzle 594, TIM-3-BV650, CD194/CCR4-APC, CD4-VioGreen, TIGIT-PerCP-eFluor 710, CD183-BV711, CD69-APC-R700, CD95-BUV737, CD127-PE-Cy7, CD103-BV786, LAG-3-APC-eFluor 780). Bar graph presented are percentage of CD4+ or CD8+ TIL of REP TIL.

[00190] Figure 59: Provides data showing higher production of IFN-γ exhibited by Gen 3.1 final product. IFNγ analysis ELISA was assessed in the culture frozen supernatant to compare both processes. For each tumor overnight stimulation with coated anti -CD3 plate, using fresh TIL product on each Harvest day. Each bar represents here are IFN-γ levels of stimulated, unstimulated and media control.

[00191] Figure 60: Provides data showing that IL-2 concentration on supernatant were comparable across exemplary embodiments of the Gen 3 process (Gen 3.0, Gen 3.1 Control, Gen 3.1 Test) using Standard media. Left panel: L4063- Gen 2 Standard Media. Right panel: L4064- CTS Optimizer Media. *ELISA performed with AIM V diluent

[00192] Figure 61: Provides data showing that metabolite concentrations were comparable on supernatant supernatants across exemplary embodiments of the Gen 3 process (Gen 3.0, Gen 3.1 Control, Gen 3.1 Test). L4063 TILs were expanded in standard media. L4064 TILs were expanded in CTS Optimizer media.

[00193] Figure 62: Telomere length analysis on exemplary embodiments of the Gen 3 process (Gen 3.0, Gen 3.1 Control, Gen 3.1 Test). Telomere length analysis for cells yielded by tumor identification numbers L4063 and L4064: the relative telomere length (RTL) value indicates the average telomere fluorescence per chromosome/genome in cells produced by the Gen 3.0, Gen 3.1 Control and Gen 3.1 Test processes over the telomere fluorescence per chromosome/genome in the control cells line (1301 Leukemia cell line) using DAKO kit.

[00194] Figure 63: Schematic of an exemplary embodiment of the Gen 3.1 Test (Gen 3.1 optimized) process (a 16-17 day process).

[00195] Figure 64: Schematic of an exemplary embodiment of the Gen 3 process (a 16-day process).

[00196] Figure 65A-65B: Comparison tables for exemplary Gen 2 and exemplary Gen 3 processes with exemplary differences highlighted.

[00197] Figure 66: Schematic of an exemplary embodiment of the Gen 3 process (a 16/17 day process) preparation timeline.

[00198] Figure 67: Schematic of an exemplary embodiment of the Gen 3 process (a 14-16 day process).

[00199] Figure 68: Summary of data from Day 16/17 of three engineering runs of an exemplary Gen 3 process embodiment.

[00200] Figure 69: Data regarding the extended phenotype of TIL: shown are the differentiation characteristics against TIL identity (ID) specifications for cells produced by two engineering runs of an exemplary Gen 3 process embodiment.

[00201] Figure 70: Data regarding the extended phenotype of TIL expanded from lung tumors: shown are the differentiation characteristics against TIL identity (ID) specifications for cells produced by two process development (PD) runs of an exemplary Gen 3 process embodiment using lung tumor tissues.

[00202] Figure 71: Data regarding the extended phenotype (purity, identity and memory) of TIL expanded from ovarian tumors: shown are the purity, identity and memory phenotypic characteristics of cells expanded from ovarian tumors using exemplary Gen 2, Gen 3.1, and FR ER (Frozen tumor, Early REP) process embodiments; * indicates condition not tested; Y indicates sampling issue, low TVC count or non-viable cells on thawing.

[00203] Figure 72: Shown is the gating strategy for characterization of TIL (gating hierarchy is shown) and data regarding the extended phenotypic characteristics of cells produced by two engineering runs of an exemplary Gen 3 process embodiment.

[00204] Figure 73: Shown is the gating strategy for characterization of TIL (gating hierarchy is shown) and data regarding the extended phenotypic characteristics of the CD4+ subpopulation and the CD8+ subpopulation of cells produced by two engineering runs of an exemplary Gen 3 process embodiment.

[00205] Figure 74: Shown are data regarding Granzyme B ELISA analysis of cells produced by two engineering runs of an exemplary Gen 3 process embodiment.

[00206] Figure 75A-75B: Schematic of an exemplary embodiment of the Gen 3 process (a 16 day process).

[00207] Figure 76: Schematic of an exemplary embodiment of the Gen 3 process (a 16 day process).

[00208] Figure 77: Comparison of Gen 2, Gen 2.1 and an embodiment of the Gen 3 process (a 16 day process).

[00209] Figure 78: Comparison of Gen 2, Gen 2.1 and an embodiment of the Gen 3 process (a 16 day process).

[00210] Figure 79: Gen 3 embodiment components.

- [00211] Figure 80: Gen 3 embodiment flow chart comparison (Gen 3.0, Gen 3.1 control, Gen 3.1 Test).
- **[00212] Figure 81:** Total viable cell count and fold expansion are presented for exemplary Gen 3 embodiments (Gen 3.0, Gen 3.1 Control and Gen 3.1 Test) using standard cell culture media and serum free cell culture media.
- [00213] Figure 82: % viability scores upon reactivation, culture scale up and TIL harvest are presented for exemplary Gen 3 embodiments (Gen 3.0, Gen 3.1 Control and Gen 3.1 Test) using standard cell culture media and serum free cell culture media.
- [00214] Figure 83: Presented is phenotypic characterization of final TIL product produced by processing L4063 and L4064 tumor samples in exemplary Gen 3 processes (Gen 3.0, Gen 3.1 Control and Gen 3.1 Test) using standard cell culture media and CTS serum free cell culture media.
- **[00215] Figure 84:** Presented is memory marker analysis of TIL product produced by processing L4063 and L4064 tumor samples in exemplary Gen 3 processes (Gen 3.0, Gen 3.1 Control and Gen 3.1 Test) using standard cell culture media and CTS serum free cell culture media.
- **[00216] Figure 85:** Presented are activation and exhaustion markers of TIL produced by processing L4063 and L4064 tumor samples in exemplary Gen 3 processes (Gen 3.0, Gen 3.1 Control and Gen 3.1 Test) using standard cell culture media and CTS serum free cell culture media followed by CD4+ gated cell sorting.
- **[00217] Figure 86:** Presented are activation and exhaustion markers of TIL produced by processing L4063 and L4064 tumor samples in exemplary Gen 3 processes (Gen 3.0, Gen 3.1 Control and Gen 3.1 Test) using standard cell culture media and CTS serum free cell culture media followed by CD8+ gated cell sorting.
- **[00218] Figure 87:** Presented are IFN-γ production (pg/mL) scores for final TIL product produced by processing L4063 and L4064 tumor samples in exemplary Gen 3 processes (Gen 3.0, Gen 3.1 Control and Gen 3.1 Test) using standard cell culture media and CTS serum free cell culture media.
- [00219] Figure 88: Presented is IL-2 concentration (pg/mL) analysis of spent media (collected upon reactivation, culture scale up and TIL harvest) from processing L4063 and

L4064 tumor samples in exemplary Gen 3 processes (Gen 3.0, Gen 3.1 Control and Gen 3.1 Test) using standard cell culture media and CTS serum free cell culture media.

- **[00220]** Figure 89: Presented is concentration of glucose (g/L) in spent media (collected upon reactivation, culture scale up and TIL harvest) from processing L4063 and L4064 tumor samples in exemplary Gen 3 processes (Gen 3.0, Gen 3.1 Control and Gen 3.1 Test) using standard cell culture media and CTS serum free cell culture media.
- **[00221] Figure 90:** Presented is concentration of lactate (g/L) in spent media (collected upon reactivation, culture scale up and TIL harvest) from processing L4063 and L4064 tumor samples in exemplary Gen 3 processes (Gen 3.0, Gen 3.1 Control and Gen 3.1 Test) using standard cell culture media and CTS serum free cell culture media.
- [00222] Figure 91: Presented is concentration of glutamine (mmol/L) in spent media (collected upon reactivation, culture scale up and TIL harvest) from processing L4063 and L4064 tumor samples in exemplary Gen 3 processes (Gen 3.0, Gen 3.1 Control and Gen 3.1 Test) using standard cell culture media and CTS serum free cell culture media.
- [00223] Figure 92: Presented is concentration of glutamax (mmol/L) in spent media (collected upon reactivation, culture scale up and TIL harvest) from processing L4063 and L4064 tumor samples in exemplary Gen 3 processes (Gen 3.0, Gen 3.1 Control and Gen 3.1 Test) using standard cell culture media and CTS serum free cell culture media.
- [00224] Figure 93: Presented is concentration of ammonia (mmol/L) in spent media (collected upon reactivation, culture scale up and TIL harvest) from processing L4063 and L4064tumor samples in exemplary Gen 3 processes (Gen 3.0, Gen 3.1 Control and Gen 3.1 Test) using standard cell culture media and CTS serum free cell culture media. Telomere length analysis on exemplary embodiments of the Gen 3 process (Gen 3.0, Gen 3.1 Control, Gen 3.1 Test). Telomere length analysis for cells yielded by tumor identification numbers L4063 and L4064: the relative telomere length (RTL) value indicates the average telomere fluorescence per chromosome/genome in cells produced by the Gen 3.0, Gen 3.1 Control and Gen 3.1 Test processes over the telomere fluorescence per chromosome/genome in the control cells line (1301 Leukemia cell line) using DAKO kit.
- **[00225] Figure 94:** Telomere length analysis on TIL produced by exemplary embodiments of the Gen 3 process (Gen 3.0, Gen 3.1 Control, Gen 3.1 Test) using standard cell culture media and CTS serum free cell culture media. Telomere length analysis for cells yielded by tumor identification numbers L4063 and L4064: the relative telomere length (RTL) value

indicates the average telomere fluorescence per chromosome/genome in cells produced by the Gen 3.0, Gen 3.1 Control and Gen 3.1 Test processes over the telomere fluorescence per chromosome/genome in the control cells line (1301 Leukemia cell line) using DAKO kit.

[00226] Figure 95: TCR V β repertoire summary for TIL produced by exemplary embodiments of the Gen 3 process (Gen 3.0, Gen 3.1 Control, Gen 3.1 Test) using standard cell culture media and CTS serum free cell culture media. Described is the clonality of TIL for final TIL product yielded by tumor identification numbers L4063 and L4064 produced by the Gen 3.0, Gen 3.1 Control and Gen 3.1 Test processes as measured by the TCR V β repertoire of unique CDR3 sequences.

[00227] Figure 96: Comparison of TIL produced by exemplary embodiments of the Gen 3 process (Gen 3.0, Gen 3.1 Control, Gen 3.1 Test) with respect to frequency of unique CDR3 sequences in TIL harvested product from processing of L4063 tumor samples.

[00228] Figure 97: Comparison of TIL produced by exemplary embodiments of the Gen 3 process (Gen 3.0, Gen 3.1 Control, Gen 3.1 Test) with respect to percentage shared unique CDR3 sequences in TIL harvested cell product from processing of L4063 tumor samples: 975 sequences are shared between Gen 3.0 and Gen 3.1 Test final product, equivalent to 88% of top 80% of unique CDR3 sequences from Gen 3.0 shared with Gen 3.1 Test final product.

[00229] Figure 98: Comparison of TIL produced by exemplary embodiments of the Gen 3 process (Gen 3.0, Gen 3.1 Control, Gen 3.1 Test) with respect to percentage shared unique CDR3 sequences in TIL harvested cell product for from processing of L4064 tumor samples: 2163 sequences are shared between Gen 3.0 and Gen 3.1 Test final product, equivalent to 87% of top 80% of unique CDR3 sequences from Gen 3.0 shared with Gen 3.1 Test final product.

[00230] Figure 99: Comparison of TIL produced by exemplary embodiments of the Gen 3 process (Gen 3.0, Gen 3.1 Control, Gen 3.1 Test) with respect to frequency of unique CDR3 sequences in TIL harvested product from processing of L4064 tumor samples.

[00231] Figure 100: Shown are the components of an exemplary embodiment of the Gen 3 process (Gen 3-Optimized, a 16-17 day process).

[00232] Figure 101: Acceptance criteria table.

[00233] Figure 102: Cell counts reactivation Day.

[00234] Figure 103: Cell counts Scale Up Day.

- [00235] Figure 104: Cell counts Harvest L4063.
- [00236] Figure 105: Cell counts Harvest L4064.
- [00237] Figure 106: Flow data.
- [00238] Figure 107: Flow data.
- [00239] Figure 108: Flow data.
- [00240] Figure 109: Flow data.
- **[00241] Figure 110:** IFN-γ production Data Figure 7-L4063.
- [00242] Figure 111: Data IFN-γ production Figure 7-L4064.
- [00243] Figure 112: ELISA analysis of IL-2 concentration data.
- [00244] Figure 113: Metabolic data summary table.
- [00245] Figure 114: Summary data.
- [00246] Figure 115: Summary data.
- [00247] Figure 116: Shannon diversity index.

BRIEF DESCRIPTION OF THE SEQUENCE LISTING

- [00248] SEQ ID NO:1 is the amino acid sequence of the heavy chain of muromonab.
- [00249] SEQ ID NO:2 is the amino acid sequence of the light chain of muromonab.
- [00250] SEQ ID NO:3 is the amino acid sequence of a recombinant human IL-2 protein.
- [00251] SEQ ID NO:4 is the amino acid sequence of aldesleukin.
- [00252] SEQ ID NO:5 is the amino acid sequence of a recombinant human IL-4 protein.
- [00253] SEQ ID NO:6 is the amino acid sequence of a recombinant human IL-7 protein.
- [00254] SEQ ID NO:7 is the amino acid sequence of a recombinant human IL-15 protein.
- [00255] SEQ ID NO:8 is the amino acid sequence of a recombinant human IL-21 protein.
- [00256] SEQ ID NO:9 is the amino acid sequence of human 4-1BB.
- [00257] SEQ ID NO:10 is the amino acid sequence of murine 4-1BB.

[00258] SEQ ID NO:11 is the heavy chain for the 4-1BB agonist monoclonal antibody utomilumab (PF-05082566).

[00259] SEQ ID NO:12 is the light chain for the 4-1BB agonist monoclonal antibody utomilumab (PF-05082566).

[00260] SEQ ID NO:13 is the heavy chain variable region (VH) for the 4-1BB agonist monoclonal antibody utomilumab (PF-05082566).

[00261] SEQ ID NO:14 is the light chain variable region (VL) for the 4-1BB agonist monoclonal antibody utomilumab (PF-05082566).

[00262] SEQ ID NO:15 is the heavy chain CDRl for the 4-1BB agonist monoclonal antibody utomilumab (PF-05082566).

[00263] SEQ ID NO:16 is the heavy chain CDR2 for the 4-1BB agonist monoclonal antibody utomilumab (PF-05082566).

[00264] SEQ ID NO:17 is the heavy chain CDR3 for the 4-1BB agonist monoclonal antibody utomilumab (PF-05082566).

[00265] SEQ ID NO:18 is the light chain CDR1 for the 4-1BB agonist monoclonal antibody utomilumab (PF-05082566).

[00266] SEQ ID NO:19 is the light chain CDR2 for the 4-1BB agonist monoclonal antibody utomilumab (PF-05082566).

[00267] SEQ ID NO:20 is the light chain CDR3 for the 4-1BB agonist monoclonal antibody utomilumab (PF-05082566).

[00268] SEQ ID NO:21 is the heavy chain for the 4-1BB agonist monoclonal antibody urelumab (BMS-663513).

[00269] SEQ ID NO:22 is the light chain for the 4-1BB agonist monoclonal antibody urelumab (BMS-663513).

[00270] SEQ ID NO:23 is the heavy chain variable region (VH) for the 4-1BB agonist monoclonal antibody urelumab (BMS-663513).

[00271] SEQ ID NO:24 is the light chain variable region (VL) for the 4-1BB agonist monoclonal antibody urelumab (BMS-663513).

- [00272] SEQ ID NO:25 is the heavy chain CDR1 for the 4-1BB agonist monoclonal antibody urelumab (BMS-663513).
- [00273] SEQ ID NO:26 is the heavy chain CDR2 for the 4-1BB agonist monoclonal antibody urelumab (BMS-663513).
- [00274] SEQ ID NO:27 is the heavy chain CDR3 for the 4-1BB agonist monoclonal antibody urelumab (BMS-663513).
- [00275] SEQ ID NO:28 is the light chain CDR1 for the 4-1BB agonist monoclonal antibody urelumab (BMS-663513).
- [00276] SEQ ID NO:29 is the light chain CDR2 for the 4-1BB agonist monoclonal antibody urelumab (BMS-663513).
- [00277] SEQ ID NO:30 is the light chain CDR3 for the 4-1BB agonist monoclonal antibody urelumab (BMS-663513).
- [00278] SEQ ID NO:31 is an Fc domain for a TNFRSF agonist fusion protein.
- [00279] SEQ ID NO:32 is a linker for a TNFRSF agonist fusion protein.
- [00280] SEQ ID NO:33 is a linker for a TNFRSF agonist fusion protein.
- [00281] SEQ ID NO:34 is a linker for a TNFRSF agonist fusion protein.
- [00282] SEQ ID NO:35 is a linker for a TNFRSF agonist fusion protein.
- [00283] SEQ ID NO:36 is a linker for a TNFRSF agonist fusion protein.
- [00284] SEQ ID NO:37 is a linker for a TNFRSF agonist fusion protein.
- [00285] SEQ ID NO:38 is a linker for a TNFRSF agonist fusion protein.
- [00286] SEQ ID NO:39 is a linker for a TNFRSF agonist fusion protein.
- [00287] SEQ ID NO:40 is a linker for a TNFRSF agonist fusion protein.
- [00288] SEQ ID NO:41 is a linker for a TNFRSF agonist fusion protein.
- [00289] SEQ ID NO:42 is an Fc domain for a TNFRSF agonist fusion protein.
- [00290] SEQ ID NO:43 is a linker for a TNFRSF agonist fusion protein.
- [00291] SEQ ID NO:44 is a linker for a TNFRSF agonist fusion protein.
- [00292] SEQ ID NO:45 is a linker for a TNFRSF agonist fusion protein.

[00293] SEQ ID NO:46 is a 4-1BB ligand (4-1BBL) amino acid sequence.

[00294] SEQ ID NO:47 is a soluble portion of 4-1BBL polypeptide.

[00295] SEQ ID NO:48 is a heavy chain variable region (VH) for the 4-1BB agonist antibody 4B4-1-1 version 1.

[00296] SEQ ID NO:49 is a light chain variable region (VL) for the 4-1BB agonist antibody 4B4-1-1 version 1.

[00297] SEQ ID NO:50 is a heavy chain variable region (VH) for the 4-1BB agonist antibody 4B4-1-1 version 2.

[00298] SEQ ID NO:51 is a light chain variable region (VL) for the 4-1BB agonist antibody 4B4-1-1 version 2.

[00299] SEQ ID NO:52 is a heavy chain variable region (VH) for the 4-1BB agonist antibody H39E3-2.

[00300] SEQ ID NO:53 is a light chain variable region (VL) for the 4-1BB agonist antibody H39E3-2.

[00301] SEQ ID NO:54 is the amino acid sequence of human OX40.

[00302] SEQ ID NO:55 is the amino acid sequence of murine OX40.

[00303] SEQ ID NO:56 is the heavy chain for the OX40 agonist monoclonal antibody tavolixizumab (MEDI-0562).

[00304] SEQ ID NO:57 is the light chain for the OX40 agonist monoclonal antibody tavolixizumab (MEDI-0562).

[00305] SEQ ID NO:58 is the heavy chain variable region (VH) for the OX40 agonist monoclonal antibody tavolixizumab (MEDI-0562).

[00306] SEQ ID NO:59 is the light chain variable region (VL) for the OX40 agonist monoclonal antibody tavolixizumab (MEDI-0562).

[00307] SEQ ID NO:60 is the heavy chain CDRl for the OX40 agonist monoclonal antibody tavolixizumab (MEDI-0562).

[00308] SEQ ID NO:61 is the heavy chain CDR2 for the OX40 agonist monoclonal antibody tavolixizumab (MEDI-0562).

[00309] SEQ ID NO:62 is the heavy chain CDR3 for the OX40 agonist monoclonal antibody tavolixizumab (MEDI-0562).

[00310] SEQ ID NO:63 is the light chain CDR1 for the OX40 agonist monoclonal antibody tavolixizumab (MEDI-0562).

[00311] SEQ ID NO:64 is the light chain CDR2 for the OX40 agonist monoclonal antibody tavolixizumab (MEDI-0562).

[00312] SEQ ID NO:65 is the light chain CDR3 for the OX40 agonist monoclonal antibody tavolixizumab (MEDI-0562).

[00313] SEQ ID NO:66 is the heavy chain for the OX40 agonist monoclonal antibody 11D4.

[00314] SEQ ID NO:67 is the light chain for the OX40 agonist monoclonal antibody 11D4.

[00315] SEQ ID NO:68 is the heavy chain variable region (VH) for the OX40 agonist monoclonal antibody 11D4.

[00316] SEQ ID NO:69 is the light chain variable region (VL) for the OX40 agonist monoclonal antibody 11D4.

[00317] SEQ ID NO:70 is the heavy chain CDRl for the OX40 agonist monoclonal antibody 11D4.

[00318] SEQ ID NO:71 is the heavy chain CDR2 for the OX40 agonist monoclonal antibody 11D4.

[00319] SEQ ID NO:72 is the heavy chain CDR3 for the OX40 agonist monoclonal antibody 11D4.

[00320] SEQ ID NO:73 is the light chain CDR1 for the OX40 agonist monoclonal antibody 11D4.

[00321] SEQ ID NO:74 is the light chain CDR2 for the OX40 agonist monoclonal antibody 11D4.

[00322] SEQ ID NO:75 is the light chain CDR3 for the OX40 agonist monoclonal antibody 11D4.

[00323] SEQ ID NO:76 is the heavy chain for the OX40 agonist monoclonal antibody 18D8.

[00324] SEQ ID NO:77 is the light chain for the OX40 agonist monoclonal antibody 18D8.

[00325] SEQ ID NO:78 is the heavy chain variable region (VH) for the OX40 agonist monoclonal antibody 18D8.

[00326] SEQ ID NO:79 is the light chain variable region (VL) for the OX40 agonist monoclonal antibody 18D8.

[00327] SEQ ID NO:80 is the heavy chain CDRl for the OX40 agonist monoclonal antibody 18D8.

[00328] SEQ ID NO:81 is the heavy chain CDR2 for the OX40 agonist monoclonal antibody 18D8.

[00329] SEQ ID NO:82 is the heavy chain CDR3 for the OX40 agonist monoclonal antibody 18D8.

[00330] SEQ ID NO:83 is the light chain CDR1 for the OX40 agonist monoclonal antibody 18D8.

[00331] SEQ ID NO:84 is the light chain CDR2 for the OX40 agonist monoclonal antibody 18D8.

[00332] SEQ ID NO:85 is the light chain CDR3 for the OX40 agonist monoclonal antibody 18D8.

[00333] SEQ ID NO:86 is the heavy chain variable region (VH) for the OX40 agonist monoclonal antibody Hu119-122.

[00334] SEQ ID NO:87 is the light chain variable region (VL) for the OX40 agonist monoclonal antibody Hu119-122.

[00335] SEQ ID NO:88 is the heavy chain CDRl for the OX40 agonist monoclonal antibody Hu119-122.

[00336] SEQ ID NO:89 is the heavy chain CDR2 for the OX40 agonist monoclonal antibody Hu119-122.

[00337] SEQ ID NO:90 is the heavy chain CDR3 for the OX40 agonist monoclonal antibody Hu119-122.

[00338] SEQ ID NO:91 is the light chain CDR1 for the OX40 agonist monoclonal antibody Hu119-122.

[00339] SEQ ID NO:92 is the light chain CDR2 for the OX40 agonist monoclonal antibody Hu119-122.

[00340] SEQ ID NO:93 is the light chain CDR3 for the OX40 agonist monoclonal antibody Hu119-122.

[00341] SEQ ID NO:94 is the heavy chain variable region (VH) for the OX40 agonist monoclonal antibody Hu106-222.

[00342] SEQ ID NO:95 is the light chain variable region (VL) for the OX40 agonist monoclonal antibody Hu106-222.

[00343] SEQ ID NO:96 is the heavy chain CDRl for the OX40 agonist monoclonal antibody Hu106-222.

[00344] SEQ ID NO:97 is the heavy chain CDR2 for the OX40 agonist monoclonal antibody Hu106-222.

[00345] SEQ ID NO:98 is the heavy chain CDR3 for the OX40 agonist monoclonal antibody Hu106-222.

[00346] SEQ ID NO:99 is the light chain CDR1 for the OX40 agonist monoclonal antibody Hu106-222.

[00347] SEQ ID NO:100 is the light chain CDR2 for the OX40 agonist monoclonal antibody Hu106-222.

[00348] SEQ ID NO:101 is the light chain CDR3 for the OX40 agonist monoclonal antibody Hu106-222.

[00349] SEQ ID NO:102 is an OX40 ligand (OX40L) amino acid sequence.

[00350] SEQ ID NO:103 is a soluble portion of OX40L polypeptide.

[00351] SEQ ID NO:104 is an alternative soluble portion of OX40L polypeptide.

[00352] SEQ ID NO:105 is the heavy chain variable region (VH) for the OX40 agonist monoclonal antibody 008.

[00353] SEQ ID NO:106 is the light chain variable region (VL) for the OX40 agonist monoclonal antibody 008.

[00354] SEQ ID NO:107 is the heavy chain variable region (VH) for the OX40 agonist monoclonal antibody 011.

[00355] SEQ ID NO:108 is the light chain variable region (VL) for the OX40 agonist monoclonal antibody 011.

[00356] SEQ ID NO:109 is the heavy chain variable region (VH) for the OX40 agonist monoclonal antibody 021.

[00357] SEQ ID NO:110 is the light chain variable region (VL) for the OX40 agonist monoclonal antibody 021.

[00358] SEQ ID NO:111 is the heavy chain variable region (VH) for the OX40 agonist monoclonal antibody 023.

[00359] SEQ ID NO:112 is the light chain variable region (VL) for the OX40 agonist monoclonal antibody 023.

[00360] SEQ ID NO:113 is the heavy chain variable region (VH) for an OX40 agonist monoclonal antibody.

[00361] SEQ ID NO:114 is the light chain variable region (VL) for an OX40 agonist monoclonal antibody.

[00362] SEQ ID NO:115 is the heavy chain variable region (VH) for an OX40 agonist monoclonal antibody.

[00363] SEQ ID NO:116 is the light chain variable region (VL) for an OX40 agonist monoclonal antibody.

[00364] SEQ ID NO:117 is the heavy chain variable region (VH) for a humanized OX40 agonist monoclonal antibody.

[00365] SEQ ID NO:118 is the heavy chain variable region (VH) for a humanized OX40 agonist monoclonal antibody.

[00366] SEQ ID NO:119 is the light chain variable region (VL) for a humanized OX40 agonist monoclonal antibody.

[00367] SEQ ID NO:120 is the light chain variable region (VL) for a humanized OX40 agonist monoclonal antibody.

[00368] SEQ ID NO:121 is the heavy chain variable region (VH) for a humanized OX40 agonist monoclonal antibody.

[00369] SEQ ID NO:122 is the heavy chain variable region (VH) for a humanized OX40 agonist monoclonal antibody.

[00370] SEQ ID NO:123 is the light chain variable region (VL) for a humanized OX40 agonist monoclonal antibody.

[00371] SEQ ID NO:124 is the light chain variable region (VL) for a humanized OX40 agonist monoclonal antibody.

[00372] SEQ ID NO:125 is the heavy chain variable region (VH) for an OX40 agonist monoclonal antibody.

[00373] SEQ ID NO:126 is the light chain variable region (VL) for an OX40 agonist monoclonal antibody.

[00374] SEQ ID NO:127-462 are currently not assigned.

[00375] SEQ ID NO:463 is the heavy chain amino acid sequence of the PD-1 inhibitor nivolumab.

[00376] SEQ ID NO:464 is the light chain amino acid sequence of the PD-1 inhibitor nivolumab.

[00377] SEQ ID NO:465 is the heavy chain variable region (V_H) amino acid sequence of the PD-1 inhibitor nivolumab.

[00378] SEQ ID NO:466 is the light chain variable region (V_L) amino acid sequence of the PD-1 inhibitor nivolumab.

[00379] SEQ ID NO:467 is the heavy chain CDR1 amino acid sequence of the PD-1 inhibitor nivolumab.

[00380] SEQ ID NO:468 is the heavy chain CDR2 amino acid sequence of the PD-1 inhibitor nivolumab.

[00381] SEQ ID NO:469 is the heavy chain CDR3 amino acid sequence of the PD-1 inhibitor nivolumab.

[00382] SEQ ID NO:470 is the light chain CDR1 amino acid sequence of the PD-1 inhibitor nivolumab.

[00383] SEQ ID NO:471 is the light chain CDR2 amino acid sequence of the PD-1 inhibitor nivolumab.

[00384] SEQ ID NO:472 is the light chain CDR3 amino acid sequence of the PD-1 inhibitor nivolumab.

[00385] SEQ ID NO:473 is the heavy chain amino acid sequence of the PD-1 inhibitor pembrolizumab.

[00386] SEQ ID NO:474 is the light chain amino acid sequence of the PD-1 inhibitor pembrolizumab.

[00387] SEQ ID NO:475 is the heavy chain variable region (V_H) amino acid sequence of the PD-1 inhibitor pembrolizumab.

[00388] SEQ ID NO:476 is the light chain variable region (V_L) amino acid sequence of the PD-1 inhibitor pembrolizumab.

[00389] SEQ ID NO:477 is the heavy chain CDR1 amino acid sequence of the PD-1 inhibitor pembrolizumab.

[00390] SEQ ID NO:478 is the heavy chain CDR2 amino acid sequence of the PD-1 inhibitor pembrolizumab.

[00391] SEQ ID NO:479 is the heavy chain CDR3 amino acid sequence of the PD-1 inhibitor pembrolizumab.

[00392] SEQ ID NO:480 is the light chain CDR1 amino acid sequence of the PD-1 inhibitor pembrolizumab.

[00393] SEQ ID NO:481 is the light chain CDR2 amino acid sequence of the PD-1 inhibitor pembrolizumab.

[00394] SEQ ID NO:482 is the light chain CDR3 amino acid sequence of the PD-1 inhibitor pembrolizumab.

[00395] SEQ ID NO:483 is the heavy chain amino acid sequence of the PD-L1 inhibitor durvalumab.

[00396] SEQ ID NO:484 is the light chain amino acid sequence of the PD-L1 inhibitor durvalumab.

[00397] SEQ ID NO:485 is the heavy chain variable region (V_H) amino acid sequence of the PD-L1 inhibitor durvalumab.

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[00398] SEQ ID NO:486 is the light chain variable region (V_L) amino acid sequence of the PD-L1 inhibitor durvalumab.

[00399] SEQ ID NO:487 is the heavy chain CDR1 amino acid sequence of the PD-L1 inhibitor durvalumab.

[00400] SEQ ID NO:488 is the heavy chain CDR2 amino acid sequence of the PD-L1 inhibitor durvalumab.

[00401] SEQ ID NO:489 is the heavy chain CDR3 amino acid sequence of the PD-L1 inhibitor durvalumab.

[00402] SEQ ID NO:490 is the light chain CDR1 amino acid sequence of the PD-L1 inhibitor durvalumab.

[00403] SEQ ID NO:491 is the light chain CDR2 amino acid sequence of the PD-L1 inhibitor durvalumab.

[00404] SEQ ID NO:492 is the light chain CDR3 amino acid sequence of the PD-L1 inhibitor durvalumab.

[00405] SEQ ID NO:493 is the heavy chain amino acid sequence of the PD-L1 inhibitor avelumab.

[00406] SEQ ID NO:494 is the light chain amino acid sequence of the PD-L1 inhibitor avelumab.

[00407] SEQ ID NO:495 is the heavy chain variable region (V_H) amino acid sequence of the PD-L1 inhibitor avelumab.

[00408] SEQ ID NO:496 is the light chain variable region (V_L) amino acid sequence of the PD-L1 inhibitor avelumab.

[00409] SEQ ID NO:497 is the heavy chain CDR1 amino acid sequence of the PD-L1 inhibitor avelumab.

[00410] SEQ ID NO:498 is the heavy chain CDR2 amino acid sequence of the PD-L1 inhibitor avelumab.

[00411] SEQ ID NO:499 is the heavy chain CDR3 amino acid sequence of the PD-L1 inhibitor avelumab.

[00412] SEQ ID NO:500 is the light chain CDR1 amino acid sequence of the PD-L1 inhibitor avelumab.

[00413] SEQ ID NO:501 is the light chain CDR2 amino acid sequence of the PD-L1 inhibitor avelumab.

[00414] SEQ ID NO:502 is the light chain CDR3 amino acid sequence of the PD-L1 inhibitor avelumab.

[00415] SEQ ID NO:503 is the heavy chain amino acid sequence of the PD-L1 inhibitor atezolizumab.

[00416] SEQ ID NO:504 is the light chain amino acid sequence of the PD-L1 inhibitor atezolizumab.

[00417] SEQ ID NO:505 is the heavy chain variable region (V_H) amino acid sequence of the PD-L1 inhibitor atezolizumab.

[00418] SEQ ID NO:506 is the light chain variable region (V_L) amino acid sequence of the PD-L1 inhibitor atezolizumab.

[00419] SEQ ID NO:507 is the heavy chain CDR1 amino acid sequence of the PD-L1 inhibitor atezolizumab.

[00420] SEQ ID NO:508 is the heavy chain CDR2 amino acid sequence of the PD-L1 inhibitor atezolizumab.

[00421] SEQ ID NO:509 is the heavy chain CDR3 amino acid sequence of the PD-L1 inhibitor atezolizumab.

[00422] SEQ ID NO:510 is the light chain CDR1 amino acid sequence of the PD-L1 inhibitor atezolizumab.

[00423] SEQ ID NO:511 is the light chain CDR2 amino acid sequence of the PD-L1 inhibitor atezolizumab.

[00424] SEQ ID NO:512 is the light chain CDR3 amino acid sequence of the PD-L1 inhibitor atezolizumab.

[00425]

DETAILED DESCRIPTION OF THE INVENTION

I. Introduction

[00426] Adoptive cell therapy utilizing TILs cultured *ex vivo* by the Rapid Expansion Protocol (REP) has produced successful adoptive cell therapy following host immunosuppression in patients with cancer such as melanoma. Current infusion acceptance parameters rely on readouts of the composition of TILs (*e.g.*, CD28, CD8, or CD4 positivity) and on the numerical folds of expansion and viability of the REP product.

[00427] Current REP protocols give little insight into the health of the TIL that will be infused into the patient. T cells undergo a profound metabolic shift during the course of their maturation from naïve to effector T cells (see Chang, *et al.*, *Nat. Immunol.* 2016, *17*, 364, hereby expressly incorporated in its entirety, and in particular for the discussion and markers of anaerobic and aerobic metabolism). For example, naïve T cells rely on mitochondrial respiration to produce ATP, while mature, healthy effector T cells such as TIL are highly glycolytic, relying on aerobic glycolysis to provide the bioenergetics substrates they require for proliferation, migration, activation, and anti-tumor efficacy.

[00428] Current TIL manufacturing and treatment processes are limited by length, cost, sterility concerns, and other factors described herein such that the potential to treat patients which are refractory to anti-PD1 and as such have been severly limited. There is an urgent need to provide TIL manufacturing processes and therapies based on such processes that are appropriate for use in treating patients for whom very few or no viable treatment options remain. The present invention meets this need by providing a shortened manufacturing process for use in generating TILs which can then be employed in the treatment of non-small cell lung carcinoma (NSCLC) patients whom are refractory to anti-PD-1 treatment.

II. Definitions

[00429] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are incorporated by reference in their entireties.

[00430] The terms "co-administration," "co-administering," "administered in combination with," "administering in combination with," "simultaneous," and "concurrent,"

as used herein, encompass administration of two or more active pharmaceutical ingredients (in a preferred embodiment of the present invention, for example, a plurality of TILs) to a subject so that both active pharmaceutical ingredients and/or their metabolites are present in the subject at the same time. Co-administration includes simultaneous administration in separate compositions, administration at different times in separate compositions, or administration in a composition in which two or more active pharmaceutical ingredients are present. Simultaneous administration in separate compositions and administration in a composition in which both agents are present are preferred.

[00431] The term "in vivo" refers to an event that takes place in a subject's body.

[00432] The term "in vitro" refers to an event that takes places outside of a subject's body. In vitro assays encompass cell-based assays in which cells alive or dead are employed and may also encompass a cell-free assay in which no intact cells are employed.

[00433] The term "ex vivo" refers to an event which involves treating or performing a procedure on a cell, tissue and/or organ which has been removed from a subject's body. Aptly, the cell, tissue and/or organ may be returned to the subject's body in a method of surgery or treatment.

[00434] The term "rapid expansion" means an increase in the number of antigen-specific TILs of at least about 3-fold (or 4-, 5-, 6-, 7-, 8-, or 9-fold) over a period of a week, more preferably at least about 10-fold (or 20-, 30-, 40-, 50-, 60-, 70-, 80-, or 90-fold) over a period of a week, or most preferably at least about 100-fold over a period of a week. A number of rapid expansion protocols are described herein.

[00435]

[00436] By "tumor infiltrating lymphocytes" or "TILs" herein is meant a population of cells originally obtained as white blood cells that have left the bloodstream of a subject and migrated into a tumor. TILs include, but are not limited to, CD8⁺ cytotoxic T cells (lymphocytes), Th1 and Th17 CD4⁺ T cells, natural killer cells, dendritic cells and M1 macrophages. TILs include both primary and secondary TILs. "Primary TILs" are those that are obtained from patient tissue samples as outlined herein (sometimes referred to as "freshly harvested"), and "secondary TILs" are any TIL cell populations that have been expanded or proliferated as discussed herein, including, but not limited to bulk TILs and expanded TILs ("REP TILs" or "post-REP TILs"). TIL cell populations can include genetically modified TILs.

[00437] By "population of cells" (including TILs) herein is meant a number of cells that share common traits. In general, populations generally range from 1×10^6 to 1×10^{10} in number, with different TIL populations comprising different numbers. For example, initial growth of primary TILs in the presence of IL-2 results in a population of bulk TILs of roughly 1×10^8 cells. REP expansion is generally done to provide populations of 1.5×10^9 to 1.5×10^{10} cells for infusion.

[00438] By "cryopreserved TILs" herein is meant that TILs, either primary, bulk, or expanded (REP TILs), are treated and stored in the range of about -150°C to -60°C. General methods for cryopreservation are also described elsewhere herein, including in the Examples. For clarity, "cryopreserved TILs" are distinguishable from frozen tissue samples which may be used as a source of primary TILs.

[00439] By "thawed cryopreserved TILs" herein is meant a population of TILs that was previously cryopreserved and then treated to return to room temperature or higher, including but not limited to cell culture temperatures or temperatures wherein TILs may be administered to a patient.

[00440] TILs can generally be defined either biochemically, using cell surface markers, or functionally, by their ability to infiltrate tumors and effect treatment. TILs can be generally categorized by expressing one or more of the following biomarkers: CD4, CD8, TCR $\alpha\beta$, CD27, CD28, CD56, CCR7, CD45Ra, CD95, PD-1, and CD25. Additionally and alternatively, TILs can be functionally defined by their ability to infiltrate solid tumors upon reintroduction into a patient.

[00441] The term "cryopreservation media" or "cryopreservation medium" refers to any medium that can be used for cryopreservation of cells. Such media can include media comprising 7% to 10% DMSO. Exemplary media include CryoStor CS10, Hyperthermasol, as well as combinations thereof. The term "CS10" refers to a cryopreservation medium which is obtained from Stemcell Technologies or from Biolife Solutions. The CS10 medium may be referred to by the trade name "CryoStor® CS10". The CS10 medium is a serum-free, animal component-free medium which comprises DMSO.

[00442] The term "central memory T cell" refers to a subset of T cells that in the human are CD45R0+ and constitutively express CCR7 (CCR7^{hi}) and CD62L (CD62^{hi}). The surface phenotype of central memory T cells also includes TCR, CD3, CD127 (IL-7R), and IL-15R. Transcription factors for central memory T cells include BCL-6, BCL-6B, MBD2, and BMI1.

Central memory T cells primarily secret IL-2 and CD40L as effector molecules after TCR triggering. Central memory T cells are predominant in the CD4 compartment in blood, and in the human are proportionally enriched in lymph nodes and tonsils.

[00443] The term "effector memory T cell" refers to a subset of human or mammalian T cells that, like central memory T cells, are CD45R0+, but have lost the constitutive expression of CCR7 (CCR7^{lo}) and are heterogeneous or low for CD62L expression (CD62L^{lo}). The surface phenotype of central memory T cells also includes TCR, CD3, CD127 (IL-7R), and IL-15R. Transcription factors for central memory T cells include BLIMP1. Effector memory T cells rapidly secret high levels of inflammatory cytokines following antigenic stimulation, including interferon-γ, IL-4, and IL-5. Effector memory T cells are predominant in the CD8 compartment in blood, and in the human are proportionally enriched in the lung, liver, and gut. CD8+ effector memory T cells carry large amounts of perforin.

[00444] The term "closed system" refers to a system that is closed to the outside environment. Any closed system appropriate for cell culture methods can be employed with the methods of the present invention. Closed systems include, for example, but are not limited to closed G-containers. Once a tumor segment is added to the closed system, the system is no opened to the outside environment until the TILs are ready to be administered to the patient.

[00445] The terms "fragmenting," "fragment," and "fragmented," as used herein to describe processes for disrupting a tumor, includes mechanical fragmentation methods such as crushing, slicing, dividing, and morcellating tumor tissue as well as any other method for disrupting the physical structure of tumor tissue.

[00446] The terms "peripheral blood mononuclear cells" and "PBMCs" refers to a peripheral blood cell having a round nucleus, including lymphocytes (T cells, B cells, NK cells) and monocytes. When used as an antigen presenting cell (PBMCs are a type of antigen-presenting cell), the peripheral blood mononuclear cells are preferably irradiated allogeneic peripheral blood mononuclear cells.

[00447] The terms "peripheral blood lymphocytes" and "PBLs" refer to T cells expanded from peripheral blood. In some embodiments, PBLs are separated from whole blood or apheresis product from a donor. In some embodiments, PBLs are separated from whole

blood or apheresis product from a donor by positive or negative selection of a T cell phenotype, such as the T cell phenotype of CD3+ CD45+.

[00448] The term "anti-CD3 antibody" refers to an antibody or variant thereof, *e.g.*, a monoclonal antibody and including human, humanized, chimeric or murine antibodies which are directed against the CD3 receptor in the T cell antigen receptor of mature T cells. Anti-CD3 antibodies include OKT-3, also known as muromonab. Anti-CD3 antibodies also include the UHCT1 clone, also known as T3 and CD3 ϵ . Other anti-CD3 antibodies include, for example, otelizizumab, teplizumab, and visilizumab.

[00449] The term "OKT-3" (also referred to herein as "OKT3") refers to a monoclonal antibody or biosimilar or variant thereof, including human, humanized, chimeric, or murine antibodies, directed against the CD3 receptor in the T cell antigen receptor of mature T cells, and includes commercially-available forms such as OKT-3 (30 ng/mL, MACS GMP CD3 pure, Miltenyi Biotech, Inc., San Diego, CA, USA) and muromonab or variants, conservative amino acid substitutions, glycoforms, or biosimilars thereof. The amino acid sequences of the heavy and light chains of muromonab are given in Table 1 (SEQ ID NO:1 and SEQ ID NO:2). A hybridoma capable of producing OKT-3 is deposited with the American Type Culture Collection and assigned the ATCC accession number CRL 8001. A hybridoma capable of producing OKT-3 is also deposited with European Collection of Authenticated Cell Cultures (ECACC) and assigned Catalogue No. 86022706.

TABLE 1. Amino acid sequences of muromonab.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:1	QVQLQQSGAE LARPGASVKM SCKASGYTFT RYTMHWVKQR PGQGLEWIGY INPSRGYTNY	60
Muromonab heavy	NQKFKDKATL TTDKSSSTAY MQLSSLTSED SAVYYCARYY DDHYCLDYWG QGTTLTVSSA	120
chain	KTTAPSVYPL APVCGGTTGS SVTLGCLVKG YFPEPVTLTW NSGSLSSGVH TFPAVLQSDL	180
	YTLSSSVTVT SSTWPSQSIT CNVAHPASST KVDKKIEPRP KSCDKTHTCP PCPAPELLGG	240
	PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN	300
	STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE	360
	LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW	420
	QQGNVFSCSV MHEALHNHYT QKSLSLSPGK	450
SEQ ID NO:2	QIVLTQSPAI MSASPGEKVT MTCSASSSVS YMNWYQQKSG TSPKRWIYDT SKLASGVPAH	60
Muromonab light	FRGSGSGTSY SLTISGMEAE DAATYYCQQW SSNPFTFGSG TKLEINRADT APTVSIFPPS	120
chain	SEQLTSGGAS VVCFLNNFYP KDINVKWKID GSERQNGVLN SWTDQDSKDS TYSMSSTLTL	180
	TKDEYERHNS YTCEATHKTS TSPIVKSFNR NEC	213

[00450] The term "IL-2" (also referred to herein as "IL2") refers to the T cell growth factor known as interleukin-2, and includes all forms of IL-2 including human and mammalian forms, conservative amino acid substitutions, glycoforms, biosimilars, and variants thereof. IL-2 is described, *e.g.*, in Nelson, *J. Immunol.* 2004, 172, 3983-88 and Malek, *Annu. Rev. Immunol.* 2008, 26, 453-79, the disclosures of which are incorporated by reference herein.

The amino acid sequence of recombinant human IL-2 suitable for use in the invention is given in Table 2 (SEQ ID NO:3). For example, the term IL-2 encompasses human, recombinant forms of IL-2 such as aldesleukin (PROLEUKIN, available commercially from multiple suppliers in 22 million IU per single use vials), as well as the form of recombinant IL-2 commercially supplied by CellGenix, Inc., Portsmouth, NH, USA (CELLGRO GMP) or ProSpec-Tany TechnoGene Ltd., East Brunswick, NJ, USA (Cat. No. CYT-209-b) and other commercial equivalents from other vendors. Aldesleukin (des-alanyl-1, serine-125 human IL-2) is a nonglycosylated human recombinant form of IL-2 with a molecular weight of approximately 15 kDa. The amino acid sequence of aldesleukin suitable for use in the invention is given in Table 2 (SEQ ID NO:4). The term IL-2 also encompasses pegylated forms of IL-2, as described herein, including the pegylated IL2 prodrug NKTR-214, available from Nektar Therapeutics, South San Francisco, CA, USA. NKTR-214 and pegylated IL-2 suitable for use in the invention is described in U.S. Patent Application Publication No. US 2014/0328791 A1 and International Patent Application Publication No. WO 2012/065086 Al, the disclosures of which are incorporated by reference herein. Alternative forms of conjugated IL-2 suitable for use in the invention are described in U.S. Patent Nos. 4,766,106, 5,206,344, 5,089,261 and 4902,502, the disclosures of which are incorporated by reference herein. Formulations of IL-2 suitable for use in the invention are described in U.S. Patent No. 6,706,289, the disclosure of which is incorporated by reference herein.

TABLE 2. Amino acid sequences of interleukins.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:3	MAPTSSSTKK TQLQLEHLLL DLQMILNGIN NYKNPKLTRM LTFKFYMPKK ATELKHLQCL	60
recombinant	EEELKPLEEV LNLAQSKNFH LRPRDLISNI NVIVLELKGS ETTFMCEYAD ETATIVEFLN	120
human IL-2	RWITFCQSII STLT	134
(rhIL-2)		
SEQ ID NO:4	PTSSSTKKTQ LQLEHLLLDL QMILNGINNY KNPKLTRMLT FKFYMPKKAT ELKHLQCLEE	60
Aldesleukin	ELKPLEEVLN LAQSKNFHLR PRDLISNINV IVLELKGSET TFMCEYADET ATIVEFLNRW	120
	ITFSQSIIST LT	132
SEQ ID NO:5	MHKCDITLQE IIKTLNSLTE QKTLCTELTV TDIFAASKNT TEKETFCRAA TVLRQFYSHH	60
recombinant	EKDTRCLGAT AQQFHRHKQL IRFLKRLDRN LWGLAGLNSC PVKEANQSTL ENFLERLKTI	120
human IL-4	MREKYSKCSS	130
(rhIL-4)		
SEQ ID NO:6	MDCDIEGKDG KQYESVLMVS IDQLLDSMKE IGSNCLNNEF NFFKRHICDA NKEGMFLFRA	60
recombinant	ARKLRQFLKM NSTGDFDLHL LKVSEGTTIL LNCTGQVKGR KPAALGEAQP TKSLEENKSL	120
human IL-7	KEQKKLNDLC FLKRLLQEIK TCWNKILMGT KEH	153
(rhIL-7)		
SEQ ID NO:7	MNWVNVISDL KKIEDLIQSM HIDATLYTES DVHPSCKVTA MKCFLLELQV ISLESGDASI	60
recombinant	HDTVENLIIL ANNSLSSNGN VTESGCKECE ELEEKNIKEF LQSFVHIVQM FINTS	115
human IL-15		
(rhIL-15)		
SEQ ID NO:8	MQDRHMIRMR QLIDIVDQLK NYVNDLVPEF LPAPEDVETN CEWSAFSCFQ KAQLKSANTG	60
recombinant	NNERIINVSI KKLKRKPPST NAGRRQKHRL TCPSCDSYEK KPPKEFLERF KSLLQKMIHQ	120
human IL-21	HLSSRTHGSE DS	132
(rhIL-21)		

[00451] The term "IL-4" (also referred to herein as "IL4") refers to the cytokine known as interleukin 4, which is produced by Th2 T cells and by eosinophils, basophils, and mast cells. IL-4 regulates the differentiation of naïve helper T cells (Th0 cells) to Th2 T cells. Steinke and Borish, *Respir. Res.* 2001, 2, 66-70. Upon activation by IL-4, Th2 T cells subsequently produce additional IL-4 in a positive feedback loop. IL-4 also stimulates B cell proliferation and class II MHC expression, and induces class switching to IgE and IgG₁ expression from B cells. Recombinant human IL-4 suitable for use in the invention is commercially available from multiple suppliers, including ProSpec-Tany TechnoGene Ltd., East Brunswick, NJ, USA (Cat. No. CYT-211) and ThermoFisher Scientific, Inc., Waltham, MA, USA (human IL-15 recombinant protein, Cat. No. Gibco CTP0043). The amino acid sequence of recombinant human IL-4 suitable for use in the invention is given in Table 2 (SEQ ID NO:5).

[00452] The term "IL-7" (also referred to herein as "IL7") refers to a glycosylated tissuederived cytokine known as interleukin 7, which may be obtained from stromal and epithelial cells, as well as from dendritic cells. Fry and Mackall, *Blood* 2002, *99*, 3892-904. IL-7 can stimulate the development of T cells. IL-7 binds to the IL-7 receptor, a heterodimer consisting of IL-7 receptor alpha and common gamma chain receptor, which in a series of signals important for T cell development within the thymus and survival within the periphery. Recombinant human IL-7 suitable for use in the invention is commercially available from multiple suppliers, including ProSpec-Tany TechnoGene Ltd., East Brunswick, NJ, USA (Cat. No. CYT-254) and ThermoFisher Scientific, Inc., Waltham, MA, USA (human IL-15 recombinant protein, Cat. No. Gibco PHC0071). The amino acid sequence of recombinant human IL-7 suitable for use in the invention is given in Table 2 (SEQ ID NO:6).

[00453] The term "IL-15" (also referred to herein as "IL15") refers to the T cell growth factor known as interleukin-15, and includes all forms of IL-2 including human and mammalian forms, conservative amino acid substitutions, glycoforms, biosimilars, and variants thereof. IL-15 is described, *e.g.*, in Fehniger and Caligiuri, *Blood* **2001**, *97*, 14-32, the disclosure of which is incorporated by reference herein. IL-15 shares β and γ signaling receptor subunits with IL-2. Recombinant human IL-15 is a single, non-glycosylated polypeptide chain containing 114 amino acids (and an N-terminal methionine) with a molecular mass of 12.8 kDa. Recombinant human IL-15 is commercially available from multiple suppliers, including ProSpec-Tany TechnoGene Ltd., East Brunswick, NJ, USA (Cat. No. CYT-230-b) and ThermoFisher Scientific, Inc., Waltham, MA, USA (human IL-15

recombinant protein, Cat. No. 34-8159-82). The amino acid sequence of recombinant human IL-15 suitable for use in the invention is given in Table 2 (SEQ ID NO:7).

[00454] The term "IL-21" (also referred to herein as "IL21") refers to the pleiotropic cytokine protein known as interleukin-21, and includes all forms of IL-21 including human and mammalian forms, conservative amino acid substitutions, glycoforms, biosimilars, and variants thereof. IL-21 is described, *e.g.*, in Spolski and Leonard, *Nat. Rev. Drug. Disc.* 2014, 13, 379-95, the disclosure of which is incorporated by reference herein. IL-21 is primarily produced by natural killer T cells and activated human CD4⁺ T cells. Recombinant human IL-21 is a single, non-glycosylated polypeptide chain containing 132 amino acids with a molecular mass of 15.4 kDa. Recombinant human IL-21 is commercially available from multiple suppliers, including ProSpec-Tany TechnoGene Ltd., East Brunswick, NJ, USA (Cat. No. CYT-408-b) and ThermoFisher Scientific, Inc., Waltham, MA, USA (human IL-21 recombinant protein, Cat. No. 14-8219-80). The amino acid sequence of recombinant human IL-21 suitable for use in the invention is given in Table 2 (SEQ ID NO:8).

[00455] When "an anti-tumor effective amount", "an 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 tumor infiltrating lymphocytes (e.g. secondary TILs or genetically modified cytotoxic lymphocytes) described herein may be administered at a dosage of 10⁴ to 10¹¹ cells/kg body weight (e.g., 10^5 to 10^6 , 10^5 to 10^{10} , 10^5 to 10^{11} , 10^6 to 10^{10} , 10^6 to 10^{11} , 10^7 to 10^{11} , 10^7 to 10^{10} , 10^8 to 10^{11} , 10^8 to 10^{10} , 10^9 to 10^{11} , or 10^9 to 10^{10} cells/kg body weight), including all integer values within those ranges. Tumor infiltrating lymphocytes (including in some cases, genetically modified cytotoxic lymphocytes) compositions may also be administered multiple times at these dosages. The tumor infiltrating lymphocytes (inlcuding in some cases, genetically) 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). The optimal dosage and treatment regime for a particular patient can readily be determined by one skilled in the art of medicine by monitoring the patient for signs of disease and adjusting the treatment accordingly.

[00456] The term "hematological malignancy", "hematologic malignancy" or terms of correlative meaning refer to mammalian cancers and tumors of the hematopoietic and

lymphoid tissues, including but not limited to tissues of the blood, bone marrow, lymph nodes, and lymphatic system. Hematological malignancies are also referred to as "liquid tumors." Hematological malignancies include, but are not limited to, acute lymphoblastic leukemia (ALL), chronic lymphocytic lymphoma (CLL), small lymphocytic lymphoma (SLL), acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), acute monocytic leukemia (AMoL), Hodgkin's lymphoma, and non-Hodgkin's lymphomas. The term "B cell hematological malignancy" refers to hematological malignancies that affect B cells.

[00457] The term "liquid tumor" refers to an abnormal mass of cells that is fluid in nature. Liquid tumor cancers include, but are not limited to, leukemias, myelomas, and lymphomas, as well as other hematological malignancies. TILs obtained from liquid tumors may also be referred to herein as marrow infiltrating lymphocytes (MILs). TILs obtained from liquid tumors, including liquid tumors circulating in peripheral blood, may also be referred to herein as PBLs. The terms MIL, TIL, and PBL are used interchangeably herein and differ only based on the tissue type from which the cells are derived.

[00458] The term "microenvironment," as used herein, may refer to the solid or hematological tumor microenvironment as a whole or to an individual subset of cells within the microenvironment. The tumor microenvironment, as used herein, refers to a complex mixture of "cells, soluble factors, signaling molecules, extracellular matrices, and mechanical cues that promote neoplastic transformation, support tumor growth and invasion, protect the tumor from host immunity, foster therapeutic resistance, and provide niches for dominant metastases to thrive," as described in Swartz, *et al.*, *Cancer Res.*, **2012**, *72*, 2473. Although tumors express antigens that should be recognized by T cells, tumor clearance by the immune system is rare because of immune suppression by the microenvironment.

[00459] In an embodiment, the invention includes a method of treating a cancer with a population of TILs, wherein a patient is pre-treated with non-myeloablative chemotherapy prior to an infusion of TILs according to the invention. In some embodiments, the population of TILs may be provided wherein a patient is pre-treated with nonmyeloablative chemotherapy prior to an infusion of TILs according to the present invention. In an embodiment, the non-myeloablative chemotherapy is cyclophosphamide 60 mg/kg/d for 2 days (days 27 and 26 prior to TIL infusion) and fludarabine 25 mg/m2/d for 5 days (days 27 to 23 prior to TIL infusion). In an embodiment, after non-myeloablative chemotherapy and

TIL infusion (at day 0) according to the invention, the patient receives an intravenous infusion of IL-2 intravenously at 720,000 IU/kg every 8 hours to physiologic tolerance.

[00460] Experimental findings indicate that lymphodepletion prior to adoptive transfer of tumor-specific T lymphocytes plays a key role in enhancing treatment efficacy by eliminating regulatory T cells and competing elements of the immune system ("cytokine sinks"). Accordingly, some embodiments of the invention utilize a lymphodepletion step (sometimes also referred to as "immunosuppressive conditioning") on the patient prior to the introduction of the rTILs of the invention.

[00461] The term "effective amount" or "therapeutically effective amount" refers to that amount of a compound or combination of compounds as described herein that is sufficient to effect the intended application including, but not limited to, disease treatment. A therapeutically effective amount may vary depending upon the intended application (in vitro or in vivo), or the subject and disease condition being treated (e.g., the weight, age and gender of the subject), the severity of the disease condition, or the manner of administration. The term also applies to a dose that will induce a particular response in target cells (e.g., the reduction of platelet adhesion and/or cell migration). The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether the compound is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which the compound is carried.

pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a disease and/or adverse effect attributable to the disease. "Treatment", as used herein, covers any treatment of a disease in a mammal, particularly in a human, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development or progression; and (c) relieving the disease, i.e., causing regression of the disease and/or relieving one or more disease symptoms. "Treatment" is also meant to encompass delivery of an agent in order to provide for a pharmacologic effect, even in the absence of a disease or condition. For example, "treatment" encompasses delivery of a composition that can elicit an immune response or confer immunity in the absence of a disease condition, e.g., in the case of a vaccine.

[00463] The term "heterologous" when used with reference to portions of a nucleic acid or protein indicates that the nucleic acid or protein comprises two or more subsequences that are not found in the same relationship to each other in nature. For instance, the nucleic acid is typically recombinantly produced, having two or more sequences from unrelated genes arranged to make a new functional nucleic acid, e.g., a promoter from one source and a coding region from another source, or coding regions from different sources. Similarly, a heterologous protein indicates that the protein comprises two or more subsequences that are not found in the same relationship to each other in nature (e.g., a fusion protein).

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[00464] The terms "sequence identity," "percent identity," and "sequence percent identity" (or synonyms thereof, e.g., "99% identical") in the context of two or more nucleic acids or polypeptides, refer to two or more sequences or subsequences that are the same or have a specified percentage of nucleotides or amino acid residues that are the same, when compared and aligned (introducing gaps, if necessary) for maximum correspondence, not considering any conservative amino acid substitutions as part of the sequence identity. The percent identity can be measured using sequence comparison software or algorithms or by visual inspection. Various algorithms and software are known in the art that can be used to obtain alignments of amino acid or nucleotide sequences. Suitable programs to determine percent sequence identity include for example the BLAST suite of programs available from the U.S. Government's National Center for Biotechnology Information BLAST web site. Comparisons between two sequences can be carried using either the BLASTN or BLASTP algorithm. BLASTN is used to compare nucleic acid sequences, while BLASTP is used to compare amino acid sequences. ALIGN, ALIGN-2 (Genentech, South San Francisco, California) or MegAlign, available from DNASTAR, are additional publicly available software programs that can be used to align sequences. One skilled in the art can determine appropriate parameters for maximal alignment by particular alignment software. In certain embodiments, the default parameters of the alignment software are used.

[00465] As used herein, the term "variant" encompasses but is not limited to antibodies or fusion proteins which comprise an amino acid sequence which differs from the amino acid sequence of a reference antibody by way of one or more substitutions, deletions and/or additions at certain positions within or adjacent to the amino acid sequence of the reference antibody. The variant may comprise one or more conservative substitutions in its amino acid sequence as compared to the amino acid sequence of a reference antibody. Conservative substitutions may involve, e.g., the substitution of similarly charged or uncharged amino

acids. The variant retains the ability to specifically bind to the antigen of the reference antibody. The term variant also includes pegylated antibodies or proteins.

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[00466] By "tumor infiltrating lymphocytes" or "TILs" herein is meant a population of cells originally obtained as white blood cells that have left the bloodstream of a subject and migrated into a tumor. TILs include, but are not limited to, CD8⁺ cytotoxic T cells (lymphocytes), Th1 and Th17 CD4⁺ T cells, natural killer cells, dendritic cells and M1 macrophages. TILs include both primary and secondary TILs. "Primary TILs" are those that are obtained from patient tissue samples as outlined herein (sometimes referred to as "freshly harvested"), and "secondary TILs" are any TIL cell populations that have been expanded or proliferated as discussed herein, including, but not limited to bulk TILs, expanded TILs ("REP TILs") as well as "reREP TILs" as discussed herein. reREP TILs can include for example second expansion TILs or second additional expansion TILs (such as, for example, those described in Step D of Figure 8, including TILs referred to as reREP TILs).

[00467] TILs can generally be defined either biochemically, using cell surface markers, or functionally, by their ability to infiltrate tumors and effect treatment. TILs can be generally categorized by expressing one or more of the following biomarkers: CD4, CD8, TCR αβ, CD27, CD28, CD56, CCR7, CD45Ra, CD95, PD-1, and CD25. Additionally, and alternatively, TILs can be functionally defined by their ability to infiltrate solid tumors upon reintroduction into a patient. TILS may further be characterized by potency – for example, TILS may be considered potent if, for example, interferon (IFN) release is greater than about 50 pg/mL, greater than about 100 pg/mL, greater than about 150 pg/mL, or greater than about 200 pg/mL.

[00468] The term "deoxyribonucleotide" encompasses natural and synthetic, unmodified and modified deoxyribonucleotides. Modifications include changes to the sugar moiety, to the base moiety and/or to the linkages between deoxyribonucleotide in the oligonucleotide.

[00469] The term "RNA" defines a molecule comprising at least one ribonucleotide residue. The term "ribonucleotide" defines a nucleotide with a hydroxyl group at the 2' position of a b-D-ribofuranose moiety. The term RNA includes double-stranded RNA, single-stranded RNA, isolated RNA such as partially purified RNA, essentially pure RNA, synthetic RNA, recombinantly produced RNA, as well as altered RNA that differs from naturally occurring RNA by the addition, deletion, substitution and/or alteration of one or more nucleotides. Nucleotides of the RNA molecules described herein may also comprise non-standard

nucleotides, such as non-naturally occurring nucleotides or chemically synthesized nucleotides or deoxynucleotides. These altered RNAs can be referred to as analogs of naturally-occurring RNA.

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[00470] The terms "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" are intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and inert ingredients. The use of such pharmaceutically acceptable carriers or pharmaceutically acceptable excipients for active pharmaceutical ingredients is well known in the art. Except insofar as any conventional pharmaceutically acceptable carrier or pharmaceutically acceptable excipient is incompatible with the active pharmaceutical ingredient, its use in therapeutic compositions of the invention is contemplated. Additional active pharmaceutical ingredients, such as other drugs, can also be incorporated into the described compositions and methods.

[00471] The terms "about" and "approximately" mean within a statistically meaningful range of a value. Such a range can be within an order of magnitude, preferably within 50%, more preferably within 20%, more preferably still within 10%, and even more preferably within 5% of a given value or range. The allowable variation encompassed by the terms "about" or "approximately" depends on the particular system under study, and can be readily appreciated by one of ordinary skill in the art. Moreover, as used herein, the terms "about" and "approximately" mean that dimensions, sizes, formulations, parameters, shapes and other quantities and characteristics are not and need not be exact, but may be approximate and/or larger or smaller, as desired, reflecting tolerances, conversion factors, rounding off, measurement error and the like, and other factors known to those of skill in the art. In general, a dimension, size, formulation, parameter, shape or other quantity or characteristic is "about" or "approximate" whether or not expressly stated to be such. It is noted that embodiments of very different sizes, shapes and dimensions may employ the described arrangements.

[00472] The transitional terms "comprising," "consisting essentially of," and "consisting of," when used in the appended claims, in original and amended form, define the claim scope with respect to what unrecited additional claim elements or steps, if any, are excluded from the scope of the claim(s). The term "comprising" is intended to be inclusive or open-ended and does not exclude any additional, unrecited element, method, step or material. The term "consisting of" excludes any element, step or material other than those specified in the claim

and, in the latter instance, impurities ordinary associated with the specified material(s). The term "consisting essentially of" limits the scope of a claim to the specified elements, steps or material(s) and those that do not materially affect the basic and novel characteristic(s) of the claimed invention. All compositions, methods, and kits described herein that embody the present invention can, in alternate embodiments, be more specifically defined by any of the transitional terms "comprising," "consisting essentially of," and "consisting of."

[00473] The terms "antibody" and its plural form "antibodies" refer to whole immunoglobulins and any antigen-binding fragment ("antigen-binding portion") or single chains thereof. An "antibody" further refers to a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, or an antigen-binding portion thereof. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as V_H) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as V_L) and a light chain constant region. The light chain constant region is comprised of one domain, C_L. The V_H and V_L regions of an antibody may be further subdivided into regions of hypervariability, which are referred to as complementarity determining regions (CDR) or hypervariable regions (HVR), and which can be interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen epitope or epitopes. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (Clq) of the classical complement system.

[00474] The term "antigen" refers to a substance that induces an immune response. In some embodiments, an antigen is a molecule capable of being bound by an antibody or a TCR if presented by major histocompatibility complex (MHC) molecules. The term "antigen", as used herein, also encompasses T cell epitopes. An antigen is additionally capable of being recognized by the immune system. In some embodiments, an antigen is capable of inducing a humoral immune response or a cellular immune response leading to the activation of B lymphocytes and/or T lymphocytes. In some cases, this may require that the antigen contains or is linked to a Th cell epitope. An antigen can also have one or more epitopes (*e.g.*, B- and T-epitopes). In some embodiments, an antigen will preferably react,

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typically in a highly specific and selective manner, with its corresponding antibody or TCR and not with the multitude of other antibodies or TCRs which may be induced by other antigens.

[00475] The terms "monoclonal antibody," "mAb," "monoclonal antibody composition," or their plural forms refer to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope. Monoclonal antibodies specific to certain receptors can be made using knowledge and skill in the art of injecting test subjects with suitable antigen and then isolating hybridomas expressing antibodies having the desired sequence or functional characteristics. DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the monoclonal antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as E. coli cells, simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. Recombinant production of antibodies will be described in more detail below.

[00476] The terms "antigen-binding portion" or "antigen-binding fragment" of an antibody (or simply "antibody portion" or "fragment"), as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen. It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigenbinding portion" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the V_L, V_H, C_L and CH1 domains; (ii) a F(ab')2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and CH1 domains; (iv) a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (v) a domain antibody (dAb) fragment (Ward, et al., Nature, 1989, 341, 544-546), which may consist of a V_H or a V_L domain; and (vi) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, V_L and V_H, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the V_L and V_H regions pair to form monovalent molecules known as single

chain Fv (scFv); see, e.g., Bird, et al., Science 1988, 242, 423-426; and Huston, et al., Proc. Natl. Acad. Sci. USA 1988, 85, 5879-5883). Such scFv antibodies are also intended to be encompassed within the terms "antigen-binding portion" or "antigen-binding fragment" of an antibody. These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

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[00477] The term "human antibody," as used herein, is intended to include antibodies having variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. Furthermore, if the antibody contains a constant region, the constant region also is derived from human germline immunoglobulin sequences. The human antibodies of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*). The term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

[00478] The term "human monoclonal antibody" refers to antibodies displaying a single binding specificity which have variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. In an embodiment, the human monoclonal antibodies are produced by a hybridoma which includes a B cell obtained from a transgenic nonhuman animal, *e.g.*, a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell.

The term "recombinant human antibody", as used herein, includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as (a) antibodies isolated from an animal (such as a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom (described further below), (b) antibodies isolated from a host cell transformed to express the human antibody, *e.g.*, from a transfectoma, (c) antibodies isolated from a recombinant, combinatorial human antibody library, and (d) antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable regions in which the framework and CDR regions are derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies can be subjected to *in*

vitro mutagenesis (or, when an animal transgenic for human Ig sequences is used, in vivo somatic mutagenesis) and thus the amino acid sequences of the V_H and V_L regions of the recombinant antibodies are sequences that, while derived from and related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire in vivo.

[00480] As used herein, "isotype" refers to the antibody class (e.g., IgM or IgG1) that is encoded by the heavy chain constant region genes.

[00481] The phrases "an antibody recognizing an antigen" and "an antibody specific for an antigen" are used interchangeably herein with the term "an antibody which binds specifically to an antigen."

[00482] The term "human antibody derivatives" refers to any modified form of the human antibody, including a conjugate of the antibody and another active pharmaceutical ingredient or antibody. The terms "conjugate," "antibody-drug conjugate", "ADC," or "immunoconjugate" refers to an antibody, or a fragment thereof, conjugated to another therapeutic moiety, which can be conjugated to antibodies described herein using methods available in the art.

The terms "humanized antibody," "humanized antibodies," and "humanized" [00483] are intended to refer to antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences. Additional framework region modifications may be made within the human framework sequences. Humanized forms of non-human (for example, murine) antibodies are chimeric antibodies that contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region of the recipient are replaced by residues from a 15 hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or nonhuman primate 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, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond

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to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin sequence. The humanized antibody optionally also will 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 1986, 321, 522-525; Riechmann, et al., Nature 1988, 332, 323-329; and Presta, Curr. Op. Struct. Biol. 1992, 2, 593-596. The antibodies described herein may also be modified to employ any Fc variant which is known to impart an improvement (e.g., reduction) in effector function and/or FcR binding. The Fc variants may include, for example, any one of the amino acid substitutions disclosed in International Patent Application Publication Nos. WO 1988/07089 A1, WO 1996/14339 A1, WO 1998/05787 A1, WO 1998/23289 A1, WO 1999/51642 A1, WO 99/58572 A1, WO 2000/09560 A2, WO 2000/32767 A1, WO 2000/42072 A2, WO 2002/44215 A2, WO 2002/060919 A2, WO 2003/074569 A2, WO 2004/016750 A2, WO 2004/029207 A2, WO 2004/035752 A2, WO 2004/063351 A2, WO 2004/074455 A2, WO 2004/099249 A2, WO 2005/040217 A2, WO 2005/070963 A1, WO 2005/077981 A2, WO 2005/092925 A2, WO 2005/123780 A2, WO 2006/019447 A1, WO 2006/047350 A2, and WO 2006/085967 A2; and U.S. Patent Nos. 5,648,260; 5,739,277; 5,834,250; 5,869,046; 6,096,871; 6,121,022; 6,194,551; 6,242,195; 6,277,375; 6,528,624; 6,538,124; 6,737,056; 6,821,505; 6,998,253; and 7,083,784; the disclosures of which are incorporated by reference herein.

[00484] The term "chimeric antibody" is intended to refer to antibodies in which the variable region sequences are derived from one species and the constant region sequences are derived from another species, such as an antibody in which the variable region sequences are derived from a mouse antibody and the constant region sequences are derived from a human antibody.

A "diabody" is a small antibody fragment with two antigen-binding sites. The [00485] fragments comprises a heavy chain variable domain (V_H) connected to a light chain variable domain (V_L) in the same polypeptide chain (V_H-V_L or V_L-V_H). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, e.g., European Patent No. EP 404,097, International Patent Publication No. WO 93/11161; and Bolliger, et al., Proc. Natl. Acad. Sci. USA 1993, 90, 6444-6448.

[00486] The term "glycosylation" refers to a modified derivative of an antibody. An aglycoslated antibody lacks glycosylation. Glycosylation can be altered to, for example, increase the affinity of the antibody for antigen. Such carbohydrate modifications can be accomplished by, for example, altering one or more sites of glycosylation within the antibody sequence. For example, one or more amino acid substitutions can be made that result in elimination of one or more variable region framework glycosylation sites to thereby eliminate glycosylation at that site. Aglycosylation may increase the affinity of the antibody for antigen, as described in U.S. Patent Nos. 5,714,350 and 6,350,861. Additionally or alternatively, an antibody can be made that has an altered type of glycosylation, such as a hypofucosylated antibody having reduced amounts of fucosyl residues or an antibody having increased bisecting GlcNac structures. Such altered glycosylation patterns have been demonstrated to increase the ability of antibodies. Such carbohydrate modifications can be accomplished by, for example, expressing the antibody in a host cell with altered glycosylation machinery. Cells with altered glycosylation machinery have been described in the art and can be used as host cells in which to express recombinant antibodies of the invention to thereby produce an antibody with altered glycosylation. For example, the cell lines Ms704, Ms705, and Ms709 lack the fucosyltransferase gene, FUT8 (alpha (1,6) fucosyltransferase), such that antibodies expressed in the Ms704, Ms705, and Ms709 cell lines lack fucose on their carbohydrates. The Ms704, Ms705, and Ms709 FUT8-/- cell lines were created by the targeted disruption of the FUT8 gene in CHO/DG44 cells using two replacement vectors (see e.g. U.S. Patent Publication No. 2004/0110704 or Yamane-Ohnuki, et al., Biotechnol. Bioeng., 2004, 87, 614-622). As another example, European Patent No. EP 1,176,195 describes a cell line with a functionally disrupted FUT8 gene, which encodes a fucosyl transferase, such that antibodies expressed in such a cell line exhibit hypofucosylation by reducing or eliminating the alpha 1,6 bond-related enzyme, and also describes cell lines which have a low enzyme activity for adding fucose to the Nacetylglucosamine that binds to the Fc region of the antibody or does not have the enzyme activity, for example the rat myeloma cell line YB2/0 (ATCC CRL 1662). International Patent Publication WO 03/035835 describes a variant CHO cell line, Lec 13 cells, with reduced ability to attach fucose to Asn(297)-linked carbohydrates, also resulting in hypofucosylation of antibodies expressed in that host cell (see also Shields, et al., J. Biol. Chem. 2002, 277, 26733-26740. International Patent Publication WO 99/54342 describes cell lines engineered to express glycoprotein-modifying glycosyl transferases (e.g., beta(1,4)-N-acetylglucosaminyltransferase III (GnTIII)) such that antibodies expressed in the

ADCC activity of the antibodies (see also Umana, *et al.*, *Nat. Biotech.* **1999**, *17*, 176-180). Alternatively, the fucose residues of the antibody may be cleaved off using a fucosidase enzyme. For example, the fucosidase alpha-L-fucosidase removes fucosyl residues from antibodies as described in Tarentino, *et al.*, *Biochem.* **1975**, *14*, 5516-5523.

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[00487] "Pegylation" refers to a modified antibody, or a fragment thereof, that typically is reacted with polyethylene glycol (PEG), such as a reactive ester or aldehyde derivative of PEG, under conditions in which one or more PEG groups become attached to the antibody or antibody fragment. Pegylation may, for example, increase the biological (e.g., serum) half life of the antibody. Preferably, the pegylation is carried out via an acylation reaction or an alkylation reaction with a reactive PEG molecule (or an analogous reactive water-soluble polymer). As used herein, the term "polyethylene glycol" is intended to encompass any of the forms of PEG that have been used to derivatize other proteins, such as mono (C₁-C₁₀)alkoxy- or aryloxy-polyethylene glycol or polyethylene glycol-maleimide. The antibody to be pegylated may be an aglycosylated antibody. Methods for pegylation are known in the art and can be applied to the antibodies of the invention, as described for example in European Patent Nos. EP 0154316 and EP 0401384 and U.S. Patent No. 5,824,778, the disclosures of each of which are incorporated by reference herein.

[00488] The term "biosimilar" means a biological product, including a monoclonal antibody or protein, that is highly similar to a U.S. licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product. Furthermore, a similar biological or "biosimilar" medicine is a biological medicine that is similar to another biological medicine that has already been authorized for use by the European Medicines Agency. The term "biosimilar" is also used synonymously by other national and regional regulatory agencies. Biological products or biological medicines are medicines that are made by or derived from a biological source, such as a bacterium or yeast. They can consist of relatively small molecules such as human insulin or erythropoietin, or complex molecules such as monoclonal antibodies. For example, if the reference IL-2 protein is aldesleukin (PROLEUKIN), a protein approved by drug regulatory authorities with reference to aldesleukin is a "biosimilar to" aldesleukin or is a "biosimilar thereof" of aldesleukin. In Europe, a similar biological or "biosimilar" medicine is a biological medicine that is similar

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to another biological medicine that has already been authorized for use by the European Medicines Agency (EMA). The relevant legal basis for similar biological applications in Europe is Article 6 of Regulation (EC) No 726/2004 and Article 10(4) of Directive 2001/83/EC, as amended and therefore in Europe, the biosimilar may be authorized, approved for authorization or subject of an application for authorization under Article 6 of Regulation (EC) No 726/2004 and Article 10(4) of Directive 2001/83/EC. The already authorized original biological medicinal product may be referred to as a "reference medicinal product" in Europe. Some of the requirements for a product to be considered a biosimilar are outlined in the CHMP Guideline on Similar Biological Medicinal Products. In addition, product specific guidelines, including guidelines relating to monoclonal antibody biosimilars, are provided on a product-by-product basis by the EMA and published on its website. A biosimilar as described herein may be similar to the reference medicinal product by way of quality characteristics, biological activity, mechanism of action, safety profiles and/or efficacy. In addition, the biosimilar may be used or be intended for use to treat the same conditions as the reference medicinal product. Thus, a biosimilar as described herein may be deemed to have similar or highly similar quality characteristics to a reference medicinal product. Alternatively, or in addition, a biosimilar as described herein may be deemed to have similar or highly similar biological activity to a reference medicinal product. Alternatively, or in addition, a biosimilar as described herein may be deemed to have a similar or highly similar safety profile to a reference medicinal product. Alternatively, or in addition, a biosimilar as described herein may be deemed to have similar or highly similar efficacy to a reference medicinal product. As described herein, a biosimilar in Europe is compared to a reference medicinal product which has been authorized by the EMA. However, in some instances, the biosimilar may be compared to a biological medicinal product which has been authorized outside the European Economic Area (a non-EEA authorized "comparator") in certain studies. Such studies include for example certain clinical and in vivo non-clinical studies. As used herein, the term "biosimilar" also relates to a biological medicinal product which has been or may be compared to a non-EEA authorized comparator. Certain biosimilars are proteins such as antibodies, antibody fragments (for example, antigen binding portions) and fusion proteins. A protein biosimilar may have an amino acid sequence that has minor modifications in the amino acid structure (including for example deletions, additions, and/or substitutions of amino acids) which do not significantly affect the function of the polypeptide. The biosimilar may comprise an amino acid sequence having a sequence identity of 97% or greater to the amino acid sequence of its reference

medicinal product, e.g., 97%, 98%, 99% or 100%. The biosimilar may comprise one or more post-translational modifications, for example, although not limited to, glycosylation, oxidation, deamidation, and/or truncation which is/are different to the post-translational modifications of the reference medicinal product, provided that the differences do not result in a change in safety and/or efficacy of the medicinal product. The biosimilar may have an identical or different glycosylation pattern to the reference medicinal product. Particularly, although not exclusively, the biosimilar may have a different glycosylation pattern if the differences address or are intended to address safety concerns associated with the reference medicinal product. Additionally, the biosimilar may deviate from the reference medicinal product in for example its strength, pharmaceutical form, formulation, excipients and/or presentation, providing safety and efficacy of the medicinal product is not compromised. The biosimilar may comprise differences in for example pharmacokinetic (PK) and/or pharmacodynamic (PD) profiles as compared to the reference medicinal product but is still deemed sufficiently similar to the reference medicinal product as to be authorized or considered suitable for authorization. In certain circumstances, the biosimilar exhibits different binding characteristics as compared to the reference medicinal product, wherein the different binding characteristics are considered by a Regulatory Authority such as the EMA not to be a barrier for authorization as a similar biological product. The term "biosimilar" is also used synonymously by other national and regional regulatory agencies.

III. TIL Manufacturing Processes – 2A

[00489] An exemplary TIL process known as process 2A containing some of these features is depicted in Figure 2, and some of the advantages of this embodiment of the present invention over process 1C are described in Figures F and G. An embodiment of process 2A is shown Figure 1.

[00490] As discussed herein, the present invention can include a step relating to the restimulation of cryopreserved TILs to increase their metabolic activity and thus relative health prior to transplant into a patient, and methods of testing said metabolic health. As generally outlined herein, TILs are generally taken from a patient sample and manipulated to expand their number prior to transplant into a patient. In some embodiments, the TILs may be optionally genetically manipulated as discussed below.

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[00491] In some embodiments, the TILs may be cryopreserved. Once thawed, they may also be restimulated to increase their metabolism prior to infusion into a patient.

[00492] In some embodiments, the first expansion (including processes referred to as the preREP as well as processes shown in Figure 1 as Step A) is shortened to 3 to 14 days and the second expansion (including processes referred to as the REP as well as processes shown in Figure 1 as Step B) is shorted to 7 to 14 days, as discussed in detail below as well as in the examples and figures. In some embodiments, the first expansion (for example, an expansion described as Step B in Figure 1) is shortened to 11 days and the second expansion (for example, an expansion as described in Step D in Figure 1) is shortened to 11 days. In some embodiments, the combination of the first expansion and second expansion (for example, expansions described as Step B and Step D in Figure 1) is shortened to 22 days, as discussed in detail below and in the examples and figures.

[00493] The "Step" Designations A, B, C, etc., below are in reference to Figure 1 and in reference to certain embodiments described herein. The ordering of the Steps below and in Figure 1 is exemplary and any combination or order of steps, as well as additional steps, repetition of steps, and/or omission of steps is contemplated by the present application and the methods disclosed herein.

STEP A: Obtain Patient tumor sample A.

[00494] In general, TILs are initially obtained from a patient tumor sample ("primary TILs") and then expanded into a larger population for further manipulation as described herein, optionally cryopreserved, restimulated as outlined herein and optionally evaluated for phenotype and metabolic parameters as an indication of TIL health.

[00495] A patient tumor sample may be obtained using methods known in the art, generally via surgical resection, needle biopsy, core biopsy, small biopsy, or other means for obtaining a sample that contains a mixture of tumor and TIL cells. In some embodiments, multilesional sampling is used. In some embodiments, surgical resection, needle biopsy, core biopsy, small biopsy, or other means for obtaining a sample that contains a mixture of tumor and TIL cells includes multilesional sampling (i.e., obtaining samples from one or more tumor cites and/or locations in the patient, as well as one or more tumors in the same location or in close proximity). In general, the tumor sample may be from any solid tumor, including primary tumors, invasive tumors or metastatic tumors. The tumor sample may also be a liquid tumor, such as a tumor obtained from a hematological malignancy. The solid tumor may be of lung

tissue. In some embodiments, useful TILs are obtained from non-small cell lung carcinoma (NSCLC).

[00496] Once obtained, the tumor sample is generally fragmented using sharp dissection into small pieces of between 1 to about 8 mm³, with from about 2-3 mm³ being particularly useful. The TILs are cultured from these fragments using enzymatic tumor digests. Such tumor digests may be produced by incubation in enzymatic media (e.g., Roswell Park Memorial Institute (RPMI) 1640 buffer, 2 mM glutamate, 10 mcg/mL gentamicine, 30 units/mL of DNase and 1.0 mg/mL of collagenase) followed by mechanical dissociation (e.g., using a tissue dissociator). Tumor digests may be produced by placing the tumor in enzymatic media and mechanically dissociating the tumor for approximately 1 minute, followed by incubation for 30 minutes at 37 °C in 5% CO₂, followed by repeated cycles of mechanical dissociation and incubation under the foregoing conditions until only small tissue pieces are present. At the end of this process, if the cell suspension contains a large number of red blood cells or dead cells, a density gradient separation using FICOLL branched hydrophilic polysaccharide may be performed to remove these cells. Alternative methods known in the art may be used, such as those described in U.S. Patent Application Publication No. 2012/0244133 A1, the disclosure of which is incorporated by reference herein. Any of the foregoing methods may be used in any of the embodiments described herein for methods of expanding TILs or methods treating a cancer.

[00497] As indicated above, in some embodiments, the TILs are derived from solid tumors. In some embodiments, the solid tumors are not fragmented and are subjected to enzymatic digestion as whole tumors. In some embodiments, the tumors are digested in in an enzyme mixture comprising collagenase, DNase, and hyaluronidase. In some embodiments, the tumors are digested in in an enzyme mixture comprising collagenase, DNase, and hyaluronidase for 1-2 hours. In some embodiments, the tumors are digested in in an enzyme mixture comprising collagenase, DNase, and hyaluronidase for 1-2 hours at 37°C, 5% CO₂. In some embodiments, the tumors are digested in in an enzyme mixture comprising collagenase, DNase, and hyaluronidase for 1-2 hours at 37°C, 5% CO₂ with rotation. In some embodiments, the tumors are digested overnight with constant rotation. In some embodiments, the tumors are digested overnight at 37°C, 5% CO₂ with constant rotation. In some embodiments, the whole tumor is combined with with the enzymes to form a tumor digest reaction mixture.

[00498] In some embodiments, the tumor is reconstituted with the lyophilized enzymes in a sterile buffer. In some embodiments, the buffer is sterile HBSS.

[00499] In some embodiments, the enxyme mixture comprises collagenase. In some embodiments, the collagenase is collagenase IV. In some embodiments, the working stock for the collagenase is a 100 mg/ml 10X working stock.

[00500] In some embodiments, the enzyme mixture comprises DNAse. In some embodiments, the working stock for the DNAse is a 10,000IU/ml 10X working stock.

[00501] In some embodiments, the enzyme mixture comprises hyaluronidase. In some embodiments, the working stock for the hyaluronidase is a 10-mg/ml 10X working stock.

[00502] In some embodiments, the enzyme mixture comprises 10 mg/ml collagenase, 1000 IU/ml DNAse, and 1 mg/ml hyaluronidase.

[00503] In some embodiments, the enzyme mixture comprises 10 mg/ml collagenase, 500 IU/ml DNAse, and 1 mg/ml hyaluronidase.

[00504] In general, the harvested cell suspension is called a "primary cell population" or a "freshly harvested" cell population.

[00505] In some embodiments, fragmentation includes physical fragmentation, including for example, dissection as well as digestion. In some embodiments, the fragmentation is physical fragmentation. In some embodiments, the fragmentation is dissection. In some embodiments, the fragmentation is by digestion. In some embodiments, TILs can be initially cultured from enzymatic tumor digests and tumor fragments obtained from patients. In an embodiment, TILs can be initially cultured from enzymatic tumor digests and tumor fragments obtained from patients.

[00506] In some embodiments, where the tumor is a solid tumor, the tumor undergoes physical fragmentation after the tumor sample is obtained in, for example, Step A (as provided in Figure 1). In some embodiments, the fragmentation occurs before cryopreservation. In some embodiments, the fragmentation occurs after cryopreservation. In some embodiments, the fragmentation occurs after obtaining the tumor and in the absence of any cryopreservation. In some embodiments, the tumor is fragmented and 10, 20, 30, 40 or more fragments or pieces are placed in each container for the first expansion. In some embodiments, the tumor is fragmented and 30 or 40 fragments or pieces are placed in each container for the first expansion. In some embodiments, the tumor is fragmented and 40

fragments or pieces are placed in each container for the first expansion. In some embodiments, the multiple fragments comprise about 4 to about 50 fragments, wherein each fragment has a volume of about 27 mm³. In some embodiments, the multiple fragments comprise about 30 to about 60 fragments with a total volume of about 1300 mm³ to about 1500 mm³. In some embodiments, the multiple fragments comprise about 50 fragments with a total volume of about 1350 mm³. In some embodiments, the multiple fragments comprise about 50 fragments with a total mass of about 1 gram to about 1.5 grams. In some embodiments, the multiple fragments comprise about 4 fragments.

[00507] In some embodiments, the TILs are obtained from tumor fragments. In some embodiments, the tumor fragment is obtained by sharp dissection. In some embodiments, the tumor fragment is between about 1 mm³ and 10 mm³. In some embodiments, the tumor fragment is about 1 mm³ and 8 mm³. In some embodiments, the tumor fragment is about 2 mm³. In some embodiments, the tumor fragment is about 2 mm³. In some embodiments, the tumor fragment is about 5 mm³. In some embodiments, the tumor fragment is about 5 mm³. In some embodiments, the tumor fragment is about 5 mm³. In some embodiments, the tumor fragment is about 7 mm³. In some embodiments, the tumor fragment is about 8 mm³. In some embodiments, the tumor fragment is about 10 mm³. In some embodiments, the tumor fragment is about 10 mm³. In some embodiments, the tumors are 1-4 mm x 1-4 mm x 1-4 mm. In some embodiments, the tumors are 2 mm x 2 mm x 2 mm. In some embodiments, the tumors are 3 mm x 3 mm x 3 mm. In some embodiments, the tumors are 4 mm x 4 mm x 4 mm.

[00508] In some embodiments, the tumors are resected in order to minimize the amount of hemorrhagic, necrotic, and/or fatty tissues on each piece. In some embodiments, the tumors are resected in order to minimize the amount of hemorrhagic tissue on each piece. In some embodiments, the tumors are resected in order to minimize the amount of necrotic tissue on each piece. In some embodiments, the tumors are resected in order to minimize the amount of fatty tissue on each piece.

[00509] In some embodiments, the tumor fragmentation is performed in order to maintain the tumor internal structure. In some embodiments, the tumor fragmentation is performed without preforming a sawing motion with a scalpel. In some embodiments, the TILs are obtained from tumor digests. In some embodiments, tumor digests were generated by incubation in enzyme media, for example but not limited to RPMI 1640, 2 mM GlutaMAX,

10 mg/mL gentamicin, 30 U/mL DNase, and 1.0 mg/mL collagenase, followed by mechanical dissociation (GentleMACS, Miltenyi Biotec, Auburn, CA). After placing the tumor in enzyme media, the tumor can be mechanically dissociated for approximately 1 minute. The solution can then be incubated for 30 minutes at 37 °C in 5% CO₂ and it then mechanically disrupted again for approximately 1 minute. After being incubated again for 30 minutes at 37 °C in 5% CO₂, the tumor can be mechanically disrupted a third time for approximately 1 minute. In some embodiments, after the third mechanical disruption if large pieces of tissue were present, 1 or 2 additional mechanical dissociations were applied to the sample, with or without 30 additional minutes of incubation at 37 °C in 5% CO₂. In some embodiments, at the end of the final incubation if the cell suspension contained a large number of red blood cells or dead cells, a density gradient separation using Ficoll can be performed to remove these cells.

[00510] In some embodiments, the harvested cell suspension prior to the first expansion step is called a "primary cell population" or a "freshly harvested" cell population.

[00511] In some embodiments, cells can be optionally frozen after sample harvest and stored frozen prior to entry into the expansion described in Step B, which is described in further detail below, as well as exemplified in Figure 1.

B. STEP B: First Expansion

[00512] In some embodiments, the present methods provide for obtaining young TILs, which are capable of increased replication cycles upon administration to a subject/patient and as such may provide additional therapeutic benefits over older TILs (*i.e.*, TILs which have further undergone more rounds of replication prior to administration to a subject/patient). Features of young TILs have been described in the literature, for example Donia, at al., *Scandinavian Journal of Immunology*, 75:157–167 (2012); Dudley et al., *Clin Cancer Res*, 16:6122-6131 (2010); Huang et al., *J Immunother*, 28(3):258–267 (2005); Besser et al., *Clin Cancer Res*, 19(17):OF1-OF9 (2013); Besser et al., *J Immunother* 32:415–423 (2009); Robbins, et al., *J Immunol* 2004; 173:7125-7130; Shen et al., J Immunother, 30:123–129 (2007); Zhou, et al., *J Immunother*, 28:53–62 (2005); and Tran, et al., J Immunother, 31:742–751 (2008), all of which are incorporated herein by reference in their entireties.

[00513] The diverse antigen receptors of T and B lymphocytes are produced by somatic recombination of a limited, but large number of gene segments. These gene segments: V (variable), D (diversity), J (joining), and C (constant), determine the binding

specificity and downstream applications of immunoglobulins and T-cell receptors (TCRs). The present invention provides a method for generating TILs which exhibit and increase the T-cell repertoire diversity. In some embodiments, the TILs obtained by the present method exhibit an increase in the T-cell repertoire diversity. In some embodiments, the TILs obtained by the present method exhibit an increase in the T-cell repertoire diversity as compared to freshly harvested TILs and/or TILs prepared using other methods than those provide herein including for example, methods other than those embodied in Figure 1. In some embodiments, the TILs obtained by the present method exhibit an increase in the T-cell repertoire diversity as compared to freshly harvested TILs and/or TILs prepared using methods referred to as process 1C, as exemplified in Figure 5 and/or Figure 6. In some embodiments, the TILs obtained in the first expansion exhibit an increase in the T-cell repertoire diversity. In some embodiments, the increase in diversity is an increase in the immunoglobulin diversity and/or the T-cell receptor diversity. In some embodiments, the diversity is in the immunoglobulin is in the immunoglobulin heavy chain. In some embodiments, the diversity is in the immunoglobulin is in the immunoglobulin light chain. In some embodiments, the diversity is in the T-cell receptor. In some embodiments, the diversity is in one of the T-cell receptors selected from the group consisting of alpha, beta, gamma, and delta receptors. In some embodiments, there is an increase in the expression of T-cell receptor (TCR) alpha and/or beta. In some embodiments, there is an increase in the expression of Tcell receptor (TCR) alpha. In some embodiments, there is an increase in the expression of Tcell receptor (TCR) beta. In some embodiments, there is an increase in the expression of TCRab (i.e., TCR α/β).

[00514] After dissection or digestion of tumor fragments, for example such as described in Step A of Figure 1, the resulting cells are cultured in serum containing IL-2 under conditions that favor the growth of TILs over tumor and other cells. In some embodiments, the tumor digests are incubated in 2 mL wells in media comprising inactivated human AB serum with 6000 IU/mL of IL-2. This primary cell population is cultured for a period of days, generally from 3 to 14 days, resulting in a bulk TIL population, generally about 1×10^8 bulk TIL cells. In some embodiments, this primary cell population is cultured for a period of 7 to 14 days, resulting in a bulk TIL population, generally about 1×10^8 bulk TIL cells. In some embodiments, this primary cell population is cultured for a period of 10 to 14 days, resulting in a bulk TIL population, generally about 1×10^8 bulk TIL cells. In some embodiments, this primary cell population is cultured for a period of 10 to 14 days, resulting in a bulk TIL population, generally about 1×10^8 bulk TIL cells. In some embodiments, this

primary cell population is cultured for a period of about 11 days, resulting in a bulk TIL population, generally about 1×10^8 bulk TIL cells.

[00515] In a preferred embodiment, expansion of TILs may be performed using an initial bulk TIL expansion step (for example such as those described in Step B of Figure 1, which can include processes referred to as pre-REP) as described below and herein, followed by a second expansion (Step D, including processes referred to as rapid expansion protocol (REP) steps) as described below under Step D and herein, followed by optional cryopreservation, and followed by a second Step D (including processes referred to as restimulation REP steps) as described below and herein. The TILs obtained from this process may be optionally characterized for phenotypic characteristics and metabolic parameters as described herein.

[00516] In embodiments where TIL cultures are initiated in 24-well plates, for example, using Costar 24-well cell culture cluster, flat bottom (Corning Incorporated, Corning, NY, each well can be seeded with 1×10^6 tumor digest cells or one tumor fragment in 2 mL of complete medium (CM) with IL-2 (6000 IU/mL; Chiron Corp., Emeryville, CA). In some embodiments, the tumor fragment is between about 1 mm³ and 10 mm³.

[00517] In some embodiments, the first expansion culture medium is referred to as "CM", an abbreviation for culture media. In some embodiments, CM for Step B consists of RPMI 1640 with GlutaMAX, supplemented with 10% human AB serum, 25 mM Hepes, and 10 mg/mL gentamicin. In embodiments where cultures are initiated in gas-permeable flasks with a 40 mL capacity and a 10 cm² gas-permeable silicon bottom (for example, G-Rex10; Wilson Wolf Manufacturing, New Brighton, MN) (Fig. 1), each flask was loaded with 10–40 × 10⁶ viable tumor digest cells or 5–30 tumor fragments in 10–40 mL of CM with IL-2. Both the G-Rex10 and 24-well plates were incubated in a humidified incubator at 37°C in 5% CO₂ and 5 days after culture initiation, half the media was removed and replaced with fresh CM and IL-2 and after day 5, half the media was changed every 2–3 days.

[00518] After preparation of the tumor fragments, the resulting cells (*i.e.*, fragments) are cultured in serum containing IL-2 under conditions that favor the growth of TILs over tumor and other cells. In some embodiments, the tumor digests are incubated in 2 mL wells in media comprising inactivated human AB serum (or, in some cases, as outlined herein, in the presence of aAPC cell population) with 6000 IU/mL of IL-2. This primary cell population is cultured for a period of days, generally from 10 to 14 days, resulting in a bulk TIL population, generally about 1×10^8 bulk TIL cells. In some embodiments, the growth media

during the first expansion comprises IL-2 or a variant thereof. In some embodiments, the IL is recombinant human IL-2 (rhIL-2). In some embodiments the IL-2 stock solution has a specific activity of 20-30×10⁶ IU/mg for a 1 mg vial. In some embodiments the IL-2 stock solution has a specific activity of 20×10⁶ IU/mg for a 1 mg vial. In some embodiments the IL-2 stock solution has a specific activity of 25×10⁶ IU/mg for a 1 mg vial. In some embodiments the IL-2 stock solution has a specific activity of 30×10⁶ IU/mg for a 1 mg vial. In some embodiments, the IL-2 stock solution has a final concentration of 4-8×10⁶ IU/mg of IL-2. In some embodiments, the IL-2 stock solution has a final concentration of 5-7×10⁶ IU/mg of IL-2. In some embodiments, the IL-2 stock solution has a final concentration of 6×10⁶ IU/mg of IL-2. In some embodiments, the IL-2 stock solution is prepare as described in Example 5. In some embodiments, the first expansion culture media comprises about 10,000 IU/mL of IL-2, about 9,000 IU/mL of IL-2, about 8,000 IU/mL of IL-2, about 7,000 IU/mL of IL-2, about 6000 IU/mL of IL-2 or about 5,000 IU/mL of IL-2. In some embodiments, the first expansion culture media comprises about 9,000 IU/mL of IL-2 to about 5,000 IU/mL of IL-2. In some embodiments, the first expansion culture media comprises about 8,000 IU/mL of IL-2 to about 6,000 IU/mL of IL-2. In some embodiments, the first expansion culture media comprises about 7,000 IU/mL of IL-2 to about 6,000 IU/mL of IL-2. In some embodiments, the first expansion culture media comprises about 6,000 IU/mL of IL-2. In an embodiment, the cell culture medium further comprises IL-2. In some embodiments, the cell culture medium comprises about 3000 IU/mL of IL-2. In an embodiment, the cell culture medium further comprises IL-2. In a preferred embodiment, the cell culture medium comprises about 3000 IU/mL of IL-2. In an embodiment, the cell culture medium comprises about 1000 IU/mL, about 1500 IU/mL, about 2000 IU/mL, about 2500 IU/mL, about 3000 IU/mL, about 3500 IU/mL, about 4000 IU/mL, about 4500 IU/mL, about 5000 IU/mL, about 5500 IU/mL, about 6000 IU/mL, about 6500 IU/mL, about 7000 IU/mL, about 7500 IU/mL, or about 8000 IU/mL of IL-2. In an embodiment, the cell culture medium comprises between 1000 and 2000 IU/mL, between 2000 and 3000 IU/mL, between 3000 and 4000 IU/mL, between 4000 and 5000 IU/mL, between 5000 and 6000 IU/mL, between 6000 and 7000 IU/mL, between 7000 and 8000 IU/mL, or about 8000 IU/mL of IL-2.

[00519] In some embodiments, first expansion culture media comprises about 500 IU/mL of IL-15, about 400 IU/mL of IL-15, about 300 IU/mL of IL-15, about 200 IU/mL of IL-15, about 180 IU/mL of IL-15, about 160 IU/mL of IL-15, about 140 IU/mL of IL-15, about 120 IU/mL of IL-15, or about 100 IU/mL of IL-15. In some embodiments, the first expansion

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culture media comprises about 500 IU/mL of IL-15 to about 100 IU/mL of IL-15. In some embodiments, the first expansion culture media comprises about 400 IU/mL of IL-15 to about 100 IU/mL of IL-15. In some embodiments, the first expansion culture media comprises about 300 IU/mL of IL-15 to about 100 IU/mL of IL-15. In some embodiments, the first expansion culture media comprises about 200 IU/mL of IL-15. In some embodiments, the cell culture medium comprises about 180 IU/mL of IL-15. In an embodiment, the cell culture medium further comprises IL-15. In a preferred embodiment, the cell culture medium comprises about 180 IU/mL of IL-15.

[00520] In some embodiments, first expansion culture media comprises about 20 IU/mL of IL-21, about 15 IU/mL of IL-21, about 12 IU/mL of IL-21, about 10 IU/mL of IL-21, about 5 IU/mL of IL-21, about 4 IU/mL of IL-21, about 3 IU/mL of IL-21, about 2 IU/mL of IL-21, about 1 IU/mL of IL-21, or about 0.5 IU/mL of IL-21. In some embodiments, the first expansion culture media comprises about 20 IU/mL of IL-21 to about 0.5 IU/mL of IL-21. In some embodiments, the first expansion culture media comprises about 15 IU/mL of IL-21 to about 0.5 IU/mL of IL-21. In some embodiments, the first expansion culture media comprises about 12 IU/mL of IL-21 to about 0.5 IU/mL of IL-21. In some embodiments, the first expansion culture media comprises about 10 IU/mL of IL-21 to about 0.5 IU/mL of IL-21. In some embodiments, the first expansion culture media comprises about 5 IU/mL of IL-21 to about 1 IU/mL of IL-21. In some embodiments, the first expansion culture media comprises about 2 IU/mL of IL-21. In some embodiments, the cell culture medium comprises about 1 IU/mL of IL-21. In some embodiments, the cell culture medium comprises about 0.5 IU/mL of IL-21. In an embodiment, the cell culture medium further comprises IL-21. In a preferred embodiment, the cell culture medium comprises about 1 IU/mL of IL-21.

[00521] In an embodiment, the cell culture medium comprises OKT-3 antibody. In some embodiments, the cell culture medium comprises about 30 ng/mL of OKT-3 antibody. In an embodiment, the cell culture medium comprises about 0.1 ng/mL, about 0.5 ng/mL, about 1 ng/mL, about 2.5 ng/mL, about 5 ng/mL, about 7.5 ng/mL, about 10 ng/mL, about 15 ng/mL, about 20 ng/mL, about 25 ng/mL, about 30 ng/mL, about 35 ng/mL, about 40 ng/mL, about 50 ng/mL, about 60 ng/mL, about 70 ng/mL, about 80 ng/mL, about 90 ng/mL, about 100 ng/mL, about 200 ng/mL, about 500 ng/mL, and about 1 μg/mL of OKT-3 antibody. In an embodiment, the cell culture medium comprises between 0.1 ng/mL and 1 ng/mL, between 1 ng/mL and 5 ng/mL, between 5 ng/mL and 10 ng/mL, between 10 ng/mL and 20 ng/mL, between 20 ng/mL and 30 ng/mL, between 30 ng/mL and 40 ng/mL, between 40 ng/mL and

50 ng/mL, and between 50 ng/mL and 100 ng/mL of OKT-3 antibody. In some embodiments, the cell culture medium does not comprise OKT-3 antibody. In some embodiments, the OKT-3 antibody is muromonab.

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TABLE 3: Amino acid sequences of muromonab (exemplary OKT-3 antibody)

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:1	QVQLQQSGAE LARPGASVKM SCKASGYTFT RYTMHWVKQR PGQGLEWIGY INPSRGYTNY	60
Muromonab heavy	NQKFKDKATL TTDKSSSTAY MQLSSLTSED SAVYYCARYY DDHYCLDYWG QGTTLTVSSA	120
chain	KTTAPSVYPL APVCGGTTGS SVTLGCLVKG YFPEPVTLTW NSGSLSSGVH TFPAVLQSDL	180
	YTLSSSVTVT SSTWPSQSIT CNVAHPASST KVDKKIEPRP KSCDKTHTCP PCPAPELLGG	240
	PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN	300
	STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE	360
	LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW	420
	QQGNVFSCSV MHEALHNHYT QKSLSLSPGK	450
SEQ ID NO:2	QIVLTQSPAI MSASPGEKVT MTCSASSSVS YMNWYQQKSG TSPKRWIYDT SKLASGVPAH	60
Muromonab light	FRGSGSGTSY SLTISGMEAE DAATYYCQQW SSNPFTFGSG TKLEINRADT APTVSIFPPS	120
chain	SEQLTSGGAS VVCFLNNFYP KDINVKWKID GSERQNGVLN SWTDQDSKDS TYSMSSTLTL	180
	TKDEYERHNS YTCEATHKTS TSPIVKSFNR NEC	213

[00522] In some embodiments, the cell culture medium comprises one or more TNFRSF agonists in a cell culture medium. In some embodiments, the TNFRSF agonist comprises a 4-1BB agonist. In some embodiments, the TNFRSF agonist is a 4-1BB agonist, and the 4-1BB agonist is selected from the group consisting of urelumab, utomilumab, EU-101, a fusion protein, and fragments, derivatives, variants, biosimilars, and combinations thereof. In some embodiments, the TNFRSF agonist is added at a concentration sufficient to achieve a concentration in the cell culture medium of between $0.1~\mu g/mL$ and $100~\mu g/mL$. In some embodiments, the TNFRSF agonist is added at a concentration sufficient to achieve a concentration in the cell culture medium of between $20~\mu g/mL$ and $40~\mu g/mL$.

[00523] In some embodiments, in addition to one or more TNFRSF agonists, the cell culture medium further comprises IL-2 at an initial concentration of about 3000 IU/mL and OKT-3 antibody at an initial concentration of about 30 ng/mL, and wherein the one or more TNFRSF agonists comprises a 4-1BB agonist.

[00524] In some embodiments, the first expansion culture medium is referred to as "CM", an abbreviation for culture media. In some embodiments, it is referred to as CM1 (culture medium 1). In some embodiments, CM consists of RPMI 1640 with GlutaMAX, supplemented with 10% human AB serum, 25 mM Hepes, and 10 mg/mL gentamicin. In embodiments where cultures are initiated in gas-permeable flasks with a 40 mL capacity and a 10cm² gas-permeable silicon bottom (for example, G-Rex10; Wilson Wolf Manufacturing, New Brighton, MN) (Fig. 1), each flask was loaded with 10–40x106 viable tumor digest cells

or 5–30 tumor fragments in 10–40mL of CM with IL-2. Both the G-Rex10 and 24-well plates were incubated in a humidified incubator at 37°C in 5% CO₂ and 5 days after culture initiation, half the media was removed and replaced with fresh CM and IL-2 and after day 5, half the media was changed every 2–3 days. In some embodiments, the CM is the CM1 described in the Examples, see, Example 1. In some embodiments, the first expansion occurs in an initial cell culture medium or a first cell culture medium. In some embodiments, the initial cell culture medium or the first cell culture medium comprises IL-2.

[00525] In some embodiments, the first expansion (including processes such as for example those described in Step B of Figure 1, which can include those sometimes referred to as the pre-REP) process is shortened to 3-14 days, as discussed in the examples and figures. In some embodiments, the first expansion (including processes such as for example those described in Step B of Figure 1, which can include those sometimes referred to as the pre-REP) is shortened to 7 to 14 days, as discussed in the Examples and shown in Figures 4 and 5, as well as including for example, an expansion as described in Step B of Figure 1. In some embodiments, the first expansion of Step B is shortened to 10-14 days. In some embodiments, the first expansion is shortened to 11 days, as discussed in, for example, an expansion as described in Step B of Figure 1.

[00526] In some embodiments, the first TIL expansion can proceed for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, or 14 days. In some embodiments, the first TIL expansion can proceed for 1 day to 14 days. In some embodiments, the first TIL expansion can proceed for 2 days to 14 days. In some embodiments, the first TIL expansion can proceed for 3 days to 14 days. In some embodiments, the first TIL expansion can proceed for 4 days to 14 days. In some embodiments, the first TIL expansion can proceed for 5 days to 14 days. In some embodiments, the first TIL expansion can proceed for 6 days to 14 days. In some embodiments, the first TIL expansion can proceed for 7 days to 14 days. In some embodiments, the first TIL expansion can proceed for 8 days to 14 days. In some embodiments, the first TIL expansion can proceed for 9 days to 14 days. In some embodiments, the first TIL expansion can proceed for 10 days to 14 days. In some embodiments, the first TIL expansion can proceed for 11 days to 14 days. In some embodiments, the first TIL expansion can proceed for 12 days to 14 days. In some embodiments, the first TIL expansion can proceed for 13 days to 14 days. In some embodiments, the first TIL expansion can proceed for 14 days. In some embodiments, the

first TIL expansion can proceed for 1 day to 11 days. In some embodiments, the first TIL expansion can proceed for 2 days to 11 days. In some embodiments, the first TIL expansion can proceed for 3 days to 11 days. In some embodiments, the first TIL expansion can proceed for 4 days to 11 days. In some embodiments, the first TIL expansion can proceed for 5 days to 11 days. In some embodiments, the first TIL expansion can proceed for 6 days to 11 days. In some embodiments, the first TIL expansion can proceed for 7 days to 11 days. In some embodiments, the first TIL expansion can proceed for 8 days to 11 days. In some embodiments, the first TIL expansion can proceed for 9 days to 11 days. In some embodiments, the first TIL expansion can proceed for 10 days to 11 days. In some embodiments, the first TIL expansion can proceed for 10 days to 11 days. In some

[00527] In some embodiments, a combination of IL-2, IL-7, IL-15, and/or IL-21 are employed as a combination during the first expansion. In some embodiments, IL-2, IL-7, IL-15, and/or IL-21 as well as any combinations thereof can be included during the first expansion, including for example during a Step B processes according to Figure 1, as well as described herein. In some embodiments, a combination of IL-2, IL-15, and IL-21 are employed as a combination during the first expansion. In some embodiments, IL-2, IL-15, and IL-21 as well as any combinations thereof can be included during Step B processes according to Figure 1 and as described herein.

[00528] In some embodiments, the first expansion (including processes referred to as the pre-REP; for example, Step B according to Figure 1) process is shortened to 3 to 14 days, as discussed in the examples and figures. In some embodiments, the first expansion of Step B is shortened to 7 to 14 days. In some embodiments, the first expansion of Step B is shortened to 10 to 14 days. In some embodiments, the first expansion is shortened to 11 days.

[00529] In some embodiments, the first expansion, for example, Step B according to Figure 1, is performed in a closed system bioreactor. In some embodiments, a closed system is employed for the TIL expansion, as described herein. In some embodiments, a single bioreactor is employed. In some embodiments, the single bioreactor employed is for example a G-REX -10 or a G-REX -100. In some embodiments, the closed system bioreactor is a single bioreactor.

C. STEP C: First Expansion to Second Expansion Transition

[00530] In some cases, the bulk TIL population obtained from the first expansion, including for example the TIL population obtained from for example, Step B as indicated in Figure 1,

can be cryopreserved immediately, using the protocols discussed herein below. Alternatively, the TIL population obtained from the first expansion, referred to as the second TIL population, can be subjected to a second expansion (which can include expansions sometimes referred to as REP) and then cryopreserved as discussed below. Similarly, in the case where genetically modified TILs will be used in therapy, the first TIL population (sometimes referred to as the bulk TIL population) or the second TIL population (which can in some embodiments include populations referred to as the REP TIL populations) can be subjected to genetic modifications for suitable treatments prior to expansion or after the first expansion and prior to the second expansion.

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[00531] In some embodiments, the TILs obtained from the first expansion (for example, from Step B as indicated in Figure 1) are stored until phenotyped for selection. In some embodiments, the TILs obtained from the first expansion (for example, from Step B as indicated in Figure 1) are not stored and proceed directly to the second expansion. In some embodiments, the TILs obtained from the first expansion are not cryopreserved after the first expansion and prior to the second expansion. In some embodiments, the transition from the first expansion to the second expansion occurs at about 3 days, 4, days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, or 14 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs at about 3 days to 14 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs at about 4 days to 14 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs at about 4 days to 10 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs at about 7 days to 14 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs at about 14 days from when fragmentation occurs.

[00532] In some embodiments, the transition from the first expansion to the second expansion occurs at 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, or 14 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs 1 day to 14 days from when fragmentation occurs. In some embodiments, the first TIL expansion can proceed for 2 days to 14 days. In some embodiments, the transition from the first expansion to the second expansion occurs 3 days to 14 days from when fragmentation occurs. In some

embodiments, the transition from the first expansion to the second expansion occurs 4 days to 14 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs 5 days to 14 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs 6 days to 14 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs 7 days to 14 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs 8 days to 14 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs 9 days to 14 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs 10 days to 14 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs 11 days to 14 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs 12 days to 14 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs 13 days to 14 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs 14 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs 1 day to 11 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs 2 days to 11 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs 3 days to 11 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs 4 days to 11 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs 5 days to 11 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs 6 days to 11 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs 7 days to 11 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs 8 days to 11 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs 9 days to 11 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs 10 days

to 11 days from when fragmentation occurs. In some embodiments, the transition from the first expansion to the second expansion occurs 11 days from when fragmentation occurs.

[00533] In some embodiments, the TILs are not stored after the first expansion and prior to the second expansion, and the TILs proceed directly to the second expansion (for example, in some embodiments, there is no storage during the transition from Step B to Step D as shown in Figure 1). In some embodiments, the transition occurs in closed system, as described herein. In some embodiments, the TILs from the first expansion, the second population of TILs, proceeds directly into the second expansion with no transition period.

[00534] In some embodiments, the transition from the first expansion to the second expansion, for example, Step C according to Figure 1, is performed in a closed system bioreactor. In some embodiments, a closed system is employed for the TIL expansion, as described herein. In some embodiments, a single bioreactor is employed. In some embodiments, the single bioreactor employed is for example a G-REX -10 or a G-REX -100. In some embodiments, the closed system bioreactor is a single bioreactor.

1. Cytokines

[00535] The expansion methods described herein generally use culture media with high doses of a cytokine, in particular IL-2, as is known in the art.

[00536] Alternatively, using combinations of cytokines for the rapid expansion and or second expansion of TILS is additionally possible, with combinations of two or more of IL-2, IL-15 and IL-21 as is generally outlined in International Publication No. WO 2015/189356 and W International Publication No. WO 2015/189357, hereby expressly incorporated by reference in their entirety. Thus, possible combinations include IL-2 and IL-15, IL-2 and IL-21, IL-15 and IL-21 and IL-21, with the latter finding particular use in many embodiments. The use of combinations of cytokines specifically favors the generation of lymphocytes, and in particular T-cells as described therein.

TABLE 4: Amino acid sequences of interleukins.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:3	MAPTSSSTKK TQLQLEHLLL DLQMILNGIN NYKNPKLTRM LTFKFYMPKK ATELKHLQCL	60
recombinant	EEELKPLEEV LNLAQSKNFH LRPRDLISNI NVIVLELKGS ETTFMCEYAD ETATIVEFLN	120
human IL-2	RWITFCQSII STLT	134
(rhIL-2)		
SEQ ID NO:4	PTSSSTKKTQ LQLEHLLLDL QMILNGINNY KNPKLTRMLT FKFYMPKKAT ELKHLQCLEE	60
Aldesleukin	ELKPLEEVLN LAQSKNFHLR PRDLISNINV IVLELKGSET TFMCEYADET ATIVEFLNRW	120
	ITFSQSIIST LT	132
SEQ ID NO:5	MHKCDITLQE IIKTLNSLTE QKTLCTELTV TDIFAASKNT TEKETFCRAA TVLRQFYSHH	60
	EKDTRCLGAT AQQFHRHKQL IRFLKRLDRN LWGLAGLNSC PVKEANQSTL ENFLERLKTI	120

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recombinant human IL-4 (rhIL-4)	MREKYSKCSS	130
SEQ ID NO:6	MDCDIEGKDG KQYESVLMVS IDQLLDSMKE IGSNCLNNEF NFFKRHICDA NKEGMFLFRA	60
recombinant human IL-7 (rhIL-7)	ARKLRQFLKM NSTGDFDLHL LKVSEGTTIL LNCTGQVKGR KPAALGEAQP TKSLEENKSL KEQKKLNDLC FLKRLLQEIK TCWNKILMGT KEH	120 153
SEQ ID NO:7 recombinant human IL-15 (rhIL-15)	MNWVNVISDL KKIEDLIQSM HIDATLYTES DVHPSCKVTA MKCFLLELQV ISLESGDASI HDTVENLIIL ANNSLSSNGN VTESGCKECE ELEEKNIKEF LQSFVHIVQM FINTS	60 115
SEQ ID NO:8 recombinant human IL-21 (rhIL-21)	MQDRHMIRMR QLIDIVDQLK NYVNDLVPEF LPAPEDVETN CEWSAFSCFQ KAQLKSANTG NNERIINVSI KKLKRKPPST NAGRRQKHRL TCPSCDSYEK KPPKEFLERF KSLLQKMIHQ HLSSRTHGSE DS	60 120 132

D. STEP D: Second Expansion

[00537] In some embodiments, the TIL cell population is expanded in number after harvest and initial bulk processing for example, after Step A and Step B, and the transition referred to as Step C, as indicated in Figure 1). This further expansion is referred to herein as the second expansion, which can include expansion processes generally referred to in the art as a rapid expansion process (REP; as well as processes as indicated in Step D of Figure 1). The second expansion is generally accomplished using a culture media comprising a number of components, including feeder cells, a cytokine source, and an anti-CD3 antibody, in a gaspermeable container.

[00538] In some embodiments, the second expansion or second TIL expansion (which can include expansions sometimes referred to as REP; as well as processes as indicated in Step D of Figure 1) of TIL can be performed using any TIL flasks or containers known by those of skill in the art. In some embodiments, the second TIL expansion can proceed for 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, or 14 days. In some embodiments, the second TIL expansion can proceed for about 7 days to about 14 days. In some embodiments, the second TIL expansion can proceed for about 8 days to about 14 days. In some embodiments, the second TIL expansion can proceed for about 9 days to about 14 days. In some embodiments, the second TIL expansion can proceed for about 10 days to about 14 days. In some embodiments, the second TIL expansion can proceed for about 11 days to about 14 days. In some embodiments, the second TIL expansion can proceed for about 12 days to about 14 days. In some embodiments, the second TIL expansion can proceed for about 12 days to about 14 days. In some embodiments, the second TIL expansion can proceed for about 13 days to about 14 days. In some embodiments, the second TIL expansion can proceed for about 13 days to about 14 days. In some embodiments, the second TIL expansion can proceed for about 14 days.

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[00539] In an embodiment, the second expansion can be performed in a gas permeable container using the methods of the present disclosure (including for example, expansions referred to as REP; as well as processes as indicated in Step D of Figure 1). For example, TILs can be rapidly expanded using non-specific T-cell receptor stimulation in the presence of interleukin-2 (IL-2) or interleukin-15 (IL-15). The non-specific T-cell receptor stimulus can include, for example, an anti-CD3 antibody, such as about 30 ng/ml of OKT3, a mouse monoclonal anti-CD3 antibody (commercially available from Ortho-McNeil, Raritan, NJ or Miltenyi Biotech, Auburn, CA) or UHCT-1 (commercially available from BioLegend, San Diego, CA, USA). TILs can be expanded to induce further stimulation of the TILs in vitro by including one or more antigens during the second expansion, including antigenic portions thereof, such as epitope(s), of the cancer, which can be optionally expressed from a vector, such as a human leukocyte antigen A2 (HLA-A2) binding peptide, e.g., 0.3 µM MART-1:26-35 (27 L) or gpl 00:209-217 (210M), optionally in the presence of a T-cell growth factor, such as 300 IU/mL IL-2 or IL-15. Other suitable antigens may include, e.g., NY-ESO-1, TRP-1, TRP-2, tyrosinase cancer antigen, MAGE-A3, SSX-2, and VEGFR2, or antigenic portions thereof. TIL may also be rapidly expanded by re-stimulation with the same antigen(s) of the cancer pulsed onto HLA-A2-expressing antigen-presenting cells. Alternatively, the TILs can be further re-stimulated with, e.g., example, irradiated, autologous lymphocytes or with irradiated HLA-A2+ allogeneic lymphocytes and IL-2. In some embodiments, the re-stimulation occurs as part of the second expansion. In some embodiments, the second expansion occurs in the presence of irradiated, autologous lymphocytes or with irradiated HLA-A2+ allogeneic lymphocytes and IL-2.

[00540] In an embodiment, the cell culture medium further comprises IL-2. In some embodiments, the cell culture medium comprises about 3000 IU/mL of IL-2. In an embodiment, the cell culture medium comprises about 1000 IU/mL, about 1500 IU/mL, about 2000 IU/mL, about 2500 IU/mL, about 3000 IU/mL, about 3500 IU/mL, about 4000 IU/mL, about 4500 IU/mL, about 5000 IU/mL, about 5500 IU/mL, about 6000 IU/mL, about 6500 IU/mL, about 7000 IU/mL, about 7500 IU/mL, or about 8000 IU/mL of IL-2. In an embodiment, the cell culture medium comprises between 1000 and 2000 IU/mL, between 2000 and 3000 IU/mL, between 3000 and 4000 IU/mL, between 4000 and 5000 IU/mL, between 5000 and 6000 IU/mL, between 6000 and 7000 IU/mL, between 7000 and 8000 IU/mL, or between 8000 IU/mL of IL-2.

[00541] In an embodiment, the cell culture medium comprises OKT-3 antibody. In some embodiments, the cell culture medium comprises about 30 ng/mL of OKT-3 antibody. In an embodiment, the cell culture medium comprises about 0.1 ng/mL, about 0.5 ng/mL, about 1 ng/mL, about 2.5 ng/mL, about 5 ng/mL, about 7.5 ng/mL, about 10 ng/mL, about 15 ng/mL, about 20 ng/mL, about 25 ng/mL, about 30 ng/mL, about 35 ng/mL, about 40 ng/mL, about 50 ng/mL, about 60 ng/mL, about 70 ng/mL, about 80 ng/mL, about 90 ng/mL, about 100 ng/mL, about 200 ng/mL, about 500 ng/mL, and about 1 μg/mL of OKT-3 antibody. In an embodiment, the cell culture medium comprises between 0.1 ng/mL and 1 ng/mL, between 1 ng/mL and 5 ng/mL, between 5 ng/mL and 10 ng/mL, between 10 ng/mL and 20 ng/mL, between 20 ng/mL and 30 ng/mL, between 30 ng/mL and 40 ng/mL, between 40 ng/mL and 50 ng/mL, and between 50 ng/mL and 100 ng/mL of OKT-3 antibody. In some embodiments, the cell culture medium does not comprise OKT-3 antibody. In some embodiments, the OKT-3 antibody is muromonab.

[00542] In some embodiments, the cell culture medium comprises one or more TNFRSF agonists in a cell culture medium. In some embodiments, the TNFRSF agonist comprises a 4-1BB agonist. In some embodiments, the TNFRSF agonist is a 4-1BB agonist, and the 4-1BB agonist is selected from the group consisting of urelumab, utomilumab, EU-101, a fusion protein, and fragments, derivatives, variants, biosimilars, and combinations thereof. In some embodiments, the TNFRSF agonist is added at a concentration sufficient to achieve a concentration in the cell culture medium of between 0.1 µg/mL and 100 µg/mL. In some embodiments, the TNFRSF agonist is added at a concentration sufficient to achieve a concentration in the cell culture medium of between 20 µg/mL and 40 µg/mL.

[00543] In some embodiments, in addition to one or more TNFRSF agonists, the cell culture medium further comprises IL-2 at an initial concentration of about 3000 IU/mL and OKT-3 antibody at an initial concentration of about 30 ng/mL, and wherein the one or more TNFRSF agonists comprises a 4-1BB agonist.

[00544] In some embodiments, a combination of IL-2, IL-7, IL-15, and/or IL-21 are employed as a combination during the second expansion. In some embodiments, IL-2, IL-7, IL-15, and/or IL-21 as well as any combinations thereof can be included during the second expansion, including for example during a Step D processes according to Figure 1, as well as described herein. In some embodiments, a combination of IL-2, IL-15, and IL-21 are employed as a combination during the second expansion. In some embodiments, IL-2, IL-15,

and IL-21 as well as any combinations thereof can be included during Step D processes according to Figure 1 and as described herein.

[00545] In some embodiments, the second expansion can be conducted in a supplemented cell culture medium comprising IL-2, OKT-3, antigen-presenting feeder cells, and optionally a TNFRSF agonist. In some embodiments, the second expansion occurs in a supplemented cell culture medium. In some embodiments, the supplemented cell culture medium comprises IL-2, OKT-3, and antigen-presenting feeder cells. In some embodiments, the second cell culture medium comprises IL-2, OKT-3, and antigen-presenting cells (APCs; also referred to as antigen-presenting feeder cells). In some embodiments, the second expansion occurs in a cell culture medium comprising IL-2, OKT-3, and antigen-presenting feeder cells (*i.e.*, antigen presenting cells).

[00546] In some embodiments, the second expansion culture media comprises about 500 IU/mL of IL-15, about 400 IU/mL of IL-15, about 300 IU/mL of IL-15, about 200 IU/mL of IL-15, about 180 IU/mL of IL-15, about 160 IU/mL of IL-15, about 140 IU/mL of IL-15, about 120 IU/mL of IL-15, or about 100 IU/mL of IL-15. In some embodiments, the second expansion culture media comprises about 500 IU/mL of IL-15 to about 100 IU/mL of IL-15. In some embodiments, the second expansion culture media comprises about 400 IU/mL of IL-15 to about 100 IU/mL of IL-15. In some embodiments, the second expansion culture media comprises about 300 IU/mL of IL-15 to about 100 IU/mL of IL-15. In some embodiments, the second expansion culture media comprises about 200 IU/mL of IL-15. In some embodiments, the cell culture medium comprises about 180 IU/mL of IL-15. In an embodiment, the cell culture medium further comprises IL-15. In a preferred embodiment, the cell culture medium comprises about 180 IU/mL of IL-15.

[00547] In some embodiments, the second expansion culture media comprises about 20 IU/mL of IL-21, about 15 IU/mL of IL-21, about 12 IU/mL of IL-21, about 10 IU/mL of IL-21, about 5 IU/mL of IL-21, about 4 IU/mL of IL-21, about 3 IU/mL of IL-21, about 2 IU/mL of IL-21, about 1 IU/mL of IL-21, or about 0.5 IU/mL of IL-21. In some embodiments, the second expansion culture media comprises about 20 IU/mL of IL-21 to about 0.5 IU/mL of IL-21. In some embodiments, the second expansion culture media comprises about 15 IU/mL of IL-21 to about 0.5 IU/mL of IL-21. In some embodiments, the second expansion culture media comprises about 12 IU/mL of IL-21 to about 0.5 IU/mL of IL-21. In some embodiments, the second expansion culture media comprises about 10 IU/mL of IL-21 to about 0.5 IU/mL of IL-21. In some embodiments, the second expansion culture media comprises about 10 IU/mL of IL-21 to

comprises about 5 IU/mL of IL-21 to about 1 IU/mL of IL-21. In some embodiments, the second expansion culture media comprises about 2 IU/mL of IL-21. In some embodiments, the cell culture medium comprises about 1 IU/mL of IL-21. In some embodiments, the cell culture medium comprises about 0.5 IU/mL of IL-21. In an embodiment, the cell culture medium further comprises IL-21. In a preferred embodiment, the cell culture medium comprises about 1 IU/mL of IL-21.

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[00548] In some embodiments the antigen-presenting feeder cells (APCs) are PBMCs. In an embodiment, the ratio of TILs to PBMCs and/or antigen-presenting cells in the rapid expansion and/or the second expansion is about 1 to 25, about 1 to 50, about 1 to 100, about 1 to 125, about 1 to 150, about 1 to 175, about 1 to 200, about 1 to 225, about 1 to 250, about 1 to 275, about 1 to 300, about 1 to 325, about 1 to 350, about 1 to 375, about 1 to 400, or about 1 to 500. In an embodiment, the ratio of TILs to PBMCs in the rapid expansion and/or the second expansion is between 1 to 50 and 1 to 300. In an embodiment, the ratio of TILs to PBMCs in the rapid expansion and/or the second expansion is between 1 to 100 and 1 to 200.

[00549] In an embodiment, REP and/or the second expansion is performed in flasks with the bulk TILs being mixed with a 100- or 200-fold excess of inactivated feeder cells, 30 mg/mL OKT3 anti-CD3 antibody and 3000 IU/mL IL-2 in 150 ml media. Media replacement is done (generally 2/3 media replacement via respiration with fresh media) until the cells are transferred to an alternative growth chamber. Alternative growth chambers include G-REX flasks and gas permeable containers as more fully discussed below.

[00550] In some embodiments, the second expansion (which can include processes referred to as the REP process) is shortened to 7-14 days, as discussed in the examples and figures. In some embodiments, the second expansion is shortened to 11 days.

[00551] In an embodiment, REP and/or the second expansion may be performed using T-175 flasks and gas permeable bags as previously described (Tran, *et al.*, *J. Immunother.* 2008, 31, 742-51; Dudley, *et al.*, *J. Immunother.* 2003, 26, 332-42) or gas permeable cultureware (G-Rex flasks). In some embodiments, the second expansion (including expansions referred to as rapid expansions) is performed in T-175 flasks, and about 1 x 10⁶ TILs suspended in 150 mL of media may be added to each T-175 flask. The TILs may be cultured in a 1 to 1 mixture of CM and AIM-V medium, supplemented with 3000 IU per mL of IL-2 and 30 ng per ml of anti-CD3. The T-175 flasks may be incubated at 37° C in 5% CO₂. Half the media may be exchanged on day 5 using 50/50 medium with 3000 IU per mL of IL-2. In some

embodiments, on day 7 cells from two T-175 flasks may be combined in a 3 L bag and 300 mL of AIM V with 5% human AB serum and 3000 IU per mL of IL-2 was added to the 300 ml of TIL suspension. The number of cells in each bag was counted every day or two and fresh media was added to keep the cell count between 0.5 and 2.0×10^6 cells/mL.

[00552] In an embodiment, the second expansion (which can include expansions referred to as REP, as well as those referred to in Step D of Figure 1) may be performed in 500 mL capacity gas permeable flasks with 100 cm gas-permeable silicon bottoms (G-Rex 100, commercially available from Wilson Wolf Manufacturing Corporation, New Brighton, MN, USA), 5×10^6 or 10×10^6 TIL may be cultured with PBMCs in 400 mL of 50/50 medium, supplemented with 5% human AB serum, 3000 IU per mL of IL-2 and 30 ng per ml of anti-CD3 (OKT3). The G-Rex 100 flasks may be incubated at 37°C in 5% CO₂. On day 5, 250 mL of supernatant may be removed and placed into centrifuge bottles and centrifuged at 1500 rpm (491 × g) for 10 minutes. The TIL pellets may be re-suspended with 150 mL of fresh medium with 5% human AB serum, 3000 IU per mL of IL-2, and added back to the original G-Rex 100 flasks. When TIL are expanded serially in G-Rex 100 flasks, on day 7 the TIL in each G-Rex 100 may be suspended in the 300 mL of media present in each flask and the cell suspension may be divided into 3 100 mL aliquots that may be used to seed 3 G-Rex 100 flasks. Then 150 mL of AIM-V with 5% human AB serum and 3000 IU per mL of IL-2 may be added to each flask. The G-Rex 100 flasks may be incubated at 37° C in 5% CO₂ and after 4 days 150 mL of AIM-V with 3000 IU per mL of IL-2 may be added to each G-REX 100 flask. The cells may be harvested on day 14 of culture.

[00553] In an embodiment, the second expansion (including expansions referred to as REP) is performed in flasks with the bulk TILs being mixed with a 100- or 200-fold excess of inactivated feeder cells, 30 mg/mL OKT3 anti-CD3 antibody and 3000 IU/mL IL-2 in 150 ml media. In some embodiments, media replacement is done until the cells are transferred to an alternative growth chamber. In some embodiments, 2/3 of the media is replaced by respiration with fresh media. In some embodiments, alternative growth chambers include G-REX flasks and gas permeable containers as more fully discussed below.

[00554] In an embodiment, the second expansion (including expansions referred to as REP) is performed and further comprises a step wherein TILs are selected for superior tumor reactivity. Any selection method known in the art may be used. For example, the methods described in U.S. Patent Application Publication No. 2016/0010058 A1, the disclosures of

which are incorporated herein by reference, may be used for selection of TILs for superior tumor reactivity.

[00555] Optionally, a cell viability assay can be performed after the second expansion (including expansions referred to as the REP expansion), using standard assays known in the art. For example, a trypan blue exclusion assay can be done on a sample of the bulk TILs, which selectively labels dead cells and allows a viability assessment. In some embodiments, TIL samples can be counted and viability determined using a Cellometer K2 automated cell counter (Nexcelom Bioscience, Lawrence, MA). In some embodiments, viability is determined according to the standard Cellometer K2 Image Cytometer Automatic Cell Counter protocol.

[00556] In some embodiments, the second expansion (including expansions referred to as REP) of TIL can be performed using T-175 flasks and gas-permeable bags as previously described (Tran KQ, Zhou J, Durflinger KH, et al., 2008, J Immunother., 31:742-751, and Dudley ME, Wunderlich JR, Shelton TE, et al. 2003, J Immunother., 26:332-342) or gas-permeable G-Rex flasks. In some embodiments, the second expansion is performed using flasks. In some embodiments, the second expansion is performed using gas-permeable G-Rex flasks. In some embodiments, the second expansion is performed in T-175 flasks, and about 1×10^6 TIL are suspended in about 150 mL of media and this is added to each T-175 flask. The TIL are cultured with irradiated (50 Gy) allogeneic PBMC as "feeder" cells at a ratio of 1 to 100 and the cells were cultured in a 1 to 1 mixture of CM and AIM-V medium (50/50 medium), supplemented with 3000 IU/mL of IL-2 and 30 ng/mL of anti-CD3. The T-175 flasks are incubated at 37°C in 5% CO₂. In some embodiments, half the media is changed on day 5 using 50/50 medium with 3000 IU/mL of IL-2. In some embodiments, on day 7, cells from 2 T-175 flasks are combined in a 3 L bag and 300 mL of AIM-V with 5% human AB serum and 3000 IU/mL of IL-2 is added to the 300 mL of TIL suspension. The number of cells in each bag can be counted every day or two and fresh media can be added to keep the cell count between about 0.5 and about 2.0×10^6 cells/mL.

[00557] In some embodiments, the second expansion (including expansions referred to as REP) are performed in 500 mL capacity flasks with 100 cm² gas-permeable silicon bottoms (G-Rex 100, Wilson Wolf) (Fig. 1), about $5x10^6$ or $10x10^6$ TIL are cultured with irradiated allogeneic PBMC at a ratio of 1 to 100 in 400 mL of 50/50 medium, supplemented with 3000 IU/mL of IL-2 and 30 ng/mL of anti-CD3. The G-Rex 100 flasks are incubated at 37°C in 5% CO₂. In some embodiments, on day 5, 250mL of supernatant is removed and placed into

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centrifuge bottles and centrifuged at 1500 rpm (491g) for 10 minutes. The TIL pellets can then be resuspended with 150 mL of fresh 50/50 medium with 3000 IU/ mL of IL-2 and added back to the original G-Rex 100 flasks. In embodiments where TILs are expanded serially in G-Rex 100 flasks, on day 7 the TIL in each G-Rex 100 are suspended in the 300 mL of media present in each flask and the cell suspension was divided into three 100 mL aliquots that are used to seed 3 G-Rex 100 flasks. Then 150 mL of AIM-V with 5% human AB serum and 3000 IU/mL of IL-2 is added to each flask. The G-Rex 100 flasks are incubated at 37°C in 5% CO₂ and after 4 days 150 mL of AIM-V with 3000 IU/mL of IL-2 is added to each G-Rex 100 flask. The cells are harvested on day 14 of culture.

[00558] The diverse antigen receptors of T and B lymphocytes are produced by somatic recombination of a limited, but large number of gene segments. These gene segments: V (variable), D (diversity), J (joining), and C (constant), determine the binding specificity and downstream applications of immunoglobulins and T-cell receptors (TCRs). The present invention provides a method for generating TILs which exhibit and increase the T-cell repertoire diversity. In some embodiments, the TILs obtained by the present method exhibit an increase in the T-cell repertoire diversity. In some embodiments, the TILs obtained in the second expansion exhibit an increase in the T-cell repertoire diversity. In some embodiments, the increase in diversity is an increase in the immunoglobulin diversity and/or the T-cell receptor diversity. In some embodiments, the diversity is in the immunoglobulin is in the immunoglobulin heavy chain. In some embodiments, the diversity is in the immunoglobulin is in the immunoglobulin light chain. In some embodiments, the diversity is in the T-cell receptor. In some embodiments, the diversity is in one of the T-cell receptors selected from the group consisting of alpha, beta, gamma, and delta receptors. In some embodiments, there is an increase in the expression of T-cell receptor (TCR) alpha and/or beta. In some embodiments, there is an increase in the expression of T-cell receptor (TCR) alpha. In some embodiments, there is an increase in the expression of T-cell receptor (TCR) beta. In some embodiments, there is an increase in the expression of TCRab (i.e., TCR α/β).

[00559] In some embodiments, the second expansion culture medium (e.g., sometimes referred to as CM2 or the second cell culture medium), comprises IL-2, OKT-3, as well as the antigen-presenting feeder cells (APCs), as discussed in more detail below.

[00560] In some embodiments, the second expansion, for example, Step D according to Figure 1, is performed in a closed system bioreactor. In some embodiments, a closed system is employed for the TIL expansion, as described herein. In some embodiments, a single

bioreactor is employed. In some embodiments, the single bioreactor employed is for example a G-REX -10 or a G-REX -100. In some embodiments, the closed system bioreactor is a single bioreactor.

1. Feeder Cells and Antigen Presenting Cells

[00561] In an embodiment, the second expansion procedures described herein (for example including expansion such as those described in Step D from Figure 1, as well as those referred to as REP) require an excess of feeder cells during REP TIL expansion and/or during the second expansion. In many embodiments, the feeder cells are peripheral blood mononuclear cells (PBMCs) obtained from standard whole blood units from healthy blood donors. The PBMCs are obtained using standard methods such as Ficoll-Paque gradient separation.

[00562] In general, the allogenic PBMCs are inactivated, either via irradiation or heat treatment, and used in the REP procedures, as described in the examples, which provides an exemplary protocol for evaluating the replication incompetence of irradiate allogeneic PBMCs.

[00563] In some embodiments, PBMCs are considered replication incompetent and accepted for use in the TIL expansion procedures described herein if the total number of viable cells on day 14 is less than the initial viable cell number put into culture on day 0 of the REP and/or day 0 of the second expansion (*i.e.*, the start day of the second expansion).

[00564] In some embodiments, PBMCs are considered replication incompetent and accepted for use in the TIL expansion procedures described herein if the total number of viable cells, cultured in the presence of OKT3 and IL-2, on day 7 and day 14 has not increased from the initial viable cell number put into culture on day 0 of the REP and/or day 0 of the second expansion (*i.e.*, the start day of the second expansion). In some embodiments, the PBMCs are cultured in the presence of 30 ng/ml OKT3 antibody and 3000 IU/ml IL-2.

[00565] In some embodiments, PBMCs are considered replication incompetent and accepted for use in the TIL expansion procedures described herein if the total number of viable cells, cultured in the presence of OKT3 and IL-2, on day 7 and day 14 has not increased from the initial viable cell number put into culture on day 0 of the REP and/or day 0 of the second expansion (*i.e.*, the start day of the second expansion). In some embodiments, the PBMCs are cultured in the presence of 5-60 ng/ml OKT3 antibody and 1000-6000 IU/ml IL-2. In some embodiments, the PBMCs are cultured in the presence of 10-50 ng/ml OKT3 antibody and

2000-5000 IU/ml IL-2. In some embodiments, the PBMCs are cultured in the presence of 20-40 ng/ml OKT3 antibody and 2000-4000 IU/ml IL-2. In some embodiments, the PBMCs are cultured in the presence of 25-35 ng/ml OKT3 antibody and 2500-3500 IU/ml IL-2.

[00566] In some embodiments, the antigen-presenting feeder cells are PBMCs. In some embodiments, the antigen-presenting feeder cells are artificial antigen-presenting feeder cells. In an embodiment, the ratio of TILs to antigen-presenting feeder cells in the second expansion is about 1 to 25, about 1 to 50, about 1 to 100, about 1 to 125, about 1 to 150, about 1 to 175, about 1 to 200, about 1 to 225, about 1 to 250, about 1 to 275, about 1 to 300, about 1 to 325, about 1 to 350, about 1 to 375, about 1 to 400, or about 1 to 500. In an embodiment, the ratio of TILs to antigen-presenting feeder cells in the second expansion is between 1 to 50 and 1 to 300. In an embodiment, the ratio of TILs to antigen-presenting feeder cells in the second expansion is between 1 to 100 and 1 to 200.

[00567] In an embodiment, the second expansion procedures described herein require a ratio of about 2.5×10^9 feeder cells to about 100×10^6 TILs. In another embodiment, the second expansion procedures described herein require a ratio of about 2.5×10^9 feeder cells to about 50×10^6 TILs. In yet another embodiment, the second expansion procedures described herein require about 2.5×10^9 feeder cells to about 25×10^6 TILs.

[00568] In an embodiment, the second expansion procedures described herein require an excess of feeder cells during the second expansion. In many embodiments, the feeder cells are peripheral blood mononuclear cells (PBMCs) obtained from standard whole blood units from healthy blood donors. The PBMCs are obtained using standard methods such as Ficoll-Paque gradient separation. In an embodiment, artificial antigen-presenting (aAPC) cells are used in place of PBMCs.

[00569] In general, the allogenic PBMCs are inactivated, either via irradiation or heat treatment, and used in the TIL expansion procedures described herein, including the exemplary procedures described in the figures and examples.

[00570] In an embodiment, artificial antigen presenting cells are used in the second expansion as a replacement for, or in combination with, PBMCs.

2. Cytokines

[00571] The expansion methods described herein generally use culture media with high doses of a cytokine, in particular IL-2, as is known in the art.

[00572] Alternatively, using combinations of cytokines for the rapid expansion and or second expansion of TILS is additionally possible, with combinations of two or more of IL-2, IL-15 and IL-21 as is generally outlined in International Publication No. WO 2015/189356 and W International Publication No. WO 2015/189357, hereby expressly incorporated by reference in their entirety. Thus, possible combinations include IL-2 and IL-15, IL-2 and IL-21, IL-15 and IL-21 and IL-2, IL-15 and IL-21, with the latter finding particular use in many embodiments. The use of combinations of cytokines specifically favors the generation of lymphocytes, and in particular T-cells as described therein.

E. **STEP E: Harvest TILS**

[00573] After the second expansion step, cells can be harvested. In some embodiments the TILs are harvested after one, two, three, four or more expansion steps, for example as provided in Figure 1. In some embodiments the TILs are harvested after two expansion steps, for example as provided in Figure 1.

[00574] TILs can be harvested in any appropriate and sterile manner, including for example by centrifugation. Methods for TIL harvesting are well known in the art and any such know methods can be employed with the present process. In some embodiments, TILS are harvest using an automated system.

[00575] Cell harvesters and/or cell processing systems are commercially available from a variety of sources, including, for example, Fresenius Kabi, Tomtec Life Science, Perkin Elmer, and Inotech Biosystems International, Inc. Any cell based harvester can be employed with the present methods. In some embodiments, the cell harvester and/or cell processing systems is a membrane-based cell harvester. In some embodiments, cell harvesting is via a cell processing system, such as the LOVO system (manufactured by Fresenius Kabi). The term "LOVO cell processing system" also refers to any instrument or device manufactured by any vendor that can pump a solution comprising cells through a membrane or filter such as a spinning membrane or spinning filter in a sterile and/or closed system environment, allowing for continuous flow and cell processing to remove supernatant or cell culture media without pelletization. In some embodiments, the cell harvester and/or cell processing system can perform cell separation, washing, fluid-exchange, concentration, and/or other cell processing steps in a closed, sterile system.

[00576] In some embodiments, the harvest, for example, Step E according to Figure 1, is performed from a closed system bioreactor. In some embodiments, a closed system is

employed for the TIL expansion, as described herein. In some embodiments, a single bioreactor is employed. In some embodiments, the single bioreactor employed is for example a G-REX -10 or a G-REX -100. In some embodiments, the closed system bioreactor is a single bioreactor.

[00577] In some embodiments, Step E according to Figure 1, is performed according to the processes described in Example G. In some embodiments, the closed system is accessed via syringes under sterile conditions in order to maintain the sterility and closed nature of the system. In some embodiments, a closed system as described in Example G is employed.

[00578] In some embodiments, TILs are harvested according to the methods described in Example G. In some embodiments, TILs between days 1 and 11 are harvested using the methods as described in Section 8.5 (referred to as the Day 11 TIL harvest in Example G). In some embodiments, TILs between days 12 and 22 are harvested using the methods as described in Section 8.12 (referred to as the Day 22 TIL harvest in Example G).

F. STEP F: Final Formulation/ Transfer to Infusion Bag

[00579] After Steps A through E as provided in an exemplary order in Figure 1 and as outlined in detailed above and herein are complete, cells are transferred to a container for use in administration to a patient. In some embodiments, once a therapeutically sufficient number of TILs are obtained using the expansion methods described above, they are transferred to a container for use in administration to a patient.

[00580] In an embodiment, TILs expanded using APCs of the present disclosure are administered to a patient as a pharmaceutical composition. In an embodiment, the pharmaceutical composition is a suspension of TILs in a sterile buffer. TILs expanded using PBMCs of the present disclosure may be administered by any suitable route as known in the art. In some embodiments, the T-cells are administered as a single intra-arterial or intravenous infusion, which preferably lasts approximately 30 to 60 minutes. Other suitable routes of administration include intraperitoneal, intrathecal, and intralymphatic.

G. Optional Cell Medium Components

1. Anti-CD3 Antibodies

[00581] In some embodiments, the culture media used in expansion methods described herein (including those referred to as REP, see for example, Figure 1) also includes an anti-CD3 antibody. An anti-CD3 antibody in combination with IL-2 induces T cell activation and

cell division in the TIL population. This effect can be seen with full length antibodies as well as Fab and F(ab')2 fragments, with the former being generally preferred; see, *e.g.*, Tsoukas *et al.*, *J. Immunol.* **1985**, *135*, 1719, hereby incorporated by reference in its entirety.

[00582] As will be appreciated by those in the art, there are a number of suitable anti-human CD3 antibodies that find use in the invention, including anti-human CD3 polyclonal and monoclonal antibodies from various mammals, including, but not limited to, murine, human, primate, rat, and canine antibodies. In particular embodiments, the OKT3 anti-CD3 antibody is used (commercially available from Ortho-McNeil, Raritan, NJ or Miltenyi Biotech, Auburn, CA).

TABLE 5: Amino acid sequences of muromonab (exemplary OKT-3 antibody)

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:1	QVQLQQSGAE LARPGASVKM SCKASGYTFT RYTMHWVKQR PGQGLEWIGY INPSRGYTNY	60
Muromonab heavy	NOKFKDKATL TTDKSSSTAY MOLSSLTSED SAVYYCARYY DDHYCLDYWG QGTTLTVSSA	120
chain	KTTAPSVYPL APVCGGTTGS SVTLGCLVKG YFPEPVTLTW NSGSLSSGVH TFPAVLQSDL	180
	YTLSSSVTVT SSTWPSQSIT CNVAHPASST KVDKKIEPRP KSCDKTHTCP PCPAPELLGG	240
	PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN	300
	STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE	360
	LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW	420
	QQGNVFSCSV MHEALHNHYT QKSLSLSPGK	450
SEQ ID NO:2	QIVLTQSPAI MSASPGEKVT MTCSASSSVS YMNWYQQKSG TSPKRWIYDT SKLASGVPAH	60
Muromonab light	FRGSGSGTSY SLTISGMEAE DAATYYCQQW SSNPFTFGSG TKLEINRADT APTVSIFPPS	120
chain	SEQLTSGGAS VVCFLNNFYP KDINVKWKID GSERQNGVLN SWTDQDSKDS TYSMSSTLTL	180
	TKDEYERHNS YTCEATHKTS TSPIVKSFNR NEC	213

2. 4-1BB (CD137) AGONISTS

[00583] In an embodiment, the TNFRSF agonist is a 4-1BB (CD137) agonist. The 4-1BB agonist may be any 4-1BB binding molecule known in the art. The 4-1BB binding molecule may be a monoclonal antibody or fusion protein capable of binding to human or mammalian 4-1BB. The 4-1BB agonists or 4-1BB binding molecules may comprise an immunoglobulin heavy chain of any isotype (*e.g.*, IgG, IgE, IgM, IgD, IgA, and IgY), class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. The 4-1BB agonist or 4-1BB binding molecule may have both a heavy and a light chain. As used herein, the term binding molecule also includes antibodies (including full length antibodies), monoclonal antibodies (including full length monoclonal antibodies), polyclonal antibodies, multispecific antibodies (*e.g.*, bispecific antibodies), human, humanized or chimeric antibodies, and antibody fragments, *e.g.*, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, epitope-binding fragments of any of the above, and engineered forms of antibodies, *e.g.*, scFv molecules, that bind to 4-1BB. In an embodiment, the 4-1BB agonist is

an antigen binding protein that is a fully human antibody. In an embodiment, the 4-1BB agonist is an antigen binding protein that is a humanized antibody. In some embodiments, 4-1BB agonists for use in the presently disclosed methods and compositions include anti-4-1BB antibodies, human anti-4-1BB antibodies, mouse anti-4-1BB antibodies, mammalian anti-4-1BB antibodies, monoclonal anti-4-1BB antibodies, polyclonal anti-4-1BB antibodies, chimeric anti-4-1BB antibodies, anti-4-1BB adnectins, anti-4-1BB domain antibodies, single chain anti-4-1BB fragments, heavy chain anti-4-1BB fragments, light chain anti-4-1BB fragments, anti-4-1BB fusion proteins, and fragments, derivatives, conjugates, variants, or biosimilars thereof. Agonistic anti-4-1BB antibodies are known to induce strong immune responses. Lee, et al., PLOS One 2013, 8, e69677. In a preferred embodiment, the 4-1BB agonist is an agonistic, anti-4-1BB humanized or fully human monoclonal antibody (i.e., an antibody derived from a single cell line). In an embodiment, the 4-1BB agonist is EU-101 (Eutilex Co. Ltd.), utomilumab, or urelumab, or a fragment, derivative, conjugate, variant, or biosimilar thereof. In a preferred embodiment, the 4-1BB agonist is utomilumab or urelumab, or a fragment, derivative, conjugate, variant, or biosimilar thereof.

[00584] In a preferred embodiment, the 4-1BB agonist or 4-1BB binding molecule may also be a fusion protein. In a preferred embodiment, a multimeric 4-1BB agonist, such as a trimeric or hexameric 4-1BB agonist (with three or six ligand binding domains), may induce superior receptor (4-1BBL) clustering and internal cellular signaling complex formation compared to an agonistic monoclonal antibody, which typically possesses two ligand binding domains. Trimeric (trivalent) or hexameric (or hexavalent) or greater fusion proteins comprising three TNFRSF binding domains and IgG1-Fc and optionally further linking two or more of these fusion proteins are described, e.g., in Gieffers, et al., Mol. Cancer Therapeutics 2013, 12, 2735-47.

[00585] Agonistic 4-1BB antibodies and fusion proteins are known to induce strong immune responses. In a preferred embodiment, the 4-1BB agonist is a monoclonal antibody or fusion protein that binds specifically to 4-1BB antigen in a manner sufficient to reduce toxicity. In some embodiments, the 4-1BB agonist is an agonistic 4-1BB monoclonal antibody or fusion protein that abrogates antibody-dependent cellular toxicity (ADCC), for example NK cell cytotoxicity. In some embodiments, the 4-1BB agonist is an agonistic 4-1BB monoclonal antibody or fusion protein that abrogates antibody-dependent cell phagocytosis (ADCP). In some embodiments, the 4-1BB agonist is an agonistic 4-1BB monoclonal antibody or fusion protein that abrogates complement-dependent cytotoxicity (CDC). In some embodiments, the

4-1BB agonist is an agonistic 4-1BB monoclonal antibody or fusion protein which abrogates Fc region functionality.

[00586] In some embodiments, the 4-1BB agonists are characterized by binding to human 4-1BB (SEQ ID NO:9) with high affinity and agonistic activity. In an embodiment, the 4-1BB agonist is a binding molecule that binds to human 4-1BB (SEQ ID NO:9). In an embodiment, the 4-1BB agonist is a binding molecule that binds to murine 4-1BB (SEQ ID NO:10). The amino acid sequences of 4-1BB antigen to which a 4-1BB agonist or binding molecule binds are summarized in Table 6.

TABLE 6. Amino acid sequences of 4-1BB antigens.

Identifier		Seque	nce (One-l	Letter Ami	no Acid Sy	ymbols)	
SEQ ID NO:9	MGNSCYNIVA 7	TLLLVLNFER	TRSLQDPCSN	CPAGTFCDNN	RNQICSPCPP	NSFSSAGGQR	60
human 4-1BB,	TCDICRQCKG V	VFRTRKECSS	TSNAECDCTP	GFHCLGAGCS	MCEQDCKQGQ	ELTKKGCKDC	120
Tumor necrosis	CFGTFNDQKR (GICRPWTNCS	LDGKSVLVNG	TKERDVVCGP	SPADLSPGAS	SVTPPAPARE	180
factor receptor	PGHSPQIISF H	FLALTSTALL	FLLFFLTLRF	SVVKRGRKKL	LYIFKQPFMR	PVQTTQEEDG	240
superfamily,	CSCRFPEEEE C	GGCEL					255
member 9 (Homo							
sapiens)							
SEQ ID NO:10	MGNNCYNVVV]	IVLLLVGCEK	VGAVQNSCDN	CQPGTFCRKY	NPVCKSCPPS	TFSSIGGQPN	60
murine 4-1BB,	CNICRVCAGY H	FRFKKFCSST	HNAECECIEG	FHCLGPQCTR	CEKDCRPGQE	LTKQGCKTCS	120
Tumor necrosis	LGTFNDQNGT (GVCRPWTNCS	LDGRSVLKTG	TTEKDVVCGP	PVVSFSPSTT	ISVTPEGGPG	180
factor receptor	GHSLQVLTLF I	LALTSALLLA	LIFITLLFSV	LKWIRKKFPH	IFKQPFKKTT	GAAQEEDACS	240
superfamily,	CRCPQEEEGG (GGGYEL					256
member 9 (Mus							
musculus)							

[00587] In some embodiments, the compositions, processes and methods described include a 4-1BB agonist that binds human or murine 4-1BB with a K_D of about 100 pM or lower, binds human or murine 4-1BB with a K_D of about 90 pM or lower, binds human or murine 4-1BB with a K_D of about 70 pM or lower, binds human or murine 4-1BB with a K_D of about 70 pM or lower, binds human or murine 4-1BB with a K_D of about 50 pM or lower, binds human or murine 4-1BB with a K_D of about 40 pM or lower, or binds human or murine 4-1BB with a K_D of about 30 pM or lower.

[00588] In some embodiments, the compositions, processes and methods described include a 4-1BB agonist that binds to human or murine 4-1BB with a k_{assoc} of about 7.5×10^5 1/M·s or faster, binds to human or murine 4-1BB with a k_{assoc} of about 7.5×10^5 1/M·s or faster, binds to human or murine 4-1BB with a k_{assoc} of about 8×10^5 1/M·s or faster, binds to human or murine 4-1BB with a k_{assoc} of about 8.5×10^5 1/M·s or faster, binds to human or murine 4-1BB with a k_{assoc} of about 9×10^5 1/M·s or faster, binds to human or murine 4-1BB with a k_{assoc} of about 9.5×10^5 1/M·s or faster, or binds to human or murine 4-1BB with a k_{assoc} of about 9.5×10^5 1/M·s or faster, or binds to human or murine 4-1BB with a k_{assoc} of about 1×10^6 1/M·s or faster.

[00589] In some embodiments, the compositions, processes and methods described include a 4-1BB agonist that binds to human or murine 4-1BB with a k_{dissoc} of about 2×10^{-5} 1/s or slower, binds to human or murine 4-1BB with a k_{dissoc} of about 2.1×10^{-5} 1/s or slower, binds to human or murine 4-1BB with a k_{dissoc} of about 2.2×10^{-5} 1/s or slower, binds to human or murine 4-1BB with a k_{dissoc} of about 2.3×10^{-5} 1/s or slower, binds to human or murine 4-1BB with a k_{dissoc} of about 2.4×10^{-5} 1/s or slower, binds to human or murine 4-1BB with a k_{dissoc} of about 2.5×10^{-5} 1/s or slower, binds to human or murine 4-1BB with a k_{dissoc} of about 2.6×10^{-5} 1/s or slower or binds to human or murine 4-1BB with a k_{dissoc} of about 2.8×10^{-5} 1/s or slower, binds to human or murine 4-1BB with a k_{dissoc} of about 2.8×10^{-5} 1/s or slower, binds to human or murine 4-1BB with a k_{dissoc} of about 2.9×10^{-5} 1/s or slower, or binds to human or murine 4-1BB with a k_{dissoc} of about 2.9×10^{-5} 1/s or slower, or binds to human or murine 4-1BB with a k_{dissoc} of about 2.9×10^{-5} 1/s or slower.

[00590] In some embodiments, the compositions, processes and methods described include a 4-1BB agonist that binds to human or murine 4-1BB with an IC₅₀ of about 10 nM or lower, binds to human or murine 4-1BB with an IC₅₀ of about 9 nM or lower, binds to human or murine 4-1BB with an IC₅₀ of about 8 nM or lower, binds to human or murine 4-1BB with an IC₅₀ of about 7 nM or lower, binds to human or murine 4-1BB with an IC₅₀ of about 6 nM or lower, binds to human or murine 4-1BB with an IC₅₀ of about 5 nM or lower, binds to human or murine 4-1BB with an IC₅₀ of about 3 nM or lower, binds to human or murine 4-1BB with an IC₅₀ of about 2 nM or lower, or binds to human or murine 4-1BB with an IC₅₀ of about 2 nM or lower, or binds to human or murine 4-1BB with an IC₅₀ of about 1 nM or lower.

[00591] In a preferred embodiment, the 4-1BB agonist is utomilumab, also known as PF-05082566 or MOR-7480, or a fragment, derivative, variant, or biosimilar thereof. Utomilumab is available from Pfizer, Inc. Utomilumab is an immunoglobulin G2-lambda, anti-[*Homo sapiens* TNFRSF9 (tumor necrosis factor receptor (TNFR) superfamily member 9, 4-1BB, T cell antigen ILA, CD137)], *Homo sapiens* (fully human) monoclonal antibody. The amino acid sequences of utomilumab are set forth in Table EE. Utomilumab comprises glycosylation sites at Asn59 and Asn292; heavy chain intrachain disulfide bridges at positions 22-96 (V_H-V_L), 143-199 (C_H1-C_L), 256-316 (C_H2) and 362-420 (C_H3); light chain intrachain disulfide bridges at positions 22'-87' (V_H-V_L) and 136'-195' (C_H1-C_L); interchain heavy chain-heavy chain disulfide bridges at IgG2A isoform positions 218-218, 219-219, 222-222, and 225-225, at IgG2A/B isoform positions 218-130, 219-219, 222-222, and 225-225, and at IgG2B isoform positions 219-130 (2), 222-222, and 225-225; and interchain heavy chain-light chain disulfide bridges at IgG2A isoform positions 130-213' (2), IgG2A/B

isoform positions 218-213' and 130-213', and at IgG2B isoform positions 218-213' (2). The preparation and properties of utomilumab and its variants and fragments are described in U.S. Patent Nos. 8,821,867; 8,337,850; and 9,468,678, and International Patent Application Publication No. WO 2012/032433 A1, the disclosures of each of which are incorporated by reference herein. Preclinical characteristics of utomilumab are described in Fisher, *et al.*, *Cancer Immunolog. & Immunother.* **2012**, *61*, 1721-33. Current clinical trials of utomilumab in a variety of hematological and solid tumor indications include U.S. National Institutes of Health clinicaltrials.gov identifiers NCT02444793, NCT01307267, NCT02315066, and NCT02554812.

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[00592] In an embodiment, a 4-1BB agonist comprises a heavy chain given by SEQ ID NO:11 and a light chain given by SEQ ID NO:12. In an embodiment, a 4-1BB agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:11 and SEQ ID NO:12, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:11 and SEQ ID NO:12, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:11 and SEQ ID NO:12, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:11 and SEQ ID NO:12, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:11 and SEQ ID NO:12, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:11 and SEQ ID NO:12, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:11 and SEQ ID NO:12, respectively.

[00593] In an embodiment, the 4-1BB agonist comprises the heavy and light chain CDRs or variable regions (VRs) of utomilumab. In an embodiment, the 4-1BB agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:13, and the 4-1BB agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:14, and conservative amino acid substitutions thereof. In an embodiment, a 4-1BB agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:13 and SEQ ID NO:14, respectively. In an embodiment, a 4-1BB agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:13 and SEQ ID NO:14, respectively. In an embodiment, a 4-1BB agonist comprises V_H and V_L

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regions that are each at least 97% identical to the sequences shown in SEQ ID NO:13 and SEQ ID NO:14, respectively. In an embodiment, a 4-1BB agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:13 and SEQ ID NO:14, respectively. In an embodiment, a 4-1BB agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:13 and SEQ ID NO:14, respectively. In an embodiment, a 4-1BB agonist comprises an scFv antibody comprising V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:13 and SEQ ID NO:14.

[00594] In an embodiment, a 4-1BB agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:15, SEQ ID NO:16, and SEQ ID NO:17, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:18, SEQ ID NO:19, and SEQ ID NO:20, respectively, and conservative amino acid substitutions thereof.

[00595] In an embodiment, the 4-1BB agonist is a 4-1BB agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to utomilumab. In an embodiment, the biosimilar monoclonal antibody comprises an 4-1BB antibody comprising an amino acid sequence which has at least 97% sequence identity, e.g., 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is utomilumab. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a 4-1BB agonist antibody authorized or submitted for authorization, wherein the 4-1BB agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is utomilumab. The 4-1BB agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is utomilumab. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is utomilumab.

TABLE 7. Amino acid sequences for 4-1BB agonist antibodies related to utomilumab.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:11	EVQLVQSGAE VKKPGESLRI SCKGSGYSFS TYWISWVRQM PGKGLEWMGK IYPGDSYTNY	60
heavy chain for	SPSFQGQVTI SADKSISTAY LQWSSLKASD TAMYYCARGY GIFDYWGQGT LVTVSSASTK	120
utomilumab	GPSVFPLAPC SRSTSESTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS	180
	LSSVVTVPSS NFGTQTYTCN VDHKPSNTKV DKTVERKCCV ECPPCPAPPV AGPSVFLFPP	240
	KPKDTLMISR TPEVTCVVVD VSHEDPEVQF NWYVDGVEVH NAKTKPREEQ FNSTFRVVSV	300
	LTVVHQDWLN GKEYKCKVSN KGLPAPIEKT ISKTKGQPRE PQVYTLPPSR EEMTKNQVSL	360
	TCLVKGFYPS DIAVEWESNG QPENNYKTTP PMLDSDGSFF LYSKLTVDKS RWQQGNVFSC	420
	SVMHEALHNH YTQKSLSLSP G	441
SEQ ID NO:12	SYELTQPPSV SVSPGQTASI TCSGDNIGDQ YAHWYQQKPG QSPVLVIYQD KNRPSGIPER	60
light chain for	FSGSNSGNTA TLTISGTQAM DEADYYCATY TGFGSLAVFG GGTKLTVLGQ PKAAPSVTLF	120
utomilumab	PPSSEELQAN KATLVCLISD FYPGAVTVAW KADSSPVKAG VETTTPSKQS NNKYAASSYL	180
	SLTPEQWKSH RSYSCQVTHE GSTVEKTVAP TECS	214
SEQ ID NO:13	EVQLVQSGAE VKKPGESLRI SCKGSGYSFS TYWISWVRQM PGKGLEWMG KIYPGDSYTN	60
heavy chain	YSPSFQGQVT ISADKSISTA YLQWSSLKAS DTAMYYCARG YGIFDYWGQ GTLVTVSS	118
variable region		
for utomilumab		
SEQ ID NO:14	SYELTQPPSV SVSPGQTASI TCSGDNIGDQ YAHWYQQKPG QSPVLVIYQD KNRPSGIPER	60
light chain	FSGSNSGNTA TLTISGTQAM DEADYYCATY TGFGSLAVFG GGTKLTVL	108
variable region		
for utomilumab		
SEQ ID NO:15	STYWIS	6
heavy chain CDR1		
for utomilumab		
SEQ ID NO:16	KIYPGDSYTN YSPSFQG	17
heavy chain CDR2		
for utomilumab		
SEQ ID NO:17	RGYGIFDY	8
heavy chain CDR3		
for utomilumab		
SEQ ID NO:18	SGDNIGDQYA H	11
light chain CDR1		
for utomilumab		
SEQ ID NO:19	QDKNRPS	7
light chain CDR2		
for utomilumab		
SEQ ID NO:20	ATYTGFGSLA V	11
light chain CDR3		
for utomilumab		

[00596] In a preferred embodiment, the 4-1BB agonist is the monoclonal antibody urelumab, also known as BMS-663513 and 20H4.9.h4a, or a fragment, derivative, variant, or biosimilar thereof. Urelumab is available from Bristol-Myers Squibb, Inc., and Creative Biolabs, Inc. Urelumab is an immunoglobulin G4-kappa, anti-[*Homo sapiens* TNFRSF9 (tumor necrosis factor receptor superfamily member 9, 4-1BB, T cell antigen ILA, CD137)], *Homo sapiens* (fully human) monoclonal antibody. The amino acid sequences of urelumab are set forth in Table EE. Urelumab comprises N-glycosylation sites at positions 298 (and 298"); heavy chain intrachain disulfide bridges at positions 22-95 (V_H-V_L), 148-204 (C_H1-C_L), 262-322 (C_H2) and 368-426 (C_H3) (and at positions 22"-95", 148"-204", 262"-322", and 368"-426"); light chain intrachain disulfide bridges at positions 23'-88' (V_H-V_L) and 136'-196'

(C_H1-C_L) (and at positions 23""-88"" and 136""-196""); interchain heavy chain-heavy chain disulfide bridges at positions 227-227" and 230-230"; and interchain heavy chain-light chain disulfide bridges at 135-216' and 135"-216". The preparation and properties of urelumab and its variants and fragments are described in U.S. Patent Nos. 7,288,638 and 8,962,804, the disclosures of which are incorporated by reference herein. The preclinical and clinical characteristics of urelumab are described in Segal, et al., Clin. Cancer Res. 2016, available at http:/dx.doi.org/10.1158/1078-0432.CCR-16-1272. Current clinical trials of urelumab in a variety of hematological and solid tumor indications include U.S. National Institutes of Health clinicaltrials gov identifiers NCT01775631, NCT02110082, NCT02253992, and NCT01471210.

[00597] In an embodiment, a 4-1BB agonist comprises a heavy chain given by SEQ ID NO:21 and a light chain given by SEQ ID NO:22. In an embodiment, a 4-1BB agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively.

[00598] In an embodiment, the 4-1BB agonist comprises the heavy and light chain CDRs or variable regions (VRs) of urelumab. In an embodiment, the 4-1BB agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:23, and the 4-1BB agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:24, and conservative amino acid substitutions thereof. In an embodiment, a 4-1BB agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively. In an embodiment, a 4-1BB agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:23

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and SEQ ID NO:24, respectively. In an embodiment, a 4-1BB agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively. In an embodiment, a 4-1BB agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively. In an embodiment, a 4-1BB agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively. In an embodiment, a 4-1BB agonist comprises an scFv antibody comprising V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:23 and SEQ ID NO:24.

[00599] In an embodiment, a 4-1BB agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:25, SEQ ID NO:26, and SEQ ID NO:27, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:28, SEQ ID NO:29, and SEQ ID NO:30, respectively, and conservative amino acid substitutions thereof.

[00600] In an embodiment, the 4-1BB agonist is a 4-1BB agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to urelumab. In an embodiment, the biosimilar monoclonal antibody comprises an 4-1BB antibody comprising an amino acid sequence which has at least 97% sequence identity, e.g., 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is urelumab. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a 4-1BB agonist antibody authorized or submitted for authorization, wherein the 4-1BB agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is urelumab. The 4-1BB agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is urelumab.

In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is urelumab.

TABLE 8: Amino acid sequences for 4-1BB agonist antibodies related to urelumab.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:21	QVQLQQWGAG LLKPSETLSL TCAVYGGSFS GYYWSWIRQS PEKGLEWIGE INHGGYVTYN	60
heavy chain for	PSLESRVTIS VDTSKNQFSL KLSSVTAADT AVYYCARDYG PGNYDWYFDL WGRGTLVTVS	120
urelumab	SASTKGPSVF PLAPCSRSTS ESTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS	180
	SGLYSLSSVV TVPSSSLGTK TYTCNVDHKP SNTKVDKRVE SKYGPPCPPC PAPEFLGGPS	240
	VFLFPPKPKD TLMISRTPEV TCVVVDVSQE DPEVQFNWYV DGVEVHNAKT KPREEQFNST	300
	YRVVSVLTVL HQDWLNGKEY KCKVSNKGLP SSIEKTISKA KGQPREPQVY TLPPSQEEMT	360
	KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSR LTVDKSRWQE	420
	GNVFSCSVMH EALHNHYTQK SLSLSLGK	448
SEQ ID NO:22	EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD ASNRATGIPA	60
light chain for	RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPPALTF CGGTKVEIKR TVAAPSVFIF	120
urelumab	PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYSLSST	180
	LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC	216
SEQ ID NO:23	MKHLWFFLLL VAAPRWVLSQ VQLQQWGAGL LKPSETLSLT CAVYGGSFSG YYWSWIRQSP	60
variable heavy	EKGLEWIGEI NHGGYVTYNP SLESRVTISV DTSKNQFSLK LSSVTAADTA VYYCARDYGP	120
chain for		
urelumab		
SEQ ID NO:24	MEAPAQLLFL LLLWLPDTTG EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP	60
variable light	GQAPRLLIYD ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ	110
chain for		
urelumab		
SEQ ID NO:25	GYYWS	5
heavy chain CDR1		
for urelumab		
SEQ ID NO:26	EINHGGYVTY NPSLES	16
heavy chain CDR2		
for urelumab		
SEQ ID NO:27	DYGPGNYDWY FDL	13
heavy chain CDR3		
for urelumab		
SEQ ID NO:28	RASQSVSSYL A	11
light chain CDR1		
for urelumab		
SEQ ID NO:29	DASNRAT	7
light chain CDR2		
for urelumab		
SEQ ID NO:30	QQRSDWPPAL T	11
light chain CDR3		
for urelumab		

[00601] In an embodiment, the 4-1BB agonist is selected from the group consisting of 1D8, 3Elor, 4B4 (BioLegend 309809), H4-1BB-M127 (BD Pharmingen 552532), BBK2 (Thermo Fisher MS621PABX), 145501 (Leinco Technologies B591), the antibody produced by cell line deposited as ATCC No. HB-11248 and disclosed in U.S. Patent No. 6,974,863, 5F4 (BioLegend 31 1503), C65-485 (BD Pharmingen 559446), antibodies disclosed in U.S. Patent Application Publication No. US 2005/0095244, antibodies disclosed in U.S. Patent No. 7,288,638 (such as 20H4.9-IgGl (BMS-663031)), antibodies disclosed in U.S. Patent No. 6,887,673 (such as 4E9 or BMS-554271), antibodies disclosed in U.S. Patent No. 6,569,997, antibodies disclosed in U.S. Patent No. 6,905,685 (such as 4E9 or BMS-554271),

antibodies disclosed in U.S. Patent No. 6,362,325 (such as 1D8 or BMS-469492; 3H3 or BMS-469497; or 3El), antibodies disclosed in U.S. Patent No. 6,974,863 (such as 53A2); antibodies disclosed in U.S. Patent No. 6,210,669 (such as 1D8, 3B8, or 3El), antibodies described in U.S. Patent No. 5,928,893, antibodies disclosed in U.S. Patent No. 6,303,121, antibodies disclosed in U.S. Patent No. 6,569,997, antibodies disclosed in International Patent Application Publication Nos. WO 2012/177788, WO 2015/119923, and WO 2010/042433, and fragments, derivatives, conjugates, variants, or biosimilars thereof, wherein the disclosure of each of the foregoing patents or patent application publications is incorporated by reference here.

[00602] In an embodiment, the 4-1BB agonist is a 4-1BB agonistic fusion protein described in International Patent Application Publication Nos. WO 2008/025516 A1, WO 2009/007120 A1, WO 2010/003766 A1, WO 2010/010051 A1, and WO 2010/078966 A1; U.S. Patent Application Publication Nos. US 2011/0027218 A1, US 2015/0126709 A1, US 2011/0111494 A1, US 2015/0110734 A1, and US 2015/0126710 A1; and U.S. Patent Nos. 9,359,420, 9,340,599, 8,921,519, and 8,450,460, the disclosures of which are incorporated by reference herein.

[00603] In an embodiment, the 4-1BB agonist is a 4-1BB agonistic fusion protein as depicted in Structure I-A (C-terminal Fc-antibody fragment fusion protein) or Structure I-B (N-terminal Fc-antibody fragment fusion protein), or a fragment, derivative, conjugate, variant, or biosimilar thereof (see, Figure 50). In structures I-A and I-B, the cylinders refer to individual polypeptide binding domains. Structures I-A and I-B comprise three linearlylinked TNFRSF binding domains derived from e.g., 4-1BBL or an antibody that binds 4-1BB, which fold to form a trivalent protein, which is then linked to a second triavelent protein through IgG1-Fc (including C_H3 and C_H2 domains) is then used to link two of the trivalent proteins together through disulfide bonds (small elongated ovals), stabilizing the structure and providing an agonists capable of bringing together the intracellular signaling domains of the six receptors and signaling proteins to form a signaling complex. The TNFRSF binding domains denoted as cylinders may be scFv domains comprising, e.g., a V_H and a V_L chain connected by a linker that may comprise hydrophilic residues and Gly and Ser sequences for flexibility, as well as Glu and Lys for solubility. Any scFv domain design may be used, such as those described in de Marco, Microbial Cell Factories, 2011, 10, 44; Ahmad, et al., Clin. & Dev. Immunol. 2012, 980250; Monnier, et al., Antibodies, 2013, 2, 193-208; or in references incorporated elsewhere herein. Fusion protein structures of this

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form are described in U.S. Patent Nos. 9,359,420, 9,340,599, 8,921,519, and 8,450,460, the

disclosures of which are incorporated by reference herein.

polypeptides.

[00604] Amino acid sequences for the other polypeptide domains of structure I-A are given in Table GG. The Fc domain preferably comprises a complete constant domain (amino acids 17-230 of SEQ ID NO:31) the complete hinge domain (amino acids 1-16 of SEQ ID NO:31) or a portion of the hinge domain (*e.g.*, amino acids 4-16 of SEQ ID NO:31). Preferred linkers for connecting a C-terminal Fc-antibody may be selected from the embodiments given in SEQ ID NO:32 to SEQ ID NO:41, including linkers suitable for fusion of additional

TABLE 9: Amino acid sequences for TNFRSF fusion proteins, including 4-1BB fusion proteins, with C-terminal Fc-antibody fragment fusion protein design (structure I-A).

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:31	KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW	60
Fc domain	YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS	120
	KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV	180
	LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK	230
SEQ ID NO:32 linker	GGPGSSKSCD KTHTCPPCPA PE	22
SEQ ID NO:33 linker	GGSGSSKSCD KTHTCPPCPA PE	22
SEQ ID NO:34 linker	GGPGSSSSS SKSCDKTHTC PPCPAPE	27
SEQ ID NO:35 linker	GGSGSSSSS SKSCDKTHTC PPCPAPE	27
SEQ ID NO:36 linker	GGPGSSSSS SSSKSCDKTH TCPPCPAPE	29
SEQ ID NO:37 linker	GGSGSSSSS SSSKSCDKTH TCPPCPAPE	29
SEQ ID NO:38 linker	GGPGSSGSGS SDKTHTCPPC PAPE	24
SEQ ID NO:39 linker	GGPGSSGSGS DKTHTCPPCP APE	23
SEQ ID NO:40 linker	GGPSSSGSDK THTCPPCPAP E	21
SEQ ID NO:41 linker	GGSSSSSSS GSDKTHTCPP CPAPE	25

[00605] Amino acid sequences for the other polypeptide domains of structure I-B are given in Table HH. If an Fc antibody fragment is fused to the N-terminus of an TNRFSF fusion protein as in structure I-B, the sequence of the Fc module is preferably that shown in SEQ ID NO:42, and the linker sequences are preferably selected from those embodiments set forth in SED ID NO:43 to SEQ ID NO:45.

TABLE 10: Amino acid sequences for TNFRSF fusion proteins, including 4-1BB fusion proteins, with N-terminal Fc-antibody fragment fusion protein design (structure I-B).

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:42	METDTLLLWV LLLWVPAGNG DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT 60	
Fc domain	CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK 120	
	CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE 180	

	WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS	240
	LSLSPG	246
SEQ ID NO:43	SGSGSGSGS S	11
linker		
SEQ ID NO:44	SSSSSGSGS GS	12
linker		
SEQ ID NO:45	SSSSSGSGS GSGSGS	16
linker		

[00606] In an embodiment, a 4-1BB agonist fusion protein according to structures I-A or I-B comprises one or more 4-1BB binding domains selected from the group consisting of a variable heavy chain and variable light chain of utomilumab, a variable heavy chain and variable light chain of urelumab, a variable heavy chain and variable light chain of utomilumab, a variable heavy chain and variable light chain selected from the variable heavy chains and variable light chains described in Table GG, any combination of a variable heavy chain and variable light chain of the foregoing, and fragments, derivatives, conjugates, variants, and biosimilars thereof.

[00607] In an embodiment, a 4-1BB agonist fusion protein according to structures I-A or I-B comprises one or more 4-1BB binding domains comprising a 4-1BBL sequence. In an embodiment, a 4-1BB agonist fusion protein according to structures I-A or I-B comprises one or more 4-1BB binding domains comprising a sequence according to SEQ ID NO:46. In an embodiment, a 4-1BB agonist fusion protein according to structures I-A or I-B comprises one or more 4-1BB binding domains comprising a soluble 4-1BBL sequence. In an embodiment, a 4-1BB agonist fusion protein according to structures I-A or I-B comprises one or more 4-1BB binding domains comprising a sequence according to SEQ ID NO:47.

[00608] In an embodiment, a 4-1BB agonist fusion protein according to structures I-A or I-B comprises one or more 4-1BB binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:13 and SEQ ID NO:14, respectively, wherein the V_H and V_L domains are connected by a linker. In an embodiment, a 4-1BB agonist fusion protein according to structures I-A or I-B comprises one or more 4-1BB binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively, wherein the V_H and V_L domains are connected by a linker. In an embodiment, a 4-1BB agonist fusion protein according to structures I-A or I-B comprises one or more 4-1BB binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the V_H and V_L sequences given in Table 11, wherein the V_H and V_L domains are connected by a linker.

TABLE 11: Additional polypeptide domains useful as 4-1BB binding domains in fusion proteins or as scFv 4-1BB agonist antibodies.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:46	MEYASDASLD PEAPWPPAPR ARACRVLPWA LVAGLLLLLL LAAACAVFLA CPWAVSGARA	60
4-1BBL	SPGSAASPRL REGPELSPDD PAGLLDLRQG MFAQLVAQNV LLIDGPLSWY SDPGLAGVSL	120
	TGGLSYKEDT KELVVAKAGV YYVFFQLELR RVVAGEGSGS VSLALHLQPL RSAAGAAALA	180
	LTVDLPPASS EARNSAFGFQ GRLLHLSAGQ RLGVHLHTEA RARHAWQLTQ GATVLGLFRV	240
	TPEIPAGLPS PRSE	254
SEQ ID NO:47	LRQGMFAQLV AQNVLLIDGP LSWYSDPGLA GVSLTGGLSY KEDTKELVVA KAGVYYVFFQ	60
4-1BBL soluble	LELRRVVAGE GSGSVSLALH LQPLRSAAGA AALALTVDLP PASSEARNSA FGFQGRLLHL	120
domain	SAGQRLGVHL HTEARARHAW QLTQGATVLG LFRVTPEIPA GLPSPRSE	168
SEQ ID NO:48	QVQLQQPGAE LVKPGASVKL SCKASGYTFS SYWMHWVKQR PGQVLEWIGE INPGNGHTNY	60
variable heavy	NEKFKSKATL TVDKSSSTAY MQLSSLTSED SAVYYCARSF TTARGFAYWG QGTLVTVS	118
chain for 4B4-1-		
1 version 1		
SEQ ID NO:49	DIVMTQSPAT QSVTPGDRVS LSCRASQTIS DYLHWYQQKS HESPRLLIKY ASQSISGIPS	60
variable light	RFSGSGSGSD FTLSINSVEP EDVGVYYCQD GHSFPPTFGG GTKLEIK	107
chain for 4B4-1-		
1 version 1		
SEQ ID NO:50	QVQLQQPGAE LVKPGASVKL SCKASGYTFS SYWMHWVKQR PGQVLEWIGE INPGNGHTNY	60
variable heavy	NEKFKSKATL TVDKSSSTAY MQLSSLTSED SAVYYCARSF TTARGFAYWG QGTLVTVSA	119
chain for 4B4-1-		
1 version 2		
SEQ ID NO:51	DIVMTQSPAT QSVTPGDRVS LSCRASQTIS DYLHWYQQKS HESPRLLIKY ASQSISGIPS	60
variable light	RFSGSGSGSD FTLSINSVEP EDVGVYYCQD GHSFPPTFGG GTKLEIKR	108
chain for 4B4-1-		
1 version 2		
SEQ ID NO:52	MDWTWRILFL VAAATGAHSE VQLVESGGGL VQPGGSLRLS CAASGFTFSD YWMSWVRQAP	60
variable heavy	GKGLEWVADI KNDGSYTNYA PSLTNRFTIS RDNAKNSLYL QMNSLRAEDT AVYYCARELT	120
chain for H39E3-		
2		
SEQ ID NO:53	MEAPAQLLFL LLLWLPDTTG DIVMTQSPDS LAVSLGERAT INCKSSQSLL SSGNQKNYL	60
variable light	WYQQKPGQPP KLLIYYASTR QSGVPDRFSG SGSGTDFTLT ISSLQAEDVA	110
chain for H39E3- 2		

[00609] In an embodiment, the 4-1BB agonist is a 4-1BB agonistic single-chain fusion polypeptide comprising (i) a first soluble 4-1BB binding domain, (ii) a first peptide linker, (iii) a second soluble 4-1BB binding domain, (iv) a second peptide linker, and (v) a third soluble 4-1BB binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, and wherein the additional domain is a Fab or Fc fragment domain. In an embodiment, the 4-1BB agonist is a 4-1BB agonistic single-chain fusion polypeptide comprising (i) a first soluble 4-1BB binding domain, (ii) a first peptide linker, (iii) a second soluble 4-1BB binding domain, (iv) a second peptide linker, and (v) a third soluble 4-1BB binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, wherein the additional domain is a Fab or Fc fragment domain, wherein each of the soluble 4-1BB domains lacks a stalk region (which contributes to trimerisation and provides a certain distance to the cell membrane, but is not part of the 4-1BB binding domain) and the first and the second peptide linkers independently have a length of 3-8 amino acids.

[00610] In an embodiment, the 4-1BB agonist is a 4-1BB agonistic single-chain fusion polypeptide comprising (i) a first soluble tumor necrosis factor (TNF) superfamily cytokine domain, (ii) a first peptide linker, (iii) a second soluble TNF superfamily cytokine domain,

(iv) a second peptide linker, and (v) a third soluble TNF superfamily cytokine domain, wherein each of the soluble TNF superfamily cytokine domains lacks a stalk region and the first and the second peptide linkers independently have a length of 3-8 amino acids, and wherein each TNF superfamily cytokine domain is a 4-1BB binding domain.

[00611] In an embodiment, the 4-1BB agonist is a 4-1BB agonistic scFv antibody comprising any of the foregoing V_H domains linked to any of the foregoing V_L domains.

[00612] In an embodiment, the 4-1BB agonist is BPS Bioscience 4-1BB agonist antibody catalog no. 79097-2, commercially available from BPS Bioscience, San Diego, CA, USA. In an embodiment, the 4-1BB agonist is Creative Biolabs 4-1BB agonist antibody catalog no. MOM-18179, commercially available from Creative Biolabs, Shirley, NY, USA.

3. OX40 (CD134) AGONISTS

[00613] In an embodiment, the TNFRSF agonist is an OX40 (CD134) agonist. The OX40 agonist may be any OX40 binding molecule known in the art. The OX40 binding molecule may be a monoclonal antibody or fusion protein capable of binding to human or mammalian OX40. The OX40 agonists or OX40 binding molecules may comprise an immunoglobulin heavy chain of any isotype (e.g., IgG, IgE, IgM, IgD, IgA, and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. The OX40 agonist or OX40 binding molecule may have both a heavy and a light chain. As used herein, the term binding molecule also includes antibodies (including full length antibodies), monoclonal antibodies (including full length monoclonal antibodies), polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), human, humanized or chimeric antibodies, and antibody fragments, e.g., Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, epitope-binding fragments of any of the above, and engineered forms of antibodies, e.g., scFv molecules, that bind to OX40. In an embodiment, the OX40 agonist is an antigen binding protein that is a fully human antibody. In an embodiment, the OX40 agonist is an antigen binding protein that is a humanized antibody. In some embodiments, OX40 agonists for use in the presently disclosed methods and compositions include anti-OX40 antibodies, human anti-OX40 antibodies, mouse anti-OX40 antibodies, mammalian anti-OX40 antibodies, monoclonal anti-OX40 antibodies, polyclonal anti-OX40 antibodies, chimeric anti-OX40 antibodies, anti-OX40 adnectins, anti-OX40 domain antibodies, single chain anti-OX40 fragments, heavy chain anti-OX40 fragments, light chain anti-OX40 fragments, anti-OX40 fusion proteins, and fragments, derivatives, conjugates, variants, or

biosimilars thereof. In a preferred embodiment, the OX40 agonist is an agonistic, anti-OX40 humanized or fully human monoclonal antibody (*i.e.*, an antibody derived from a single cell line).

[00614] In a preferred embodiment, the OX40 agonist or OX40 binding molecule may also be a fusion protein. OX40 fusion proteins comprising an Fc domain fused to OX40L are described, for example, in Sadun, *et al.*, *J. Immunother*. 2009, *182*, 1481-89. In a preferred embodiment, a multimeric OX40 agonist, such as a trimeric or hexameric OX40 agonist (with three or six ligand binding domains), may induce superior receptor (OX40L) clustering and internal cellular signaling complex formation compared to an agonistic monoclonal antibody, which typically possesses two ligand binding domains. Trimeric (trivalent) or hexameric (or hexavalent) or greater fusion proteins comprising three TNFRSF binding domains and IgG1-Fc and optionally further linking two or more of these fusion proteins are described, *e.g.*, in Gieffers, *et al.*, *Mol. Cancer Therapeutics* 2013, *12*, 2735-47.

[00615] Agonistic OX40 antibodies and fusion proteins are known to induce strong immune responses. Curti, *et al.*, *Cancer Res.* 2013, 73, 7189-98. In a preferred embodiment, the OX40 agonist is a monoclonal antibody or fusion protein that binds specifically to OX40 antigen in a manner sufficient to reduce toxicity. In some embodiments, the OX40 agonist is an agonistic OX40 monoclonal antibody or fusion protein that abrogates antibody-dependent cellular toxicity (ADCC), for example NK cell cytotoxicity. In some embodiments, the OX40 agonist is an agonistic OX40 monoclonal antibody or fusion protein that abrogates antibody-dependent cell phagocytosis (ADCP). In some embodiments, the OX40 agonist is an agonistic OX40 monoclonal antibody or fusion protein that abrogates complement-dependent cytotoxicity (CDC). In some embodiments, the OX40 agonist is an agonistic OX40 monoclonal antibody or fusion protein which abrogates Fc region functionality.

[00616] In some embodiments, the OX40 agonists are characterized by binding to human OX40 (SEQ ID NO:54) with high affinity and agonistic activity. In an embodiment, the OX40 agonist is a binding molecule that binds to human OX40 (SEQ ID NO:54). In an embodiment, the OX40 agonist is a binding molecule that binds to murine OX40 (SEQ ID NO:55). The amino acid sequences of OX40 antigen to which an OX40 agonist or binding molecule binds are summarized in Table 12.

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TABLE 12: Amino acid sequences of OX40 antigens.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:54	MCVGARRLGR GPCAALLLLG LGLSTVTGLH CVGDTYPSND RCCHECRPGN GMVSRCSRSQ	60
human OX40	NTVCRPCGPG FYNDVVSSKP CKPCTWCNLR SGSERKQLCT ATQDTVCRCR AGTQPLDSYK	120
(Homo sapiens)	PGVDCAPCPP GHFSPGDNQA CKPWTNCTLA GKHTLQPASN SSDAICEDRD PPATQPQETQ	180
	GPPARPITVQ PTEAWPRTSQ GPSTRPVEVP GGRAVAAILG LGLVLGLLGP LAILLALYLL	240
	RRDQRLPPDA HKPPGGGSFR TPIQEEQADA HSTLAKI	277
SEQ ID NO:55	MYVWVQQPTA LLLLGLTLGV TARRLNCVKH TYPSGHKCCR ECQPGHGMVS RCDHTRDTLC	60
murine OX40	HPCETGFYNE AVNYDTCKQC TQCNHRSGSE LKQNCTPTQD TVCRCRPGTQ PRQDSGYKLG	120
(Mus musculus)	VDCVPCPPGH FSPGNNQACK PWTNCTLSGK QTRHPASDSL DAVCEDRSLL ATLLWETQRP	180
	TFRPTTVQST TVWPRTSELP SPPTLVTPEG PAFAVLLGLG LGLLAPLTVL LALYLLRKAW	240
	RLPNTPKPCW GNSFRTPIQE EHTDAHFTLA KI	272

[00617] In some embodiments, the compositions, processes and methods described include a OX40 agonist that binds human or murine OX40 with a K_D of about 100 pM or lower, binds human or murine OX40 with a K_D of about 90 pM or lower, binds human or murine OX40 with a K_D of about 80 pM or lower, binds human or murine OX40 with a K_D of about 70 pM or lower, binds human or murine OX40 with a K_D of about 60 pM or lower, binds human or murine OX40 with a K_D of about 40 pM or lower, or binds human or murine OX40 with a K_D of about 30 pM or lower.

[00618] In some embodiments, the compositions, processes and methods described include a OX40 agonist that binds to human or murine OX40 with a k_{assoc} of about 7.5×10^5 1/M·s or faster, binds to human or murine OX40 with a k_{assoc} of about 7.5×10^5 1/M·s or faster, binds to human or murine OX40 with a k_{assoc} of about 8×10^5 1/M·s or faster, binds to human or murine OX40 with a k_{assoc} of about 8.5×10^5 1/M·s or faster, binds to human or murine OX40 with a k_{assoc} of about 9×10^5 1/M·s or faster, binds to human or murine OX40 with a k_{assoc} of about 9.5×10^5 1/M·s or faster, or binds to human or murine OX40 with a k_{assoc} of about 1×10^6 1/M·s or faster.

[00619] In some embodiments, the compositions, processes and methods described include a OX40 agonist that binds to human or murine OX40 with a k_{dissoc} of about 2×10^{-5} 1/s or slower, binds to human or murine OX40 with a k_{dissoc} of about 2.1×10^{-5} 1/s or slower, binds to human or murine OX40 with a k_{dissoc} of about 2.2×10^{-5} 1/s or slower, binds to human or murine OX40 with a k_{dissoc} of about 2.3×10^{-5} 1/s or slower, binds to human or murine OX40 with a k_{dissoc} of about 2.4×10^{-5} 1/s or slower, binds to human or murine OX40 with a k_{dissoc} of about 2.5×10^{-5} 1/s or slower, binds to human or murine OX40 with a k_{dissoc} of about 2.6×10^{-5} 1/s or slower or binds to human or murine OX40 with a k_{dissoc} of about 2.7×10^{-5} 1/s or slower, binds to human or murine OX40 with a k_{dissoc} of about 2.8×10^{-5} 1/s or slower, binds to human or murine OX40 with a k_{dissoc} of about 2.9×10^{-5} 1/s or slower, or binds to human or murine OX40 with a k_{dissoc} of about 2.9×10^{-5} 1/s or slower, or binds to human or murine OX40 with a k_{dissoc} of about 2.9×10^{-5} 1/s or slower, or binds to human or murine OX40 with a k_{dissoc} of about 2.9×10^{-5} 1/s or slower, or binds to human or murine OX40 with a k_{dissoc} of about 2.9×10^{-5} 1/s or slower, or binds to human or murine OX40 with a k_{dissoc} of about 3×10^{-5} 1/s or slower.

[00620] In some embodiments, the compositions, processes and methods described include OX40 agonist that binds to human or murine OX40 with an IC₅₀ of about 10 nM or lower, binds to human or murine OX40 with an IC₅₀ of about 9 nM or lower, binds to human or murine OX40 with an IC₅₀ of about 8 nM or lower, binds to human or murine OX40 with an IC₅₀ of about 7 nM or lower, binds to human or murine OX40 with an IC₅₀ of about 6 nM or lower, binds to human or murine OX40 with an IC₅₀ of about 5 nM or lower, binds to human or murine OX40 with an IC₅₀ of about 3 nM or lower, binds to human or murine OX40 with an IC₅₀ of about 2 nM or lower, or binds to human or murine OX40 with an IC₅₀ of about 1 nM or lower.

[00621] In some embodiments, the OX40 agonist is tavolixizumab, also known as MEDI0562 or MEDI-0562. Tavolixizumab is available from the MedImmune subsidiary of AstraZeneca, Inc. Tavolixizumab is immunoglobulin G1-kappa, anti-[Homo sapiens TNFRSF4 (tumor necrosis factor receptor (TNFR) superfamily member 4, OX40, CD134)], humanized and chimeric monoclonal antibody. The amino acid sequences of tavolixizumab are set forth in Table KK. Tavolixizumab comprises N-glycosylation sites at positions 301 and 301", with fucosylated complex bi-antennary CHO-type glycans; heavy chain intrachain disulfide bridges at positions 22-95 (V_H-V_L), 148-204 (C_H1-C_L), 265-325 (C_H2) and 371-429 (C_H3) (and at positions 22"-95", 148"-204", 265"-325", and 371"-429"); light chain intrachain disulfide bridges at positions 23'-88' (V_H-V_L) and 134'-194' (C_H1-C_L) (and at positions 23"-88" and 134"'-194"'); interchain heavy chain-heavy chain disulfide bridges at positions 230-230" and 233-233"; and interchain heavy chain-light chain disulfide bridges at 224-214' and 224"-214"'. Current clinical trials of tavolixizumab in a variety of solid tumor indications include U.S. National Institutes of Health clinicaltrials.gov identifiers NCT02318394 and NCT02705482.

[00622] In an embodiment, a OX40 agonist comprises a heavy chain given by SEQ ID NO:56 and a light chain given by SEQ ID NO:57. In an embodiment, a OX40 agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:56 and SEQ ID NO:57, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:56 and SEQ ID NO:57, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:56 and SEQ ID NO:57, respectively. In an embodiment, a OX40 agonist

comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:56 and SEQ ID NO:57, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:56 and SEQ ID NO:57, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:56 and SEQ ID NO:57, respectively.

[00623] In an embodiment, the OX40 agonist comprises the heavy and light chain CDRs or variable regions (VRs) of tavolixizumab. In an embodiment, the OX40 agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:58, and the OX40 agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:59, and conservative amino acid substitutions thereof. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:58 and SEQ ID NO:59, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:58 and SEQ ID NO:59, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:58 and SEQ ID NO:59, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:58 and SEQ ID NO:59, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:58 and SEQ ID NO:59, respectively. In an embodiment, an OX40 agonist comprises an scFv antibody comprising V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:58 and SEQ ID NO:59.

[00624] In an embodiment, a OX40 agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:60, SEQ ID NO:61, and SEQ ID NO:62, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, respectively, and conservative amino acid substitutions thereof.

[00625] In an embodiment, the OX40 agonist is a OX40 agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to tavolixizumab. In an embodiment, the biosimilar monoclonal antibody comprises an OX40 antibody comprising an amino acid sequence which has at least 97% sequence identity, *e.g.*, 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or

reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is tavolixizumab. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a OX40 agonist antibody authorized or submitted for authorization, wherein the OX40 agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is tavolixizumab. The OX40 agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is tavolixizumab. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is tavolixizumab.

TABLE 13: Amino acid sequences for OX40 agonist antibodies related to tavolixizumab.

Identifier		Seque	nce (One-l	Letter Ami	no Acid Sy	ymbols)	
SEQ ID NO:56	QVQLQESGPG I	LVKPSQTLSL	TCAVYGGSFS	SGYWNWIRKH	PGKGLEYIGY	ISYNGITYHN	60
heavy chain for	PSLKSRITIN F	RDTSKNQYSL	QLNSVTPEDT	AVYYCARYKY	DYDGGHAMDY	WGQGTLVTVS	120
tavolixizumab	SASTKGPSVF F	PLAPSSKSTS	GGTAALGCLV	KDYFPEPVTV	SWNSGALTSG	VHTFPAVLQS	180
	SGLYSLSSVV I	CVPSSSLGTQ	TYICNVNHKP	SNTKVDKRVE	PKSCDKTHTC	PPCPAPELLG	240
	GPSVFLFPPK F	RKDTLMISRT	PEVTCVVVDV	SHEDPEVKFN	WYVDGVEVHN	AKTKPREEQY	300
	NSTYRVVSVL I	VLHQDWLNG	KEYKCKVSNK	ALPAPIEKTI	SKAKGQPREP	QVYTLPPSRE	360
	EMTKNQVSLT C	CLVKGFYPSD	IAVEWESNGQ	PENNYKTTPP	VLDSDGSFFL	YSKLTVDKSR	420
	WQQGNVFSCS V	MHEALHNHY	TQKSLSLSPG	K			451
SEQ ID NO:57	DIQMTQSPSS I	LSASVGDRVT	ITCRASQDIS	NYLNWYQQKP	GKAPKLLIYY	TSKLHSGVPS	60
light chain for	RFSGSGSGTD Y	TLTISSLQP	EDFATYYCQQ	GSALPWTFGQ	GTKVEIKRTV	AAPSVFIFPP	120
tavolixizumab	SDEQLKSGTA S	SVVCLLNNFY	PREAKVQWKV	DNALQSGNSQ	ESVTEQDSKD	STYSLSSTLT	180
	LSKADYEKHK V	/YACEVTHQG	LSSPVTKSFN	RGEC			214
SEQ ID NO:58	QVQLQESGPG I	LVKPSQTLSL	TCAVYGGSFS	SGYWNWIRKH	PGKGLEYIGY	ISYNGITYHN	60
heavy chain	PSLKSRITIN F	RDTSKNQYSL	QLNSVTPEDT	AVYYCARYKY	DYDGGHAMDY	WGQGTLVT	118
variable region							
for							
tavolixizumab							
SEQ ID NO:59	DIQMTQSPSS I	LSASVGDRVT	ITCRASQDIS	NYLNWYQQKP	GKAPKLLIYY	TSKLHSGVPS	60
light chain	RFSGSGSGTD Y	TLTISSLQP	EDFATYYCQQ	GSALPWTFGQ	GTKVEIKR		108
variable region							
for							
tavolixizumab							
SEQ ID NO:60	GSFSSGYWN						9
heavy chain CDR1							
for							
tavolixizumab							

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SEQ ID NO:61	YIGYISYNGI TYH	13
heavy chain CDR2		
for		
tavolixizumab		
SEQ ID NO:62	RYKYDYDGGH AMDY	14
heavy chain CDR3		
for		
tavolixizumab		
SEQ ID NO:63	QDISNYLN	8
light chain CDR1		
for		
tavolixizumab		
SEQ ID NO:64	LLIYYTSKLH S	11
light chain CDR2		
for		
tavolixizumab		
SEQ ID NO:65	QQGSALPW	8
light chain CDR3		
for		
tavolixizumab		

[00626] In some embodiments, the OX40 agonist is 11D4, which is a fully human antibody available from Pfizer, Inc. The preparation and properties of 11D4 are described in U.S. Patent Nos. 7,960,515; 8,236,930; and 9,028,824, the disclosures of which are incorporated by reference herein. The amino acid sequences of 11D4 are set forth in Table LL.

[00627] In an embodiment, a OX40 agonist comprises a heavy chain given by SEQ ID NO:66 and a light chain given by SEQ ID NO:67. In an embodiment, a OX40 agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:66 and SEQ ID NO:67, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:66 and SEQ ID NO:67, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:66 and SEQ ID NO:67, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:66 and SEQ ID NO:67, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:66 and SEQ ID NO:67, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:66 and SEQ ID NO:67, respectively.

[00628] In an embodiment, the OX40 agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 11D4. In an embodiment, the OX40 agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:68, and the OX40 agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:69, and conservative amino acid substitutions thereof. In an embodiment, a OX40 agonist comprises

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V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:68 and SEQ ID NO:69, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:68 and SEQ ID NO:69, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:68 and SEQ ID NO:69, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:68 and SEQ ID NO:69, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:68 and SEQ ID NO:69, respectively.

[00629] In an embodiment, a OX40 agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:70, SEQ ID NO:71, and SEQ ID NO:72, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:73, SEQ ID NO:74, and SEQ ID NO:75, respectively, and conservative amino acid substitutions thereof.

[00630] In an embodiment, the OX40 agonist is a OX40 agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to 11D4. In an embodiment, the biosimilar monoclonal antibody comprises an OX40 antibody comprising an amino acid sequence which has at least 97% sequence identity, e.g., 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 11D4. In some embodiments, the one or more posttranslational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a OX40 agonist antibody authorized or submitted for authorization, wherein the OX40 agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 11D4. The OX40 agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product,

wherein the reference medicinal product or reference biological product is 11D4. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 11D4.

TABLE 14: Amino acid sequences for OX40 agonist antibodies related to 11D4.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:66	EVQLVESGGG LVQPGGSLRL SCAASGFTFS SYSMNWVRQA PGKGLEWVSY ISSSSSTIDY	60
heavy chain for	ADSVKGRFTI SRDNAKNSLY LQMNSLRDED TAVYYCARES GWYLFDYWGQ GTLVTVSSAS	120
11D4	TKGPSVFPLA PCSRSTSEST AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL	180
	YSLSSVVTVP SSNFGTQTYT CNVDHKPSNT KVDKTVERKC CVECPPCPAP PVAGPSVFLF	240
	PPKPKDTLMI SRTPEVTCVV VDVSHEDPEV QFNWYVDGVE VHNAKTKPRE EQFNSTFRVV	300
	SVLTVVHQDW LNGKEYKCKV SNKGLPAPIE KTISKTKGQP REPQVYTLPP SREEMTKNQV	360
	SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPMLDSDGS FFLYSKLTVD KSRWQQGNVF	420
	SCSVMHEALH NHYTQKSLSL SPGK	444
SEQ ID NO:67	DIQMTQSPSS LSASVGDRVT ITCRASQGIS SWLAWYQQKP EKAPKSLIYA ASSLQSGVPS	60
light chain for	RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YNSYPPTFGG GTKVEIKRTV AAPSVFIFPP	120
11D4	SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT	180
	LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	214
SEQ ID NO:68	EVQLVESGGG LVQPGGSLRL SCAASGFTFS SYSMNWVRQA PGKGLEWVSY ISSSSSTIDY	60
heavy chain	ADSVKGRFTI SRDNAKNSLY LQMNSLRDED TAVYYCARES GWYLFDYWGQ GTLVTVSS	118
variable region		
for 11D4		
SEQ ID NO:69	DIQMTQSPSS LSASVGDRVT ITCRASQGIS SWLAWYQQKP EKAPKSLIYA ASSLQSGVPS	60
light chain	RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YNSYPPTFGG GTKVEIK	107
variable region		
for 11D4		
SEQ ID NO:70	SYSMN	5
heavy chain CDR1		
for 11D4		
SEQ ID NO:71	YISSSSSTID YADSVKG	17
heavy chain CDR2		
for 11D4		
SEQ ID NO:72	ESGWYLFDY	9
heavy chain CDR3		
for 11D4		
SEQ ID NO:73	RASQGISSWL A	11
light chain CDR1		
for 11D4		
SEQ ID NO:74	AASSLQS	7
light chain CDR2		
for 11D4		
SEQ ID NO:75	QQYNSYPPT	9
light chain CDR3		
for 11D4		

[00631] In some embodiments, the OX40 agonist is 18D8, which is a fully human antibody available from Pfizer, Inc. The preparation and properties of 18D8 are described in U.S. Patent Nos. 7,960,515; 8,236,930; and 9,028,824, the disclosures of which are incorporated by reference herein. The amino acid sequences of 18D8 are set forth in Table MM.

[00632] In an embodiment, a OX40 agonist comprises a heavy chain given by SEQ ID NO:76 and a light chain given by SEQ ID NO:77. In an embodiment, a OX40 agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively, or antigen binding fragments, Fab fragments, single-chain variable

fragments (scFv), variants, or conjugates thereof. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively.

[00633] In an embodiment, the OX40 agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 18D8. In an embodiment, the OX40 agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:78, and the OX40 agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:79, and conservative amino acid substitutions thereof. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:78 and SEQ ID NO:79, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:78 and SEQ ID NO:79, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:78 and SEQ ID NO:79, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:78 and SEQ ID NO:79, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:78 and SEQ ID NO:79, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:78 and SEQ ID NO:79, respectively.

[00634] In an embodiment, a OX40 agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:80, SEQ ID NO:81, and SEQ ID NO:82, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:83, SEQ ID NO:84, and SEQ ID NO:85, respectively, and conservative amino acid substitutions thereof.

[00635] In an embodiment, the OX40 agonist is a OX40 agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to 18D8. In an embodiment,

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the biosimilar monoclonal antibody comprises an OX40 antibody comprising an amino acid sequence which has at least 97% sequence identity, e.g., 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 18D8. In some embodiments, the one or more posttranslational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a OX40 agonist antibody authorized or submitted for authorization, wherein the OX40 agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 18D8. The OX40 agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 18D8. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 18D8.

TABLE 15: Amino acid sequences for OX40 agonist antibodies related to 18D8.

Identifier	Seque	ence (One-l	Letter Ami	no Acid S	ymbols)	
SEQ ID NO:76	EVQLVESGGG LVQPGRSLRL	SCAASGFTFD	DYAMHWVRQA	PGKGLEWVSG	ISWNSGSIGY	60
heavy chain for	ADSVKGRFTI SRDNAKNSLY	LQMNSLRAED	TALYYCAKDQ	STADYYFYYG	MDVWGQGTTV	120
18D8	TVSSASTKGP SVFPLAPCSR	STSESTAALG	CLVKDYFPEP	VTVSWNSGAL	TSGVHTFPAV	180
	LQSSGLYSLS SVVTVPSSNF	GTQTYTCNVD	HKPSNTKVDK	TVERKCCVEC	PPCPAPPVAG	240
	PSVFLFPPKP KDTLMISRTP	EVTCVVVDVS	HEDPEVQFNW	YVDGVEVHNA	KTKPREEQFN	300
	STFRVVSVLT VVHQDWLNGK	EYKCKVSNKG	LPAPIEKTIS	KTKGQPREPQ	VYTLPPSREE	360
	MTKNQVSLTC LVKGFYPSDI	AVEWESNGQP	ENNYKTTPPM	LDSDGSFFLY	SKLTVDKSRW	420
	QQGNVFSCSV MHEALHNHYT	QKSLSLSPGK				450
SEQ ID NO:77	EIVVTQSPAT LSLSPGERAT	LSCRASQSVS	SYLAWYQQKP	GQAPRLLIYD	ASNRATGIPA	60
light chain for	RFSGSGSGTD FTLTISSLEP	EDFAVYYCQQ	RSNWPTFGQG	TKVEIKRTVA	APSVFIFPPS	120
18D8	DEQLKSGTAS VVCLLNNFYP	REAKVQWKVD	NALQSGNSQE	SVTEQDSKDS	TYSLSSTLTL	180
	SKADYEKHKV YACEVTHQGL	SSPVTKSFNR	GEC			213
SEQ ID NO:78	EVQLVESGGG LVQPGRSLRL	SCAASGFTFD	DYAMHWVRQA	PGKGLEWVSG	ISWNSGSIGY	60
heavy chain	ADSVKGRFTI SRDNAKNSLY	LQMNSLRAED	TALYYCAKDQ	STADYYFYYG	MDVWGQGTTV	120
variable region	TVSS					124
for 18D8						
SEQ ID NO:79	EIVVTQSPAT LSLSPGERAT	LSCRASQSVS	SYLAWYQQKP	GQAPRLLIYD	ASNRATGIPA	60
light chain	RFSGSGSGTD FTLTISSLEP	EDFAVYYCQQ	RSNWPTFGQG	TKVEIK		106
variable region						
for 18D8						

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SEQ ID NO:80	DYAMH	5
heavy chain CDR1		
for 18D8		
SEQ ID NO:81	GISWNSGSIG YADSVKG	17
heavy chain CDR2		
for 18D8		
SEQ ID NO:82	DQSTADYYFY YGMDV	15
heavy chain CDR3		
for 18D8		
SEQ ID NO:83	RASQSVSSYL A	11
light chain CDR1		
for 18D8		
SEQ ID NO:84	DASNRAT	7
light chain CDR2		
for 18D8		
SEQ ID NO:85	QQRSNWPT	8
light chain CDR3		
for 18D8		

[00636] In some embodiments, the OX40 agonist is Hu119-122, which is a humanized antibody available from GlaxoSmithKline plc. The preparation and properties of Hu119-122 are described in U.S. Patent Nos. 9,006,399 and 9,163,085, and in International Patent Publication No. WO 2012/027328, the disclosures of which are incorporated by reference herein. The amino acid sequences of Hu119-122 are set forth in Table NN.

[00637] In an embodiment, the OX40 agonist comprises the heavy and light chain CDRs or variable regions (VRs) of Hu119-122. In an embodiment, the OX40 agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:86, and the OX40 agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:87, and conservative amino acid substitutions thereof. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:86 and SEQ ID NO:87, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:86 and SEQ ID NO:87, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:86 and SEQ ID NO:87, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:86 and SEQ ID NO:87, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:86 and SEQ ID NO:87, respectively.

[00638] In an embodiment, a OX40 agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:88, SEQ ID NO:89, and SEQ ID NO:90, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:91, SEQ ID NO:92, and SEQ ID NO:93, respectively, and conservative amino acid substitutions thereof.

[00639] In an embodiment, the OX40 agonist is a OX40 agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to Hu119-122. In an embodiment, the biosimilar monoclonal antibody comprises an OX40 antibody comprising an amino acid sequence which has at least 97% sequence identity, e.g., 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is Hu119-122. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a OX40 agonist antibody authorized or submitted for authorization, wherein the OX40 agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is Hu119-122. The OX40 agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is Hull9-122. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is Hull9-122.

TABLE 16: Amino acid sequences for OX40 agonist antibodies related to Hu119-122.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:86	EVQLVESGGG LVQPGGSLRL SCAASEYEFP SHDMSWVRQA PGKGLELVAA INSDGGSTYY	60
heavy chain variable region for Hull9-122	PDTMERRFTI SRDNAKNSLY LQMNSLRAED TAVYYCARHY DDYYAWFAYW GQGTMVTVSS	120
SEQ ID NO:87	EIVLTQSPAT LSLSPGERAT LSCRASKSVS TSGYSYMHWY QQKPGQAPRL LIYLASNLES	60
light chain variable region for Hull9-122	GVPARFSGSG SGTDFTLTIS SLEPEDFAVY YCQHSRELPL TFGGGTKVEI K	111
SEQ ID NO:88 heavy chain CDRl for Hull9-122	SHDMS	5
SEQ ID NO:89 heavy chain CDR2 for Hull9-122	AINSDGGSTY YPDTMER	17

SEQ ID NO:90	HYDDYYAWFA Y	11
heavy chain CDR3		
for Hull9-122		
SEQ ID NO:91	RASKSVSTSG YSYMH	15
light chain CDR1		
for Hull9-122		
SEQ ID NO:92	LASNLES	7
light chain CDR2		
for Hull9-122		
SEQ ID NO:93	QHSRELPLT	9
light chain CDR3		
for Hull9-122		

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[00640] In some embodiments, the OX40 agonist is Hu106-222, which is a humanized antibody available from GlaxoSmithKline plc. The preparation and properties of Hu106-222 are described in U.S. Patent Nos. 9,006,399 and 9,163,085, and in International Patent Publication No. WO 2012/027328, the disclosures of which are incorporated by reference herein. The amino acid sequences of Hu106-222 are set forth in Table OO.

[00641] In an embodiment, the OX40 agonist comprises the heavy and light chain CDRs or variable regions (VRs) of Hu106-222. In an embodiment, the OX40 agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:94, and the OX40 agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:95, and conservative amino acid substitutions thereof. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:94 and SEQ ID NO:95, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:94 and SEQ ID NO:95, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:94 and SEQ ID NO:95, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:94 and SEQ ID NO:95, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:94 and SEQ ID NO:95, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:94 and SEQ ID NO:95, respectively.

[00642] In an embodiment, a OX40 agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:96, SEQ ID NO:97, and SEQ ID NO:98, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:99, SEQ ID NO:100, and SEQ ID NO:101, respectively, and conservative amino acid substitutions thereof.

[00643] In an embodiment, the OX40 agonist is a OX40 agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to Hu106-222. In an embodiment, the biosimilar monoclonal antibody comprises an OX40 antibody comprising an amino acid sequence which has at least 97% sequence identity, e.g., 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is Hu106-222. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a OX40 agonist antibody authorized or submitted for authorization, wherein the OX40 agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is Hu106-222. The OX40 agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is Hu106-222. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is Hu106-222.

TABLE 17: Amino acid sequences for OX40 agonist antibodies related to Hu106-222.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:94	QVQLVQSGSE LKKPGASVKV SCKASGYTFT DYSMHWVRQA PGQGLKWMGW INTETGEPTY	60
heavy chain	ADDFKGRFVF SLDTSVSTAY LQISSLKAED TAVYYCANPY YDYVSYYAMD YWGQGTTVTV	120
variable region	ss	122
for Hu106-222		
SEQ ID NO:95	DIQMTQSPSS LSASVGDRVT ITCKASQDVS TAVAWYQQKP GKAPKLLIYS ASYLYTGVPS	60
light chain	RFSGSGSGTD FTFTISSLQP EDIATYYCQQ HYSTPRTFGQ GTKLEIK	107
variable region		
for Hu106-222		
SEQ ID NO:96	DYSMH	5
heavy chain CDR1		
for Hu106-222		
SEQ ID NO:97	WINTETGEPT YADDFKG	17
heavy chain CDR2		
for Hu106-222		

SEQ ID NO:98	PYYDYVSYYA MDY	13
heavy chain CDR3		
for Hu106-222		
SEQ ID NO:99	KASQDVSTAV A	11
light chain CDR1		
for Hu106-222		
SEQ ID NO:100	SASYLYT	7
light chain CDR2		
for Hu106-222		
SEQ ID NO:101	QQHYSTPRT	9
light chain CDR3		
for Hu106-222		

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[00644] In some embodiments, the OX40 agonist antibody is MEDI6469 (also referred to as 9B12). MEDI6469 is a murine monoclonal antibody. Weinberg, et al., J. Immunother. 2006, 29, 575-585. In some embodiments the OX40 agonist is an antibody produced by the 9B12 hybridoma, deposited with Biovest Inc. (Malvern, MA, USA), as described in Weinberg, et al., J. Immunother. 2006, 29, 575-585, the disclosure of which is hereby incorporated by reference in its entirety. In some embodiments, the antibody comprises the CDR sequences of MEDI6469. In some embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of MEDI6469.

[00645] In an embodiment, the OX40 agonist is L106 BD (Pharmingen Product #340420). In some embodiments, the OX40 agonist comprises the CDRs of antibody L106 (BD Pharmingen Product #340420). In some embodiments, the OX40 agonist comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody L106 (BD Pharmingen Product #340420). In an embodiment, the OX40 agonist is ACT35 (Santa Cruz Biotechnology, Catalog #20073). In some embodiments, the OX40 agonist comprises the CDRs of antibody ACT35 (Santa Cruz Biotechnology, Catalog #20073). In some embodiments, the OX40 agonist comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody ACT35 (Santa Cruz Biotechnology, Catalog #20073). In an embodiment, the OX40 agonist is the murine monoclonal antibody anti-mCD134/mOX40 (clone OX86), commercially available from InVivoMAb, BioXcell Inc, West Lebanon, NH.

[00646] In an embodiment, the OX40 agonist is selected from the OX40 agonists described in International Patent Application Publication Nos. WO 95/12673, WO 95/21925, WO 2006/121810, WO 2012/027328, WO 2013/028231, WO 2013/038191, and WO 2014/148895; European Patent Application EP 0672141; U.S. Patent Application Publication Nos. US 2010/136030, US 2014/377284, US 2015/190506, and US 2015/132288 (including clones 20E5 and 12H3); and U.S. Patent Nos. 7,504,101, 7,550,140, 7,622,444, 7,696,175,

7,960,515, 7,961,515, 8,133,983, 9,006,399, and 9,163,085, the disclosure of each of which is incorporated herein by reference in its entirety.

[00647] In an embodiment, the OX40 agonist is an OX40 agonistic fusion protein as depicted in Structure I-A (C-terminal Fc-antibody fragment fusion protein) or Structure I-B (N-terminal Fc-antibody fragment fusion protein), or a fragment, derivative, conjugate, variant, or biosimilar thereof. The properties of structures I-A and I-B are described above and in U.S. Patent Nos. 9,359,420, 9,340,599, 8,921,519, and 8,450,460, the disclosures of which are incorporated by reference herein. Amino acid sequences for the polypeptide domains of structure I-A are given in Table GG. The Fc domain preferably comprises a complete constant domain (amino acids 17-230 of SEQ ID NO:31) the complete hinge domain (amino acids 1-16 of SEQ ID NO:31) or a portion of the hinge domain (e.g., amino acids 4-16 of SEQ ID NO:31). Preferred linkers for connecting a C-terminal Fc-antibody may be selected from the embodiments given in SEQ ID NO:32 to SEQ ID NO:41, including linkers suitable for fusion of additional polypeptides. Likewise, amino acid sequences for the polypeptide domains of structure I-B are given in Table HH. If an Fc antibody fragment is fused to the N-terminus of an TNRFSF fusion protein as in structure I-B, the sequence of the Fc module is preferably that shown in SEQ ID NO:42, and the linker sequences are preferably selected from those embodiments set forth in SED ID NO:43 to SEQ ID NO:45.

[00648] In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains selected from the group consisting of a variable heavy chain and variable light chain of tavolixizumab, a variable heavy chain and variable light chain of 11D4, a variable heavy chain and variable light chain of 18D8, a variable heavy chain and variable light chain of Hu119-122, a variable heavy chain and variable light chain of Hu106-222, a variable heavy chain and variable light chain selected from the variable heavy chains and variable light chains described in Table OO, any combination of a variable heavy chain and variable light chain of the foregoing, and fragments, derivatives, conjugates, variants, and biosimilars thereof.

[00649] In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains comprising an OX40L sequence. In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains comprising a sequence according to SEQ ID NO:102. In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains comprising a soluble OX40L sequence. In an

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embodiment, a OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains comprising a sequence according to SEQ ID NO:103. In an embodiment, a OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains comprising a sequence according to SEQ ID NO:104.

[00650] In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:58 and SEQ ID NO:59, respectively, wherein the V_H and V_L domains are connected by a linker. In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:68 and SEQ ID NO:69, respectively, wherein the V_H and V_L domains are connected by a linker. In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:78 and SEQ ID NO:79, respectively, wherein the V_H and V_L domains are connected by a linker. In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:86 and SEQ ID NO:87, respectively, wherein the V_H and V_L domains are connected by a linker. In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:94 and SEQ ID NO:95, respectively, wherein the V_H and V_L domains are connected by a linker. In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the V_H and V_L sequences given in Table 18, wherein the V_H and V_L domains are connected by a linker.

TABLE 18: Additional polypeptide domains useful as OX40 binding domains in fusion proteins (e.g., structures I-A and I-B) or as scFv OX40 agonist antibodies.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:102	MERVQPLEEN VGNAARPRFE RNKLLLVASV IQGLGLLLCF TYICLHFSAL QVSHRYPRIQ	60
OX40L	SIKVQFTEYK KEKGFILTSQ KEDEIMKVQN NSVIINCDGF YLISLKGYFS QEVNISLHYQ	120
	KDEEPLFQLK KVRSVNSLMV ASLTYKDKVY LNVTTDNTSL DDFHVNGGEL ILIHQNPGEF	180
	CVL	183

SEQ ID NOI-108 SEQ ID NOI-108 SEQ ID NOI-06 SEQ ID NOI-06 SEQ ID NOI-06 SEQ ID NOI-07 SEQ ID NOI-08 SEQ ID NOI-08 SEQ ID NOI-09 SEQ ID NOI-10 SEQ								
Seg. ID NO.104 OKHOL Soluble OKHOL Soluble Seg. ID NO.105 Seg. ID NO.104 A FYELESKYNG FIRTHKYNG ILTSQYERDER MKVQRNSVII NOOSPYLISL KOYESQEVNI 228 SILVKROERP FEFEKKYRS MASHMARSLYY KDEVYLANTY DATSLODEN NOGELILING 129 SEG. ID NO.105 SEG. ID NO.106 VARIABLE Heavy Chain for 108 SEG. ID NO.106 SEG. ID NO.106 SEG. ID NO.106 SEG. ID NO.106 SEG. ID NO.107 SEG. ID NO.108 SEG. ID NO.108 SEG. ID NO.109 VARIABLE Hight Chain for 101 SEG. ID NO.110 VARIABLE Hight Chain for 101 SEG. ID NO.110 VARIABLE Hight Chain for 101 SEG. ID NO.110 VARIABLE HEAVY VARIABLE HIGHT CHAIN FOR SEG. ID NO.110 VARIABLE HIGHT CHAIN FOR SEG. ID NO.110 VARIABLE HEAVY VARIABLE HIGHT CHAIN FOR SEG. ID NO.110 VARIABLE HEAVY VARIABLE HEAVY VARIABLE HEAVY SHOWNERS SEGIOTALL SURVEAUGUVAY TYDIGYENAN PROGETYAVE SEG. ID NO.111 SEG. ID NO.1110 VARIABLE HEAVY SHOWNERS SEGIOTALL SURVEAUGUVAY TYDIGYENAN PROGETYAVE SEG. ID NO.1110 VARIABLE HEAVY SHOWNERS SEGIOTALL SURVEAUGUVAY TYDIGYENAN PROGETYAVE SEG. ID NO.1110 VARIABLE HEAVY SHOWNERS SEGIOTALL SURVEAUGUVAY TYDIGYENAN PROGETYAVE SEG. ID NO.1110 SEG. ID	SEQ ID NO:103	SHRYPRIQSI	KVQFTEYKKE	KGFILTSQKE	DEIMKVQNNS	VIINCDGFYL	ISLKGYFSQE	60
SSQ ID NOTION TOURISHED SHYLDESSAYS PETYKERREN LIPSCRIPT BRYCHING BORDEN GOOD STATE OF THE STAT	OX40L soluble	VNISLHYQKD	EEPLFQLKKV	RSVNSLMVAS	LTYKDKVYLN	VTTDNTSLDD	FHVNGGELIL	120
SKUNÇKORE İ EÇLEKYARSA MILMÜYASLIY KORÜYLMIYT DMYSLDƏFIN MƏSELÜLING 120 (Alternative) NOSEPÜL (Alternative) NO	domain	IHQNPGEFCV	L					131
domein (alternative) STO ID NO:165 STO ID NO:165 STO ID NO:165 STO ID NO:166 STO ID NO:167 STO ID NO:168 STO ID NO:169 STO ID NO:160 STO ID NO:162 STO ID NO:163 STO ID NO:164 STO ID NO:165 STO ID NO:165 STO ID NO:165 STO ID NO:167 STO ID NO	SEQ ID NO:104	YPRIQSIKVQ	FTEYKKEKGF	ILTSQKEDEI	MKVQNNSVII	NCDGFYLISL	KGYFSQEVNI	60
Section Sect	OX40L soluble	SLHYOKDEEP	LFOLKKVRSV	NSLMVASLTY	KDKVYLNVTT	DNTSLDDFHV	NGGELILIHO	120
SEQ IR NO:105 **EVOLUCISED & LOVPROSERS LOVPROSERS SYMMET SYMMENT SENSITIVE LONG STRUCK LOVERS SOUTHER SYMMET SENSITIVE LONG STRUCK LOVERS SET SYMMET SENSITIVE LONG STRUCK SYMMET SYMMET SENSITIVE LONG STRUCK SYMMET SYMMET SENSITIVE LONG STRUCK SYMMET SYMMET SENSITIVE SYMMET			~				~	
SEQ IR NO:105 **EVOLUCISED & LOVPROSERS LOVPROSERS SYMMET SYMMENT SENSITIVE LONG STRUCK LOVERS SOUTHER SYMMET SENSITIVE LONG STRUCK LOVERS SET SYMMET SENSITIVE LONG STRUCK SYMMET SYMMET SENSITIVE LONG STRUCK SYMMET SYMMET SENSITIVE LONG STRUCK SYMMET SYMMET SENSITIVE SYMMET	(alternative)							
AGSYMCRET SERNSKRYL LORMSLARE TATYLCARGE SECULTURES 120 SEQ ID NO:106 SEQ ID NO:107 Variable light SOVORPESS GEOTETIK: SKYZAZDOWY YTOQCYTNIE TYROGTIK ORAL FOR 108 SEQ ID NO:107 Variable light SOVORPESS GEOTETIK: SKYZAZDOWY TYROGTINE TYROGTIK ORAL FOR 108 SEQ ID NO:108 VARIABLE MARRY VARIABL		EVOLVESGGG	LVOPGGSLRL	SCAASGETES	NYTMNWVROA	PGKGLEWVSA	TSGSGGSTYY	60
Sep 10 No:106 Variable light Chain for 008 SEQ 10 No:107 SEQ 10 No:107 SEQ 10 No:107 SEQ 10 No:107 SEQ 10 No:108 SEQ 10 No:108 SEQ 10 No:108 SEQ 10 No:108 SEQ 10 No:109 Variable beavy Chain for 011 SEQ 10 No:100	. ~							
SEQ IE NO:105 SEQ ID NO:107 VARIABIO INDUSTRASS GOSTOPPERUS SYMPASSEVOV YYOQQYINNE TITOGOTY OF VARIABIO INDUSTRIANS INDUSTRI		ADSVINGINITI	SKDNSKNILI	DÖLINDLIVED	IAVIICANDN	IDQVIITADDI	MGGGITALAD	120
SOUTH NOTES AND ACTION OF SOUTH STRUCKERS OF STRUCKER S		DIAMEOGDDG	I DVIIIDCEDAC	TCCDCCCCTT	HCMCVMVIDW	VIOVACOCDO	TITVICONDA	
chain for 008 SSQ IB NO:107 vorlable heavy chain for 011 SSQ IB NO:108 SRIGHTISE DMSNNITHIQ MNNHARABETA TYTONNYGA PGKGLEWYS ISGSSTYTAD 60 vorlable heavy chain for 011 SSQ IB NO:109 SSQ ID NO:109 SVQLVESGGG LVQPKGSERI SCASSGTIS SYMMNYGAP PGKGLEWYS ISGSSTYTAD 108 chain for 021 SSQ ID NO:109 ADSVAGRETI SENSENTHY LQMSLERDED TYTOGERS ISCSSSOLI HINGYNYLDW TYQKAGGSPG LLIYLGSNRA 60 vorlable heavy chain for 021 SSQ ID NO:109 SVQLVESGGG LVQPKGSERI SCASSGTIS SYMMNYGA PGKGLEWYA ISTOGERNYY 60 ADSVAGRETI SENSENTHY LQMSLERED TAYYCAKOR TITLEMALCY MOGOTIVTYS 120 SSQ ID NO:100 SSQ ID NO:100 SVQLVESGGG LVQPKGSERI SCASSGVIS LHNGYNYLDW TYQCAGGSPG LLIYLGSNRA 60 SSQ ID NO:100 SSQ ID NO:101 SSQ ID NO:102 SSQ ID NO:102 SSQ ID NO:102 SSQ ID NO:103 SSQ ID NO:103 SSQ ID NO:104 SSQ ID NO:105 SSQ ID NO:107 SSQ ID NO:107 SSQ ID NO:107 SSQ ID NO:107 SSQ ID NO:108 SSQ ID NO:109 SSQ ID NO:10	. ~						LLIILGSNKA	
SNC ID NOTION AVAILABED HEAVY Chein for Oll SNC ID NOTION AVAILABED HEAVY Chein for Oll SNC ID NOTION AVAILABED HIGHT Chein for Oll SNC ID NOTION		SGVPDRFSGS	GSGTDFTLKI	SRVEAEDVGV	YYCQQYYNHP	TTFGQGTK		108
SEC ID NO:109 VARIABLE DE NO:109 SEC ID NO:109 VARIABLE DI DIVENÇASES ESCRIPTER SECRESÇASEL HANGVENYLDY YLQXAGQSFQ BLIYLGSNAM 60 SEC ID NO:109 VARIABLE DISTRICTURE SECRESCASEL HANGVENYLDY YLQXAGQSFQ BLIYLGSNAM 60 VARIABLE DISTRICTURE SECRESCASEL HANGVENYLDY YLQXAGQSFQ BLIYLGSNAM 60 VARIABLE DI NO:109 SEC ID NO:110 DIGNYCOSEVE DEVPEGERAS ISCRASGETTS SYAMMAVROA PERGLEWAW ISYDOSNATY LONGARD FOR ADSWERFTIS SADNANTHY LQNASLARD TAWYCAROR YITLERALDY WGQGTLATVS 120 CHAIR FOR 221 SEC ID NO:111 VARIABLE DI NO:112 SEC ID NO:111 VARIABLE DI NO:112 SEC ID NO:113 SEC ID NO:113 SEC ID NO:114 SEC ID NO:115 SEC ID NO:116 SEC ID NO:117 SEC ID NO:117 SEC ID NO:118 SEC ID NO:128 SEC ID NO:128 SEC ID NO:128								
chain for 011 SEQ 1D NO198	_							
SEC ID NO:108 VARIABLE HIGH Chain for 011 SEC ID NO:109 VARIABLE HIGH Chain for 021 SEC ID NO:109 VARIABLE HIGH Chain for 021 SEC ID NO:109 VARIABLE HIGH CHAIN FOR 021 SEC ID NO:110 VARIABLE HIGH CHAIN FOR 021 SEC ID NO:110 DICHTOSPES LPYTPEGERAS ISCRESSUL HENGYMYLDW YLCHROGGSTEV 120 SEC ID NO:110 DICHTOSPES LPYTPEGERAS ISCRESSUL HENGYMYLDW YLCHROGGSTE LITHGENRA 60 VARIABLE HIGH CHAIN FOR 021 SEC ID NO:110 DICHTOSPES LPYTPEGERAS ISCRESSUL HENGYMYLDW YLCHROGGSTE LITHGENRA 60 SEC ID NO:111 VARIABLE HIGH CHAIN FOR 021 SEC ID NO:112 VARIABLE HIGH CHAIN FOR 022 SEC ID NO:112 VARIABLE HIGH CHAIN FOR 023 SEC ID NO:112 VARIABLE HIGH CHAIN FOR 023 SEC ID NO:113 EVOLUCESGGG LVHPGGSIRL SCAGSGFTES SYAMHWYROA PGKGLEWYSA IGTGGGTYYA 60 DSWMGRFTIS ROMSKNITLY CANNELRADED ANYYCARCH WAGLYWEDUR GCGTLYTYSS 120 SEC ID NO:112 VARIABLE HIGH CHAIN FOR 023 SEC ID NO:113 EVOLUCESGGG LVHPGGSIRL SCAGSGFTES SYAMHWYROA PGKGLEWYSA IGTGGGTYYA 60 SEC ID NO:113 FOR 100 SEC ID NO:113 FOR 100 SEC ID NO:113 FOR 100 SEC ID NO:114 FOR 100 F		SRKGRFTISR	DNSKNTLYLQ	MNNLRAEDTA	VYYCARDRYF	RQQNAFDYWG	QGTLVTVSSA	120
SEC ID NO:119 SEC ID NO:120 SEC ID								
Sep ID NO:119 Sep ID NO:119 Sep ID NO:110 Sep ID NO:110 Sep ID NO:110 Dichtische heavy chain for 02:1 Sep ID NO:111 Variable heavy chain for 02:1 Sep ID NO:112 Devices of the sep in the se	_						LLIYLGSNRA	
SEQ ID NO:109 **EQUIVESGOG LYMPROSLEN SCARSGITTS SYAMINYSQA PGGGLENVAN ISTSUGSINKTY 60 **Chain for 021 **SEQ ID NO:110 **DIGNTQSFVS LPVIPOGERAS ISCSSSSSLE HENGYNYLDMY YLCKFGGGSPG LLIYLGSNRA 60 **CANTAGALE Hight Chain for 021 **SEQ ID NO:111 **EQUIVESGOG LYMPGGGLEN SCARSGITTS SYAMINYSQA PGGGLENVAN IGTSUGGTYYA 60 **SEQ ID NO:112 **EQUIVESGOG LYMPGGGLEN SCARSGITTS SYAMINYSQA PGGGLENVAN IGTSUGGTYYA 60 **SEQ ID NO:112 **EVUITQSFAT LSLSFGERAT LSCRASGITTS SYAMINYSQA PGGGLENVAN IGTSUGGTYYA 60 **SEQ ID NO:112 **EVUITQSFAT LSLSFGERAT LSCRASGITTS SYAMINYSQA PGGGLENVAN IGTSUGGTYYA 60 **RESCRESSORTD FTUTISSLEP EDFAVYYCQQ SHAMPPAFGG GTMVSTER 108 **SEQ ID NO:113 **EVUITQSFAT LSLSFGERAT LSCRASGINS SYLAWYQQE GQAPALLIYD ANNANTGIPA 60 **RESCRASGIN FTUTISSLEP EDFAVYYCQQ SHAMPPAFGG GTMVSTER 108 **SEQ ID NO:113 **EVUITQSFAT LSLSFGERAT LSCRASGINS SYLAWYQQE GGAPALLIYD ANNANTGIPA 60 **RESCRASGIN FTUTISSLEP EDFAVYYCQQ SHAMPPAFGG GTMVSTER 108 **SEQ ID NO:114 **Light chain NEKKGATL TSSKASSTAY MESSLEDS SAVYYCQAMY GSSLEMDYMG QCTSTVTSS 119 **RESCRESSORTD YSJITISHLEQ EDIATYFCQQ GMTLFWTFGG GTMLSTER 108 **SEQ ID NO:115 **SEQ ID NO:116 **LEVALCOUGH PART AND ANNANTGIA PGGGLENGAMY GRASGINDY GRASGIND ANNANTGAT PGGG ANTHAFTGYPD 60 **RESCRESSORTD YSJITISHLEQ EDIATYFCQQ GMTLFWTFGG GTMLSTER 108 **RESCRESSORTD YSJITISHLEQ EDIATYFCQQ GMTLFWTFGG GTMLSTER 108 **RESCRESSORTD YSJITISHLEQ EDIATYFCQQ THINFIFTGG GTMLSTER 108 **RESCRESSORTD TTITISHTYSE EDITOFTCQQ YNANTYCAMM YHOPHOPEN WAGATYTVYS 120 **VARIABLE region 108 **SEQ ID NO:116 **LIGHT Chain NEW AND ANNANT STREAM STREAM HINDERS YNANTYCAM PGGLENMAM HINTSTGEPTY 60 **REDCH NO:116 **LIGHT Chain NEW AND ANNANT STREAM STREAM YMPORT PGGLENMAM HINTSTGEPTY 60 **REDCH NO:117 **RESCRESSORTD TTITISHTYSE EDITOFTCQQ YNANTYCAMP YMYGAYMAM WAGATYTVY 120 **SEQ ID NO:118 **RESCRESSORTD TTITISHTYSE EDITOFTCQQ YNANTYCAMP YMYGAYMAM WAGATYTVY 120 **RESCRESSORTD TTITISHTYSE EDITOFTCQQ YNANTYCAMP YMYGAYMAM WAGATYTY 120 **RESCRESSORTD TTITISHTYSE EDITOFTCQQ YNANTYCAMP YMYGAYMAM WAGATYTY 12	variable light	SGVPDRFSGS	GSGTDFTLKI	SRVEAEDVGV	YYCQQYYNHP	TTFGQGTK		108
ADSWERFT SRÜNSKHTLY LOMNSLRAED TAVYYCAKUR YITLPHALDY WGGGLVTVS chain for 021 SEG ID NG:110 Chain for 021 SGVPERPSS GSGSTFTIKK SNYZAEDVGV YYCQQYKNNP PTFGGGTK 108 SGVPERPSS GSGSTFTLKK SNYZAEDVGV YYCQQYKNNP PTFGGGTK 108 SGVPERPSS GSGSTFTIKK SNYZAEDVGV YYCQQYKNNP PTFGGGTYA 60 Chain for 021 SEG ID NG:111 EVOLVESGGG LVHEGGSLAL SCASSGTTS SYAHHWYRGA PSKKLEKVSA IGTGGGTYA 60 CANADA COLOR OF CO	chain for 011							
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variable region of humanized antibody							
SEQ ID NO:124	EIVLTQSPAT	LSLSPGERAT	LSCRASKSVS	TSGYSYMHWY	QQKPGQAPRL	LIYLASNLES	60
light chain	GVPARFSGSG	SGTDFTLTIS	SLEPEDFAVY	YCQHSRELPL	TFGGGTKVEI	K	111
variable region							
of humanized							
antibody							
SEQ ID NO:125	MYLGLNYVFI	VFLLNGVQSE	VKLEESGGGL	VQPGGSMKLS	CAASGFTFSD	AWMDWVRQSP	60
heavy chain	EKGLEWVAEI	RSKANNHATY	YAESVNGRFT	ISRDDSKSSV	YLQMNSLRAE	DTGIYYCTWG	120
variable region	EVFYFDYWGQ	GTTLTVSS					138
SEQ ID NO:126	MRPSIQFLGL	LLFWLHGAQC	DIQMTQSPSS	LSASLGGKVT	ITCKSSQDIN	KYIAWYQHKP	60
light chain	GKGPRLLIHY	TSTLQPGIPS	RFSGSGSGRD	YSFSISNLEP	EDIATYYCLQ	YDNLLTFGAG	120
variable region	TKLELK						126

In an embodiment, the OX40 agonist is a OX40 agonistic single-chain fusion polypeptide comprising (i) a first soluble OX40 binding domain, (ii) a first peptide linker, (iii) a second soluble OX40 binding domain, (iv) a second peptide linker, and (v) a third soluble OX40 binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, and wherein the additional domain is a Fab or Fc fragment domain. In an embodiment, the OX40 agonist is a OX40 agonistic single-chain fusion polypeptide comprising (i) a first soluble OX40 binding domain, (ii) a first peptide linker, (iii) a second soluble OX40 binding domain, (iv) a second peptide linker, and (v) a third soluble OX40 binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, wherein the additional domain is a Fab or Fc fragment domain wherein each of the soluble OX40 binding domains lacks a stalk region (which contributes to trimerisation and provides a certain distance to the cell membrane, but is not part of the OX40 binding domain) and the first and the second peptide linkers independently have a length of 3-8 amino acids.

[00652] In an embodiment, the OX40 agonist is an OX40 agonistic single-chain fusion polypeptide comprising (i) a first soluble tumor necrosis factor (TNF) superfamily cytokine domain, (ii) a first peptide linker, (iii) a second soluble TNF superfamily cytokine domain, (iv) a second peptide linker, and (v) a third soluble TNF superfamily cytokine domain, wherein each of the soluble TNF superfamily cytokine domains lacks a stalk region and the first and the second peptide linkers independently have a length of 3-8 amino acids, and wherein the TNF superfamily cytokine domain is an OX40 binding domain.

[00653] In some embodiments, the OX40 agonist is MEDI6383. MEDI6383 is an OX40 agonistic fusion protein and can be prepared as described in U.S. Patent No. 6,312,700, the disclosure of which is incorporated by reference herein.

[00654] In an embodiment, the OX40 agonist is an OX40 agonistic scFv antibody comprising any of the foregoing V_H domains linked to any of the foregoing V_L domains.

[00655] In an embodiment, the OX40 agonist is Creative Biolabs OX40 agonist monoclonal antibody MOM-18455, commercially available from Creative Biolabs, Inc., Shirley, NY, USA.

[00656] In an embodiment, the OX40 agonist is OX40 agonistic antibody clone Ber-ACT35 commercially available from BioLegend, Inc., San Diego, CA, USA.

H. Optional Cell Viability Analyses

[00657] Optionally, a cell viability assay can be performed after the first expansion (sometimes referred to as the initial bulk expansion), using standard assays known in the art. For example, a trypan blue exclusion assay can be done on a sample of the bulk TILs, which selectively labels dead cells and allows a viability assessment. Other assays for use in testing viability can include but are not limited to the Alamar blue assay; and the MTT assay.

1. Cell Counts, Viability, Flow Cytometry

[00658] In some embodiments, cell counts and/or viability are measured. The expression of markers such as but not limited CD3, CD4, CD8, and CD56, as well as any other disclosed or described herein, can be measured by flow cytometry with antibodies, for example but not limited to those commercially available from BD Bio-sciences (BD Biosciences, San Jose, CA) using a FACSCantoTM flow cytometer (BD Biosciences). The cells can be counted manually using a disposable c-chip hemocytometer (VWR, Batavia, IL) and viability can be assessed using any method known in the art, including but not limited to trypan blue staining. The cell viability can also be assayed based on USSN 15/863,634, incorporated by reference herein in its entirety.

[00659] In some cases, the bulk TIL population can be cryopreserved immediately, using the protocols discussed below. Alternatively, the bulk TIL population can be subjected to REP and then cryopreserved as discussed below. Similarly, in the case where genetically modified TILs will be used in therapy, the bulk or REP TIL populations can be subjected to genetic modifications for suitable treatments.

[00660] According to the present disclosure, a method for assaying TILs for viability and/or further use in administration to a subject. In some embodiments, the method for assay tumor infiltrating lymphocytes (TILs) comprises:

(i) obtaining a first population of TILs;

- (ii) performing a first expansion by culturing the first population of TILs in a cell culture medium comprising IL-2, and optionally OKT-3, to produce a second population of TILs; and
- (iii) performing a second expansion by supplementing the cell culture medium of the second population of TILs with additional IL-2, OKT-3, and antigen presenting cells (APCs), to produce a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs;
- (iv) harvesting, washing, and cryopreserving the third population of TILs;
- (v) storing the cryopreserved TILs at a cryogenic temperature;
- (vi) thawing the third population of TILs to provide a thawed third population of TILs; and
- (vii) performing an additional second expansion of a portion of the thawed third population of TILs by supplementing the cell culture medium of the third population with IL-2, OKT-3, and APCs for an additional expansion period (sometimes referred to as a reREP period) of at least 3 days, wherein the third expansion is performed to obtain a fourth population of TILs, wherein the number of TILs in the fourth population of TILs is compared to the number of TILs in the third population of TILs to obtain a ratio;
- (viii) determining based on the ratio in step (vii) whether the thawed population of TILs is suitable for administration to a patient;
- (ix) administering a therapeutically effective dosage of the thawed third population of TILs to the patient when the ratio of the number of TILs in the fourth population of TILs to the number of TILs in the third population of TILs is determined to be greater than 5:1 in step (viii).
- [00661] In some embodiments, the TILs are assayed for viability after step (vii).
- [00662] The present disclosure also provides further methods for assaying TILs. In some embodiments, the disclosure provides a method for assaying TILs comprising:
 - (i) obtaining a portion of a first population of cryopreserved TILs;
 - (ii) thawing the portion of the first population of cryopreserved TILs;
 - (iii) performing a first expansion by culturing the portion of the first population of

TILs in a cell culture medium comprising IL-2, OKT-3, and antigen presenting cells (APCs) for an additional expansion period (sometimes referred to as a reREP period) of at least 3 days, to produce a second population of TILs, wherein the portion from the first population of TILs is compared to the second population of TILs to obtain a ratio of the number of TILs, wherein the ratio of the number of TILs in the second population of TILs to the number of TILs in the portion of the first population of TILs is greater than 5:1;

- (iv) determining based on the ratio in step (iii) whether the first population of TILs is suitable for use in therapeutic administration to a patient;
- (v) determining the first population of TILs is suitable for use in therapeutic administration when the ratio of the number of TILs in the second population of TILs to the number of TILs in the first population of TILs is determined to be greater than 5:1 in step (iv).

[00663] In some embodiments, the ratio of the number of TILs in the second population of TILs to the number of TILs in the portion of the first population of TILs is greater than 50:1.

[00664] In some embodiments, the method further comprises performing expansion of the entire first population of cryopreserved TILs from step (i) according to the methods as described in any of the embodiments provided herein.

[00665] In some embodiments, the method further comprises administering the entire first population of cryopreserved TILs from step (i) to the patient.

2. Cell Cultures

[00666] In an embodiment, a method for expanding TILs, including those discussed above as well as exemplified in Figure 1, may include using about 5,000 mL to about 25,000 mL of cell medium, about 5,000 mL to about 10,000 mL of cell medium, or about 5,800 mL to about 8,700 mL of cell medium. In some embodiments, the media is a serum free medium. In some embodiments, the media in the first expansion is serum free. In some embodiments, the media in the first expansion and the second expansion is serum free. In some embodiments, the media in the first expansion and the second are both serum free. In an embodiment, expanding the number of TILs uses no more than one type of cell culture medium. Any suitable cell culture medium may be used, *e.g.*, AIM-V cell medium (L-glutamine, 50 μM streptomycin sulfate, and 10 μM gentamicin sulfate) cell culture medium (Invitrogen, Carlsbad CA). In this regard, the

inventive methods advantageously reduce the amount of medium and the number of types of medium required to expand the number of TIL. In an embodiment, expanding the number of TIL may comprise feeding the cells no more frequently than every third or fourth day. Expanding the number of cells in a gas permeable container simplifies the procedures necessary to expand the number of cells by reducing the feeding frequency necessary to expand the cells.

[00667] In an embodiment, the cell medium in the first and/or second gas permeable container is unfiltered. The use of unfiltered cell medium may simplify the procedures necessary to expand the number of cells. In an embodiment, the cell medium in the first and/or second gas permeable container lacks beta-mercaptoethanol (BME).

[00668] In an embodiment, the duration of the method comprising obtaining a tumor tissue sample from the mammal; culturing the tumor tissue sample in a first gas permeable container containing cell medium therein; obtaining TILs from the tumor tissue sample; expanding the number of TILs in a second gas permeable container containing cell medium for a duration of about 7 to 14 days, *e.g.*, about 11 days. In some embodiments pre-REP is about 7 to 14 days, *e.g.*, about 11 days. In some embodiments, REP is about 7 to 14 days, *e.g.*, about 11 days.

[00669] In an embodiment, TILs are expanded in gas-permeable containers. Gas-permeable containers have been used to expand TILs using PBMCs using methods, compositions, and devices known in the art, including those described in U.S. Patent Application Publication No. 2005/0106717 A1, the disclosures of which are incorporated herein by reference. In an embodiment, TILs are expanded in gas-permeable bags. In an embodiment, TILs are expanded using a cell expansion system that expands TILs in gas permeable bags, such as the Xuri Cell Expansion System W25 (GE Healthcare). In an embodiment, TILs are expanded using a cell expansion system that expands TILs in gas permeable bags, such as the WAVE Bioreactor System, also known as the Xuri Cell Expansion System W5 (GE Healthcare). In an embodiment, the cell expansion system includes a gas permeable cell bag with a volume selected from the group consisting of about 100 mL, about 200 mL, about 300 mL, about 400 mL, about 500 mL, about 600 mL, about 700 mL, about 800 mL, about 900 mL, about 1 L, about 2 L, about 3 L, about 4 L, about 5 L, about 6 L, about 7 L, about 8 L, about 9 L, and about 10 L.

[00670] In an embodiment, TILs can be expanded in G-Rex flasks (commercially available from Wilson Wolf Manufacturing). Such embodiments allow for cell populations to expand from about 5x10⁵ cells/cm² to between 10x10⁶ and 30x10⁶ cells/cm². In an embodiment this is without feeding. In an embodiment, this is without feeding so long as medium resides at a height of about 10 cm in the G-Rex flask. In an embodiment this is without feeding but with the addition of one or more cytokines. In an embodiment, the cytokine can be added as a bolus without any need to mix the cytokine with the medium. Such containers, devices, and methods are known in the art and have been used to expand TILs, and include those described in U.S. Patent Application Publication No. US 2014/0377739A1, International Publication No. WO 2014/210036 A1, U.S. Patent Application Publication No. us 2013/0115617 A1, International Publication No. WO 2013/188427 A1, U.S. Patent Application Publication No. US 2011/0136228 A1, U.S. Patent No. US 8,809,050 B2, International publication No. WO 2011/072088 A2, U.S. Patent Application Publication No. US 2016/0208216 A1, U.S. Patent Application Publication No. US 2012/0244133 A1, International Publication No. WO 2012/129201 A1, U.S. Patent Application Publication No. US 2013/0102075 A1, U.S. Patent No. US 8,956,860 B2, International Publication No. WO 2013/173835 A1, U.S. Patent Application Publication No. US 2015/0175966 A1, the disclosures of which are incorporated herein by reference. Such processes are also described in Jin et al., J. Immunotherapy, 2012, 35:283-292.

I. Optional Genetic Engineering of TILs

[00671] In some embodiments, the TILs are optionally genetically engineered to include additional functionalities, including, but not limited to, a high-affinity T cell receptor (TCR), *e.g.*, a TCR targeted at a tumor-associated antigen such as MAGE-1, HER2, or NY-ESO-1, or a chimeric antigen receptor (CAR) which binds to a tumor-associated cell surface molecule (*e.g.*, mesothelin) or lineage-restricted cell surface molecule (*e.g.*, CD19).

J. Optional Cryopreservation of TILs

[00672] As discussed above, and exemplified in Steps A through E as provided in Figure 1, cryopreservation can occur at numerous points throughout the TIL expansion process. In some embodiments, the expanded population of TILs after the second expansion (as provided for example, according to Step D of Figure 1) can be cryopreserved. Cryopreservation can be generally accomplished by placing the TIL population into a freezing solution, *e.g.*, 85% complement inactivated AB serum and 15% dimethyl sulfoxide (DMSO). The cells in

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solution are placed into cryogenic vials and stored for 24 hours at -80 °C, with optional transfer to gaseous nitrogen freezers for cryopreservation. See Sadeghi, et al., Acta Oncologica 2013, 52, 978-986. In some embodiments, the TILs are cryopreserved in 5% DMSO. In some embodiments, the TILs are cryopreserved in cell culture media plus 5% DMSO. In some embodiments, the TILs are cryopreserved according to the methods provided in Examples F and G.

[00673] When appropriate, the cells are removed from the freezer and thawed in a 37 °C water bath until approximately 4/5 of the solution is thawed. The cells are generally resuspended in complete media and optionally washed one or more times. In some embodiments, the thawed TILs can be counted and assessed for viability as is known in the art.

Closed Systems for TIL Manufacturing K.

[00674] The present invention provides for the use of closed systems during the TIL culturing process. Such closed systems allow for preventing and/or reducing microbial contamination, allow for the use of fewer flasks, and allow for cost reductions. In some embodiments, the closed system uses two containers.

[00675] Such closed systems are well-known in the art and can be found, for example, at http://www.fda.gov/cber/guidelines.htm and https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/G uidances/Blood/ucm076779.htm.

[00676] Sterile connecting devices (STCDs) produce sterile welds between two pieces of compatible tubing. This procedure permits sterile connection of a variety of containers and tube diameters. In some embodiments, the closed systems include luer lock and heat sealed systems as described in for example, Example G. In some embodiments, the closed system is accessed via syringes under sterile conditions in order to maintain the sterility and closed nature of the system. In some embodiments, a closed system as described in Example G is employed. In some embodiments, the TILs are formulated into a final product formulation container according to the method described in Example G, section "Final Formulation and Fill".

[00677] In some embodiments, the closed system uses one container from the time the tumor fragments are obtained until the TILs are ready for administration to the patient or cryopreserving. In some embodiments when two containers are used, the first container is a

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closed G-container and the population of TILs is centrifuged and transferred to an infusion bag without opening the first closed G-container. In some embodiments, when two containers are used, the infusion bag is a HypoThermosol-containing infusion bag. A closed system or closed TIL cell culture system is characterized in that once the tumor sample and/or tumor fragments have been added, the system is tightly sealed from the outside to form a closed environment free from the invasion of bacteria, fungi, and/or any other microbial contamination.

[00678] In some embodiments, the reduction in microbial contamination is between about 5% and about 100%. In some embodiments, the reduction in microbial contamination is between about 5% and about 95%. In some embodiments, the reduction in microbial contamination is between about 5% and about 90%. In some embodiments, the reduction in microbial contamination is between about 10% and about 90%. In some embodiments, the reduction in microbial contamination is between about 15% and about 85%. In some embodiments, the reduction in microbial contamination is about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 95%, about 95%, about 97%, about 98%, about 99%, or about 100%.

[00679] The closed system allows for TIL growth in the absence and/or with a significant reduction in microbial contamination.

[00680] Moreover, pH, carbon dioxide partial pressure and oxygen partial pressure of the TIL cell culture environment each vary as the cells are cultured. Consequently, even though a medium appropriate for cell culture is circulated, the closed environment still needs to be constantly maintained as an optimal environment for TIL proliferation. To this end, it is desirable that the physical factors of pH, carbon dioxide partial pressure and oxygen partial pressure within the culture liquid of the closed environment be monitored by means of a sensor, the signal whereof is used to control a gas exchanger installed at the inlet of the culture environment, and the that gas partial pressure of the closed environment be adjusted in real time according to changes in the culture liquid so as to optimize the cell culture environment. In some embodiments, the present invention provides a closed cell culture system which incorporates at the inlet to the closed environment a gas exchanger equipped with a monitoring device which measures the pH, carbon dioxide partial pressure and oxygen partial pressure of the closed environment, and optimizes the cell culture environment by automatically adjusting gas concentrations based on signals from the monitoring device.

[00681] In some embodiments, the pressure within the closed environment is continuously or intermittently controlled. That is, the pressure in the closed environment can be varied by means of a pressure maintenance device for example, thus ensuring that the space is suitable for growth of TILs in a positive pressure state, or promoting exudation of fluid in a negative pressure state and thus promoting cell proliferation. By applying negative pressure intermittently, moreover, it is possible to uniformly and efficiently replace the circulating liquid in the closed environment by means of a temporary shrinkage in the volume of the closed environment.

[00682] In some embodiments, optimal culture components for proliferation of the TILs can be substituted or added, and including factors such as IL-2 and/or OKT3, as well as combination, can be added.

L. Optional Cryopreservation of TILs

[00683] Either the bulk TIL population or the expanded population of TILs can be optionally cryopreserved. In some embodiments, cryopreservation occurs on therapeutic TIL population. In some embodiments, cryopreservation occurs on the TILs harvested after the second expansion. In some embodiments, cryopreservation occurs on the TILs in exemplary Step F of Figure 1. In some embodiments, the TILs are cryopreserved in the infusion bag. In some embodiments, the TILs are cryopreserved prior to placement in an infusion bag. In some embodiments, the TILs are cryopreserved and not placed in an infusion bag. In some embodiments, cryopreservation is performed using a cryopreservation medium. In some embodiments, the cryopreservation media contains dimethylsulfoxide (DMSO). This is generally accomplished by putting the TIL population into a freezing solution, e.g. 85% complement inactivated AB serum and 15% dimethyl sulfoxide (DMSO). The cells in solution are placed into cryogenic vials and stored for 24 hours at -80 °C, with optional transfer to gaseous nitrogen freezers for cryopreservation. See, Sadeghi, *et al.*, *Acta Oncologica* 2013, *52*, 978-986.

[00684] When appropriate, the cells are removed from the freezer and thawed in a 37 °C water bath until approximately 4/5 of the solution is thawed. The cells are generally resuspended in complete media and optionally washed one or more times. In some embodiments, the thawed TILs can be counted and assessed for viability as is known in the art.

[00685] In a preferred embodiment, a population of TILs is cryopreserved using CS10 cryopreservation media (CryoStor 10, BioLife Solutions). In a preferred embodiment, a population of TILs is cryopreserved using a cryopreservation media containing dimethylsulfoxide (DMSO). In a preferred embodiment, a population of TILs is cryopreserved using a 1:1 (vol:vol) ratio of CS10 and cell culture media. In a preferred embodiment, a population of TILs is cryopreserved using about a 1:1 (vol:vol) ratio of CS10 and cell culture media, further comprising additional IL-2.

[00686] As discussed above in Steps A through E, cryopreservation can occur at numerous points throughout the TIL expansion process. In some embodiments, the bulk TIL population after the first expansion according to Step B or the expanded population of TILs after the one or more second expansions according to Step D can be cryopreserved. Cryopreservation can be generally accomplished by placing the TIL population into a freezing solution, *e.g.*, 85% complement inactivated AB serum and 15% dimethyl sulfoxide (DMSO). The cells in solution are placed into cryogenic vials and stored for 24 hours at -80 °C, with optional transfer to gaseous nitrogen freezers for cryopreservation. See Sadeghi, *et al.*, *Acta Oncologica* 2013, 52, 978-986.

[00687] When appropriate, the cells are removed from the freezer and thawed in a 37 °C water bath until approximately 4/5 of the solution is thawed. The cells are generally resuspended in complete media and optionally washed one or more times. In some embodiments, the thawed TILs can be counted and assessed for viability as is known in the art.

[00688] In some cases, the Step B TIL population can be cryopreserved immediately, using the protocols discussed below. Alternatively, the bulk TIL population can be subjected to Step C and Step D and then cryopreserved after Step D. Similarly, in the case where genetically modified TILs will be used in therapy, the Step B or Step D TIL populations can be subjected to genetic modifications for suitable treatments.

IV. TIL Manufacturing Processes (Embodiments of GEN3 Processes, optionally including Defined Media)

[00689] Without being limited to any particular theory, it is believed that the priming first expansion that primes an activation of T cells followed by the rapid second expansion that boosts the activation of T cells as described in the methods of the invention allows the preparation of expanded T cells that retain a "younger" phenotype, and as such the expanded T cells of the invention are expected to exhibit greater cytotoxicity against cancer cells than T

cells expanded by other methods. In particular, it is believed that an activation of T cells that is primed by exposure to an anti-CD3 antibody (e.g. OKT-3), IL-2 and optionally antigenpresenting cells (APCs) and then boosted by subsequent exposure to additional anti-CD-3 antibody (e.g. OKT-3), IL-2 and APCs as taught by the methods of the invention limits or avoids the maturation of T cells in culture, yielding a population of T cells with a less mature phenotype, which T cells are less exhausted by expansion in culture and exhibit greater cytotoxicity against cancer cells. In some embodiments, the step of rapid second expansion is split into a plurality of steps to achieve a scaling up of the culture by: (a) performing the rapid second expansion by culturing T cells in a small scale culture in a first container, e.g., a G-REX 100MCS container, for a period of about 3 to 4 days, and then (b) effecting the transfer of the T cells in the small scale culture to a second container larger than the first container, e.g., a G-REX 500MCS container, and culturing the T cells from the small scale culture in a larger scale culture in the second container for a period of about 4 to 7 days. In some embodiments, the step of rapid expansion is split into a plurality of steps to achieve a scaling out of the culture by: (a) performing the rapid second expansion by culturing T cells in a first small scale culture in a first container, e.g., a G-REX 100MCS container, for a period of about 3 to 4 days, and then (b) effecting the transfer and apportioning of the T cells from the first small scale culture into and amongst at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 second containers that are equal in size to the first container, wherein in each second container the portion of the T cells from first small scale culture transferred to such second container is cultured in a second small scale culture for a period of about 4 to 7 days. In some embodiments, the step of rapid expansion is split into a plurality of steps to achieve a scaling out and scaling up of the culture by: (a) performing the rapid second expansion by culturing T cells in a small scale culture in a first container, e.g., a G-REX 100MCS container, for a period of about 3 to 4 days, and then (b) effecting the transfer and apportioning of the T cells from the small scale culture into and amongst at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 second containers that are larger in size than the first container, e.g., G-REX 500MCS containers, wherein in each second container the portion of the T cells from the small scale culture transferred to such second container is cultured in a larger scale culture for a period of about 4 to 7 days. In some embodiments, the step of rapid expansion is split into a plurality of steps to achieve a scaling out and scaling up of the culture by: (a) performing the rapid second expansion by culturing T cells in a small scale culture in a first container, e.g., a G-REX 100MCS container, for a period of about 4 days, and then (b) effecting the transfer and apportioning of the T cells from the small scale

culture into and amongst 2, 3 or 4 second containers that are larger in size than the first container, e.g., G-REX 500MCS containers, wherein in each second container the portion of the T cells from the small scale culture transferred to such second container is cultured in a larger scale culture for a period of about 5 days.

[00690] In some embodiments, the rapid second expansion is performed after the activation of T cells effected by the priming first expansion begins to decrease, abate, decay or subside.

[00691] In some embodiments, the rapid second expansion is performed after the activation of T cells effected by the priming first expansion has decreased by at or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 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, or 100%.

[00692] In some embodiments, the rapid second expansion is performed after the activation of T cells effected by the priming first expansion has decreased by a percentage in the range of at or about 1% to 100%.

[00693] In some embodiments, the rapid second expansion is performed after the activation of T cells effected by the priming first expansion has decreased by a percentage in the range of at or about 1% to 10%, 10% to 20%, 20% to 30%, 30% to 40%, 40% to 50%, 50% to 60%, 60% to 70%, 70% to 80%, 80% to 90%, or 90% to 100%.

[00694] In some embodiments, the rapid second expansion is performed after the activation of T cells effected by the priming first expansion has decreased by at least at or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 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, or 99%.

[00695] In some embodiments, the rapid second expansion is performed after the activation of T cells effected by the priming first expansion has decreased by up to at or about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 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 or 100%.

[00696] In some embodiments, the decrease in the activation of T cells effected by the priming first expansion is determined by a reduction in the amount of interferon gamma released by the T cells in response to stimulation with antigen.

[00697] In some embodiments, the priming first expansion of T cells is performed during a period of up to at or about 7 days or about 8 days.

[00698] In some embodiments, the priming first expansion of T cells is performed during a period of up to at or about 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, or 8 days.

[00699] In some embodiments, the priming first expansion of T cells is performed during a period of 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, or 8 days.

[00700] In some embodiments, the rapid second expansion of T cells is performed during a period of up to at or about 11 days.

[00701] In some embodiments, the rapid second expansion of T cells is performed during a period of up to at or about 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days or 11 days.

[00702] In some embodiments, the rapid second expansion of T cells is performed during a period of 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days or 11 days.

[00703] In some embodiments, the priming first expansion of T cells is performed during a period of from at or about 1 day to at or about 7 days and the rapid second expansion of T cells is performed during a period of from at or about 1 day to at or about 11 days.

[00704] In some embodiments, the priming first expansion of T cells is performed during a period of up to at or about 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, or 8 days and the rapid second expansion of T cells is performed during a period of up to at or about 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days or 11 days.

[00705] In some embodiments, the priming first expansion of T cells is performed during a period of from at or about 1 day to at or about 8 days and the rapid second expansion of T cells is performed during a period of from at or about 1 day to at or about 9 days.

[00706] In some embodiments, the priming first expansion of T cells is performed during a period of 8 days and the rapid second expansion of T cells is performed during a period of 9 days.

[00707] In some embodiments, the priming first expansion of T cells is performed during a period of from at or about 1 day to at or about 7 days and the rapid second expansion of T cells is performed during a period of from at or about 1 day to at or about 9 days.

[00708] In some embodiments, the priming first expansion of T cells is performed during a period of 7 days and the rapid second expansion of T cells is performed during a period of 9 days.

[00709] In some embodiments, the T cells are tumor infiltrating lymphocytes (TILs).

[00710] In some embodiments, the T cells are marrow infiltrating lymphocytes (MILs).

[00711] In some embodiments, the T cells are peripheral blood lymphocytes (PBLs).

[00712] In some embodiments, the T cells are obtained from a donor suffering from a cancer.

[00713] In some embodiments, the T cells are TILs obtained from a tumor excised from a patient suffering from a cancer.

[00714] In some embodiments, the T cells are MILs obtained from bone marrow of a patient suffering from a hematologic malignancy.

[00715] In some embodiments, the T cells are PBLs obtained from peripheral blood mononuclear cells (PBMCs) from a donor. In some embodiments, the donor is suffering from a cancer. In some embodiments, the cancer is the cancer is selected from the group consisting of melanoma, ovarian cancer, endometrial cancer, thyroid cancer, cervical cancer, non-small-cell lung cancer (NSCLC), lung cancer, bladder cancer, breast cancer, cancer caused by human papilloma virus, head and neck cancer (including head and neck squamous cell carcinoma (HNSCC)), glioblastoma (including GBM), gastrointestinal cancer, renal cancer, and renal cell carcinoma. In some embodiments, the cancer is selected from the group consisting of melanoma, ovarian cancer, cervical cancer, non-small-cell lung cancer (NSCLC), lung cancer, bladder cancer, breast cancer, cancer caused by human papilloma virus, head and neck cancer (including head and neck squamous cell carcinoma (HNSCC)), glioblastoma (including GBM), gastrointestinal cancer, renal cancer, and renal cell carcinoma. In some embodiments, the donor is suffering from a tumor. In some embodiments, the tumor is a liquid tumor. In some embodiments, the tumor is a solid tumor. In some embodiments, the donor is suffering from a hematologic malignancy.

[00716] In certain aspects of the present disclosure, immune effector cells, e.g., 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, optionally, to place the cells in an appropriate buffer or media for subsequent processing steps. In one embodiment, the cells are washed with phosphate buffered saline (PBS). In an alternative embodiment, the wash solution lacks calcium and may lack magnesium or may lack many if not all divalent cations. 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 PERCOLL gradient or by counterflow centrifugal elutriation.

[00717] In some embodiments, the T cells are PBLs separated from whole blood or apheresis product enriched for lymphocytes from a donor. In some embodiments, the donor is suffering from a cancer. In some embodiments, the cancer is the cancer is selected from the group consisting of melanoma, ovarian cancer, endometrial cancer, thyroid cancer, cervical cancer, non-small-cell lung cancer (NSCLC), lung cancer, bladder cancer, breast cancer, cancer caused by human papilloma virus, head and neck cancer (including head and neck squamous cell carcinoma (HNSCC)), glioblastoma (including GBM), gastrointestinal cancer, renal cancer, and renal cell carcinoma. In some embodiments, the cancer is selected from the group consisting of melanoma, ovarian cancer, cervical cancer, non-small-cell lung cancer (NSCLC), lung cancer, bladder cancer, breast cancer, cancer caused by human papilloma virus, head and neck cancer (including head and neck squamous cell carcinoma (HNSCC)), glioblastoma (including GBM), gastrointestinal cancer, renal cancer, and renal cell carcinoma. In some embodments, the donor is suffering from a tumor. In some embodiments, the tumor is a liquid tumor. In some embodiments, the tumor is a solid tumor. In some embodiments, the donor is suffering from a hematologic malignancy. In some embodiments, the PBLs are isolated from whole blood or apheresis product enriched for lymphocytes by using positive or negative selection methods, i.e., removing the PBLs using a marker(s), e.g., CD3+ CD45+, for T cell phenotype, or removing non-T cell phenotype cells, leaving PBLs. In other embodiments, the PBLs are isolated by gradient centrifugation. Upon isolation of PBLs from donor tissue, the priming first expansion of PBLs can be initiated by

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seeding a suitable number of isolated PBLs (in some embodiments, approximately 1×10^7 PBLs) in the priming first expansion culture according to the priming first expansion step of any of the methods described herein.

[00718] An exemplary TIL process known as process 3 (also referred to herein as GEN3) containing some of these features is depicted in Figure 8 (in particular, *e.g.*, Figure 8B and/or Figure 8C), and some of the advantages of this embodiment of the present invention over process 2A are described in Figures 1, 2, 30, and 31 (in particular, *e.g.*, Figure 8B and/or Figure 8C). Two embodiments of process 3 are shown in Figures 1 and 30 (in particular, *e.g.*, Figure 8B and/or Figure 8C). Process 2A or Gen 2 is also described in U.S. Patent Publication No. 2018/0280436, incorporated by reference herein in its entirety. The Gen 3 process is also described in USSN 62/755,954 filed on November 5, 2018 (116983-5045-PR).

[00719] As discussed and generally outlined herein, TILs are taken from a patient sample and manipulated to expand their number prior to transplant into a patient using the TIL expansion process described herein and referred to as Gen 3. In some embodiments, the TILs may be optionally genetically manipulated as discussed below. In some embodiments, the TILs may be cryopreserved prior to or after expansion. Once thawed, they may also be restimulated to increase their metabolism prior to infusion into a patient.

[00720] In some embodiments, the priming first expansion (including processes referred herein as the pre-Rapid Expansion (Pre-REP), as well as processes shown in Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C) as Step B) is shortened to 1 to 8 days and the rapid second expansion (including processes referred to herein as Rapid Expansion Protocol (REP) as well as processes shown in Figure 1 (in particular, e.g., Figure 8B and/or Figure 8C) as Step D) is shortened to 1 to 9 days, as discussed in detail below as well as in the examples and figures. In some embodiments, the priming first expansion (including processes referred herein as the pre-Rapid Expansion (Pre-REP), as well as processes shown in Figure 1 (in particular, e.g., Figure 8B and/or Figure 8C) as Step B) is shortened to 1 to 8 days and the rapid second expansion (including processes referred to herein as Rapid Expansion Protocol (REP) as well as processes shown in Figure 1 (in particular, e.g., Figure 8B and/or Figure 8C) as Step D) is shortened to 1 to 8 days, as discussed in detail below as well as in the examples and figures. In some embodiments, the priming first expansion (including processes referred herein as the pre-Rapid Expansion (Pre-REP), as well as processes shown in Figure 1 (in particular, e.g., Figure 8B and/or Figure 8C) as Step B) is shortened to 1 to 7 days and the rapid second expansion (including processes referred to herein as Rapid Expansion Protocol

(REP) as well as processes shown in Figure 1 (in particular, e.g., Figure 8B and/or Figure 8C) as Step D) is shortened to 1 to 9 days, as discussed in detail below as well as in the examples and figures. In some embodiments, the priming first expansion (including processes referred herein as the pre-Rapid Expansion (Pre-REP), as well as processes shown in Figure 1 (in particular, e.g., Figure 1B and/or Figure 8C) as Step B) is 1 to 7 days and the rapid second expansion (including processes referred to herein as Rapid Expansion Protocol (REP) as well as processes shown in Figure 1 (in particular, e.g., Figure 8B and/or Figure 8C) as Step D) is 1 to 10 days, as discussed in detail below as well as in the examples and figures. In some embodiments, the priming first expansion (for example, an expansion described as Step B in Figure 1 (in particular, e.g., Figure 8B and/or Figure 8C)) is shortened to 8 days and the rapid second expansion (for example, an expansion as described in Step D in Figure 1 (in particular, e.g., Figure 8B and/or Figure 8C)) is 7 to 9 days. In some embodiments, the priming first expansion (for example, an expansion described as Step B in Figure 1 (in particular, e.g., Figure 8B and/or Figure 8C)) is 8 days and the rapid second expansion (for example, an expansion as described in Step D in Figure 1 (in particular, e.g., Figure 8B) and/or Figure 8C)) is 8 to 9 days. In some embodiments, the priming first expansion (for example, an expansion described as Step B in Figure 1 (in particular, e.g., Figure 8B and/or Figure 8C)) is shortened to 7 days and the rapid second expansion (for example, an expansion as described in Step D in Figure 1 (in particular, e.g., Figure 8B and/or Figure 8C)) is 7 to 8 days. In some embodiments, the priming first expansion (for example, an expansion described as Step B in Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C)) is shortened to 8 days and the rapid second expansion (for example, an expansion as described in Step D in Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C)) is 8 days. In some embodiments, the priming first expansion (for example, an expansion described as Step B in Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C)) is 8 days and the rapid second expansion (for example, an expansion as described in Step D in Figure 8 (in particular, e.g., Figure 8B) and/or Figure 8C)) is 9 days. In some embodiments, the priming first expansion (for example, an expansion described as Step B in Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C)) is 8 days and the rapid second expansion (for example, an expansion as described in Step D in Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C)) is 10 days. In some embodiments, the priming first expansion (for example, an expansion described as Step B in Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C)) is 7 days and the rapid second expansion (for example, an expansion as described in Step D in Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C)) is 7 to 10 days. In some embodiments, the priming first

expansion (for example, an expansion described as Step B in Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C)) is 7 days and the rapid second expansion (for example, an expansion as described in Step D in Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C)) is 8 to 10 days. In some embodiments, the priming first expansion (for example, an expansion described as Step B in Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C)) is 7 days and the rapid second expansion (for example, an expansion as described in Step D in Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C)) is 9 to 10 days. In some embodiments, the priming first expansion (for example, an expansion described as Step B in Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C)) is shortened to 7 days and the rapid second expansion (for example, an expansion as described in Step D in Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C)) is 7 to 9 days. In some embodiments, the combination of the priming first expansion and rapid second expansion (for example, expansions described as Step B and Step D in Figure 1 (in particular, e.g., Figure 1B and/or Figure 8C)) is 14-16 days, as discussed in detail below and in the examples and figures. Particularly, it is considered that certain embodiments of the present invention comprise a priming first expansion step in which TILs are activated by exposure to an anti-CD3 antibody, e.g., OKT-3 in the presence of IL-2 or exposure to an antigen in the presence of at least IL-2 and an anti-CD3 antibody e.g. OKT-3. In certain embodiments, the TILs which are activated in the priming first expansion step as described above are a first population of TILs i.e., which are a primary cell population.

[00721] The "Step" Designations A, B, C, *etc.*, below are in reference to the non-limiting example in Figure 8 (in particular, *e.g.*, Figure 8B and/or Figure 8C) and in reference to certain non-limiting embodiments described herein. The ordering of the Steps below and in Figure 8 (in particular, *e.g.*, Figure 8B and/or Figure 8C) is exemplary and any combination or order of steps, as well as additional steps, repetition of steps, and/or omission of steps is contemplated by the present application and the methods disclosed herein.

A. STEP A: Obtain Patient tumor sample

[00722] In general, TILs are initially obtained from a patient tumor sample ("primary TILs") or from circulating lymphocytes, such as peripheral blood lymphocytes, including peripheral blood lymphocytes having TIL-like characteristics, and are then expanded into a larger population for further manipulation as described herein, optionally cryopreserved, and optionally evaluated for phenotype and metabolic parameters as an indication of TIL health.

[00723] A patient tumor sample may be obtained using methods known in the art, generally via surgical resection, needle biopsy or other means for obtaining a sample that contains a mixture of tumor and TIL cells. In general, the tumor sample may be from any solid tumor, including primary tumors, invasive tumors or metastatic tumors. The tumor sample may also be a liquid tumor, such as a tumor obtained from a hematological malignancy. The solid tumor may be of any cancer type, including, but not limited to, breast, pancreatic, prostate, colorectal, lung, brain, renal, stomach, and skin (including but not limited to squamous cell carcinoma, basal cell carcinoma, and melanoma). In some embodiments, the cancer is selected from cervical cancer, head and neck cancer (including, for example, head and neck squamous cell carcinoma (HNSCC)), glioblastoma (GBM), gastrointestinal cancer, ovarian cancer, sarcoma, pancreatic cancer, bladder cancer, breast cancer, triple negative breast cancer, and non-small cell lung carcinoma. In some embodiments, useful TILs are obtained from malignant melanoma tumors, as these have been reported to have particularly high levels of TILs.

[00724] Once obtained, the tumor sample is generally fragmented using sharp dissection into small pieces of between 1 to about 8 mm³, with from about 2-3 mm³ being particularly useful. The TILs are cultured from these fragments using enzymatic tumor digests. Such tumor digests may be produced by incubation in enzymatic media (e.g., Roswell Park Memorial Institute (RPMI) 1640 buffer, 2 mM glutamate, 10 mcg/mL gentamicine, 30 units/mL of DNase and 1.0 mg/mL of collagenase) followed by mechanical dissociation (e.g., using a tissue dissociator). Tumor digests may be produced by placing the tumor in enzymatic media and mechanically dissociating the tumor for approximately 1 minute, followed by incubation for 30 minutes at 37 °C in 5% CO₂, followed by repeated cycles of mechanical dissociation and incubation under the foregoing conditions until only small tissue pieces are present. At the end of this process, if the cell suspension contains a large number of red blood cells or dead cells, a density gradient separation using FICOLL branched hydrophilic polysaccharide may be performed to remove these cells. Alternative methods known in the art may be used, such as those described in U.S. Patent Application Publication No. 2012/0244133 A1, the disclosure of which is incorporated by reference herein. Any of the foregoing methods may be used in any of the embodiments described herein for methods of expanding TILs or methods treating a cancer.

[00725] As indicated above, in some embodiments, the TILs are derived from solid tumors. In some embodiments, the solid tumors are not fragmented. In some embodiments, the solid

tumors are not fragmented and are subjected to enzymatic digestion as whole tumors. In some embodiments, the tumors are digested in in an enzyme mixture comprising collagenase, DNase, and hyaluronidase. In some embodiments, the tumors are digested in in an enzyme mixture comprising collagenase, DNase, and hyaluronidase for 1-2 hours. In some embodiments, the tumors are digested in in an enzyme mixture comprising collagenase, DNase, and hyaluronidase for 1-2 hours at 37°C, 5% CO₂. In some embodiments, the tumors are digested in in an enzyme mixture comprising collagenase, DNase, and hyaluronidase for 1-2 hours at 37°C, 5% CO₂ with rotation. In some embodiments, the tumors are digested overnight with constant rotation. In some embodiments, the tumors are digested overnight at 37°C, 5% CO₂ with constant rotation. In some embodiments, the whole tumor is combined with with the enzymes to form a tumor digest reaction mixture.

[00726] In some embodiments, the tumor is reconstituted with the lyophilized enzymes in a sterile buffer. In some embodiments, the buffer is sterile HBSS.

[00727] In some embodiments, the enxyme mixture comprises collagenase. In some embodiments, the collagenase is collagenase IV. In some embodiments, the working stock for the collagenase is a 100 mg/ml 10X working stock.

[00728] In some embodiments, the enzyme mixture comprises DNAse. In some embodiments, the working stock for the DNAse is a 10,000 IU/ml 10X working stock.

[00729] In some embodiments, the enzyme mixture comprises hyaluronidase. In some embodiments, the working stock for the hyaluronidase is a 10-mg/ml 10X working stock.

[00730] In some embodiments, the enzyme mixture comprises 10 mg/ml collagenase, 1000 IU/ml DNAse, and 1 mg/ml hyaluronidase.

[00731] In some embodiments, the enzyme mixture comprises 10 mg/ml collagenase, 500 IU/ml DNAse, and 1 mg/ml hyaluronidase.

[00732] In general, the cell suspension obtained from the tumor is called a "primary cell population" or a "freshly obtained" or a "freshly isolated" cell population. In certain embodiments, the freshly obtained cell population of TILs is exposed to a cell culture medium comprising antigen presenting cells, IL-12 and OKT-3.

[00733] In some embodiments, fragmentation includes physical fragmentation, including, for example, dissection as well as digestion. In some embodiments, the fragmentation is physical fragmentation. In some embodiments, the fragmentation is dissection. In some

embodiments, the fragmentation is by digestion. In some embodiments, TILs can be initially cultured from enzymatic tumor digests and tumor fragments obtained from patients. In an embodiment, TILs can be initially cultured from enzymatic tumor digests and tumor fragments obtained from patients.

[00734] In some embodiments, where the tumor is a solid tumor, the tumor undergoes physical fragmentation after the tumor sample is obtained in, for example, Step A (as provided in Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C)). In some embodiments, the fragmentation occurs before cryopreservation. In some embodiments, the fragmentation occurs after cryopreservation. In some embodiments, the fragmentation occurs after obtaining the tumor and in the absence of any cryopreservation. In some embodiments, the step of fragmentation is an in vitro or ex-vivo process. In some embodiments, the tumor is fragmented and 10, 20, 30, 40 or more fragments or pieces are placed in each container for the priming first expansion. In some embodiments, the tumor is fragmented and 30 or 40 fragments or pieces are placed in each container for the priming first expansion. In some embodiments, the tumor is fragmented and 40 fragments or pieces are placed in each container for the priming first expansion. In some embodiments, the multiple fragments comprise about 4 to about 50 fragments, wherein each fragment has a volume of about 27 mm³. In some embodiments, the multiple fragments comprise about 30 to about 60 fragments with a total volume of about 1300 mm³ to about 1500 mm³. In some embodiments, the multiple fragments comprise about 50 fragments with a total volume of about 1350 mm³. In some embodiments, the multiple fragments comprise about 50 fragments with a total mass of about 1 gram to about 1.5 grams. In some embodiments, the multiple fragments comprise about 4 fragments.

[00735] In some embodiments, the TILs are obtained from tumor fragments. In some embodiments, the tumor fragment is obtained by sharp dissection. In some embodiments, the tumor fragment is between about 1 mm³ and 10 mm³. In some embodiments, the tumor fragment is about 1 mm³ and 8 mm³. In some embodiments, the tumor fragment is about 2 mm³. In some embodiments, the tumor fragment is about 2 mm³. In some embodiments, the tumor fragment is about 4 mm³. In some embodiments, the tumor fragment is about 5 mm³. In some embodiments, the tumor fragment is about 5 mm³. In some embodiments, the tumor fragment is about 7 mm³. In some embodiments, the tumor fragment is about 8 mm³. In some embodiments, the tumor fragment is about 9 mm³. In some embodiments, the tumor fragment

is about 10 mm^3 . In some embodiments, the tumor fragments are $1\text{-}4 \text{ mm} \times 1\text{-}4 \text{ mm} \times 1\text{-}4$ mm. In some embodiments, the tumor fragments are $1 \text{ mm} \times 1 \text{ mm} \times 1 \text{ mm}$. In some embodiments, the tumor fragments are $2 \text{ mm} \times 2 \text{ mm} \times 2 \text{ mm}$. In some embodiments, the tumor fragments are $3 \text{ mm} \times 3 \text{ mm} \times 3 \text{ mm}$. In some embodiments, the tumor fragments are $4 \text{ mm} \times 4 \text{ mm} \times 4 \text{ mm}$.

[00736] In some embodiments, the tumors are fragmented in order to minimize the amount of hemorrhagic, necrotic, and/or fatty tissues on each piece. In some embodiments, the tumors are fragmented in order to minimize the amount of hemorrhagic tissue on each piece. In some embodiments, the tumors are fragmented in order to minimize the amount of necrotic tissue on each piece. In some embodiments, the tumors are fragmented in order to minimize the amount of fatty tissue on each piece. In certain embodiments, the step of fragmentation of the tumor is an *in vitro* or *ex-vivo* method.

[00737] In some embodiments, the tumor fragmentation is performed in order to maintain the tumor internal structure. In some embodiments, the tumor fragmentation is performed without preforming a sawing motion with a scalpel. In some embodiments, the TILs are obtained from tumor digests. In some embodiments, tumor digests were generated by incubation in enzyme media, for example but not limited to RPMI 1640, 2 mM GlutaMAX, 10 mg/mL gentamicin, 30 U/mL DNase, and 1.0 mg/mL collagenase, followed by mechanical dissociation (GentleMACS, Miltenyi Biotec, Auburn, CA). After placing the tumor in enzyme media, the tumor can be mechanically dissociated for approximately 1 minute. The solution can then be incubated for 30 minutes at 37 °C in 5% CO₂ and it then mechanically disrupted again for approximately 1 minute. After being incubated again for 30 minutes at 37 °C in 5% CO₂, the tumor can be mechanically disrupted a third time for approximately 1 minute. In some embodiments, after the third mechanical disruption if large pieces of tissue were present, 1 or 2 additional mechanical dissociations were applied to the sample, with or without 30 additional minutes of incubation at 37 °C in 5% CO₂. In some embodiments, at the end of the final incubation if the cell suspension contained a large number of red blood cells or dead cells, a density gradient separation using Ficoll can be performed to remove these cells.

[00738] In some embodiments, the cell suspension prior to the priming first expansion step is called a "primary cell population" or a "freshly obtained" or "freshly isolated" cell population.

[00739] In some embodiments, cells can be optionally frozen after sample isolation (*e.g.*, after obtaining the tumor sample and/or after obtaining the cell suspension from the tumor sample) and stored frozen prior to entry into the expansion described in Step B, which is described in further detail below, as well as exemplified in Figure 8 (in particular, *e.g.*, Figure 8B).

1. <u>Core/Small Biopsy Derived TILS</u>

[00740] In some embodiments, TILs are initially obtained from a patient tumor sample ("primary TILs") obtained by a core biopsy or similar procedure and then expanded into a larger population for further manipulation as described herein, optionally cryopreserved, and optionally evaluated for phenotype and metabolic parameters.

[00741] In some emboidments, a patient tumor sample may be obtained using methods known in the art, generally via small biopsy, core biopsy, needle biopsy or other means for obtaining a sample that contains a mixture of tumor and TIL cells. In general, the tumor sample may be from any solid tumor, including primary tumors, invasive tumors or metastatic tumors. The tumor sample may also be a liquid tumor, such as a tumor obtained from a hematological malignancy. In some embodiments, the sample can be from multiple small tumor samples or biopsies. In some embodiments, the sample can comprise multiple tumor samples from a single tumor from the same patient. In some embodiments, the sample can comprise multiple tumor samples from one, two, three, or four tumors from the same patient. In some embodiments, the sample can comprise multiple tumor samples from multiple tumors from the same patient. The solid tumor may of lung and/or non-small cell lung carcinoma (NSCLC).

[00742] In general, the cell suspension obtained from the tumor core or fragment is called a "primary cell population" or a "freshly obtained" or a "freshly isolated" cell population. In certain embodiments, the freshly obtained cell population of TILs is exposed to a cell culture medium comprising antigen presenting cells, IL-2 and OKT-3.

[00743] In some embodiments, if the tumor is metastatic and the primary lesion has been efficiently treated/removed in the past, removal of one of the metastatic lesions may be needed. In some embodiments, the least invasive approach is to remove a skin lesion, or a lymph node on the neck or axillary area when available. In some embodiments, a skin lesion is removed or small biopsy thereof is removed. In some embodiments, a lymph node or small

biopsy thereof is removed. In some embodiments, a lung or liver metastatic lesion, or an intra-abdominal or thoracic lymph node or small biopsy can thereof can be employed.

[00744] In some embodiments, the tumor is a melanoma. In some embodiments, the small biopsy for a melanoma comprises a mole or portion thereof.

[00745] In some embodiments, the small biopsy is a punch biopsy. In some embodiments, the punch biopsy is obtained with a circular blade pressed into the skin. In some embodiments, the punch biopsy is obtained with a circular blade pressed into the skin. around a suspicious mole. In some embodiments, the punch biopsy is obtained with a circular blade pressed into the skin, and a round piece of skin is removed. In some embodiments, the small biopsy is a punch biopsy and round portion of the tumor is removed.

[00746] In some embodiments, the small biopsy is an excisional biopsy. In some embodiments, the small biopsy is an excisional biopsy and the entire mole or growth is removed. In some embodiments, the small biopsy is an excisional biopsy and the entire mole or growth is removed along with a small border of normal-appearing skin.

[00747] In some embodiments, the small biopsy is an incisional biopsy. In some embodiments, the small biopsy is an incisional biopsy and only the most irregular part of a mole or growth is taken. In some embodiments, the small biopsy is an incisional biopsy and the incisional biopsy is used when other techniques can't be completed, such as if a suspicious mole is very large.

[00748] In some embodiments, the small biopsy is a lung biopsy. In some embodiments, the small biopsy is obtained by bronchoscopy. Generally, bronchoscopy, the patient is put under anesthesia, and a small tool goes through the nose or mouth, down the throat, and into the bronchial passages, where small tools are used to remove some tissue. In some embodiments, where the tumor or growth cannot be reached via bronchoscopy, a transthoracic needle biopsy can be employed. Generally, for a transthoracic needle biopsy, the patient is also under anesthesia and a needle is inserted through the skin directly into the suspicious spot to remove a small sample of tissue. In some embodiments, a transthoracic needle biopsy may require interventional radiology (for example, the use of x-rays or CT scan to guide the needle). In some embodiments, the small biopsy is obtained by needle biopsy. In some embodiments, the small biopsy is obtained endoscopic ultrasound (for example, an endoscope with a light and is placed through the mouth into the esophagus). In some embodiments, the small biopsy is obtained surgically.

[00749] In some embodiments, the small biopsy is a head and neck biopsy. In some embodiments, the small biopsy is an incisional biopsy. In some embodiments, the small biopsy is an incisional biopsy, wherein a small piece of tissue is cut from an abnormal-looking area. In some embodiments, if the abnormal region is easily accessed, the sample may be taken without hospitalization. In some embodiments, if the tumor is deeper inside the mouth or throat, the biopsy may need to be done in an operating room, with general anesthesia. In some embodiments, the small biopsy is an excisional biopsy. In some embodiments, the small biopsy is an excisional biopsy, wherein the whole area is removed. In some embodiments, the small biopsy is a fine needle aspiration (FNA). In some embodiments, the small biopsy is a fine needle aspiration (FNA), wherein a very thin needle attached to a syringe is used to extract (aspirate) cells from a tumor or lump. In some embodiments, the small biopsy is a punch biopsy. In some embodiments, the small biopsy is a punch biopsy, wherein punch forceps are used to remove a piece of the suspicious area.

[00750] In some embodiments, the small biopsy is a cervical biopsy. In some embodiments, the small biopsy is obtained via colposcopy. Generally, colposcopy methods employ the use of a lighted magnifying instrument attached to magnifying binoculars (a colposcope) which is then used to biopsy a small section of the surface of the cervix. In some embodiments, the small biopsy is a conization/cone biopsy. In some embodiments, the small biopsy is a conization/cone biopsy, wherein an outpatient surgery may be needed to remove a larger piece of tissue from the cervix. In some embodiments, the cone biopsy, in addition to helping to confirm a diagnosis, a cone biopsy can serve as an initial treatment.

[00751] The term "solid tumor" refers to an abnormal mass of tissue that usually does not contain cysts or liquid areas. Solid tumors may be benign or malignant. The term "solid tumor cancer refers to malignant, neoplastic, or cancerous solid tumors. Solid tumor cancers include cancers of the lung. In some embodiments, the cancer is non-small cell lung carcinoma (NSCLC). The tissue structure of solid tumors includes interdependent tissue compartments including the parenchyma (cancer cells) and the supporting stromal cells in which the cancer cells are dispersed and which may provide a supporting microenvironment.

[00752] In some embodiments, the sample from the tumor is obtained as a fine needle aspirate (FNA), a core biopsy, a small biopsy (including, for example, a punch biopsy). In some embodiments, sample is placed first into a G-Rex 10. In some embodiments, sample is placed first into a G-Rex 10 when there are 1 or 2 core biopsy and/or small biopsy samples. In some embodiments, sample is placed first into a G-Rex 100 when there are 3, 4, 5, 6, 8, 9,

or 10 or more core biopsy and/or small biopsy samples. In some embodiments, sample is placed first into a G-Rex 500 when there are 3, 4, 5, 6, 8, 9, or 10 or more core biopsy and/or small biopsy samples.

[00753] The FNA can be obtained from a lung tumor, including, for example, an NSCLC. In some embodiments, the FNA is obtained from a lung tumor, such as a lung tumor from a patient with non-small cell lung cancer (NSCLC). In some cases, the patient with NSCLC has previously undergone a surgical treatment.

[00754] TILs described herein can be obtained from an FNA sample. In some cases, the FNA sample is obtained or isolated from the patient using a fine gauge needle ranging from an 18 gauge needle to a 25 gauge needle. The fine gauge needle can be 18 gauge, 19 gauge, 20 gauge, 21 gauge, 22 gauge, 23 gauge, 24 gauge, or 25 gauge. In some embodiments, the FNA sample from the patient can contain at least 400,000 TILs, *e.g.*, 400,000 TILs, 450,000 TILs, 500,000 TILs, 550,000 TILs, 600,000 TILs, 650,000 TILs, 700,000 TILs, 750,000 TILs, 800,000 TILs, 850,000 TILs, 900,000 TILs, 950,000 TILs, or more.

[00755] In some cases, the TILs described herein are obtained from a core biopsy sample. In some cases, the core biopsy sample is obtained or isolated from the patient using a surgical or medical needle ranging from an 11 gauge needle to a 16 gauge needle. The needle can be 11 gauge, 12 gauge, 13 gauge, 14 gauge, 15 gauge, or 16 gauge. In some embodiments, the core biopsy sample from the patient can contain at least 400,000 TILs, *e.g.*, 400,000 TILs, 450,000 TILs, 500,000 TILs, 550,000 TILs, 600,000 TILs, 650,000 TILs, 700,000 TILs, 750,000 TILs, 800,000 TILs, 850,000 TILs, 900,000 TILs, 950,000 TILs, or more.

[00756] In general, the harvested cell suspension is called a "primary cell population" or a "freshly harvested" cell population.

[00757] In some embodiments, the TILs are not obtained from tumor digests. In some embodiments, the solid tumor cores are not fragmented.

[00758] In some embodiments, the TILs are obtained from tumor digests. In some embodiments, tumor digests were generated by incubation in enzyme media, for example but not limited to RPMI 1640, 2mM GlutaMAX, 10 mg/mL gentamicin, 30 U/mL DNase, and 1.0 mg/mL collagenase, followed by mechanical dissociation (GentleMACS, Miltenyi Biotec, Auburn, CA). After placing the tumor in enzyme media, the tumor can be mechanically dissociated for approximately 1 minute. The solution can then be incubated for 30 minutes at 37 °C in 5% CO₂ and it then mechanically disrupted again for approximately 1

minute. After being incubated again for 30 minutes at 37 °C in 5% CO₂, the tumor can be mechanically disrupted a third time for approximately 1 minute. In some embodiments, after the third mechanical disruption if large pieces of tissue were present, 1 or 2 additional mechanical dissociations were applied to the sample, with or without 30 additional minutes of incubation at 37 °C in 5% CO₂. In some embodiments, at the end of the final incubation if the cell suspension contained a large number of red blood cells or dead cells, a density gradient separation using Ficoll can be performed to remove these cells.

2. <u>Methods of Expanding Peripheral Blood Lymphocytes (PBLs) from Peripheral Blood</u>

[00759] PBL Method 1. In an embodiment of the invention, PBLs are expanded using the processes described herein. In an embodiment of the invention, the method comprises obtaining a PBMC sample from whole blood. In an embodiment, the method comprises enriching T-cells by isolating pure T-cells from PBMCs using negative selection of a non-CD19+ fraction. In an embodiment, the method comprises enriching T-cells by isolating pure T-cells from PBMCs using magnetic bead-based negative selection of a non-CD19+ fraction.

[00760] In an embodiment of the invention, PBL Method 1 is performed as follows: On Day 0, a cryopreserved PBMC sample is thawed and PBMCs are counted. T-cells are isolated using a Human Pan T-Cell Isolation Kit and LS columns (Miltenyi Biotec).

[00761] PBL Method 2. In an embodiment of the invention, PBLs are expanded using PBL Method 2, which comprises obtaining a PBMC sample from whole blood. The T-cells from the PBMCs are enriched by incubating the PBMCs for at least three hours at 37°C and then isolating the non-adherent cells.

[00762] In an embodiment of the invention, PBL Method 2 is performed as follows: On Day 0, the cryopreserved PMBC sample is thawed and the PBMC cells are seeded at 6 million cells per well in a 6 well plate in CM-2 media and incubated for 3 hours at 37 degrees Celsius. After 3 hours, the non-adherent cells, which are the PBLs, are removed and counted.

[00763] PBL Method 3. In an embodiment of the invention, PBLs are expanded using PBL Method 3, which comprises obtaining a PBMC sample from peripheral blood. B-cells are isolated using a CD19+ selection and T-cells are selected using negative selection of the non-CD19+ fraction of the PBMC sample.

[00764] In an embodiment of the invention, PBL Method 3 is performed as follows: On Day 0, cryopreserved PBMCs derived from peripheral blood are thawed and counted. CD19+ B-cells are sorted using a CD19 Multisort Kit, Human (Miltenyi Biotec). Of the non-CD19+ cell fraction, T-cells are purified using the Human Pan T-cell Isolation Kit and LS Columns (Miltenyi Biotec).

[00765] In an embodiment, PBMCs are isolated from a whole blood sample. In an embodiment, the PBMC sample is used as the starting material to expand the PBLs. In an embodiment, the sample is cryopreserved prior to the expansion process. In another embodiment, a fresh sample is used as the starting material to expand the PBLs. In an embodiment of the invention, T-cells are isolated from PBMCs using methods known in the art. In an embodiment, the T-cells are isolated using a Human Pan T-cell isolation kit and LS columns. In an embodiment of the invention, T-cells are isolated from PBMCs using antibody selection methods known in the art, for example, CD19 negative selection.

[00766] In an embodiment of the invention, the PBMC sample is incubated for a period of time at a desired temperature effective to identify the non-adherent cells. In an embodiment of the invention, the incubation time is about 3 hours. In an embodiment of the invention, the temperature is about 37° Celsius. The non-adherent cells are then expanded using the process described above.

[00767] In some embodiments, the PBMC sample is from a subject or patient who has been optionally pre-treated with a regimen comprising a kinase inhibitor or an ITK inhibitor. In some embodiments, the tumor sample is from a subject or patient who has been pre-treated with a regimen comprising a kinase inhibitor or an ITK inhibitor. In some embodiments, the PBMC sample is from a subject or patient who has been pre-treated with a regimen comprising a kinase inhibitor or an ITK inhibitor, has undergone treatment for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, or 1 year or more. In another embodiment, the PBMCs are derived from a patient who is currently on an ITK inhibitor regimen, such as ibrutinib.

[00768] In some embodiments, the PBMC sample is from a subject or patient who has been pre-treated with a regimen comprising a kinase inhibitor or an ITK inhibitor and is refractory to treatment with a kinase inhibitor or an ITK inhibitor, such as ibrutinib.

[00769] In some embodiments, the PBMC sample is from a subject or patient who has been pre-treated with a regimen comprising a kinase inhibitor or an ITK inhibitor but is no longer

undergoing treatment with a kinase inhibitor or an ITK inhibitor. In some embodiments, the PBMC sample is from a subject or patient who has been pre-treated with a regimen comprising a kinase inhibitor or an ITK inhibitor but is no longer undergoing treatment with a kinase inhibitor or an ITK inhibitor and has not undergone treatment for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, or at least 1 year or more. In another embodiment, the PBMCs are derived from a patient who has prior exposure to an ITK inhibitor, but has not been treated in at least 3 months, at least 6 months, at least 9 months, or at least 1 year.

[00770] In an embodment of the invention, at Day 0, cells are selected for CD19+ and sorted accordingly. In an embodiment of the invention, the selection is made using antibody binding beads. In an embodiment of the invention, pure T-cells are isolated on Day 0 from the PBMCs.

[00771] In an embodiment of the invention, for patients that are not pre-treated with ibrutinib or other ITK inhibitor, 10-15ml of Buffy Coat will yield about 5×10^9 PBMC, which, in turn, will yield about 5.5×10^7 PBLs.

[00772] In an embodiment of the invention, for patients that are pre-treated with ibrutinib or other ITK inhibitor, the expansion process will yield about 20×10^9 PBLs. In an embodiment of the invention, 40.3×10^6 PBMCs will yield about 4.7×10^5 PBLs.

[00773] In any of the foregoing embodiments, PBMCs may be derived from a whole blood sample, by apheresis, from the buffy coat, or from any other method known in the art for obtaining PBMCs.

3. <u>Methods of Expanding Marrow Infiltrating Lymphocytes (MILs) from PBMCs Derived from Bone Marrow</u>

[00774] MIL Method 3. In an embodiment of the invention, the method comprises obtaining PBMCs from the bone marrow. On Day 0, the PBMCs are selected for CD3+/CD33+/CD20+/CD14+ and sorted, and the non-CD3+/CD33+/CD20+/CD14+ cell fraction is sonicated and a portion of the sonicated cell fraction is added back to the selected cell fraction.

[00775] In an embodiment of the invention, MIL Method 3 is performed as follows: On Day 0, a cryopreserved sample of PBMCs is thawed and PBMCs are counted. The cells are stained with CD3, CD33, CD20, and CD14 antibodies and sorted using a S3e cell sorted (Bio-Rad). The cells are sorted into two fractions – an immune cell fraction (or the MIL fraction) (CD3+CD33+CD20+CD14+) and an AML blast cell fraction (non-CD3+CD33+CD20+CD14+).

[00776] In an embodiment of the invention, PBMCs are obtained from bone marrow. In an embodiment, the PBMCs are obtained from the bone marrow through apheresis, aspiration, needle biopsy, or other similar means known in the art. In an embodiment, the PBMCs are fresh. In another embodiment, the PBMCs are cryopreserved.

[00777] In an embodiment of the invention, MILs are expanded from 10-50 ml of bone marrow aspirate. In an embodiment of the invention, 10ml of bone marrow aspirate is obtained from the patient. In another embodiment, 20ml of bone marrow aspirate is obtained from the patient. In another embodiment, 30ml of bone marrow aspirate is obtained from the patient. In another embodiment, 40ml of bone marrow aspirate is obtained from the patient. In another embodiment, 50ml of bone marrow aspirate is obtained from the patient.

[00778] In an embodiment of the invention, the number of PBMCs yielded from about 10-50ml of bone marrow aspirate is about 5×10^7 to about 10×10^7 PBMCs. In another embodiment, the number of PMBCs yielded is about 7×10^7 PBMCs.

[00779] In an embodiment of the invention, about 5×10^7 to about 10×10^7 PBMCs, yields about 0.5×10^6 to about 1.5×10^6 MILs. In an embodiment of the invention, about 1×10^6 MILs is yielded.

[00780] In an embodiment of the invention, 12×10^6 PBMC derived from bone marrow aspirate yields approximately 1.4×10^5 MILs.

[00781] In any of the foregoing embodiments, PBMCs may be derived from a whole blood sample, from bone marrow, by apheresis, from the buffy coat, or from any other method known in the art for obtaining PBMCs.

B. STEP B: Priming First Expansion

[00782] In some embodiments, the present methods provide for younger TILs, which may provide additional therapeutic benefits over older TILs (i.e., TILs which have further

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undergone more rounds of replication prior to administration to a subject/patient). Features of young TILs have been described in the literature, for example Donia, at al., Scandinavian Journal of Immunology, 75:157-167 (2012); Dudley et al., Clin Cancer Res, 16:6122-6131 (2010); Huang et al., J Immunother, 28(3):258–267 (2005); Besser et al., Clin Cancer Res, 19(17):OF1-OF9 (2013); Besser et al., J Immunother 32:415–423 (2009); Robbins, et al., J *Immunol* 2004; 173:7125-7130; Shen et al., J Immunother, 30:123–129 (2007); Zhou, et al., J Immunother, 28:53-62 (2005); and Tran, et al., J Immunother, 31:742-751 (2008), all of which are incorporated herein by reference in their entireties.

[00783] After dissection or digestion of tumor fragments and/or tumor fragments, for example such as described in Step A of Figure 1 (in particular, e.g., Figure 1B and/or Figure 8C), the resulting cells are cultured in serum containing IL-2, OKT-3, and feeder cells (e.g., antigen-presenting feeder cells), under conditions that favor the growth of TILs over tumor and other cells. In some embodiments, the IL-2, OKT-3, and feeder cells are added at culture initiation along with the tumor digest and/or tumor fragments (e.g., at Day 0). In some embodiments, the tumor digests and/or tumor fragments are incubated in a container with up to 60 fragments per container and with 6000 IU/mL of IL-2. In some embodiments, this primary cell population is cultured for a period of days, generally from 1 to 8 days, resulting in a bulk TIL population, generally about 1×10^8 bulk TIL cells. In some embodiments, this primary cell population is cultured for a period of days, generally from 1 to 7 days, resulting in a bulk TIL population, generally about 1×10^8 bulk TIL cells. In some embodiments, priming first expansion occurs for a period of 1 to 8 days, resulting in a bulk TIL population, generally about 1×10^8 bulk TIL cells. In some embodiments, priming first expansion occurs for a period of 1 to 7 days, resulting in a bulk TIL population, generally about 1×10^8 bulk TIL cells. In some embodiments, this priming first expansion occurs for a period of 5 to 8 days, resulting in a bulk TIL population, generally about 1×10^8 bulk TIL cells. In some embodiments, this priming first expansion occurs for a period of 5 to 7 days, resulting in a bulk TIL population, generally about 1×10^8 bulk TIL cells. In some embodiments, this priming first expansion occurs for a period of about 6 to 8 days, resulting in a bulk TIL population, generally about 1×10^8 bulk TIL cells. In some embodiments, this priming first expansion occurs for a period of about 6 to 7 days, resulting in a bulk TIL population, generally about 1×10^8 bulk TIL cells. In some embodiments, this priming first expansion occurs for a period of about 7 to 8 days, resulting in a bulk TIL population, generally about 1 × 10⁸ bulk TIL cells. In some embodiments, this priming first expansion occurs for a period

of about 7 days, resulting in a bulk TIL population, generally about 1×10^8 bulk TIL cells. In some embodiments, this priming first expansion occurs for a period of about 8 days, resulting in a bulk TIL population, generally about 1×10^8 bulk TIL cells.

[00784] In a preferred embodiment, expansion of TILs may be performed using a priming first expansion step (for example such as those described in Step B of Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C), which can include processes referred to as pre-REP or priming REP and which contains feeder cells from Day 0 and/or from culture initiation) as described below and herein, followed by a rapid second expansion (Step D, including processes referred to as rapid expansion protocol (REP) steps) as described below under Step D and herein, followed by optional cryopreservation, and followed by a second Step D (including processes referred to as restimulation REP steps) as described below and herein. The TILs obtained from this process may be optionally characterized for phenotypic characteristics and metabolic parameters as described herein. In some embodiments, the tumor fragment is between about 1 mm³ and 10 mm³.

[00785] In some embodiments, the first expansion culture medium is referred to as "CM", an abbreviation for culture media. In some embodiments, CM for Step B consists of RPMI 1640 with GlutaMAX, supplemented with 10% human AB serum, 25 mM Hepes, and 10 mg/mL gentamicin.

[00786] In some embodiments, there are less than or equal to 240 tumor fragments. In some embodiments, there are less than or equal to 240 tumor fragments placed in less than or equal to 4 containers. In some embodiments, the containers are GREX100 MCS flasks. In some embodiments, less than or equal to 60 tumor fragments are placed in 1 container. In some embodiments, each container comprises less than or equal to 500 mL of media per container. In some embodiments, the media comprises IL-2. In some embodiments, the media comprises antigen-presenting feeder cells (also referred to herein as "antigen-presenting cells"). In some embodiments, the media comprises 2.5×10^8 antigen-presenting feeder cells per container. In some embodiments, the media comprises 30 ng/mL of OKT-3 per container. In some embodiments, the container is a GREX100 MCS flask. In some embodiments, the media comprises 6000 IU/mL of IL-2, 30 ng of OKT-3, and 2.5×10^8 antigen-presenting feeder cells. In some embodiments, the media comprises 6000 IU/mL of IL-2, 30 ng of OKT-3, and 2.5×10^8 antigen-presenting feeder cells. In some embodiments, the media comprises 6000 IU/mL of IL-2, 30 ng/mL of OKT-3, and 2.5×10^8 antigen-presenting feeder cells per container.

[00787] After preparation of the tumor fragments, the resulting cells (i.e., fragments which is a primary cell population) are cultured in media containing IL-2, antigen-presenting feeder cells and OKT-3 under conditions that favor the growth of TILs over tumor and other cells and which allow for TIL priming and accelerated growth from initiation of the culture on Day 0. In some embodiments, the tumor digests and/or tumor fragments are incubated in with 6000 IU/mL of IL-2, as well as antigen-presenting feeder cells and OKT-3. This primary cell population is cultured for a period of days, generally from 1 to 8 days, resulting in a bulk TIL population, generally about 1×10^8 bulk TIL cells. In some embodiments, the growth media during the priming first expansion comprises IL-2 or a variant thereof, as well as antigenpresenting feeder cells and OKT-3. In some embodiments, this primary cell population is cultured for a period of days, generally from 1 to 7 days, resulting in a bulk TIL population, generally about 1×10^8 bulk TIL cells. In some embodiments, the growth media during the priming first expansion comprises IL-2 or a variant thereof, as well as antigen-presenting feeder cells and OKT-3. In some embodiments, the IL-2 is recombinant human IL-2 (rhIL-2). In some embodiments the IL-2 stock solution has a specific activity of 20-30×10⁶ IU/mg for a 1 mg vial. In some embodiments the IL-2 stock solution has a specific activity of 20×10^6 IU/mg for a 1 mg vial. In some embodiments the IL-2 stock solution has a specific activity of 25×10⁶ IU/mg for a 1 mg vial. In some embodiments the IL-2 stock solution has a specific activity of 30×10^6 IU/mg for a 1 mg vial. In some embodiments, the IL- 2 stock solution has a final concentration of 4-8×10⁶ IU/mg of IL-2. In some embodiments, the IL-2 stock solution has a final concentration of 5-7×10⁶ IU/mg of IL-2. In some embodiments, the IL-2 stock solution has a final concentration of 6×10⁶ IU/mg of IL-2. In some embodiments, the IL-2 stock solution is prepare as described in Example C. In some embodiments, the priming first expansion culture media comprises about 10,000 IU/mL of IL-2, about 9,000 IU/mL of IL-2, about 8,000 IU/mL of IL-2, about 7,000 IU/mL of IL-2, about 6000 IU/mL of IL-2 or about 5,000 IU/mL of IL-2. In some embodiments, the priming first expansion culture media comprises about 9,000 IU/mL of IL-2 to about 5,000 IU/mL of IL-2. In some embodiments, the priming first expansion culture media comprises about 8,000 IU/mL of IL-2 to about 6,000 IU/mL of IL-2. In some embodiments, the priming first expansion culture media comprises about 7,000 IU/mL of IL-2 to about 6,000 IU/mL of IL-2. In some embodiments, the priming first expansion culture media comprises about 6,000 IU/mL of IL-2. In an embodiment, the cell culture medium further comprises IL-2. In some embodiments, the priming first expansion cell culture medium comprises about 3000 IU/mL of IL-2. In an embodiment, the priming first expansion cell culture medium further comprises IL-2. In a

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preferred embodiment, the priming first expansion cell culture medium comprises about 3000 IU/mL of IL-2. In an embodiment, the priming first expansion cell culture medium comprises about 1000 IU/mL, about 1500 IU/mL, about 2000 IU/mL, about 2500 IU/mL, about 3000 IU/mL, about 3500 IU/mL, about 4000 IU/mL, about 4500 IU/mL, about 5000 IU/mL, about 5500 IU/mL, about 6000 IU/mL, about 6500 IU/mL, about 7000 IU/mL, about 7500 IU/mL, or about 8000 IU/mL of IL-2. In an embodiment, the priming first expansion cell culture medium comprises between 1000 and 2000 IU/mL, between 2000 and 3000 IU/mL, between 3000 and 4000 IU/mL, between 4000 and 5000 IU/mL, between 5000 and 6000 IU/mL, between 6000 and 7000 IU/mL, between 7000 and 8000 IU/mL, or about 8000 IU/mL of IL-2.

[00788] In some embodiments, priming first expansion culture media comprises about 500 IU/mL of IL-15, about 400 IU/mL of IL-15, about 300 IU/mL of IL-15, about 200 IU/mL of IL-15, about 180 IU/mL of IL-15, about 160 IU/mL of IL-15, about 140 IU/mL of IL-15, about 120 IU/mL of IL-15, or about 100 IU/mL of IL-15. In some embodiments, the priming first expansion culture media comprises about 500 IU/mL of IL-15 to about 100 IU/mL of IL-15. In some embodiments, the priming first expansion culture media comprises about 400 IU/mL of IL-15 to about 100 IU/mL of IL-15. In some embodiments, the priming first expansion culture media comprises about 300 IU/mL of IL-15 to about 100 IU/mL of IL-15. In some embodiments, the priming first expansion culture media comprises about 200 IU/mL of IL-15. In some embodiments, the priming first expansion cell culture medium comprises about 180 IU/mL of IL-15. In an embodiment, the priming first expansion cell culture medium further comprises IL-15. In a preferred embodiment, the priming first expansion cell culture medium comprises about 180 IU/mL of IL-15.

[00789] In some embodiments, priming first expansion culture media comprises about 20 IU/mL of IL-21, about 15 IU/mL of IL-21, about 12 IU/mL of IL-21, about 10 IU/mL of IL-21, about 5 IU/mL of IL-21, about 4 IU/mL of IL-21, about 3 IU/mL of IL-21, about 2 IU/mL of IL-21, about 1 IU/mL of IL-21, or about 0.5 IU/mL of IL-21. In some embodiments, the priming first expansion culture media comprises about 20 IU/mL of IL-21 to about 0.5 IU/mL of IL-21. In some embodiments, the priming first expansion culture media comprises about 15 IU/mL of IL-21 to about 0.5 IU/mL of IL-21. In some embodiments, the priming first expansion culture media comprises about 12 IU/mL of IL-21 to about 0.5 IU/mL of IL-21. In some embodiments, the priming first expansion culture media comprises about 10 IU/mL of IL-21 to about 0.5 IU/mL of IL-21. In some embodiments, the priming first

expansion culture media comprises about 5 IU/mL of IL-21 to about 1 IU/mL of IL-21. In some embodiments, the priming first expansion culture media comprises about 2 IU/mL of IL-21. In some embodiments, the priming first expansion cell culture medium comprises about 1 IU/mL of IL-21. In some embodiments, the priming first expansion cell culture medium comprises about 0.5 IU/mL of IL-21. In an embodiment, the cell culture medium further comprises IL-21. In a preferred embodiment, the priming first expansion cell culture medium comprises about 1 IU/mL of IL-21.

[00790] In an embodiment, the priming first expansion cell culture medium comprises OKT-3 antibody. In some embodiments, the priming first expansion cell culture medium comprises about 30 ng/mL of OKT-3 antibody. In an embodiment, the priming first expansion cell culture medium comprises about 0.1 ng/mL, about 0.5 ng/mL, about 1 ng/mL, about 2.5 ng/mL, about 5 ng/mL, about 7.5 ng/mL, about 10 ng/mL, about 15 ng/mL, about 20 ng/mL, about 25 ng/mL, about 30 ng/mL, about 35 ng/mL, about 40 ng/mL, about 50 ng/mL, about 60 ng/mL, about 70 ng/mL, about 80 ng/mL, about 90 ng/mL, about 100 ng/mL, about 200 ng/mL, about 500 ng/mL, and about 1 μg/mL of OKT-3 antibody. In an embodiment, the cell culture medium comprises between 0.1 ng/mL and 1 ng/mL, between 1 ng/mL and 5 ng/mL and 30 ng/mL and 10 ng/mL and 40 ng/mL, between 40 ng/mL and 50 ng/mL, and between 50 ng/mL and 100 ng/mL of OKT-3 antibody. In an embodiment, the cell culture medium comprises between 15 ng/ml and 30 ng/mL of OKT-3 antibody. In an embodiment, the cell culture medium comprises between 15 ng/ml and 30 ng/mL of OKT-3 antibody. In some embodiments, the OKT-3 antibody is muromonab.

TABLE 19: Amino acid sequences of muromonab (exemplary OKT-3 antibody)

Identifier	Sequence (One-Letter Amino Acid Symbols)			
SEQ ID NO:1	QVQLQQSGAE LARPGASVKM SCKASGYTFT	RYTMHWVKQR PGQGLEWIGY INPSRGYTNY	60	
Muromonab heavy	NQKFKDKATL TTDKSSSTAY MQLSSLTSED	SAVYYCARYY DDHYCLDYWG QGTTLTVSSA	120	
chain	KTTAPSVYPL APVCGGTTGS SVTLGCLVKG	YFPEPVTLTW NSGSLSSGVH TFPAVLQSDL	180	
	YTLSSSVTVT SSTWPSQSIT CNVAHPASST	KVDKKIEPRP KSCDKTHTCP PCPAPELLGG	240	
	PSVFLFPPKP KDTLMISRTP EVTCVVVDVS	HEDPEVKFNW YVDGVEVHNA KTKPREEQYN	300	
	STYRVVSVLT VLHQDWLNGK EYKCKVSNKA	LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE	360	
	LTKNQVSLTC LVKGFYPSDI AVEWESNGQE	ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW	420	
	QQGNVFSCSV MHEALHNHYT QKSLSLSPGK		450	
SEQ ID NO:2	QIVLTQSPAI MSASPGEKVT MTCSASSSVS	YMNWYQQKSG TSPKRWIYDT SKLASGVPAH	60	
Muromonab light	FRGSGSGTSY SLTISGMEAE DAATYYCQQW	SSNPFTFGSG TKLEINRADT APTVSIFPPS	120	
chain	SEQLTSGGAS VVCFLNNFYP KDINVKWKII	GSERQNGVLN SWTDQDSKDS TYSMSSTLTL	180	
	TKDEYERHNS YTCEATHKTS TSPIVKSFNF	NEC	213	

[00791] In some embodiments, the priming first expansion cell culture medium comprises one or more TNFRSF agonists in a cell culture medium. In some embodiments, the TNFRSF agonist comprises a 4-1BB agonist. In some embodiments, the TNFRSF agonist is a 4-1BB agonist, and the 4-1BB agonist is selected from the group consisting of urelumab, utomilumab, EU-101, a fusion protein, and fragments, derivatives, variants, biosimilars, and combinations thereof. In some embodiments, the TNFRSF agonist is added at a concentration sufficient to achieve a concentration in the cell culture medium of between 0.1 μ g/mL and 100 μ g/mL. In some embodiments, the TNFRSF agonist is added at a concentration sufficient to achieve a concentration in the cell culture medium of between 20 μ g/mL and 40 μ g/mL.

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[00792] In some embodiments, in addition to one or more TNFRSF agonists, the priming first expansion cell culture medium further comprises IL-2 at an initial concentration of about 3000 IU/mL and OKT-3 antibody at an initial concentration of about 30 ng/mL, and wherein the one or more TNFRSF agonists comprises a 4-1BB agonist. In some embodiments, in addition to one or more TNFRSF agonists, the priming first expansion cell culture medium further comprises IL-2 at an initial concentration of about 6000 IU/mL and OKT-3 antibody at an initial concentration of about 30 ng/mL, and wherein the one or more TNFRSF agonists comprises a 4-1BB agonist.

[00793] In some embodiments, the priming first expansion culture medium is referred to as "CM", an abbreviation for culture media. In some embodiments, it is referred to as CM1 (culture medium 1). In some embodiments, CM consists of RPMI 1640 with GlutaMAX, supplemented with 10% human AB serum, 25 mM Hepes, and 10 mg/mL gentamicin. In some embodiments, the CM is the CM1 described in the Examples, *see*, Example A. In some embodiments, the priming first expansion occurs in an initial cell culture medium or a first cell culture medium. In some embodiments, the priming first expansion culture medium or the initial cell culture medium or the first cell culture medium comprises IL-2, OKT-3 and antigen-presenting feeder cells (also referred to herein as feeder cells).

[00794] In some embodiments, the culture medium used in the expansion processes disclosed herein is a serum-free medium or a defined medium. In some embodiments, the serum-free or defined medium comprises a basal cell medium and a serum supplement and/or a serum replacement. In some embodiments, the serum-free or defined medium is used to prevent and/or decrease experimental variation due in part to the lot-to-lot variation of serum-containing media.

[00795] In some embodiments, the serum-free or defined medium comprises a basal cell medium and a serum supplement and/or serum replacement. In some embodiments, the basal cell medium includes, but is not limited to CTSTM OpTmizerTM T-cell Expansion Basal Medium, CTSTM OpTmizerTM T-Cell Expansion SFM, CTSTM AIM-V Medium, CTSTM AIM-V SFM, LymphoONETM T-Cell Expansion Xeno-Free Medium, Dulbecco's Modified Eagle's Medium (DMEM), Minimal Essential Medium (MEM), Basal Medium Eagle (BME), RPMI 1640, F-10, F-12, Minimal Essential Medium (αMEM), Glasgow's Minimal Essential Medium (G-MEM). RPMI growth medium, and Iscove's Modified Dulbecco's Medium.

[00796] In some embodiments, the serum supplement or serum replacement includes, but is not limited to one or more of CTSTM OpTmizer T-Cell Expansion Serum Supplement, CTSTM Immune Cell Serum Replacement, one or more albumins or albumin substitutes, one or more amino acids, one or more vitamins, one or more transferrins or transferrin substitutes, one or more antioxidants, one or more insulins or insulin substitutes, one or more collagen precursors, one or more antibiotics, and one or more trace elements. In some embodiments, the defined medium comprises albumin and one or more ingredients selected from the group consisting of glycine, L- histidine, L-isoleucine, L-methionine, L-phenylalanine, L-proline, L- hydroxyproline, L-serine, L-threonine, L-tryptophan, L-tyrosine, L-valine, thiamine, reduced glutathione, L-ascorbic acid-2-phosphate, iron saturated transferrin, insulin, and compounds containing the trace element moieties Ag⁺, Al³⁺, Ba²⁺, Cd²⁺, Co²⁺, Cr³⁺, Ge⁴⁺, Se⁴⁺, Br, T, Mn²⁺, P, Si⁴⁺, V⁵⁺, Mo⁶⁺, Ni²⁺, Rb⁺, Sn²⁺ and Zr⁴⁺. In some embodiments, the defined medium further comprises L-glutamine, sodium bicarbonate and/or 2-mercaptoethanol.

[00797] In some embodiments, the CTSTMOpTmizerTM T-cell Immune Cell Serum Replacement is used with conventional growth media, including but not limited to CTSTM OpTmizerTM T-cell Expansion Basal Medium, CTSTM OpTmizerTM T-cell Expansion SFM, CTSTM AIM-V Medium, CSTTM AIM-V SFM, LymphoONETM T-Cell Expansion Xeno-Free Medium, Dulbecco's Modified Eagle's Medium (DMEM), Minimal Essential Medium (MEM), Basal Medium Eagle (BME), RPMI 1640, F-10, F-12, Minimal Essential Medium (αMEM), Glasgow's Minimal Essential Medium (G-MEM), RPMI growth medium, and Iscove's Modified Dulbecco's Medium.

[00798] In some embodiments, the total serum replacement concentration (vol%) in the serum-free or defined medium is from about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20% by volume of the total serum-free

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or defined medium. In some embodiments, the total serum replacement concentration is about 3% of the total volume of the serum-free or defined medium. In some embodiments, the total serum replacement concentration is about 5% of the total volume of the serum-free or defined medium. In some embodiments, the total serum replacement concentration is about 10% of the total volume of the serum-free or defined medium.

[00799] In some embodiments, the serum-free or defined medium is CTSTM OpTmizer[™] T-cell Expansion SFM (ThermoFisher Scientific). Any formulation of CTS[™] OpTmizerTM is useful in the present invention. CTSTM OpTmizerTM T-cell Expansion SFM is a combination of 1L CTSTM OpTmizerTM T-cell Expansion Basal Medium and 26 mL CTSTM OpTmizerTM T-Cell Expansion Supplement, which are mixed together prior to use. In some embodiments, the CTSTM OpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTS™ Immune Cell Serum Replacement (SR) (ThermoFisher Scientific). In some embodiments, the CTSTM OpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTS™ Immune Cell Serum Replacement (SR) (ThermoFisher Scientific), along with 2-mercaptoethanol at 55mM. In some embodiments, the CTSTM OpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTSTM Immune Cell Serum Replacement (SR) (ThermoFisher Scientific) and the final concentration of 2mercaptoethanol in the media is 55µM.

[00800] In some embodiments, the defined medium is CTSTM OpTmizerTM T-cell Expansion SFM (ThermoFisher Scientific). Any formulation of CTSTM OpTmizerTM is useful in the present invention. CTSTM OpTmizerTM T-cell Expansion SFM is a combination of 1L CTSTM OpTmizerTM T-cell Expansion Basal Medium and 26 mL CTSTM OpTmizerTM T-Cell Expansion Supplement, which are mixed together prior to use. In some embodiments, the CTSTM OpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTSTM Immune Cell Serum Replacement (SR) (ThermoFisher Scientific), along with 2mercaptoethanol at 55mM. In some embodiments, the CTSTMOpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTSTM Immune Cell Serum Replacement (SR) (ThermoFisher Scientific), 55mM of 2-mercaptoethanol, and 2mM of L-glutamine. In some embodiments, the CTSTMOpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTS™ Immune Cell Serum Replacement (SR) (ThermoFisher Scientific), 55mM of 2mercaptoethanol, and 2mM of L-glutamine, and further comprises about 1000 IU/mL to about 8000 IU/mL of IL-2. In some embodiments, the CTSTMOpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTSTM Immune Cell Serum Replacement (SR)

(ThermoFisher Scientific), 55mM of 2-mercaptoethanol, and 2mM of L-glutamine, and further comprises about 3000 IU/mL of IL-2. In some embodiments, the CTSTMOpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTSTM Immune Cell Serum Replacement (SR) (ThermoFisher Scientific), 55mM of 2-mercaptoethanol, and 2mM of Lglutamine, and further comprises about 6000 IU/mL of IL-2. In some embodiments, the CTSTMOpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTSTM Immune Cell Serum Replacement (SR) (ThermoFisher Scientific) and 55mM of 2mercaptoethanol, and further comprises about 1000 IU/mL to about 8000 IU/mL of IL-2. In some embodiments, the CTSTMOpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTSTM Immune Cell Serum Replacement (SR) (ThermoFisher Scientific) and 55mM of 2-mercaptoethanol, and further comprises about 3000 IU/mL of IL-2. In some embodiments, the CTSTMOpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTSTM Immune Cell Serum Replacement (SR) (ThermoFisher Scientific) and 55mM of 2-mercaptoethanol, and further comprises about 1000 IU/mL to about 6000 IU/mL of IL-2. In some embodiments, the CTSTMOpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTSTM Immune Cell Serum Replacement (SR) (ThermoFisher Scientific) and about 2mM glutamine, and further comprises about 1000 IU/mL to about 8000 IU/mL of IL-2. In some embodiments, the CTSTMOpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTSTM Immune Cell Serum Replacement (SR) (ThermoFisher Scientific) and about 2mM glutamine, and further comprises about 3000 IU/mL of IL-2. In some embodiments, the CTSTMOpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTSTM Immune Cell Serum Replacement (SR) (ThermoFisher Scientific) and about 2mM glutamine, and further comprises about 6000 IU/mL of IL-2. In some embodiments, the CTS[™] OpTmizer[™] T-cell Expansion SFM is supplemented with about 3% of the CTSTM Immune Cell Serum Replacement (SR) (ThermoFisher Scientific) and the final concentration of 2-mercaptoethanol in the media is 55µM.

[00801] In some embodiments, the serum-free medium or defined medium is supplemented with glutamine (i.e., GlutaMAX®) at a concentration of from about 0.1mM to about 10mM, 0.5mM to about 9mM, 1mM to about 8mM, 2mM to about 7mM, 3mM to about 6mM, or 4mM to about 5 mM. In some embodiments, the serum-free medium or defined medium is supplemented with glutamine (i.e., GlutaMAX®) at a concentration of about 2mM.

[00802] In some embodiments, the serum-free medium or defined medium is supplemented with 2-mercaptoethanol at a concentration of from about 5mM to about

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150mM, 10mM to about 140mM, 15mM to about 130mM, 20mM to about 120mM, 25mM to about 110mM, 30mM to about 100mM, 35mM to about 95mM, 40mM to about 90mM, 45mM to about 85mM, 50mM to about 80mM, 55mM to about 75mM, 60mM to about 70mM, or about 65mM. In some embodiments, the serum-free medium or defined medium is supplemented with 2-mercaptoethanol at a concentration of about 55mM. In some embodiments, the final concentration of 2-mercaptoethanol in the media is $55\mu M$.

[00803] In some embodiments, the defined media described in International PCT Publication No. WO/1998/030679, which is herein incorporated by reference, are useful in the present invention. In that publication, serum-free eukaryotic cell culture media are described. The serum-free, eukaryotic cell culture medium includes a basal cell culture medium supplemented with a serum-free supplement capable of supporting the growth of cells in serum- free culture. The serum-free eukaryotic cell culture medium supplement comprises or is obtained by combining one or more ingredients selected from the group consisting of one or more albumins or albumin substitutes, one or more amino acids, one or more vitamins, one or more transferrins or transferrin substitutes, one or more antioxidants, one or more insulins or insulin substitutes, one or more collagen precursors, one or more trace elements, and one or more antibiotics. In some embodiments, the defined medium further comprises Lglutamine, sodium bicarbonate and/or beta-mercaptoethanol. In some embodiments, the defined medium comprises an albumin or an albumin substitute and one or more ingredients selected from group consisting of one or more amino acids, one or more vitamins, one or more transferrins or transferrin substitutes, one or more antioxidants, one or more insulins or insulin substitutes, one or more collagen precursors, and one or more trace elements. In some embodiments, the defined medium comprises albumin and one or more ingredients selected from the group consisting of glycine, L- histidine, L-isoleucine, L-methionine, Lphenylalanine, L-proline, L- hydroxyproline, L-serine, L-threonine, L-tryptophan, L-tyrosine, L-valine, thiamine, reduced glutathione, L-ascorbic acid-2-phosphate, iron saturated transferrin, insulin, and compounds containing the trace element moieties Ag⁺, Al³⁺, Ba²⁺, Cd²⁺, Co²⁺, Cr³⁺, Ge⁴⁺, Se⁴⁺, Br, T, Mn²⁺, P, Si⁴⁺, V⁵⁺, Mo⁶⁺, Ni²⁺, Rb⁺, Sn²⁺ and Zr⁴⁺. In some embodiments, the basal cell media is selected from the group consisting of Dulbecco's Modified Eagle's Medium (DMEM), Minimal Essential Medium (MEM), Basal Medium Eagle (BME), RPMI 1640, F-10, F-12, Minimal Essential Medium (aMEM), Glasgow's Minimal Essential Medium (G-MEM), RPMI growth medium, and Iscove's Modified Dulbecco's Medium.

[00804] In some embodiments, the concentration of glycine in the defined medium is in the range of from about 5-200 mg/L, the concentration of L- histidine is about 5-250 mg/L, the concentration of L-isoleucine is about 5-300 mg/L, the concentration of L-methionine is about 5-200 mg/L, the concentration of L-phenylalanine is about 5-400 mg/L, the concentration of L-proline is about 1-1000 mg/L, the concentration of L-hydroxyproline is about 1-45 mg/L, the concentration of L-serine is about 1-250 mg/L, the concentration of L-threonine is about 10-500 mg/L, the concentration of L-tryptophan is about 2-110 mg/L, the concentration of L-tyrosine is about 3-175 mg/L, the concentration of L-valine is about 5-500 mg/L, the concentration of thiamine is about 1-20 mg/L, the concentration of reduced glutathione is about 1-20 mg/L, the concentration of L-ascorbic acid-2-phosphate is about 1-200 mg/L, the concentration of iron saturated transferrin is about 1-50 mg/L, the concentration of insulin is about 1-100 mg/L, the concentration of sodium selenite is about 0.000001-0.0001 mg/L, and the concentration of albumin (e.g., AlbuMAX® I) is about 5000-50,000 mg/L.

[00805] In some embodiments, the non-trace element moiety ingredients in the defined medium are present in the concentration ranges listed in the column under the heading "Concentration Range in 1X Medium" in Table A below. In other embodiments, the non-trace element moiety ingredients in the defined medium are present in the final concentrations listed in the column under the heading "A Preferred Embodiment of the 1X Medium" in Table A below. In other embodiments, the defined medium is a basal cell medium comprising a serum free supplement. In some of these embodiments, the serum free supplement comprises non-trace moiety ingredients of the type and in the concentrations listed in the column under the heading "A Preferred Embodiment in Supplement" in Table A below.

Table A: Concentrations of Non-Trace Element Moiety Ingredients

Ingredient	A preferred	Concentration range	A preferred
	embodiment in	in 1X medium	embodiment in 1X
	supplement (mg/L)	(mg/L)	medium (mg/L)
	(About)	(About)	(About)
Glycine	150	5-200	53
L-Histidine	940	5-250	183
L-Isoleucine	3400	5-300	615
L-Methionine	90	5-200	44
L-Phenylalanine	1800	5-400	336
L-Proline	4000	1-1000	600
L-Hydroxyproline	100	1-45	15

L-Serine	800	1-250	162
L-Threonine	2200	10-500	425
L-Tryptophan	440	2-110	82
L-Tyrosine	77	3-175	84
L-Valine	2400	5-500	454
Thiamine	33	1-20	9
Reduced Glutathione	10	1-20	1.5
Ascorbic Acid-2-PO ₄	330	1-200	50
(Mg Salt)			
Transferrin (iron	55	1-50	8
saturated)			
Insulin	100	1-100	10
Sodium Selenite	0.07	0.000001-0.0001	0.00001
AlbuMAX [®] I	83,000	5000-50,000	12,500

[00806] In some embodiments, the osmolarity of the defined medium is between about 260 and 350 mOsmol. In some embodiments, the osmolarity is between about 280 and 310 mOsmol. In some embodiments, the defined medium is supplemented with up to about 3.7 g/L, or about 2.2 g/L sodium bicarbonate. The defined medium can be further supplemented with L-glutamine (final concentration of about 2 mM), one or more antibiotics, non-essential amino acids (NEAA; final concentration of about 100 μ M), 2-mercaptoethanol (final concentration of about 100 μ M).

[00807] In some embodiments, the defined media 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," *Clin Transl Immunology*, 4(1) 2015 (doi: 10.1038/cti.2014.31) are useful in the present invention. Briefly, RPMI or CTSTM OpTmizerTM was used as the basal cell medium, and supplemented with either 0, 2%, 5%, or 10% CTSTM Immune Cell Serum Replacement.

[00808] In an embodiment, the cell medium in the first and/or second gas permeable container is unfiltered. The use of unfiltered cell medium may simplify the procedures necessary to expand the number of cells. In an embodiment, the cell medium in the first and/or second gas permeable container lacks beta-mercaptoethanol (BME or β ME; also known as 2-mercaptoethanol, CAS 60-24-2).

[00809] In some embodiments, the priming first expansion (including processes such as for example those described in Step B of Figure 1 (in particular, *e.g.*, Figure 1B and/or Figure 8C), which can include those sometimes referred to as the pre-REP or priming REP) process is 1 to 8 days, as discussed in the examples and figures. In some embodiments, the priming

first expansion (including processes such as for example those described in Step B of Figure 1 (in particular, e.g., Figure 1B and/or Figure 8C), which can include those sometimes referred to as the pre-REP or priming REP) process is 2 to 8 days. In some embodiments, the priming first expansion (including processes such as for example those described in Step B of Figure 1 (in particular, e.g., Figure 1B and/or Figure 8C), which can include those sometimes referred to as the pre-REP or priming REP) process is 3 to 8 days. In some embodiments, the priming first expansion (including processes such as for example those described in Step B of Figure 1 (in particular, e.g., Figure 8B and/or Figure 8C), which can include those sometimes referred to as the pre-REP or priming REP) process is 4 to 8 days, as discussed in the examples and figures. In some embodiments, the priming first expansion (including processes such as for example those described in Step B of Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C), which can include those sometimes referred to as the pre-REP or priming REP) process is 1 to 7 days, as discussed in the examples and figures. In some embodiments, the priming first expansion (including processes such as for example those described in Step B of Figure 1 (in particular, e.g., Figure 1B and/or Figure 8C), which can include those sometimes referred to as the pre-REP or priming REP) process is 2 to 8 days. In some embodiments, the priming first expansion (including processes such as for example those described in Step B of Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C), which can include those sometimes referred to as the pre-REP or priming REP) process is 2 to 7 days. In some embodiments, the priming first expansion (including processes such as for example those described in Step B of Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C), which can include those sometimes referred to as the pre-REP or priming REP) process is 3 to 8 days. In some embodiments, the priming first expansion (including processes such as for example those described in Step B of Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C), which can include those sometimes referred to as the pre-REP or priming REP) process is 3 to 7 days. In some embodiments, the priming first expansion (including processes such as for example those described in Step B of Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C), which can include those sometimes referred to as the pre-REP or priming REP) process is 4 to 8 days. In some embodiments, the priming first expansion (including processes such as for example those described in Step B of Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C), which can include those sometimes referred to as the pre-REP or priming REP) process is 4 to 7 days. In some embodiments, the priming first expansion (including processes such as for example those described in Step B of Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C), which can include those sometimes referred to as the pre-REP or priming REP) process

is 5 to 8 days. In some embodiments, the priming first expansion (including processes such as for example those described in Step B of Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C), which can include those sometimes referred to as the pre-REP or priming REP) process is 5 to 7 days. In some embodiments, the priming first expansion (including processes such as for example those described in Step B of Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C), which can include those sometimes referred to as the pre-REP or priming REP) process is 6 to 8 days. In some embodiments, the priming first expansion (including processes such as for example those described in Step B of Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C), which can include those sometimes referred to as the pre-REP or priming REP) process is 6 to 7 days. In some embodiments, the priming first expansion (including processes such as for example those provided in Step B of Figure 1 (in particular, e.g., Figure 8B and/or Figure 8C), which can include those sometimes referred to as the pre-REP or priming REP) process is 7 to 8 days. In some embodiments, the priming first expansion (including processes such as for example those provided in Step B of Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C), which can include those sometimes referred to as the pre-REP or priming REP) process is 8 days. In some embodiments, the priming first expansion (including processes such as for example those provided in Step B of Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C), which can include those sometimes referred to as the pre-REP or priming REP) process is 7 days.

[00810] In some embodiments, the priming first TIL expansion can proceed for 1 days to 8 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the priming first TIL expansion can proceed for 1 days to 7 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the priming first TIL expansion can proceed for 2 days to 8 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the priming first TIL expansion can proceed for 2 days to 7 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the priming first TIL expansion can proceed for 3 days to 8 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the priming first TIL expansion can proceed for 3 days to 7 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the priming first TIL expansion can proceed for 4 days to 8 days from when fragmentation occurs and/or when the first priming expansion step is

initiated. In some embodiments, the priming first TIL expansion can proceed for 4 days to 7 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the priming first TIL expansion can proceed for 5 days to 8 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the priming first TIL expansion can proceed for 5 days to 7 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the priming first TIL expansion can proceed for 6 days to 8 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the priming first TIL expansion can proceed for 6 days to 7 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the priming first TIL expansion can proceed for 7 to 8 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the priming first TIL expansion can proceed for 8 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the priming first TIL expansion can proceed for 7 days from when fragmentation occurs and/or when the first priming expansion step is initiated.

[00811] In some embodiments, the priming first expansion of the TILs can proceed for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, or 8 days. In some embodiments, the first TIL expansion can proceed for 1 day to 8 days. In some embodiments, the first TIL expansion can proceed for 1 day to 7 days. In some embodiments, the first TIL expansion can proceed for 2 days to 8 days. In some embodiments, the first TIL expansion can proceed for 2 days to 7 days. In some embodiments, the first TIL expansion can proceed for 3 days to 8 days. In some embodiments, the first TIL expansion can proceed for 3 days to 7 days. In some embodiments, the first TIL expansion can proceed for 4 days to 8 days. In some embodiments, the first TIL expansion can proceed for 4 days to 7 days. In some embodiments, the first TIL expansion can proceed for 5 days to 8 days. In some embodiments, the first TIL expansion can proceed for 5 days to 7 days. In some embodiments, the first TIL expansion can proceed for 6 days to 8 days. In some embodiments, the first TIL expansion can proceed for 6 days to 7 days. In some embodiments, the first TIL expansion can proceed for 7 to 8 days. In some embodiments, the first TIL expansion can proceed for 8 days. In some embodiments, the first TIL expansion can proceed for 7 days.

[00812] In some embodiments, a combination of IL-2, IL-7, IL-15, and/or IL-21 are employed as a combination during the priming first expansion. In some embodiments, IL-2, IL-7, IL-15, and/or IL-21 as well as any combinations thereof can be included during the priming first expansion, including, for example during Step B processes according to Figure 8 (in particular, *e.g.*, Figure 8B and/or Figure 8C), as well as described herein. In some

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embodiments, a combination of IL-2, IL-15, and IL-21 are employed as a combination during the priming first expansion. In some embodiments, IL-2, IL-15, and IL-21 as well as any combinations thereof can be included during Step B processes according to Figure 8 (in particular, *e.g.*, Figure 8B and/or Figure 8C) and as described herein.

[00813] In some embodiments, the priming first expansion, for example, Step B according to Figure 8 (in particular, *e.g.*, Figure 8B and/or Figure 8C), is performed in a closed system bioreactor. In some embodiments, a closed system is employed for the TIL expansion, as described herein. In some embodiments, a bioreactor is employed. In some embodiments, a bioreactor is employed as the container. In some embodiments, the bioreactor employed is for example a G-REX-10 or a G-REX-100. In some embodiments, the bioreactor employed is a G-REX-10.

1. Feeder Cells and Antigen Presenting Cells

[00814] In an embodiment, the priming first expansion procedures described herein (for example including expansion such as those described in Step B from Figure 1 (in particular, *e.g.*, Figure 8B and/or Figure 8C), as well as those referred to as pre-REP or priming REP) does not require feeder cells (also referred to herein as "antigen-presenting cells") at the initiation of the TIL expansion, but rather are added during the priming first expansion. In an embodiment, the priming first expansion procedures described herein (for example including expansion such as those described in Step B from Figure 8 (in particular, *e.g.*, Figure 8B and/or Figure 8C), as well as those referred to as pre-REP or priming REP) does not require feeder cells (also referred to herein as "antigen-presenting cells") at the initiation of the TIL expansion, but rather are added during the priming first expansion at any time during days 4-8. In an embodiment, the priming first expansion procedures described herein (for example including expansion such as those described in Step B from Figure 8 (in particular, *e.g.*, Figure 8B and/or Figure 8C), as well as those referred to as pre-REP or priming REP) does not require feeder cells (also referred to herein as "antigen-presenting cells") at the initiation of the TIL expansion, but rather are added during the priming first expansion at any time

WO 2020/096989 PCT/US2019/059720 during days 4-7. In an embodiment, the priming first expansion procedures described herein (for example including expansion such as those described in Step B from Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C), as well as those referred to as pre-REP or priming REP) does not require feeder cells (also referred to herein as "antigen-presenting cells") at the initiation of the TIL expansion, but rather are added during the priming first

expansion at any time during days 5-8. In an embodiment, the priming first expansion procedures described herein (for example including expansion such as those described in Step B from Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C), as well as those referred to as pre-REP or priming REP) does not require feeder cells (also referred to herein as "antigenpresenting cells") at the initiation of the TIL expansion, but rather are added during the priming first expansion at any time during days 5-7. In an embodiment, the priming first expansion procedures described herein (for example including expansion such as those described in Step B from Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C), as well as those referred to as pre-REP or priming REP) does not require feeder cells (also referred to herein as "antigen-presenting cells") at the initiation of the TIL expansion, but rather are added during the priming first expansion at any time during days 6-8. In an embodiment, the priming first expansion procedures described herein (for example including expansion such as those described in Step B from Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C), as well as those referred to as pre-REP or priming REP) does not require feeder cells (also referred to herein as "antigen-presenting cells") at the initiation of the TIL expansion, but rather are added during the priming first expansion at any time during days 6-7. In an embodiment, the priming first expansion procedures described herein (for example including expansion such as those described in Step B from Figure 8 (in particular, e.g., Figure 8B) and/or Figure 8C), as well as those referred to as pre-REP or priming REP) does not require feeder cells (also referred to herein as "antigen-presenting cells") at the initiation of the TIL expansion, but rather are added during the priming first expansion at any time during day 7 or 8. In an embodiment, the priming first expansion procedures described herein (for example including expansion such as those described in Step B from Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C), as well as those referred to as pre-REP or priming REP) does not require feeder cells (also referred to herein as "antigen-presenting cells") at the initiation of the TIL expansion, but rather are added during the priming first expansion at any time during day 7. In an embodiment, the priming first expansion procedures described herein (for example including expansion such as those described in Step B from Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C), as well as those referred to as pre-REP or priming REP)

does not require feeder cells (also referred to herein as "antigen-presenting cells") at the initiation of the TIL expansion, but rather are added during the priming first expansion at any time during day 8

[00815] In an embodiment, the priming first expansion procedures described herein (for example including expansion such as those described in Step B from Figure 8 (in particular, *e.g.*, Figure 8B), as well as those referred to as pre-REP or priming REP) require feeder cells (also referred to herein as "antigen-presenting cells") at the initiation of the TIL expansion and during the priming first expansion. In many embodiments, the feeder cells are peripheral blood mononuclear cells (PBMCs) obtained from standard whole blood units from allogeneic healthy blood donors. The PBMCs are obtained using standard methods such as Ficoll-Paque gradient separation. In some embodiments, 2.5×10^8 feeder cells are used during the priming first expansion. In some embodiments, 2.5×10^8 feeder cells per GREX-10 are used during the priming first expansion. In some embodiments, 2.5×10^8 feeder cells per GREX-10 are used during the priming first expansion. In some embodiments, 2.5×10^8 feeder cells per GREX-10 are used during the priming first expansion. In some embodiments, 2.5×10^8 feeder cells per GREX-10 are used

[00816] In general, the allogenic PBMCs are inactivated, either via irradiation or heat treatment, and used in the REP procedures, as described in the examples, which provides an exemplary protocol for evaluating the replication incompetence of irradiate allogeneic PBMCs.

[00817] In some embodiments, PBMCs are considered replication incompetent and acceptable for use in the TIL expansion procedures described herein if the total number of viable cells on day 14 is less than the initial viable cell number put into culture on day 0 of the priming first expansion.

[00818] In some embodiments, PBMCs are considered replication incompetent and acceptable for use in the TIL expansion procedures described herein if the total number of viable cells, cultured in the presence of OKT3 and IL-2, on day 7 have not increased from the initial viable cell number put into culture on day 0 of the priming first expansion. In some embodiments, the PBMCs are cultured in the presence of 30 ng/ml OKT3 antibody and 3000 IU/ml IL-2. In some embodiments, the PBMCs are cultured in the presence of 30 ng/ml OKT3 antibody and 6000 IU/ml IL-2.

[00819] In some embodiments, PBMCs are considered replication incompetent and acceptable for use in the TIL expansion procedures described herein if the total number of

viable cells, cultured in the presence of OKT3 and IL-2, on day 7 have not increased from the initial viable cell number put into culture on day 0 of the priming first expansion. In some embodiments, the PBMCs are cultured in the presence of 5-60 ng/mL OKT3 antibody and 1000-6000 IU/mL IL-2. In some embodiments, the PBMCs are cultured in the presence of 10-50 ng/ml OKT3 antibody and 2000-5000 IU/mL IL-2. In some embodiments, the PBMCs are cultured in the presence of 20-40 ng/mL OKT3 antibody and 2000-4000 IU/mL IL-2. In some embodiments, the PBMCs are cultured in the presence of 25-35 ng/mL OKT3 antibody and 2500-3500 IU/mL IL-2. In some embodiments, the PBMCs are cultured in the presence of 30 ng/ml OKT3 antibody and 6000 IU/mL IL-2. In some embodiments, the PBMCs are cultured in the presence of 15 ng/mL OKT3 antibody and 3000 IU/mL IL-2. In some embodiments, the PBMCs are cultured in the presence of 15 ng/mL OKT3 antibody and 6000 IU/mL IL-2.

[00820] In some embodiments, the antigen-presenting feeder cells are PBMCs. In some embodiments, the antigen-presenting feeder cells are artificial antigen-presenting feeder cells. In an embodiment, the ratio of TILs to antigen-presenting feeder cells in the second expansion is about 1 to 25, about 1 to 50, about 1 to 100, about 1 to 125, about 1 to 150, about 1 to 175, about 1 to 200, about 1 to 225, about 1 to 250, about 1 to 275, about 1 to 300, about 1 to 325, about 1 to 350, about 1 to 375, about 1 to 400, or about 1 to 500. In an embodiment, the ratio of TILs to antigen-presenting feeder cells in the second expansion is between 1 to 50 and 1 to 300. In an embodiment, the ratio of TILs to antigen-presenting feeder cells in the second expansion is between 1 to 100 and 1 to 200.

[00821] In an embodiment, the priming first expansion procedures described herein require a ratio of about 2.5×10^8 feeder cells to about 100×10^6 TILs. In another embodiment, the priming first expansion procedures described herein require a ratio of about 2.5×10^8 feeder cells to about 50×10^6 TILs. In yet another embodiment, the priming first expansion described herein require about 2.5×10^8 feeder cells to about 2.5×10^6 TILs. In yet another embodiment, the priming first expansion described herein require about 2.5×10^8 feeder cells. In yet another embodiment, the priming first expansion requires one-fourth, one-third, five-twelfths, or one-half of the number of feeder cells used in the rapid second expansion.

[00822] In some embodiments, the media in the priming first expansion comprises IL-2. In some embodiments, the media in the priming first expansion comprises 6000 IU/mL of IL-2. In some embodiments, the media in the priming first expansion comprises antigen-presenting feeder cells. In some embodiments, the media in the priming first expansion comprises 2.5×10^{-2} km some embodiments, the media in the priming first expansion comprises 2.5×10^{-2} km some embodiments, the media in the priming first expansion comprises 2.5×10^{-2} km some embodiments, the media in the priming first expansion comprises 2.5×10^{-2} km some embodiments, the media in the priming first expansion comprises 2.5×10^{-2} km some embodiments, the media in the priming first expansion comprises 2.5×10^{-2} km some embodiments, the media in the priming first expansion comprises 2.5×10^{-2} km some embodiments, the media in the priming first expansion comprises 2.5×10^{-2} km some embodiments, the media in the priming first expansion comprises 2.5×10^{-2} km some embodiments, the media in the priming first expansion comprises 2.5×10^{-2} km some embodiments.

 10^8 antigen-presenting feeder cells per container. In some embodiments, the media in the priming first expansion comprises OKT-3. In some embodiments, the media comprises 30 ng of OKT-3 per container. In some embodiments, the container is a GREX100 MCS flask. In some embodiments, the media comprises 6000 IU/mL of IL-2, 30 ng/mL of OKT-3, and 2.5 \times 10⁸ antigen-presenting feeder cells. In some embodiments, the media comprises 6000 IU/mL of IL-2, 30 ng/mL of OKT-3, and 2.5 \times 10⁸ antigen-presenting feeder cells per container. In some embodiments, the media comprises 500 mL of culture medium and 15 µg of OKT-3 per 2.5 \times 10⁸ antigen-presenting feeder cells per container. In some embodiments, the media comprises 500 mL of culture medium and 15 µg of OKT-3 per container. In some embodiments, the container is a GREX100 MCS flask. In some embodiments, the media comprises 500 mL of culture medium, 6000 IU/mL of IL-2, 30 ng/mL of OKT-3, and 2.5 \times 10⁸ antigen-presenting feeder cells. In some embodiments, the media comprises 500 mL of culture medium, 6000 IU/mL of IL-2, 15 µg of OKT-3, and 2.5 \times 10⁸ antigen-presenting feeder cells per container. In some embodiments, the media comprises 500 mL of culture medium, 6000 IU/mL of IL-2, 15 µg of OKT-3, and 2.5 \times 10⁸ antigen-presenting feeder cells per container. In some embodiments, the media comprises 500 mL of culture medium and 15 µg of OKT-3 per 2.5 \times 10⁸ antigen-presenting feeder cells per container.

[00823] In an embodiment, the priming first expansion procedures described herein require an excess of feeder cells over TILs during the second expansion. In many embodiments, the feeder cells are peripheral blood mononuclear cells (PBMCs) obtained from standard whole blood units from allogeneic healthy blood donors. The PBMCs are obtained using standard methods such as Ficoll-Paque gradient separation. In an embodiment, artificial antigenpresenting (aAPC) cells are used in place of PBMCs.

[00824] In general, the allogenic PBMCs are inactivated, either via irradiation or heat treatment, and used in the TIL expansion procedures described herein, including the exemplary procedures described in the figures and examples.

[00825] In an embodiment, artificial antigen presenting cells are used in the priming first expansion as a replacement for, or in combination with, PBMCs.

2. Cytokines

[00826] The expansion methods described herein generally use culture media with high doses of a cytokine, in particular IL-2, as is known in the art.

[00827] Alternatively, using combinations of cytokines for the priming first expansion of TILs is additionally possible, with combinations of two or more of IL-2, IL-15 and IL-21 as is generally outlined in International Publication No. WO 2015/189356 and WO

2015/189357, hereby expressly incorporated by reference in their entirety. Thus, possible combinations include IL-2 and IL-15, IL-2 and IL-21, IL-15 and IL-21, and IL-2, IL-15 and IL-21, with the latter finding particular use in many embodiments. The use of combinations of cytokines specifically favors the generation of lymphocytes, and in particular T-cells as described therein.

TABLE 20: Amino acid sequences of interleukins.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:3 recombinant human IL-2 (rhIL-2)	MAPTSSSTKK TQLQLEHLLL DLQMILNGIN NYKNPKLTRM LTFKFYMPKK ATELKHLQCL EEELKPLEEV LNLAQSKNFH LRPRDLISNI NVIVLELKGS ETTFMCEYAD ETATIVEFLN RWITFCQSII STLT	60 120 134
SEQ ID NO:4 Aldesleukin	PTSSSTKKTQ LQLEHLLLDL QMILNGINNY KNPKLTRMLT FKFYMPKKAT ELKHLQCLEE ELKPLEEVLN LAQSKNFHLR PRDLISNINV IVLELKGSET TFMCEYADET ATIVEFLNRW ITFSQSIIST LT	60 120 132
SEQ ID NO:5 recombinant human IL-4 (rhIL-4)	MHKCDITLQE IIKTLNSLTE QKTLCTELTV TDIFAASKNT TEKETFCRAA TVLRQFYSHH EKDTRCLGAT AQQFHRHKQL IRFLKRLDRN LWGLAGLNSC PVKEANQSTL ENFLERLKTI MREKYSKCSS	60 120 130
SEQ ID NO:6 recombinant human IL-7 (rhIL-7)	MDCDIEGKDG KQYESVLMVS IDQLLDSMKE IGSNCLNNEF NFFKRHICDA NKEGMFLFRA ARKLRQFLKM NSTGDFDLHL LKVSEGTTIL LNCTGQVKGR KPAALGEAQP TKSLEENKSL KEQKKLNDLC FLKRLLQEIK TCWNKILMGT KEH	60 120 153
SEQ ID NO:7 recombinant human IL-15 (rhIL-15)	MNWVNVISDL KKIEDLIQSM HIDATLYTES DVHPSCKVTA MKCFLLELQV ISLESGDASI HDTVENLIIL ANNSLSSNGN VTESGCKECE ELEEKNIKEF LQSFVHIVQM FINTS	60 115
SEQ ID NO:8 recombinant human IL-21 (rhIL-21)	MQDRHMIRMR QLIDIVDQLK NYVNDLVPEF LPAPEDVETN CEWSAFSCFQ KAQLKSANTG NNERIINVSI KKLKRKPPST NAGRRQKHRL TCPSCDSYEK KPPKEFLERF KSLLQKMIHQ HLSSRTHGSE DS	60 120 132

C. STEP C: Priming First Expansion to Rapid Second Expansion Transition

[00828] In some cases, the bulk TIL population obtained from the priming first expansion (which can include expansions sometimes referred to as pre-REP), including, for example the TIL population obtained from for example, Step B as indicated in Figure 8 (in particular, *e.g.*, Figure 8B and/or Figure 8C), can be subjected to a rapid second expansion (which can include expansions sometimes referred to as Rapid Expansion Protocol (REP)) and then cryopreserved as discussed below. Similarly, in the case where genetically modified TILs will be used in therapy, the expanded TIL population from the priming first expansion or the expanded TIL population from the rapid second expansion can be subjected to genetic modifications for suitable treatments prior to the expansion step or after the priming first expansion and prior to the rapid second expansion.

[00829] In some embodiments, the TILs obtained from the priming first expansion (for example, from Step B as indicated in Figure 1 (in particular, e.g., Figure 1B and/or Figure

8C)) are stored until phenotyped for selection. In some embodiments, the TILs obtained from the priming first expansion (for example, from Step B as indicated in Figure 1 (in particular, e.g., Figure 1B and/or Figure 8C)) are not stored and proceed directly to the rapid second expansion. In some embodiments, the TILs obtained from the priming first expansion are not cryopreserved after the priming first expansion and prior to the rapid second expansion. In some embodiments, the transition from the priming first expansion to the second expansion occurs at about 2 days, 3 days, 4, days, 5 days, 6 days, 7 days, or 8 days from when tumor fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the rapid second expansion occurs at about 3 days to 7 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the rapid second expansion occurs at about 3 days to 8 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the second expansion occurs at about 4 days to 7 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the second expansion occurs at about 4 days to 8 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the second expansion occurs at about 5 days to 7 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the second expansion occurs at about 5 days to 8 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the second expansion occurs at about 6 days to 7 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the second expansion occurs at about 6 days to 8 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the second expansion occurs at about 7 days to 8 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the second expansion occurs at about 7 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the second expansion

occurs at about 8 days from when fragmentation occurs and/or when the first priming expansion step is initiated.

[00830] In some embodiments, the transition from the priming first expansion to the rapid second expansion occurs at 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, or 8 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the rapid second expansion occurs 1 day to 7 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the rapid second expansion occurs 1 day to 8 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the second expansion occurs 2 days to 7 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the second expansion occurs 2 days to 8 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the second expansion occurs 3 days to 7 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the second expansion occurs 3 days to 8 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the rapid second expansion occurs 4 days to 7 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the rapid second expansion occurs 4 days to 8 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the rapid second expansion occurs 5 days to 7 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the rapid second expansion occurs 5 days to 8 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the rapid second expansion occurs 6 days to 7 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the rapid second expansion occurs 6 days to 8 days from when fragmentation occurs and/or when the

first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the rapid second expansion occurs 7 days to 8 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the rapid second expansion occurs 7 days from when fragmentation occurs and/or when the first priming expansion step is initiated. In some embodiments, the transition from the priming first expansion to the rapid second expansion occurs 8 days from when fragmentation occurs and/or when the first priming expansion step is initiated

[00831] In some embodiments, the TILs are not stored after the primary first expansion and prior to the rapid second expansion, and the TILs proceed directly to the rapid second expansion (for example, in some embodiments, there is no storage during the transition from Step B to Step D as shown in Figure 8 (in particular, *e.g.*, Figure 8B and/or Figure 8C)). In some embodiments, the transition occurs in closed system, as described herein. In some embodiments, the TILs from the priming first expansion, the second population of TILs, proceeds directly into the rapid second expansion with no transition period.

[00832] In some embodiments, the transition from the priming first expansion to the rapid second expansion, for example, Step C according to Figure 8 (in particular, *e.g.*, Figure 8B and/or Figure 8C), is performed in a closed system bioreactor. In some embodiments, a closed system is employed for the TIL expansion, as described herein. In some embodiments, a single bioreactor is employed. In some embodiments, the single bioreactor employed is for example a GREX-10 or a GREX-100. In some embodiments, the closed system bioreactor is a single bioreactor. In some embodiments, the transition from the priming first expansion to the rapid second expansion involves a scale-up in container size. In some embodiments, the priming first expansion is performed in a smaller container than the rapid second expansion. In some embodiments, the priming first expansion is performed in a GREX-100 and the rapid second expansion is performed in a GREX-500.

D. STEP D: Rapid Second Expansion

[00833] In some embodiments, the TIL cell population is further expanded in number after harvest and the priming first expansion, after Step A and Step B, and the transition referred to as Step C, as indicated in Figure 8 (in particular, *e.g.*, Figure 8B and/or Figure 8C)). This further expansion is referred to herein as the rapid second expansion, which can include expansion processes generally referred to in the art as a rapid expansion process (Rapid

Expansion Protocol or REP; as well as processes as indicated in Step D of Figure 8 (in particular, *e.g.*, Figure 8B)). The rapid second expansion is generally accomplished using a culture media comprising a number of components, including feeder cells, a cytokine source, and an anti-CD3 antibody, in a gas-permeable container. In some embodiments, 1 day, 2 days, 3 days, or 4 days after initiation of the rapid second expansion (*i.e.*, at days 8, 9, 10, or 11 of the overall Gen 3 process), the TILs are transferred to a larger volume container.

[00834] In some embodiments, the rapid second expansion (which can include expansions sometimes referred to as REP; as well as processes as indicated in Step D of Figure 1 (in particular, e.g., Figure 1B and/or Figure 8C)) of TIL can be performed using any TIL flasks or containers known by those of skill in the art. In some embodiments, the second TIL expansion can proceed for 1 day, 2 days, 3 days, 4, days, 5 days, 6 days, 7 days, 8 days, 9 days or 10 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 1 days to about 9 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 1 days to about 10 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 2 days to about 9 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 2 days to about 10 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 3 days to about 9 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 3 days to about 10 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 4 days to about 9 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 4 days to about 10 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 5 days to about 9 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 5 days to about 10 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 6 days to about 9 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 6 days to about 10 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 7 days to about 9 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 7 days to about 10 days

after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 8 days to about 9 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 8 days to about 10 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 9 days to about 10 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 1 day after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 2 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 3 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 4 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 5 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 6 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 7 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 8 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 9 days after initiation of the rapid second expansion. In some embodiments, the second TIL expansion can proceed for about 10 days after initiation of the rapid second expansion.

[00835] In an embodiment, the rapid second expansion can be performed in a gas permeable container using the methods of the present disclosure (including, for example, expansions referred to as REP; as well as processes as indicated in Step D of Figure 8 (in particular, *e.g.*, Figure 8B and/or Figure 8C). In some embodiments, the TILs are expanded in the rapid second expansion in the presence of IL-2, OKT-3, and feeder cells (also referred herein as "antigen-presenting cells"). In some embodiments, the TILs are expanded in the rapid second expansion in the presence of IL-2, OKT-3, and feeder cells, wherein the feeder cells are added to a final concentration that is twice, 2.4 times, 2.5 times, 3 times, 3.5 times or 4 times the concentration of feeder cells present in the priming first expansion. For example, TILs can be rapidly expanded using non-specific T-cell receptor stimulation in the presence of interleukin-2 (IL-2) or interleukin-15 (IL-15). The non-specific T-cell receptor stimulus can include, for example, an anti-CD3 antibody, such as about 30 ng/ml of OKT3, a mouse monoclonal anti-CD3 antibody (commercially available from Ortho-McNeil, Raritan, NJ or Miltenyi Biotech, Auburn, CA) or UHCT-1 (commercially available from BioLegend, San

Diego, CA, USA). TILs can be expanded to induce further stimulation of the TILs *in vitro* by including one or more antigens during the second expansion, including antigenic portions thereof, such as epitope(s), of the cancer, which can be optionally expressed from a vector, such as a human leukocyte antigen A2 (HLA-A2) binding peptide, *e.g.*, 0.3 μM MART-1 :26-35 (27 L) or gpl 00:209-217 (210M), optionally in the presence of a T-cell growth factor, such as 300 IU/mL IL-2 or IL-15. Other suitable antigens may include, *e.g.*, NY-ESO-1, TRP-1, TRP-2, tyrosinase cancer antigen, MAGE-A3, SSX-2, and VEGFR2, or antigenic portions thereof. TIL may also be rapidly expanded by re-stimulation with the same antigen(s) of the cancer pulsed onto HLA-A2-expressing antigen-presenting cells. Alternatively, the TILs can be further re-stimulated with, *e.g.*, example, irradiated, autologous lymphocytes or with irradiated HLA-A2+ allogeneic lymphocytes and IL-2. In some embodiments, the re-stimulation occurs as part of the second expansion. In some embodiments, the second expansion occurs in the presence of irradiated, autologous lymphocytes or with irradiated HLA-A2+ allogeneic lymphocytes and IL-2.

[00836] In an embodiment, the cell culture medium further comprises IL-2. In some embodiments, the cell culture medium comprises about 3000 IU/mL of IL-2. In an embodiment, the cell culture medium comprises about 1000 IU/mL, about 1500 IU/mL, about 2000 IU/mL, about 2500 IU/mL, about 3000 IU/mL, about 3500 IU/mL, about 4000 IU/mL, about 4500 IU/mL, about 5000 IU/mL, about 5500 IU/mL, about 6000 IU/mL, about 6500 IU/mL, about 7000 IU/mL, about 7500 IU/mL, or about 8000 IU/mL of IL-2. In an embodiment, the cell culture medium comprises between 1000 and 2000 IU/mL, between 2000 and 3000 IU/mL, between 3000 and 4000 IU/mL, between 4000 and 5000 IU/mL, between 5000 and 6000 IU/mL, between 6000 and 7000 IU/mL, between 7000 and 8000 IU/mL, or between 8000 IU/mL of IL-2.

[00837] In an embodiment, the cell culture medium comprises OKT-3 antibody. In some embodiments, the cell culture medium comprises about 30 ng/mL of OKT-3 antibody. In an embodiment, the cell culture medium comprises about 0.1 ng/mL, about 0.5 ng/mL, about 1 ng/mL, about 2.5 ng/mL, about 5 ng/mL, about 7.5 ng/mL, about 10 ng/mL, about 15 ng/mL, about 20 ng/mL, about 25 ng/mL, about 30 ng/mL, about 35 ng/mL, about 40 ng/mL, about 50 ng/mL, about 60 ng/mL, about 70 ng/mL, about 80 ng/mL, about 90 ng/mL, about 100 ng/mL, about 200 ng/mL, about 500 ng/mL, and about 1 μg/mL of OKT-3 antibody. In an embodiment, the cell culture medium comprises between 0.1 ng/mL and 1 ng/mL, between 1 ng/mL and 5 ng/mL, between 5 ng/mL and 10 ng/mL, between 10 ng/mL and 20 ng/mL.

between 20 ng/mL and 30 ng/mL, between 30 ng/mL and 40 ng/mL, between 40 ng/mL and 50 ng/mL, and between 50 ng/mL and 100 ng/mL of OKT-3 antibody. In an embodiment, the cell culture medium comprises between 15 ng/ml and 30 ng/mL of OKT-3 antibody. In an embodiment, the cell culture medium comprises between 30 ng/ml and 60 ng/mL of OKT-3 antibody. In an embodiment, the cell culture medium comprises about 30 ng/mL OKT-3. In an embodiment, the cell culture medium comprises about 60 ng/mL OKT-3. In some embodiments, the OKT-3 antibody is muromonab.

[00838] In some embodiments, the media in the rapid second expansion comprises IL-2. In some embodiments, the media comprises 6000 IU/mL of IL-2. In some embodiments, the media in the rapid second expansion comprises antigen-presenting feeder cells. In some embodiments, the media in the rapid second expansion comprises 7.5×10^8 antigen-presenting feeder cells per container. In some embodiments, the media in the rapid second expansion comprises OKT-3. In some embodiments, the in the rapid second expansion media comprises 500 mL of culture medium and 30 μ g of OKT-3 per container. In some embodiments, the container is a GREX100 MCS flask. In some embodiments, the in the rapid second expansion media comprises 6000 IU/mL of IL-2, 60 ng/mL of OKT-3, and 7.5×10^8 antigen-presenting feeder cells. In some embodiments, the media comprises 500 mL of culture medium and 6000 IU/mL of IL-2, 30 μ g of OKT-3, and 7.5×10^8 antigen-presenting feeder cells per container.

[00839] In some embodiments, the media in the rapid second expansion comprises IL-2. In some embodiments, the media comprises 6000 IU/mL of IL-2. In some embodiments, the media in the rapid second expansion comprises antigen-presenting feeder cells. In some embodiments, the media comprises between 5×10^8 and 7.5×10^8 antigen-presenting feeder cells per container. In some embodiments, the media in the rapid second expansion comprises OKT-3. In some embodiments, the media in the rapid second expansion comprises 500 mL of culture medium and 30 μ g of OKT-3 per container. In some embodiments, the container is a GREX100 MCS flask. In some embodiments, the media in the rapid second expansion comprises 6000 IU/mL of IL-2, 60 ng/mL of OKT-3, and between 5×10^8 and 7.5×10^8 antigen-presenting feeder cells. In some embodiments, the media in the rapid second expansion comprises 500 mL of culture medium and 6000 IU/mL of IL-2, 30 μ g of OKT-3, and between 5×10^8 and 7.5×10^8 antigen-presenting feeder cells per container.

[00840] In some embodiments, the cell culture medium comprises one or more TNFRSF agonists in a cell culture medium. In some embodiments, the TNFRSF agonist comprises a 4-

1BB agonist. In some embodiments, the TNFRSF agonist is a 4-1BB agonist, and the 4-1BB agonist is selected from the group consisting of urelumab, utomilumab, EU-101, a fusion protein, and fragments, derivatives, variants, biosimilars, and combinations thereof. In some embodiments, the TNFRSF agonist is added at a concentration sufficient to achieve a concentration in the cell culture medium of between 0.1 μ g/mL and 100 μ g/mL. In some embodiments, the TNFRSF agonist is added at a concentration sufficient to achieve a concentration in the cell culture medium of between 20 μ g/mL and 40 μ g/mL.

[00841] In some embodiments, in addition to one or more TNFRSF agonists, the cell culture medium further comprises IL-2 at an initial concentration of about 3000 IU/mL and OKT-3 antibody at an initial concentration of about 30 ng/mL, and wherein the one or more TNFRSF agonists comprises a 4-1BB agonist.

[00842] In some embodiments, a combination of IL-2, IL-7, IL-15, and/or IL-21 are employed as a combination during the second expansion. In some embodiments, IL-2, IL-7, IL-15, and/or IL-21 as well as any combinations thereof can be included during the second expansion, including, for example during a Step D processes according to Figure 8 (in particular, *e.g.*, Figure 8B and/or Figure 8C), as well as described herein. In some embodiments, a combination of IL-2, IL-15, and IL-21 are employed as a combination during the second expansion. In some embodiments, IL-2, IL-15, and IL-21 as well as any combinations thereof can be included during Step D processes according to Figure 8 (in particular, *e.g.*, Figure 8B and/or Figure 8C) and as described herein.

[00843] In some embodiments, the second expansion can be conducted in a supplemented cell culture medium comprising IL-2, OKT-3, antigen-presenting feeder cells, and optionally a TNFRSF agonist. In some embodiments, the second expansion occurs in a supplemented cell culture medium. In some embodiments, the supplemented cell culture medium comprises IL-2, OKT-3, and antigen-presenting feeder cells. In some embodiments, the second cell culture medium comprises IL-2, OKT-3, and antigen-presenting cells (APCs; also referred to as antigen-presenting feeder cells). In some embodiments, the second expansion occurs in a cell culture medium comprising IL-2, OKT-3, and antigen-presenting feeder cells (*i.e.*, antigen presenting cells).

[00844] In some embodiments, the second expansion culture media comprises about 500 IU/mL of IL-15, about 400 IU/mL of IL-15, about 300 IU/mL of IL-15, about 200 IU/mL of IL-15, about 180 IU/mL of IL-15, about 160 IU/mL of IL-15, about 140 IU/mL of IL-15,

about 120 IU/mL of IL-15, or about 100 IU/mL of IL-15. In some embodiments, the second expansion culture media comprises about 500 IU/mL of IL-15 to about 100 IU/mL of IL-15. In some embodiments, the second expansion culture media comprises about 400 IU/mL of IL-15 to about 100 IU/mL of IL-15. In some embodiments, the second expansion culture media comprises about 300 IU/mL of IL-15 to about 100 IU/mL of IL-15. In some embodiments, the second expansion culture media comprises about 200 IU/mL of IL-15. In some embodiments, the cell culture medium comprises about 180 IU/mL of IL-15. In an embodiment, the cell culture medium further comprises IL-15. In a preferred embodiment, the cell culture medium comprises about 180 IU/mL of IL-15.

[00845] In some embodiments, the second expansion culture media comprises about 20 IU/mL of IL-21, about 15 IU/mL of IL-21, about 12 IU/mL of IL-21, about 10 IU/mL of IL-21, about 5 IU/mL of IL-21, about 4 IU/mL of IL-21, about 3 IU/mL of IL-21, about 2 IU/mL of IL-21, about 1 IU/mL of IL-21, or about 0.5 IU/mL of IL-21. In some embodiments, the second expansion culture media comprises about 20 IU/mL of IL-21 to about 0.5 IU/mL of IL-21. In some embodiments, the second expansion culture media comprises about 15 IU/mL of IL-21 to about 0.5 IU/mL of IL-21. In some embodiments, the second expansion culture media comprises about 12 IU/mL of IL-21 to about 0.5 IU/mL of IL-21. In some embodiments, the second expansion culture media comprises about 10 IU/mL of IL-21 to about 0.5 IU/mL of IL-21. In some embodiments, the second expansion culture media comprises about 5 IU/mL of IL-21 to about 1 IU/mL of IL-21. In some embodiments, the second expansion culture media comprises about 2 IU/mL of IL-21. In some embodiments, the cell culture medium comprises about 1 IU/mL of IL-21. In some embodiments, the cell culture medium comprises about 0.5 IU/mL of IL-21. In an embodiment, the cell culture medium further comprises IL-21. In a preferred embodiment, the cell culture medium comprises about 1 IU/mL of IL-21.

[00846] In some embodiments, the antigen-presenting feeder cells (APCs) are PBMCs. In an embodiment, the ratio of TILs to PBMCs and/or antigen-presenting cells in the rapid expansion and/or the second expansion is about 1 to 10, about 1 to 15, about 1 to 20, about 1 to 25, about 1 to 30, about 1 to 35, about 1 to 40, about 1 to 45, about 1 to 50, about 1 to 75, about 1 to 100, about 1 to 125, about 1 to 150, about 1 to 175, about 1 to 200, about 1 to 225, about 1 to 250, about 1 to 275, about 1 to 300, about 1 to 325, about 1 to 350, about 1 to 375, about 1 to 400, or about 1 to 500. In an embodiment, the ratio of TILs to PBMCs in the rapid expansion and/or the second expansion is between 1 to 50 and 1 to 300. In an embodiment,

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the ratio of TILs to PBMCs in the rapid expansion and/or the second expansion is between 1 to 100 and 1 to 200.

[00847] In an embodiment, REP and/or the rapid second expansion is performed in flasks with the bulk TILs being mixed with a 100- or 200-fold excess of inactivated feeder cells, wherein the feeder cell concentration is at least 1.1 times (1.1X), 1.2X, 1.3X, 1.4X, 1.5X, 1.6X, 1.7X, 1.8X, 1.8X, 2X, 2.1X2.2X, 2.3X, 2.4X, 2.5X, 2.6X, 2.7X, 2.8X, 2.9X, 3.0X, 3.1X, 3.2X, 3.3X, 3.4X, 3.5X, 3.6X, 3.7X, 3.8X, 3.9X or 4.0X the feeder cell concentration in the priming first expansion, 30 ng/mL OKT3 anti-CD3 antibody and 6000 IU/mL IL-2 in 150 ml media. Media replacement is done (generally 2/3 media replacement via aspiration of 2/3 of spent media and replacement with an equal volume of fresh media) until the cells are transferred to an alternative growth chamber. Alternative growth chambers include G-REX flasks and gas permeable containers as more fully discussed below.

[00848] In some embodiments, the rapid second expansion (which can include processes referred to as the REP process) is 7 to 9 days, as discussed in the examples and figures. In some embodiments, the second expansion is 7 days. In some embodiments, the second expansion is 8 days. In some embodiments, the second expansion is 9 days.

[00849] In an embodiment, the second expansion (which can include expansions referred to as REP, as well as those referred to in Step D of Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C) may be performed in 500 mL capacity gas permeable flasks with 100 cm gaspermeable silicon bottoms (G-Rex 100, commercially available from Wilson Wolf Manufacturing Corporation, New Brighton, MN, USA), 5×10^6 or 10×10^6 TIL may be cultured with PBMCs in 400 mL of 50/50 medium, supplemented with 5% human AB serum, 3000 IU per mL of IL-2 and 30 ng per ml of anti-CD3 (OKT3). The G-Rex 100 flasks may be incubated at 37°C in 5% CO₂. On day 5, 250 mL of supernatant may be removed and placed into centrifuge bottles and centrifuged at 1500 rpm (491 × g) for 10 minutes. The TIL pellets may be re-suspended with 150 mL of fresh medium with 5% human AB serum, 6000 IU per mL of IL-2, and added back to the original GREX-100 flasks. When TIL are expanded serially in GREX-100 flasks, on day 10 or 11 the TILs can be moved to a larger flask, such as a GREX-500. The cells may be harvested on day 14 of culture. The cells may be harvested on day 15 of culture. The cells may be harvested on day 16 of culture. In some embodiments, media replacement is done until the cells are transferred to an alternative growth chamber. In some embodiments, 2/3 of the media is replaced by aspiration of spent media and

replacement with an equal volume of fresh media. In some embodiments, alternative growth chambers include GREX flasks and gas permeable containers as more fully discussed below.

In some embodiments, the culture medium used in the expansion processes disclosed herein is a serum-free medium or a defined medium. In some embodiments, the serum-free or defined medium comprises a basal cell medium and a serum supplement and/or a serum replacement. In some embodiments, the serum-free or defined medium is used to prevent and/or decrease experimental variation due in part to the lot-to-lot variation of serum-containing media.

In some embodiments, the serum-free or defined medium comprises a basal cell medium and a serum supplement and/or serum replacement. In some embodiments, the basal cell medium includes, but is not limited to CTSTM OpTmizerTM T-cell Expansion Basal Medium , CTSTM OpTmizerTM T-Cell Expansion SFM, CTSTM AIM-V Medium, CTSTM AIM-V SFM, LymphoONETM T-Cell Expansion Xeno-Free Medium, Dulbecco's Modified Eagle's Medium (DMEM), Minimal Essential Medium (MEM), Basal Medium Eagle (BME), RPMI 1640, F-10, F-12, Minimal Essential Medium (αMEM), Glasgow's Minimal Essential Medium (G-MEM), RPMI growth medium, and Iscove's Modified Dulbecco's Medium.

In some embodiments, the serum supplement or serum replacement includes, but is not limited to one or more of CTS™ OpTmizer T-Cell Expansion Serum Supplement, CTS™ Immune Cell Serum Replacement, one or more albumins or albumin substitutes, one or more amino acids, one or more vitamins, one or more transferrins or transferrin substitutes, one or more antioxidants, one or more insulins or insulin substitutes, one or more collagen precursors, one or more antibiotics, and one or more trace elements. In some embodiments, the defined medium comprises albumin and one or more ingredients selected from the group consisting of glycine, L- histidine, L-isoleucine, L-methionine, L-phenylalanine, L-proline, L- hydroxyproline, L-serine, L-threonine, L-tryptophan, L-tyrosine, L-valine, thiamine, reduced glutathione, L-ascorbic acid-2-phosphate, iron saturated transferrin, insulin, and compounds containing the trace element moieties Ag⁺, Al³⁺, Ba²⁺, Cd²⁺, Co²⁺, Cr³⁺, Ge⁴⁺, Se⁴⁺, Br, T, Mn²⁺, P, Si⁴⁺, V⁵⁺, Mo⁶⁺, Ni²⁺, Rb⁺, Sn²⁺ and Zr⁴⁺. In some embodiments, the defined medium further comprises L-glutamine, sodium bicarbonate and/or 2-mercaptoethanol.

[00853] In some embodiments, the CTSTMOpTmizerTM T-cell Immune Cell Serum Replacement is used with conventional growth media, including but not limited to CTSTM

OpTmizerTM T-cell Expansion Basal Medium, CTSTM OpTmizerTM T-cell Expansion SFM, CTSTM AIM-V Medium, CSTTM AIM-V SFM, LymphoONETM T-Cell Expansion Xeno-Free Medium, Dulbecco's Modified Eagle's Medium (DMEM), Minimal Essential Medium (MEM), Basal Medium Eagle (BME), RPMI 1640, F-10, F-12, Minimal Essential Medium (αMEM), Glasgow's Minimal Essential Medium (G-MEM), RPMI growth medium, and Iscove's Modified Dulbecco's Medium.

[00854] In some embodiments, the total serum replacement concentration (vol%) in the serum-free or defined medium is from about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20% by volume of the total serum-free or defined medium. In some embodiments, the total serum replacement concentration is about 3% of the total volume of the serum-free or defined medium. In some embodiments, the total serum replacement concentration is about 5% of the total volume of the serum-free or defined medium. In some embodiments, the total serum replacement concentration is about 10% of the total volume of the serum-free or defined medium.

[00855] In some embodiments, the serum-free or defined medium is CTSTM OpTmizerTM T-cell Expansion SFM (ThermoFisher Scientific). Any formulation of CTSTM OpTmizerTM is useful in the present invention. CTSTM OpTmizerTM T-cell Expansion SFM is a combination of 1L CTSTM OpTmizerTM T-cell Expansion Basal Medium and 26 mL CTSTM OpTmizerTM T-Cell Expansion Supplement, which are mixed together prior to use. In some embodiments, the CTSTM OpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTSTM Immune Cell Serum Replacement (SR) (ThermoFisher Scientific), along with 2-mercaptoethanol at 55mM.

In some embodiments, the defined medium is CTSTM OpTmizerTM T-cell Expansion SFM (ThermoFisher Scientific). Any formulation of CTSTM OpTmizerTM is useful in the present invention. CTSTM OpTmizerTM T-cell Expansion SFM is a combination of 1L CTSTM OpTmizerTM T-cell Expansion Basal Medium and 26 mL CTSTM OpTmizerTM T-Cell Expansion Supplement, which are mixed together prior to use. In some embodiments, the CTSTM OpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTSTM Immune Cell Serum Replacement (SR) (ThermoFisher Scientific), along with 2-mercaptoethanol at 55mM. In some embodiments, the CTSTMOpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTSTM Immune Cell Serum Replacement (SR) (ThermoFisher Scientific), 55mM of 2-mercaptoethanol, and 2mM of L-glutamine. In some embodiments, the CTSTMOpTmizerTM T-cell Expansion SFM is supplemented with about 3%

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of the CTS™ Immune Cell Serum Replacement (SR) (ThermoFisher Scientific), 55mM of 2mercaptoethanol, and 2mM of L-glutamine, and further comprises about 1000 IU/mL to about 8000 IU/mL of IL-2. In some embodiments, the CTSTMOpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTSTM Immune Cell Serum Replacement (SR) (ThermoFisher Scientific), 55mM of 2-mercaptoethanol, and 2mM of L-glutamine, and further comprises about 3000 IU/mL of IL-2. In some embodiments, the CTSTMOpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTS™ Immune Cell Serum Replacement (SR) (ThermoFisher Scientific), 55mM of 2-mercaptoethanol, and 2mM of Lglutamine, and further comprises about 6000 IU/mL of IL-2. In some embodiments, the CTSTMOpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTSTM Immune Cell Serum Replacement (SR) (ThermoFisher Scientific) and 55mM of 2mercaptoethanol, and further comprises about 1000 IU/mL to about 8000 IU/mL of IL-2. In some embodiments, the CTSTMOpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTSTM Immune Cell Serum Replacement (SR) (ThermoFisher Scientific) and 55mM of 2-mercaptoethanol, and further comprises about 3000 IU/mL of IL-2. In some embodiments, the CTSTMOpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTSTM Immune Cell Serum Replacement (SR) (ThermoFisher Scientific) and 55mM of 2-mercaptoethanol, and further comprises about 1000 IU/mL to about 6000 IU/mL of IL-2. In some embodiments, the CTSTMOpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTSTM Immune Cell Serum Replacement (SR) (ThermoFisher Scientific) and about 2mM glutamine, and further comprises about 1000 IU/mL to about 8000 IU/mL of IL-2. In some embodiments, the CTSTMOpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTSTM Immune Cell Serum Replacement (SR) (ThermoFisher Scientific) and about 2mM glutamine, and further comprises about 3000 IU/mL of IL-2. In some embodiments, the CTSTMOpTmizerTM T-cell Expansion SFM is supplemented with about 3% of the CTSTM Immune Cell Serum Replacement (SR) (ThermoFisher Scientific) and about 2mM glutamine, and further comprises about 6000 IU/mL of IL-2.

[00857] In some embodiments, the serum-free medium or defined medium is supplemented with glutamine (i.e., GlutaMAX®) at a concentration of from about 0.1mM to about 10mM, 0.5mM to about 9mM, 1mM to about 8mM, 2mM to about 7mM, 3mM to about 6mM, or 4mM to about 5 mM. In some embodiments, the serum-free medium or defined medium is supplemented with glutamine (i.e., GlutaMAX®) at a concentration of about 2mM.

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[00858] In some embodiments, the serum-free medium or defined medium is supplemented with 2-mercaptoethanol at a concentration of from about 5mM to about 150mM, 10mM to about 140mM, 15mM to about 130mM, 20mM to about 120mM, 25mM to about 110mM, 30mM to about 100mM, 35mM to about 95mM, 40mM to about 90mM, 45mM to about 85mM, 50mM to about 80mM, 55mM to about 75mM, 60mM to about 70mM, or about 65mM. In some embodiments, the serum-free medium or defined medium is supplemented with 2-mercaptoethanol at a concentration of about 55mM.

[00859] In some embodiments, the defined media described in International PCT Publication No. WO/1998/030679, which is herein incorporated by reference, are useful in the present invention. In that publication, serum-free eukaryotic cell culture media are described. The serum-free, eukaryotic cell culture medium includes a basal cell culture medium supplemented with a serum-free supplement capable of supporting the growth of cells in serum- free culture. The serum-free eukarvotic cell culture medium supplement comprises or is obtained by combining one or more ingredients selected from the group consisting of one or more albumins or albumin substitutes, one or more amino acids, one or more vitamins, one or more transferrins or transferrin substitutes, one or more antioxidants, one or more insulins or insulin substitutes, one or more collagen precursors, one or more trace elements, and one or more antibiotics. In some embodiments, the defined medium further comprises L-glutamine, sodium bicarbonate and/or beta-mercaptoethanol. In some embodiments, the defined medium comprises an albumin or an albumin substitute and one or more ingredients selected from group consisting of one or more amino acids, one or more vitamins, one or more transferrins or transferrin substitutes, one or more antioxidants, one or more insulins or insulin substitutes, one or more collagen precursors, and one or more trace elements. In some embodiments, the defined medium comprises albumin and one or more ingredients selected from the group consisting of glycine, L-histidine, L-isoleucine, Lmethionine, L-phenylalanine, L-proline, L- hydroxyproline, L-serine, L-threonine, Ltryptophan, L-tyrosine, L-valine, thiamine, reduced glutathione, L-ascorbic acid-2-phosphate, iron saturated transferrin, insulin, and compounds containing the trace element moieties Ag⁺, Al³⁺, Ba²⁺, Cd²⁺, Co²⁺, Cr³⁺, Ge⁴⁺, Se⁴⁺, Br, T, Mn²⁺, P, Si⁴⁺, V⁵⁺, Mo⁶⁺, Ni²⁺, Rb⁺, Sn²⁺ and Zr⁴⁺. In some embodiments, the basal cell media is selected from the group consisting of Dulbecco's Modified Eagle's Medium (DMEM), Minimal Essential Medium (MEM), Basal Medium Eagle (BME), RPMI 1640, F-10, F-12, Minimal Essential Medium (αΜΕΜ),

Glasgow's Minimal Essential Medium (G-MEM), RPMI growth medium, and Iscove's Modified Dulbecco's Medium.

In some embodiments, the concentration of glycine in the defined medium is in the range of from about 5-200 mg/L, the concentration of L- histidine is about 5-250 mg/L, the concentration of L-isoleucine is about 5-300 mg/L, the concentration of L-methionine is about 5-200 mg/L, the concentration of L-phenylalanine is about 5-400 mg/L, the concentration of L-proline is about 1-1000 mg/L, the concentration of L- hydroxyproline is about 1-45 mg/L, the concentration of L-serine is about 1-250 mg/L, the concentration of L-threonine is about 10-500 mg/L, the concentration of L-tryptophan is about 2-110 mg/L, the concentration of L-tyrosine is about 3-175 mg/L, the concentration of L-valine is about 5-500 mg/L, the concentration of thiamine is about 1-20 mg/L, the concentration of reduced glutathione is about 1-20 mg/L, the concentration of L-ascorbic acid-2-phosphate is about 1-200 mg/L, the concentration of iron saturated transferrin is about 1-50 mg/L, the concentration of insulin is about 1-100 mg/L, the concentration of sodium selenite is about 0.000001-0.0001 mg/L, and the concentration of albumin (e.g., AlbuMAX® I) is about 5000-50,000 mg/L.

[00861] In some embodiments, the non-trace element moiety ingredients in the defined medium are present in the concentration ranges listed in the column under the heading "Concentration Range in 1X Medium" in Table A below. In other embodiments, the non-trace element moiety ingredients in the defined medium are present in the final concentrations listed in the column under the heading "A Preferred Embodiment of the 1X Medium" in Table A below. In other embodiments, the defined medium is a basal cell medium comprising a serum free supplement. In some of these embodiments, the serum free supplement comprises non-trace moiety ingredients of the type and in the concentrations listed in the column under the heading "A Preferred Embodiment in Supplement" in Table A below.

Table A: Concentrations of Non-Trace Element Moiety Ingredients

Ingredient	A preferred	Concentration range	A preferred
	embodiment in	in 1X medium	embodiment in 1X
	supplement (mg/L)	(mg/L)	medium (mg/L)
	(About)	(About)	(About)
Glycine	150	5-200	53
L-Histidine	940	5-250	183
L-Isoleucine	3400	5-300	615
L-Methionine	90	5-200	44

L-Phenylalanine	1800	5-400	336
L-Proline	4000	1~1000	600
L-Hydroxyproline	100	1-45	15
L-Serine	800	1-250	162
L-Threonine	2200	10-500	425
L-Tryptophan	440	2-110	82
L-Tyrosine	77	3-175	84
L-Valine	2400	5-500	454
Thiamine	33	1-20	9
Reduced Glutathione	10	1-20	1.5
Ascorbic Acid-2-PO ₄ (Mg Salt)	330	1-200	50
Transferrin (iron saturated)	55	1-50	S
Insulin	100	1-100	10
Sodium Selenite	0.07	0.000001-0.0001	0.00001
AlbuMAX®I	83,000	5000-50,000	12,500

In some embodiments, the osmolarity of the defined medium is between about 260 and 350 mOsmol. In some embodiments, the osmolarity is between about 280 and 310 mOsmol. In some embodiments, the defined medium is supplemented with up to about 3.7 g/L, or about 2.2 g/L sodium bicarbonate. The defined medium can be further supplemented with L-glutamine (final concentration of about 2 mM), one or more antibiotics, non-essential amino acids (NEAA; final concentration of about 100 μ M), 2-mercaptoethanol (final concentration of about 100 μ M).

[00863] In some embodiments, the defined media 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," *Clin Transl Immunology*, 4(1) 2015 (doi: 10.1038/cti.2014.31) are useful in the present invention. Briefly, RPMI or CTSTM OpTmizerTM was used as the basal cell medium, and supplemented with either 0, 2%, 5%, or 10% CTSTM Immune Cell Serum Replacement.

[00864] In an embodiment, the cell medium in the first and/or second gas permeable container is unfiltered. The use of unfiltered cell medium may simplify the procedures necessary to expand the number of cells. In an embodiment, the cell medium in the first and/or second gas permeable container lacks beta-mercaptoethanol (BME or β ME; also known as 2-mercaptoethanol, CAS 60-24-2).

[00865] In an embodiment, the rapid second expansion (including expansions referred to as REP) is performed and further comprises a step wherein TILs are selected for superior tumor

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reactivity. Any selection method known in the art may be used. For example, the methods described in U.S. Patent Application Publication No. 2016/0010058 A1, the disclosures of which are incorporated herein by reference, may be used for selection of TILs for superior tumor reactivity.

[00866] Optionally, a cell viability assay can be performed after the rapid second expansion (including expansions referred to as the REP expansion), using standard assays known in the art. For example, a trypan blue exclusion assay can be done on a sample of the bulk TILs, which selectively labels dead cells and allows a viability assessment. In some embodiments, TIL samples can be counted and viability determined using a Cellometer K2 automated cell counter (Nexcelom Bioscience, Lawrence, MA). In some embodiments, viability is determined according to the standard Cellometer K2 Image Cytometer Automatic Cell Counter protocol.

[00867] The diverse antigen receptors of T and B lymphocytes are produced by somatic recombination of a limited, but large number of gene segments. These gene segments: V (variable), D (diversity), J (joining), and C (constant), determine the binding specificity and downstream applications of immunoglobulins and T-cell receptors (TCRs). The present invention provides a method for generating TILs which exhibit and increase the T-cell repertoire diversity. In some embodiments, the TILs obtained by the present method exhibit an increase in the T-cell repertoire diversity. In some embodiments, the TILs obtained in the second expansion exhibit an increase in the T-cell repertoire diversity. In some embodiments, the increase in diversity is an increase in the immunoglobulin diversity and/or the T-cell receptor diversity. In some embodiments, the diversity is in the immunoglobulin is in the immunoglobulin heavy chain. In some embodiments, the diversity is in the immunoglobulin is in the immunoglobulin light chain. In some embodiments, the diversity is in the T-cell receptor. In some embodiments, the diversity is in one of the T-cell receptors selected from the group consisting of alpha, beta, gamma, and delta receptors. In some embodiments, there is an increase in the expression of T-cell receptor (TCR) alpha and/or beta. In some embodiments, there is an increase in the expression of T-cell receptor (TCR) alpha. In some embodiments, there is an increase in the expression of T-cell receptor (TCR) beta. In some embodiments, there is an increase in the expression of TCRab (i.e., TCR α/β).

[00868] In some embodiments, the rapid second expansion culture medium (e.g., sometimes referred to as CM2 or the second cell culture medium), comprises IL-2, OKT-3, as well as the antigen-presenting feeder cells (APCs), as discussed in more detail below. In

some embodiments, the rapid second expansion culture medium (e.g., sometimes referred to as CM2 or the second cell culture medium), comprises 6000 IU/mL IL-2, 30 ug/flask OKT-3, as well as 7.5×10^8 antigen-presenting feeder cells (APCs), as discussed in more detail below. In some embodiments, the rapid second expansion culture medium (e.g., sometimes referred to as CM2 or the second cell culture medium), comprises IL-2, OKT-3, as well as the antigen-presenting feeder cells (APCs), as discussed in more detail below. In some embodiments, the rapid second expansion culture medium (e.g., sometimes referred to as CM2 or the second cell culture medium), comprises 6000 IU/mL IL-2, 30 ug/flask OKT-3, as well as 5×10^8 antigen-presenting feeder cells (APCs), as discussed in more detail below.

[00869] In some embodiments, the rapid second expansion, for example, Step D according to Figure 8 (in particular, *e.g.*, Figure 8B and/or Figure 8C), is performed in a closed system bioreactor. In some embodiments, a closed system is employed for the TIL expansion, as described herein. In some embodiments, a bioreactor is employed. In some embodiments, a bioreactor is employed as the container. In some embodiments, the bioreactor employed is for example a G-REX-100 or a G-REX-500. In some embodiments, the bioreactor employed is a G-REX-500.

1. Feeder Cells and Antigen Presenting Cells

[00870] In an embodiment, the rapid second expansion procedures described herein (for example including expansion such as those described in Step D from Figure 8 (in particular, e.g., Figure 8B and/or Figure 8C), as well as those referred to as REP) require an excess of feeder cells during REP TIL expansion and/or during the rapid second expansion. In many embodiments, the feeder cells are peripheral blood mononuclear cells (PBMCs) obtained from standard whole blood units from healthy blood donors. The PBMCs are obtained using standard methods such as Ficoll-Paque gradient separation.

[00871] In general, the allogenic PBMCs are inactivated, either via irradiation or heat treatment, and used in the REP procedures, as described in the examples, which provides an exemplary protocol for evaluating the replication incompetence of irradiate allogeneic PBMCs.

[00872] In some embodiments, PBMCs are considered replication incompetent and acceptable for use in the TIL expansion procedures described herein if the total number of

viable cells on day 7 or 14 is less than the initial viable cell number put into culture on day 0 of the REP and/or day 0 of the second expansion (*i.e.*, the start day of the second expansion).

[00873] In some embodiments, PBMCs are considered replication incompetent and acceptable for use in the TIL expansion procedures described herein if the total number of viable cells, cultured in the presence of OKT3 and IL-2, on day 7 and day 14 has not increased from the initial viable cell number put into culture on day 0 of the REP and/or day 0 of the second expansion (*i.e.*, the start day of the second expansion). In some embodiments, the PBMCs are cultured in the presence of 30 ng/ml OKT3 antibody and 3000 IU/ml IL-2. In some embodiments, the PBMCs are cultured in the presence of 60 ng/ml OKT3 antibody and 6000 IU/ml IL-2. In some embodiments, the PBMCs are cultured in the presence of 60 ng/ml OKT3 antibody and 3000 IU/ml IL-2. In some embodiments, the PBMCs are cultured in the presence of 30 ng/ml OKT3 antibody and 6000 IU/ml IL-2.

[00874] In some embodiments, PBMCs are considered replication incompetent and acceptable for use in the TIL expansion procedures described herein if the total number of viable cells, cultured in the presence of OKT3 and IL-2, on day 7 and day 14 has not increased from the initial viable cell number put into culture on day 0 of the REP and/or day 0 of the second expansion (*i.e.*, the start day of the second expansion). In some embodiments, the PBMCs are cultured in the presence of 30-60 ng/ml OKT3 antibody and 1000-6000 IU/ml IL-2. In some embodiments, the PBMCs are cultured in the presence of 30-60 ng/ml OKT3 antibody and 2000-5000 IU/ml IL-2. In some embodiments, the PBMCs are cultured in the presence of 30-60 ng/ml OKT3 antibody and 2000-4000 IU/ml IL-2. In some embodiments, the PBMCs are cultured in the presence of 30-60 ng/ml OKT3 antibody and 2500-3500 IU/ml IL-2. In some embodiments, the PBMCs are cultured in the presence of 30-60 ng/ml OKT3 antibody and 2500-3500 IU/ml IL-2. In some embodiments, the PBMCs are cultured in the presence of 30-60 ng/ml OKT3 antibody and 6000 IU/ml IL-2.

[00875] In some embodiments, the antigen-presenting feeder cells are PBMCs. In some embodiments, the antigen-presenting feeder cells are artificial antigen-presenting feeder cells. In an embodiment, the ratio of TILs to antigen-presenting feeder cells in the second expansion is about 1 to 10, about 1 to 25, about 1 to 50, about 1 to 100, about 1 to 125, about 1 to 150, about 1 to 175, about 1 to 200, about 1 to 225, about 1 to 250, about 1 to 275, about 1 to 300, about 1 to 325, about 1 to 350, about 1 to 375, about 1 to 400, or about 1 to 500. In an embodiment, the ratio of TILs to antigen-presenting feeder cells in the second expansion is between 1 to 50 and 1 to 300. In an embodiment, the ratio of TILs to antigen-presenting feeder cells in the second expansion is between 1 to 100 and 1 to 200.

[00876] In an embodiment, the second expansion procedures described herein require a ratio of about 5×10^8 feeder cells to about 100×10^6 TILs. In an embodiment, the second expansion procedures described herein require a ratio of about 7.5×10^8 feeder cells to about 100×10^6 TILs. In another embodiment, the second expansion procedures described herein require a ratio of about 5×10^8 feeder cells to about 50×10^6 TILs. In another embodiment, the second expansion procedures described herein require a ratio of about 7.5×10^8 feeder cells to about 50×10^6 TILs. In yet another embodiment, the second expansion procedures described herein require about 5×10^8 feeder cells to about 25×10^6 TILs. In vet another embodiment, the second expansion procedures described herein require about 7.5×10^8 feeder cells to about 25×10^6 TILs. In vet another embodiment, the rapid second expansion requires twice the number of feeder cells as the rapid second expansion. In yet another embodiment, when the priming first expansion described herein requires about 2.5×10^8 feeder cells, the rapid second expansion requires about 5×10^8 feeder cells. In yet another embodiment, when the priming first expansion described herein requires about 2.5×10^8 feeder cells, the rapid second expansion requires about 7.5×10^8 feeder cells. In yet another embodiment, the rapid second expansion requires two times (2.0X), 2.5X, 3.0X, 3.5X or 4.0X the number of feeder cells as the <u>priming first</u> expansion.

[00877] In an embodiment, the rapid second expansion procedures described herein require an excess of feeder cells during the rapid second expansion. In many embodiments, the feeder cells are peripheral blood mononuclear cells (PBMCs) obtained from standard whole blood units from allogeneic healthy blood donors. The PBMCs are obtained using standard methods such as Ficoll-Paque gradient separation. In an embodiment, artificial antigen-presenting (aAPC) cells are used in place of PBMCs. In some embodiments, the PBMCs are added to the rapid second expansion at twice the concentration of PBMCs that were added to the priming first expansion.

[00878] In general, the allogenic PBMCs are inactivated, either via irradiation or heat treatment, and used in the TIL expansion procedures described herein, including the exemplary procedures described in the figures and examples.

[00879] In an embodiment, artificial antigen presenting cells are used in the rapid second expansion as a replacement for, or in combination with, PBMCs.

2. Cytokines

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[00880] The rapid second expansion methods described herein generally use culture media with high doses of a cytokine, in particular IL-2, as is known in the art.

[00881] Alternatively, using combinations of cytokines for the rapid second expansion of TILs is additionally possible, with combinations of two or more of IL-2, IL-15 and IL-21 as is generally outlined in WO 2015/189356 and WO 2015/189357, hereby expressly incorporated by reference in their entirety. Thus, possible combinations include IL-2 and IL-15, IL-2 and IL-21, IL-15 and IL-21, and IL-2, IL-15 and IL-21, with the latter finding particular use in many embodiments. The use of combinations of cytokines specifically favors the generation of lymphocytes, and in particular T-cells as described therein.

E. STEP E: Harvest TILS

[00882] After the rapid second expansion step, cells can be harvested. In some embodiments the TILs are harvested after one, two, three, four or more expansion steps, for example as provided in Figure 8 (in particular, *e.g.*, Figure 8B and/or Figure 8C). In some embodiments the TILs are harvested after two expansion steps, for example as provided in Figure 8 (in particular, *e.g.*, Figure 8B and/or Figure 8C). In some embodiments the TILs are harvested after two expansion steps, one priming first expansion and one rapid second expansion, for example as provided in Figure 8 (in particular, *e.g.*, Figure 8B and/or Figure 8C).

[00883] TILs can be harvested in any appropriate and sterile manner, including, for example by centrifugation. Methods for TIL harvesting are well known in the art and any such known methods can be employed with the present process. In some embodiments, TILS are harvested using an automated system.

[00884] Cell harvesters and/or cell processing systems are commercially available from a variety of sources, including, for example, Fresenius Kabi, Tomtec Life Science, Perkin Elmer, and Inotech Biosystems International, Inc. Any cell based harvester can be employed with the present methods. In some embodiments, the cell harvester and/or cell processing system is a membrane-based cell harvester. In some embodiments, cell harvesting is via a cell processing system, such as the LOVO system (manufactured by Fresenius Kabi). The term "LOVO cell processing system" also refers to any instrument or device manufactured by any vendor that can pump a solution comprising cells through a membrane or filter such as a spinning membrane or spinning filter in a sterile and/or closed system environment, allowing for continuous flow and cell processing to remove supernatant or cell culture media without pelletization. In some embodiments, the cell harvester and/or cell processing system can

perform cell separation, washing, fluid-exchange, concentration, and/or other cell processing steps in a closed, sterile system.

[00885] In some embodiments, the rapid second expansion, for example, Step D according to Figure 8 (in particular, *e.g.*, Figure 8B and/or Figure 8C), is performed in a closed system bioreactor. In some embodiments, a closed system is employed for the TIL expansion, as described herein. In some embodiments, a bioreactor is employed. In some embodiments, a bioreactor is employed as the container. In some embodiments, the bioreactor employed is for example a G-REX-100 or a G-REX-500. In some embodiments, the bioreactor employed is a G-REX-500.

[00886] In some embodiments, Step E according to Figure 8 (in particular, *e.g.*, Figure 8B and/or Figure 8C), is performed according to the processes described herein. In some embodiments, the closed system is accessed via syringes under sterile conditions in order to maintain the sterility and closed nature of the system. In some embodiments, a closed system as described herein is employed.

[00887] In some embodiments, TILs are harvested according to the methods described in herein. In some embodiments, TILs between days 14 and 16 are harvested using the methods as described herein. In some embodiments, TILs are harvested at 14 days using the methods as described herein. In some embodiments, TILs are harvested at 15 days using the methods as described herein. In some embodiments, TILs are harvested at 16 days using the methods as described herein.

F. STEP F: Final Formulation/ Transfer to Infusion Bag

[00888] After Steps A through E as provided in an exemplary order in Figure 8 (in particular, *e.g.*, Figure 8B) and as outlined in detailed above and herein are complete, cells are transferred to a container for use in administration to a patient. In some embodiments, once a therapeutically sufficient number of TILs are obtained using the expansion methods described above, they are transferred to a container for use in administration to a patient.

[00889] In an embodiment, TILs expanded using the methods of the present disclosure are administered to a patient as a pharmaceutical composition. In an embodiment, the pharmaceutical composition is a suspension of TILs in a sterile buffer. TILs expanded as disclosed herein may be administered by any suitable route as known in the art. In some embodiments, the TILs are administered as a single intra-arterial or intravenous infusion,

which preferably lasts approximately 30 to 60 minutes. Other suitable routes of administration include intraperitoneal, intrathecal, and intralymphatic.

G. PBMC Feeder Cell Ratios

[00890] In some embodiments, the culture media used in expansion methods described herein (see for example, Figure 8 (in particular, *e.g.*, Figure 8B and/or Figure 8C)) include an anti-CD3 antibody e.g. OKT-3. An anti-CD3 antibody in combination with IL-2 induces T cell activation and cell division in the TIL population. This effect can be seen with full length antibodies as well as Fab and F(ab')2 fragments, with the former being generally preferred; see, *e.g.*, Tsoukas *et al.*, *J. Immunol.* **1985**, *135*, 1719, hereby incorporated by reference in its entirety.

[00891] In an embodiment, the number of PBMC feeder layers is calculated as follows:

- A. Volume of a T-cell (10 μ m diameter): $V = (4/3) \pi r^3 = 523.6 \mu m^3$
- B. Columne of G-Rex 100 (M) with a 40 μ m (4 cells) height: $V = (4/3) \pi r^3 = 4 \times 10^{12} \mu m^3$
- C. Number cell required to fill column B: $4 \times 10^{12} \ \mu m^3 / 523.6 \ \mu m^3 = 7.6 \times 10^8 \ \mu m^3 * 0.64 = 4.86 \times 10^8$
- D. Number cells that can be optimally activated in 4D space: $4.86 \times 10^8 / 24 = 20.25 \times 10^6$
- E. Number of feeders and TIL extrapolated to G-Rex 500: TIL: 100×10^6 and Feeder: 2.5×10^9

In this calculation, an approximation of the number of mononuclear cells required to provide an icosahedral geometry for activation of TIL in a cylinder with a 100 cm^2 base is used. The calculation derives the experimental result of $\sim 5 \times 10^8$ for threshold activation of T-cells which closely mirrors NCI experimental data.⁽¹⁾ (C) The multiplier (0.64) is the random packing density for equivalent spheres as calculated by Jaeger and Nagel in $1992^{(2)}$. (D) The divisor 24 is the number of equivalent spheres that could contact a similar object in 4 dimensional space "the Newton number."⁽³⁾.

- (1) Jin, Jianjian, et.al., Simplified Method of the Growth of Human Tumor Infiltrating Lymphocytes (TIL) in Gas-Permeable Flasks to Numbers Needed for Patient Treatment. J Immunother. 2012 Apr; 35(3): 283–292.
- ⁽²⁾ Jaeger HM, Nagel SR. Physics of the granular state. Science. 1992 Mar 20;255(5051):1523-31.

(3) O. R. Musin (2003). "The problem of the twenty-five spheres". Russ. Math. Surv. 58 (4): 794–795.

[00892] In an embodiment, the number of antigen-presenting feeder cells exogenously supplied during the priming first expansion is approximately one-half the number of antigen-presenting feeder cells exogenously supplied during the rapid second expansion. In certain embodiments, the method comprises performing the priming first expansion in a cell culture medium which comprises approximately 50% fewer antigen presenting cells as compared to the cell culture medium of the rapid second expansion.

[00893] In another embodiment, the number of antigen-presenting feeder cells (APCs) exogenously supplied during the rapid second expansion is greater than the number of APCs exogenously supplied during the priming first expansion.

[00894] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 20:1.

[00895] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 10:1.

[00896] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 9:1.

[00897] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 8:1.

[00898] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 7:1.

[00899] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 6:1.

[00900] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 5:1.

[00901] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 4:1.

[00902] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion) is selected from a range of from at or about 1.1:1 to at or about 3:1.

[00903] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 2.9:1.

[00904] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 2.8:1.

[00905] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 2.7:1.

[00906] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 2.6:1.

[00907] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 2.5:1.

[00908] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 2.4:1.

[00909] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 2.3:1.

[00910] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 2.2:1.

[00911] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 2.1:1.

[00912] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 2:1.

[00913] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 2:1 to at or about 10:1.

[00914] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 2:1 to at or about 5:1.

[00915] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 2:1 to at or about 4:1.

[00916] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 2:1 to at or about 3:1.

[00917] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 2:1 to at or about 2.9:1.

[00918] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 2:1 to at or about 2.8:1.

[00919] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 2:1 to at or about 2.7:1.

[00920] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 2:1 to at or about 2.6:1.

[00921] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 2:1 to at or about 2.5:1.

[00922] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 2:1 to at or about 2.4:1.

[00923] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 2:1 to at or about 2.3:1.

[00924] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about about 2:1 to at or about 2.2:1.

[00925] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is selected from a range of from at or about 2:1 to at or about 2.1:1.

[00926] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is at or about 2:1.

[00927] In another embodiment, the ratio of the number of APCs exogenously supplied during the rapid second expansion to the number of APCs exogenously supplied during the priming first expansion is at or about 1.1:1, 1.2:1, 1.3:1, 1.4:1, 1.5:1, 1.6:1, 1.7:1, 1.8:1, 1.9:1, 2:1, 2.1:1, 2.2:1, 2.3:1, 2.4:1, 2.5:1, 2.6:1, 2.7:1, 2.8:1, 2.9:1, 3:1, 3.1:1, 3.2:1, 3.3:1, 3.4:1, 3.5:1, 3.6:1, 3.7:1, 3.8:1, 3.9:1, 4:1, 4.1:1, 4.2:1, 4.3:1, 4.4:1, 4.5:1, 4.6:1, 4.7:1, 4.8:1, 4.9:1, or 5:1.

[00928] In another embodiment, the number of APCs exogenously supplied during the priming first expansion is at or about 1×10^8 , 1.1×10^8 , 1.2×10^8 , 1.3×10^8 , 1.4×10^8 , 1.5×10^8 , 1.6×10^8 , 1.7×10^8 , 1.8×10^8 , 1.9×10^8 , 2×10^8 , 2.1×10^8 , 2.2×10^8 , 2.3×10^8 , 2.4×10^8 , 2.5×10^8 ,

 $2.6 \times 10^8, 2.7 \times 10^8, 2.8 \times 10^8, 2.9 \times 10^8, 3 \times 10^8, 3.1 \times 10^8, 3.2 \times 10^8, 3.3 \times 10^8, 3.4 \times 10^8 \text{ or } 3.5 \times 10^8$ APCs, and the number of APCs exogenously supplied during the rapid second expansion is at or about $3.5 \times 10^8, 3.6 \times 10^8, 3.7 \times 10^8, 3.8 \times 10^8, 3.9 \times 10^8, 4 \times 10^8, 4.1 \times 10^8, 4.2 \times 10^8, 4.3 \times 10^8, 4.4 \times 10^8, 4.5 \times 10^8, 4.6 \times 10^8, 4.7 \times 10^8, 4.8 \times 10^8, 4.9 \times 10^8, 5 \times 10^8, 5.1 \times 10^8, 5.2 \times 10^8, 5.3 \times 10^8, 5.4 \times 10^8, 5.5 \times 10^8, 5.6 \times 10^8, 5.7 \times 10^8, 5.8 \times 10^8, 5.9 \times 10^8, 6 \times 10^8, 6.1 \times 10^8, 6.2 \times 10^8, 6.3 \times 10^8, 6.4 \times 10^8, 6.5 \times 10^8, 6.6 \times 10^8, 6.7 \times 10^8, 6.8 \times 10^8, 6.9 \times 10^8, 7 \times 10^8, 7.1 \times 10^8, 7.2 \times 10^8, 7.3 \times 10^8, 7.4 \times 10^8, 7.5 \times 10^8, 7.6 \times 10^8, 7.7 \times 10^8, 7.8 \times 10^8, 7.9 \times 10^8, 8.1 \times 10^8, 8.2 \times 10^8, 8.3 \times 10^8, 8.4 \times 10^8, 8.5 \times 10^8, 8.6 \times 10^8, 8.7 \times 10^8, 8.8 \times 10^8, 8.9 \times 10^8, 9.1 \times 10^8, 9.2 \times 10^8, 9.3 \times 10^8, 9.4 \times 10^8, 9.5 \times 10^8, 9.6 \times 10^8, 9.7 \times 10^8, 9.8 \times 10^8, 9.1 \times 10^9, 9.2 \times 10^8, 9.3 \times 10^8, 9.4 \times 10^8, 9.5 \times 10^8, 9.6 \times 10^8, 9.7 \times 10^8, 9.8 \times 10^8, 9.9 \times 10^8, 9.1 \times 10^9, 9.2 \times 10^8, 9.3 \times 10^8, 9.4 \times 10^8, 9.5 \times 10^8, 9.6 \times 10^8, 9.7 \times 10^8, 9.8 \times 10^8, 9.9 \times 10^8, 9.1 \times 10^9, 9.2 \times 10^8, 9.3 \times 10^8, 9.4 \times 10^8, 9.5 \times 10^8, 9.6 \times 10^8, 9.7 \times 10^8, 9.8 \times 10^8, 9.9 \times 10^9, 9.1 \times 10^9, 9.2 \times 10^8, 9.3 \times 10^8, 9.3 \times 10^8, 9.4 \times 10^9, 9.5 \times 10^8, 9.6 \times 10^8, 9.7 \times 10^8, 9.8 \times 10^8, 9.9 \times 10^9, 9.1 \times 10^9, 9.2 \times 10^8, 9.3 \times 10^8, 9.3 \times 10^8, 9.3 \times 10^9, 9.1 \times 10^9, 9.2 \times 10^8, 9.3 \times 10^8, 9.3 \times 10^9, 9.3$

[00929] In another embodiment, the number of APCs exogenously supplied during the priming first expansion is selected from the range of at or about 1.5×10^8 APCs to at or about 3×10^8 APCs, and the number of APCs exogenously supplied during the rapid second expansion is selected from the range of at or about 4×10^8 APCs to at or about 7.5×10^8 APCs.

[00930] In another embodiment, the number of APCs exogenously supplied during the priming first expansion is selected from the range of at or about 2×10^8 APCs to at or about 2.5×10^8 APCs, and the number of APCs exogenously supplied during the rapid second expansion is selected from the range of at or about 4.5×10^8 APCs to at or about 5.5×10^8 APCs.

[00931] In another embodiment, the number of APCs exogenously supplied during the priming first expansion is at or about 2.5×10^8 APCs, and the number of APCs exogenously supplied during the rapid second expansion is at or about 5×10^8 APCs.

[00932] In an embodiment, the number of APCs (including, for example, PBMCs) added at day 0 of the priming first expansion is approximately one-half of the number of PBMCs added at day 7 of the priming first expansion (e.g., day 7 of the method). In certain embodiments, the method comprises adding antigen presenting cells at day 0 of the priming first expansion to the first population of TILs and adding antigen presenting cells at day 7 to the second population of TILs, wherein the number of antigen presenting cells added at day 0 is approximately 50% of the number of antigen presenting cells added at day 7 of the priming first expansion (e.g., day 7 of the method).

[00933] In another embodiment, the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion is greater than the number of PBMCs exogenously supplied at day 0 of the priming first expansion.

[00934] In another embodiment, the APCs exogenously supplied in the priming first expansion are seeded in the culture flask at a density selected from a range of at or about 1.0×10^6 APCs/cm² to at or about 4.5×10^6 APCs/cm².

[00935] In another embodiment, the APCs exogenously supplied in the priming first expansion are seeded in the culture flask at a density selected from a range of at or about 1.5×10^6 APCs/cm² to at or about 3.5×10^6 APCs/cm².

[00936] In another embodiment, the APCs exogenously supplied in the priming first expansion are seeded in the culture flask at a density selected from a range of at or about 2×10^6 APCs/cm² to at or about 3×10^6 APCs/cm².

[00937] In another embodiment, the APCs exogenously supplied in the priming first expansion are seeded in the culture flask at a density of at or about 2×10^6 APCs/cm².

[00938] In another embodiment, the APCs exogenously supplied in the priming first expansion are seeded in the culture flask at a density of at or about 1.0×10^6 , 1.1×10^6 , 1.2×10^6 , 1.3×10^6 , 1.4×10^6 , 1.5×10^6 , 1.6×10^6 , 1.7×10^6 , 1.8×10^6 , 1.9×10^6 , 2×10^6 , 2.1×10^6 , 2.2×10^6 , 2.3×10^6 , 2.4×10^6 , 2.5×10^6 , 2.6×10^6 , 2.7×10^6 , 2.8×10^6 , 2.9×10^6 , 3×10^6 , 3.1×10^6 , 3.2×10^6 , 3.3×10^6 , 3.4×10^6 , 3.5×10^6 , 3.6×10^6 , 3.7×10^6 , 3.8×10^6 , 3.9×10^6 , 4×10^6 , 4.1×10^6 , 4.2×10^6 , 4.3×10^6 , 4.4×10^6 or 4.5×10^6 APCs/cm².

[00939] In another embodiment, the APCs exogenously supplied in the rapid second expansion are seeded in the culture flask at a density selected from a range of at or about 2.5×10^6 APCs/cm² to at or about 7.5×10^6 APCs/cm².

[00940] In another embodiment, the APCs exogenously supplied in the rapid second expansion are seeded in the culture flask at a density selected from a range of at or about 3.5×10^6 APCs/cm² to about 6.0×10^6 APCs/cm².

[00941] In another embodiment, the APCs exogenously supplied in the rapid second expansion are seeded in the culture flask at a density selected from a range of at or about 4.0×10^6 APCs/cm² to about 5.5×10^6 APCs/cm².

[00942] In another embodiment, the APCs exogenously supplied in the rapid second expansion are seeded in the culture flask at a density selected from a range of at or about 4.0×10^6 APCs/cm².

[00943] In another embodiment, the APCs exogenously supplied in the rapid second expansion are seeded in the culture flask at a density of at or about 2.5×10^6 APCs/cm²,

 $2.6\times10^6 \text{ APCs/cm}^2, 2.7\times10^6 \text{ APCs/cm}^2, 2.8\times10^6, 2.9\times10^6, 3\times10^6, 3.1\times10^6, 3.2\times10^6, 3.3\times10^6, 3.4\times10^6, 3.5\times10^6, 3.6\times10^6, 3.7\times10^6, 3.8\times10^6, 3.9\times10^6, 4\times10^6, 4.1\times10^6, 4.2\times10^6, 4.3\times10^6, 4.4\times10^6, 4.5\times10^6, 4.6\times10^6, 4.7\times10^6, 4.8\times10^6, 4.9\times10^6, 5\times10^6, 5.1\times10^6, 5.2\times10^6, 5.3\times10^6, 5.4\times10^6, 5.5\times10^6, 5.6\times10^6, 5.7\times10^6, 5.8\times10^6, 5.9\times10^6, 6\times10^6, 6.1\times10^6, 6.2\times10^6, 6.3\times10^6, 6.4\times10^6, 6.5\times10^6, 6.5\times10^6, 6.7\times10^6, 6.8\times10^6, 6.9\times10^6, 7\times10^6, 7.1\times10^6, 7.2\times10^6, 7.3\times10^6, 7.4\times10^6 \text{ or } 7.5\times10^6 \text{ APCs/cm}^2.$

[00944] In another embodiment, the APCs exogenously supplied in the priming first expansion are seeded in the culture flask at a density of at or about 1.0×10⁶, 1.1×10⁶, 1.2×10⁶, 1.3×10⁶, 1.4×10⁶, 1.5×10⁶, 1.6×10⁶, 1.7×10⁶, 1.8×10⁶, 1.9×10⁶, 2×10⁶, 2.1×10⁶, 2.2×10⁶, 2.2×10⁶, 2.3×10⁶, 2.4×10⁶, 2.5×10⁶, 2.6×10⁶, 2.7×10⁶, 2.8×10⁶, 2.9×10⁶, 3×10⁶, 3.1×10⁶, 3.2×10⁶, 3.3×10⁶, 3.4×10⁶, 3.5×10⁶, 3.6×10⁶, 3.7×10⁶, 3.8×10⁶, 3.9×10⁶, 4×10⁶, 4.1×10⁶, 4.2×10⁶, 4.3×10⁶, 4.4×10⁶ or 4.5×10⁶ APCs/cm² and the APCs exogenously supplied in the rapid second expansion are seeded in the culture flask at a density of at or about 2.5×10⁶ APCs/cm², 2.6×10⁶ APCs/cm², 2.7×10⁶ APCs/cm², 2.8×10⁶, 2.9×10⁶, 3×10⁶, 3.1×10⁶, 3.2×10⁶, 3.3×10⁶, 3.4×10⁶, 3.5×10⁶, 3.6×10⁶, 3.7×10⁶, 3.8×10⁶, 3.9×10⁶, 4.1×10⁶, 4.1×10⁶, 4.2×10⁶, 4.3×10⁶, 4.4×10⁶, 4.5×10⁶, 4.6×10⁶, 4.7×10⁶, 4.8×10⁶, 4.9×10⁶, 5×10⁶, 5.1×10⁶, 5.2×10⁶, 5.3×10⁶, 5.4×10⁶, 5.5×10⁶, 5.6×10⁶, 5.7×10⁶, 5.8×10⁶, 5.9×10⁶, 6.1×10⁶, 6.2×10⁶, 6.3×10⁶, 6.4×10⁶, 6.5×10⁶, 6.6×10⁶, 6.7×10⁶, 6.8×10⁶, 6.9×10⁶, 7×10⁶, 7.1×10⁶, 7.2×10⁶, 7.3×10⁶, 7.4×10⁶ or 7.5×10⁶ APCs/cm².

[00945] In another embodiment, the APCs exogenously supplied in the priming first expansion are seeded in the culture flask at a density selected from a range of at or about 1.0×10^6 APCs/cm² to at or about 4.5×10^6 APCs/cm², and the APCs exogenously supplied in the rapid second expansion are seeded in the culture flask at a density selected from a range of at or about 2.5×10^6 APCs/cm² to at or about 7.5×10^6 APCs/cm².

[00946] In another embodiment, the APCs exogenously supplied in the priming first expansion are seeded in the culture flask at a density selected from a range of at or about 1.5×10^6 APCs/cm² to at or about 3.5×10^6 APCs/cm², and the APCs exogenously supplied in the rapid second expansion are seeded in the culture flask at a density selected from a range of at or about 3.5×10^6 APCs/cm² to at or about 6×10^6 APCs/cm².

[00947] In another embodiment, the APCs exogenously supplied in the priming first expansion are seeded in the culture flask at a density selected from a range of at or about 2×10^6 APCs/cm² to at or about 3×10^6 APCs/cm², and the APCs exogenously supplied in the

rapid second expansion are seeded in the culture flask at a density selected from a range of at or about 4×10^6 APCs/cm² to at or about 5.5×10^6 APCs/cm².

[00948] In another embodiment, the APCs exogenously supplied in the priming first expansion are seeded in the culture flask at a density at or about 2×10^6 APCs/cm² and the APCs exogenously supplied in the rapid second expansion are seeded in the culture flask at a density of at or about 4×10^6 APCs/cm².

[00949] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of PBMCs exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 20:1.

[00950] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of PBMCs exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 10:1.

[00951] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of PBMCs exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 9:1.

[00952] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 8:1.

[00953] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 7:1.

[00954] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 6:1.

[00955] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 5:1.

[00956] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 4:1.

[00957] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 3:1.

[00958] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 2.9:1.

[00959] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 2.8:1.

[00960] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 2.7:1.

[00961] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 2.6:1.

[00962] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 2.5:1.

[00963] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 2.4:1.

[00964] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 2.3:1.

[00965] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 2.2:1.

[00966] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 2.1:1.

[00967] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 1.1:1 to at or about 2:1.

[00968] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 2:1 to at or about 10:1.

[00969] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 2:1 to at or about 5:1.

[00970] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 2:1 to at or about 4:1.

[00971] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 2:1 to at or about 3:1.

[00972] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 2:1 to at or about 2.9:1.

[00973] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 2:1 to at or about 2.8:1.

[00974] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 2:1 to at or about 2.7:1.

[00975] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 2:1 to at or about 2.6:1.

[00976] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 2:1 to at or about 2.5:1.

[00977] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 2:1 to at or about 2.4:1.

[00978] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 2:1 to at or about 2.3:1.

[00979] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 2:1 to at or about 2.2:1.

[00980] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from a range of from at or about 2:1 to at or about 2.1:1.

[00981] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is at or about 2:1.

[00982] In another embodiment, the ratio of the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion to the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is at or about 1.1:1, 1.2:1, 1.3:1, 1.4:1, 1.5:1, 1.6:1, 1.7:1, 1.8:1, 1.9:1, 2:1, 2.1:1, 2.2:1, 2.3:1, 2.4:1, 2.5:1, 2.6:1, 2.7:1, 2.8:1, 2.9:1, 3:1, 3.1:1, 3.2:1, 3.3:1, 3.4:1, 3.5:1, 3.6:1, 3.7:1, 3.8:1, 3.9:1, 4:1, 4.1:1, 4.2:1, 4.3:1, 4.4:1, 4.5:1, 4.6:1, 4.7:1, 4.8:1, 4.9:1, or 5:1.

[00983] In another embodiment, the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is at or about 1×10⁸, 1.1×10⁸, 1.2×10⁸, 1.3×10⁸, 1.4×10⁸, 1.5×10⁸, 1.6×10⁸, 1.7×10⁸, 1.8×10⁸, 1.9×10⁸, 2×10⁸, 2.1×10⁸, 2.2×10⁸, 2.3×10⁸, 2.4×10⁸, 2.5×10⁸, 2.6×10⁸, 2.7×10⁸, 2.8×10⁸, 2.9×10⁸, 3×10⁸, 3.1×10⁸, 3.2×10⁸, 3.3×10⁸, 3.4×10⁸ or 3.5×10⁸ APCs (including, for example, PBMCs), and the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion is at or about 3.5×10⁸, 3.6×10⁸, 3.7×10⁸, 3.8×10⁸, 3.9×10⁸, 4×10⁸, 4.1×10⁸, 4.2×10⁸, 4.3×10⁸, 4.4×10⁸, 4.5×10⁸, 4.6×10⁸, 4.7×10⁸, 4.8×10⁸, 4.9×10⁸, 5×10⁸, 5.1×10⁸, 5.2×10⁸, 5.3×10⁸, 5.4×10⁸, 5.5×10⁸, 5.6×10⁸, 5.7×10⁸, 5.8×10⁸, 5.9×10⁸, 6×10⁸, 6.1×10⁸, 6.2×10⁸, 6.3×10⁸, 6.4×10⁸, 6.5×10⁸, 6.6×10⁸, 6.7×10⁸, 6.8×10⁸, 6.9×10⁸, 7×10⁸, 7.1×10⁸, 7.2×10⁸, 7.3×10⁸, 7.4×10⁸, 7.5×10⁸, 7.6×10⁸, 7.7×10⁸, 7.8×10⁸, 7.9×10⁸, 8×10⁸, 8.1×10⁸, 8.2×10⁸, 8.3×10⁸, 8.4×10⁸, 8.5×10⁸, 8.6×10⁸, 8.7×10⁸, 8.8×10⁸, 8.9×10⁸, 9×10⁸, 9×10⁸, 9×110⁸, 9.1×10⁸, 9.2×10⁸, 9.3×10⁸, 9.4×10⁸, 9.5×10⁸, 9.6×10⁸, 9.7×10⁸, 9.8×10⁸, 9.9×10⁸ or 1x10⁹ APCs (including, for example, PBMCs).

[00984] In another embodiment, the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from the range of at or about 1×10⁸ APCs (including, for example, PBMCs) to at or about 3.5×10⁸ APCs (including, for example, PBMCs), and the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion is selected from the range of at or about 3.5×10⁸ APCs (including, for example, PBMCs) to at or about 1×10⁹ APCs (including, for example, PBMCs).

[00985] In another embodiment, the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from the range of at or about 1.5×10⁸ APCs to at or about 3×10⁸ APCs (including, for example, PBMCs), and the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion is selected from the range of at or about 4×10⁸ APCs (including, for example, PBMCs) to at or about 7.5×10⁸ APCs (including, for example, PBMCs).

[00986] In another embodiment, the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is selected from the range of at or about 2×10⁸ APCs (including, for example, PBMCs) to at or about 2.5×10⁸ APCs (including, for example, PBMCs), and the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion is selected from the range of at or about 4.5×10⁸ APCs (including, for example, PBMCs) to at or about 5.5×10⁸ APCs (including, for example, PBMCs).

[00987] In another embodiment, the number of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion is at or about 2.5×10⁸ APCs (including, for example, PBMCs) and the number of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion is at or about 5×10⁸ APCs (including, for example, PBMCs)

[00988] In an embodiment, the number of layers of APCs (including, for example, PBMCs) added at day 0 of the priming first expansion is approximately one-half of the number of layers of APCs (including, for example, PBMCs) added at day 7 of the rapid second expansion. In certain embodiments, the method comprises adding antigen presenting cell layers at day 0 of the priming first expansion to the first population of TILs and adding antigen presenting cell layers at day 7 to the second population of TILs, wherein the number

of antigen presenting cell layer added at day 0 is approximately 50% of the number of antigen presenting cell layers added at day 7.

[00989] In another embodiment, the number of layers of APCs (including, for example, PBMCs) exogenously supplied at day 7 of the rapid second expansion is greater than the number of layers of APCs (including, for example, PBMCs) exogenously supplied at day 0 of the priming first expansion.

[00990] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with an average thickness of at or about 2 cell layers and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs) with an average thickness of at or about 4 cell layers.

[00991] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with an average thickness of at or about one cell layer and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs) with an average thickness of at or about 3 cell layers.

[00992] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with an average thickness of at or about 1.5 cell layers to at or about 2.5 cell layers and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs) with an average thickness of at or about 3 cell layers.

[00993] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with an average thickness of at or about one cell layer and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs) with an average thickness of at or about 2 cell layers.

[00994] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with an average thickness of of at or about 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9 or 3 cell layers and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs) with an average thickness of at or about 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9 or 8 cell layers.

[00995] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with an average thickness of at or about 1 cell layer to at or about 2 cell layers and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs) with an average thickness of at or about 3 cell layers to at or about 10 cell layers.

[00996] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with an average thickness of at or about 2 cell layers to at or about 3 cell layers and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs) with an average thickness of at or about 4 cell layers to at or about 8 cell layers.

[00997] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with an average thickness of at or about 2 cell layers and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs) with an average thickness of at or about 4 cell layers to at or about 8 cell layers.

[00998] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with an average thickness of at or about 1, 2 or 3 cell layers and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs) with an average thickness of at or about 3, 4, 5, 6, 7, 8, 9 or 10 cell layers.

[00999] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a first average thickness equal to a first number of layers of APCs (including, for example, PBMCs) and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a second average thickness equal to a second number of layers of APCs (including, for example, PBMCs), wherein the ratio of the first number of layers of APCs (including, for example, PBMCs) to the second number of layers of APCs (including, for example, PBMCs) is selected from the range of at or about 1:1.1 to at or about 1:10.

[001000] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a first average thickness equal to a first number of layers of APCs (including, for example, PBMCs) and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs)

with a second average thickness equal to a second number of layers of APCs (including, for example, PBMCs), wherein the ratio of the first number of layers of APCs (including, for example, PBMCs) to the second number of layers of APCs (including, for example, PBMCs) is selected from the range of at or about 1:1.1 to at or about 1:8.

[001001] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a first average thickness equal to a first number of layers of APCs (including, for example, PBMCs) and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a second average thickness equal to a second number of layers of APCs (including, for example, PBMCs), wherein the ratio of the first number of layers of APCs (including, for example, PBMCs) to the second number of layers of APCs (including, for example, PBMCs) is selected from the range of at or about 1:1.1 to at or about 1:7.

[001002] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a first average thickness equal to a first number of layers of APCs (including, for example, PBMCs) and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a second average thickness equal to a second number of layers of APCs (including, for example, PBMCs), wherein the ratio of the first number of layers of APCs (including, for example, PBMCs) to the second number of layers of APCs (including, for example, PBMCs) is selected from the range of at or about 1:1.1 to at or about 1:6.

[001003] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a first average thickness equal to a first number of layers of APCs (including, for example, PBMCs) and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a second average thickness equal to a second number of layers of APCs (including, for example, PBMCs), wherein the ratio of the first number of layers of APCs (including, for example, PBMCs) to the second number of layers of APCs (including, for example, PBMCs) is selected from the range of at or about 1:1.1 to at or about 1:5.

[001004] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a first average thickness equal to a first number of layers of APCs (including, for example, PBMCs) and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs)

with a second average thickness equal to a second number of layers of APCs (including, for example, PBMCs), wherein the ratio of the first number of layers of APCs (including, for example, PBMCs) to the second number of layers of APCs (including, for example, PBMCs) is selected from the range of at or about 1:1.1 to at or about 1:4.

[001005] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a first average thickness equal to a first number of layers of APCs (including, for example, PBMCs) and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a second average thickness equal to a second number of layers of APCs (including, for example, PBMCs), wherein the ratio of the first number of layers of APCs (including, for example, PBMCs) to the second number of layers of APCs (including, for example, PBMCs) is selected from the range of at or about 1:1.1 to at or about 1:3.

[001006] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a first average thickness equal to a first number of layers of APCs (including, for example, PBMCs) and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a second average thickness equal to a second number of layers of APCs (including, for example, PBMCs), wherein the ratio of the first number of layers of APCs (including, for example, PBMCs) to the second number of layers of APCs (including, for example, PBMCs) is selected from the range of at or about 1:1.1 to at or about 1:2.

[001007] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a first average thickness equal to a first number of layers of APCs (including, for example, PBMCs) and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a second average thickness equal to a second number of layers of APCs (including, for example, PBMCs), wherein the ratio of the first number of layers of APCs (including, for example, PBMCs) to the second number of layers of APCs (including, for example, PBMCs) is selected from the range of at or about 1:1.2 to at or about 1:8.

[001008] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a first average thickness equal to a first number of layers of APCs (including, for example, PBMCs) and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs)

with a second average thickness equal to a second number of layers of APCs (including, for example, PBMCs), wherein the ratio of the first number of layers of APCs (including, for example, PBMCs) to the second number of layers of APCs (including, for example, PBMCs) is selected from the range of at or about 1:1.3 to at or about 1:7.

[001009] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a first average thickness equal to a first number of layers of APCs (including, for example, PBMCs) and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a second average thickness equal to a second number of layers of APCs (including, for example, PBMCs), wherein the ratio of the first number of layers of APCs (including, for example, PBMCs) to the second number of layers of APCs (including, for example, PBMCs) is selected from the range of at or about 1:1.4 to at or about 1:6.

[001010] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a first average thickness equal to a first number of layers of APCs (including, for example, PBMCs) and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a second average thickness equal to a second number of layers of APCs (including, for example, PBMCs), wherein the ratio of the first number of layers of APCs (including, for example, PBMCs) to the second number of layers of APCs (including, for example, PBMCs) is selected from the range of at or about 1:1.5 to at or about 1:5.

[001011] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a first average thickness equal to a first number of layers of APCs (including, for example, PBMCs) and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a second average thickness equal to a second number of layers of APCs (including, for example, PBMCs), wherein the ratio of the first number of layers of APCs (including, for example, PBMCs) to the second number of layers of APCs (including, for example, PBMCs) is selected from the range of at or about 1:1.6 to at or about 1:4.

[001012] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a first average thickness equal to a first number of layers of APCs (including, for example, PBMCs) and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs)

with a second average thickness equal to a second number of layers of APCs (including, for example, PBMCs), wherein the ratio of the first number of layers of APCs (including, for example, PBMCs) to the second number of layers of APCs (including, for example, PBMCs) is selected from the range of at or about 1:1.7 to at or about 1:3.5.

[001013] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a first average thickness equal to a first number of layers of APCs (including, for example, PBMCs) and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a second average thickness equal to a second number of layers of APCs (including, for example, PBMCs), wherein the ratio of the first number of layers of APCs (including, for example, PBMCs) to the second number of layers of APCs (including, for example, PBMCs) is selected from the range of at or about 1:1.8 to at or about 1:3.

[001014] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a first average thickness equal to a first number of layers of APCs (including, for example, PBMCs) and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a second average thickness equal to a second number of layers of APCs (including, for example, PBMCs), wherein the ratio of the first number of layers of APCs (including, for example, PBMCs) to the second number of layers of APCs (including, for example, PBMCs) is selected from the range of at or about 1:1.9 to at or about 1:2.5.

[001015] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a first average thickness equal to a first number of layers of APCs (including, for example, PBMCs) and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a second average thickness equal to a second number of layers of APCs (including, for example, PBMCs), wherein the ratio of the first number of layers of APCs (including, for example, PBMCs) to the second number of layers of APCs (including, for example, PBMCs) is at or about 1: 2.

[001016] In another embodiment, day 0 of the priming first expansion occurs in the presence of layered APCs (including, for example, PBMCs) with a first average thickness equal to a first number of layers of APCs (including, for example, PBMCs) and day 7 of the rapid second expansion occurs in the presence of layered APCs (including, for example, PBMCs)

with a second average thickness equal to a second number of layers of APCs (including, for example, PBMCs), wherein the ratio of the first number of layers of APCs (including, for example, PBMCs) to the second number of layers of APCs (including, for example, PBMCs) is selected from at or about 1:1.1, 1:1.2, 1:1.3, 1:1.4, 1:1.5, 1:1.6, 1:1.7, 1:1.8, 1:1.9, 1:2, 1:2.1, 1:2.2, 1:2.3, 1:2.4, 1:2.5, 1:2.6, 1:2.7, 1:2.8, 1:2.9, 1:3, 1:3.1, 1:3.2, 1:3.3, 1:3.4, 1:3.5, 1:3.6, 1:3.7, 1:3.8, 1:3.9, 1:4, 1:4.1, 1:4.2, 1:4.3, 1:4.4, 1:4.5, 1:4.6, 1:4.7, 1:4.8, 1:4.9, 1:5, 1:5.1, 1:5.2, 1:5.3, 1:5.4, 1:5.5, 1:5.6, 1:5.7, 1:5.8, 1:5.9, 1:6, 1:6.1, 1:6.2, 1:6.3, 1:6.4, 1:6.5, 1:6.6, 1:6.7, 1:6.8, 1:6.9, 1:7, 1:7.1, 1:7.2, 1:7.3, 1:7.4, 1:7.5, 1:7.6, 1:7.7, 1:7.8, 1:7.9, 1:8, 1:8.1, 1:8.2, 1:8.3, 1:8.4, 1:8.5, 1:8.6, 1:8.7, 1:8.8, 1:8.9, 1:9, 1:9.1, 1:9.2, 1:9.3, 1:9.4, 1:9.5, 1:9.6, 1:9.7, 1:9.8, 1:9.9 or 1:10.

[001017] In some embodiments, the number of APCs in the priming first expansion is selected from the range of about 1.0×10^6 APCs/cm² to about 4.5×10^6 APCs/cm², and the number of APCs in the rapid second expansion is selected from the range of about 2.5×10^6 APCs/cm² to about 7.5×10^6 APCs/cm².

[001018] In some embodiments, the number of APCs in the priming first expansion is selected from the range of about 1.5×10^6 APCs/cm² to about 3.5×10^6 APCs/cm², and the number of APCs in the rapid second expansion is selected from the range of about 3.5×10^6 APCs/cm² to about 6.0×10^6 APCs/cm².

[001019] In some embodiments, the number of APCs in the priming first expansion is selected from the range of about 2.0×10^6 APCs/cm² to about 3.0×10^6 APCs/cm², and the number of APCs in the rapid second expansion is selected from the range of about 4.0×10^6 APCs/cm² to about 5.5×10^6 APCs/cm².

H. Optional Cell Medium Components

1. Anti-CD3 Antibodies

[001020] In some embodiments, the culture media used in expansion methods described herein (see for example, Figure 8 (in particular, e.g., Figure 8B)) include an anti-CD3 antibody. An anti-CD3 antibody in combination with IL-2 induces T cell activation and cell division in the TIL population. This effect can be seen with full length antibodies as well as

Fab and F(ab')2 fragments, with the former being generally preferred; see, *e.g.*, Tsoukas *et al.*, *J. Immunol.* **1985**, *135*, 1719, hereby incorporated by reference in its entirety.

[001021] As will be appreciated by those in the art, there are a number of suitable anti-human CD3 antibodies that find use in the invention, including anti-human CD3 polyclonal and monoclonal antibodies from various mammals, including, but not limited to, murine, human, primate, rat, and canine antibodies. In particular embodiments, the OKT3 anti-CD3 antibody is used (commercially available from Ortho-McNeil, Raritan, NJ or Miltenyi Biotech, Auburn, CA).

TABLE 21: Amino acid sequences of muromonab (exemplary OKT-3 antibody)

Identifier	Seq	uence (One-L	etter Ami	no Acid Sy	mbols)	
SEQ ID NO:1	QVQLQQSGAE LARPGASV	KM SCKASGYTFT F	RYTMHWVKQR	PGQGLEWIGY	INPSRGYTNY	60
Muromonab heavy	NQKFKDKATL TTDKSSST	AY MQLSSLTSED S	SAVYYCARYY	DDHYCLDYWG	QGTTLTVSSA	120
chain	KTTAPSVYPL APVCGGTT	GS SVTLGCLVKG	YFPEPVTLTW	NSGSLSSGVH	TFPAVLQSDL	180
	YTLSSSVTVT SSTWPSQS	IT CNVAHPASST F	KVDKKIEPRP	KSCDKTHTCP	PCPAPELLGG	240
	PSVFLFPPKP KDTLMISR	TP EVTCVVVDVS H	HEDPEVKFNW	YVDGVEVHNA	KTKPREEQYN	300
	STYRVVSVLT VLHQDWLN	GK EYKCKVSNKA I	LPAPIEKTIS	KAKGQPREPQ	VYTLPPSRDE	360
	LTKNQVSLTC LVKGFYPS	DI AVEWESNGQP E	ENNYKTTPPV	LDSDGSFFLY	SKLTVDKSRW	420
	QQGNVFSCSV MHEALHNH	YT QKSLSLSPGK				450
SEQ ID NO:2	QIVLTQSPAI MSASPGEK	VT MTCSASSSVS Y	YMNWYQQKSG	TSPKRWIYDT	SKLASGVPAH	60
Muromonab light	FRGSGSGTSY SLTISGME	AE DAATYYCQQW S	SSNPFTFGSG	TKLEINRADT	APTVSIFPPS	120
chain	SEQLTSGGAS VVCFLNNF	YP KDINVKWKID O	GSERQNGVLN	SWTDQDSKDS	TYSMSSTLTL	180
	TKDEYERHNS YTCEATHK	TS TSPIVKSFNR N	NEC			213

2. 4-1BB (CD137) AGONISTS

[001022] In an embodiment, the cell culture medium of the priming first expansion and/or the rapid second expansion comprises a TNFRSF agonist. In an embodiment, the TNFRSF agonist is a 4-1BB (CD137) agonist. The 4-1BB agonist may be any 4-1BB binding molecule known in the art. The 4-1BB binding molecule may be a monoclonal antibody or fusion protein capable of binding to human or mammalian 4-1BB. The 4-1BB agonists or 4-1BB binding molecules may comprise an immunoglobulin heavy chain of any isotype (*e.g.*, IgG, IgE, IgM, IgD, IgA, and IgY), class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. The 4-1BB agonist or 4-1BB binding molecule may have both a heavy and a light chain. As used herein, the term binding molecule also includes antibodies (including full length antibodies), monoclonal antibodies (*e.g.*, bispecific antibodies), human, humanized or chimeric antibodies, and antibody fragments, *e.g.*, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, epitope-binding fragments of any of the above, and engineered forms of antibodies, *e.g.*, scFv molecules, that

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bind to 4-1BB. In an embodiment, the 4-1BB agonist is an antigen binding protein that is a fully human antibody. In an embodiment, the 4-1BB agonist is an antigen binding protein that is a humanized antibody. In some embodiments, 4-1BB agonists for use in the presently disclosed methods and compositions include anti-4-1BB antibodies, human anti-4-1BB antibodies, mouse anti-4-1BB antibodies, mammalian anti-4-1BB antibodies, monoclonal anti-4-1BB antibodies, polyclonal anti-4-1BB antibodies, chimeric anti-4-1BB antibodies, anti-4-1BB adnectins, anti-4-1BB domain antibodies, single chain anti-4-1BB fragments, heavy chain anti-4-1BB fragments, light chain anti-4-1BB fragments, anti-4-1BB fusion proteins, and fragments, derivatives, conjugates, variants, or biosimilars thereof. Agonistic anti-4-1BB antibodies are known to induce strong immune responses. Lee, et al., PLOS One 2013, 8, e69677. In a preferred embodiment, the 4-1BB agonist is an agonistic, anti-4-1BB humanized or fully human monoclonal antibody (i.e., an antibody derived from a single cell line). In an embodiment, the 4-1BB agonist is EU-101 (Eutilex Co. Ltd.), utomilumab, or urelumab, or a fragment, derivative, conjugate, variant, or biosimilar thereof. In a preferred embodiment, the 4-1BB agonist is utomilumab or urelumab, or a fragment, derivative, conjugate, variant, or biosimilar thereof.

[001023] In a preferred embodiment, the 4-1BB agonist or 4-1BB binding molecule may also be a fusion protein. In a preferred embodiment, a multimeric 4-1BB agonist, such as a trimeric or hexameric 4-1BB agonist (with three or six ligand binding domains), may induce superior receptor (4-1BBL) clustering and internal cellular signaling complex formation compared to an agonistic monoclonal antibody, which typically possesses two ligand binding domains. Trimeric (trivalent) or hexameric (or hexavalent) or greater fusion proteins comprising three TNFRSF binding domains and IgG1-Fc and optionally further linking two or more of these fusion proteins are described, e.g., in Gieffers, et al., Mol. Cancer Therapeutics 2013, 12, 2735-47.

[001024] Agonistic 4-1BB antibodies and fusion proteins are known to induce strong immune responses. In a preferred embodiment, the 4-1BB agonist is a monoclonal antibody or fusion protein that binds specifically to 4-1BB antigen in a manner sufficient to reduce toxicity. In some embodiments, the 4-1BB agonist is an agonistic 4-1BB monoclonal antibody or fusion protein that abrogates antibody-dependent cellular toxicity (ADCC), for example NK cell cytotoxicity. In some embodiments, the 4-1BB agonist is an agonistic 4-1BB monoclonal antibody or fusion protein that abrogates antibody-dependent cell phagocytosis (ADCP). In some embodiments, the 4-1BB agonist is an agonistic 4-1BB monoclonal antibody or fusion

protein that abrogates complement-dependent cytotoxicity (CDC). In some embodiments, the 4-1BB agonist is an agonistic 4-1BB monoclonal antibody or fusion protein which abrogates Fc region functionality.

[001025] In some embodiments, the 4-1BB agonists are characterized by binding to human 4-1BB (SEQ ID NO:9) with high affinity and agonistic activity. In an embodiment, the 4-1BB agonist is a binding molecule that binds to human 4-1BB (SEQ ID NO:9). In an embodiment, the 4-1BB agonist is a binding molecule that binds to murine 4-1BB (SEQ ID NO:10). The amino acid sequences of 4-1BB antigen to which a 4-1BB agonist or binding molecule binds are summarized in Table 22.

TABLE 22. Amino acid sequences of 4-1BB antigens.

Identifier		Sequence	e (One-L	etter Ami	no Acid Sy	mbols)	
SEQ ID NO:9	MGNSCYNIVA TLL	LVLNFER TR	RSLQDPCSN	CPAGTFCDNN	RNQICSPCPP	NSFSSAGGQR	60
human 4-1BB,	TCDICRQCKG VFR	RTRKECSS TS	SNAECDCTP	GFHCLGAGCS	MCEQDCKQGQ	ELTKKGCKDC	120
Tumor necrosis	CFGTFNDQKR GIC	CRPWTNCS LD	GKSVLVNG	TKERDVVCGP	SPADLSPGAS	SVTPPAPARE	180
factor receptor	PGHSPQIISF FLA	LTSTALL FL	LIFFLTLRF	SVVKRGRKKL	LYIFKQPFMR	PVQTTQEEDG	240
superfamily,	CSCRFPEEEE GGC	CEL					255
member 9 (Homo							
sapiens)							
SEQ ID NO:10	MGNNCYNVVV IVL	LLVGCEK VG.	GAVQNSCDN	CQPGTFCRKY	NPVCKSCPPS	TFSSIGGQPN	60
murine 4-1BB,	CNICRVCAGY FRF	KKFCSST HN.	NAECECIEG	FHCLGPQCTR	CEKDCRPGQE	LTKQGCKTCS	120
Tumor necrosis	LGTFNDQNGT GVC	CRPWTNCS LD	GRSVLKTG	TTEKDVVCGP	PVVSFSPSTT	ISVTPEGGPG	180
factor receptor	GHSLQVLTLF LAL	TSALLLA LI	FITLLFSV	LKWIRKKFPH	IFKQPFKKTT	GAAQEEDACS	240
superfamily,	CRCPQEEEGG GGG	SYEL					256
member 9 (Mus							
musculus)							

[001026] In some embodiments, the compositions, processes and methods described include a 4-1BB agonist that binds human or murine 4-1BB with a K_D of about 100 pM or lower, binds human or murine 4-1BB with a K_D of about 90 pM or lower, binds human or murine 4-1BB with a K_D of about 70 pM or lower, binds human or murine 4-1BB with a K_D of about 70 pM or lower, binds human or murine 4-1BB with a K_D of about 50 pM or lower, binds human or murine 4-1BB with a K_D of about 40 pM or lower, or binds human or murine 4-1BB with a K_D of about 30 pM or lower.

[001027] In some embodiments, the compositions, processes and methods described include a 4-1BB agonist that binds to human or murine 4-1BB with a k_{assoc} of about 7.5×10^5 1/M·s or faster, binds to human or murine 4-1BB with a k_{assoc} of about 7.5×10^5 1/M·s or faster, binds to human or murine 4-1BB with a k_{assoc} of about 8×10^5 1/M·s or faster, binds to human or murine 4-1BB with a k_{assoc} of about 8.5×10^5 1/M·s or faster, binds to human or murine 4-1BB with a k_{assoc} of about 9×10^5 1/M·s or faster, binds to human or murine 4-1BB with a

 k_{assoc} of about 9.5×10^5 1/M·s or faster, or binds to human or murine 4-1BB with a k_{assoc} of about 1×10^6 1/M·s or faster.

[001028] In some embodiments, the compositions, processes and methods described include a 4-1BB agonist that binds to human or murine 4-1BB with a k_{dissoc} of about 2×10^{-5} 1/s or slower, binds to human or murine 4-1BB with a k_{dissoc} of about 2.1×10^{-5} 1/s or slower, binds to human or murine 4-1BB with a k_{dissoc} of about 2.2×10^{-5} 1/s or slower, binds to human or murine 4-1BB with a k_{dissoc} of about 2.3×10^{-5} 1/s or slower, binds to human or murine 4-1BB with a k_{dissoc} of about 2.4×10^{-5} 1/s or slower, binds to human or murine 4-1BB with a k_{dissoc} of about 2.5×10^{-5} 1/s or slower, binds to human or murine 4-1BB with a k_{dissoc} of about 2.6×10^{-5} 1/s or slower or binds to human or murine 4-1BB with a k_{dissoc} of about 2.8×10^{-5} 1/s or slower, binds to human or murine 4-1BB with a k_{dissoc} of about 2.9×10^{-5} 1/s or slower, or binds to human or murine 4-1BB with a k_{dissoc} of about 2.9×10^{-5} 1/s or slower, or binds to human or murine 4-1BB with a k_{dissoc} of about 2.9×10^{-5} 1/s or slower, or

[001029] In some embodiments, the compositions, processes and methods described include a 4-1BB agonist that binds to human or murine 4-1BB with an IC₅₀ of about 10 nM or lower, binds to human or murine 4-1BB with an IC₅₀ of about 9 nM or lower, binds to human or murine 4-1BB with an IC₅₀ of about 8 nM or lower, binds to human or murine 4-1BB with an IC₅₀ of about 7 nM or lower, binds to human or murine 4-1BB with an IC₅₀ of about 6 nM or lower, binds to human or murine 4-1BB with an IC₅₀ of about 5 nM or lower, binds to human or murine 4-1BB with an IC₅₀ of about 3 nM or lower, binds to human or murine 4-1BB with an IC₅₀ of about 2 nM or lower, or binds to human or murine 4-1BB with an IC₅₀ of about 1 nM or lower.

[001030] In a preferred embodiment, the 4-1BB agonist is utomilumab, also known as PF-05082566 or MOR-7480, or a fragment, derivative, variant, or biosimilar thereof. Utomilumab is available from Pfizer, Inc. Utomilumab is an immunoglobulin G2-lambda, anti-[*Homo sapiens* TNFRSF9 (tumor necrosis factor receptor (TNFR) superfamily member 9, 4-1BB, T cell antigen ILA, CD137)], *Homo sapiens* (fully human) monoclonal antibody. The amino acid sequences of utomilumab are set forth in Table 7. Utomilumab comprises glycosylation sites at Asn59 and Asn292; heavy chain intrachain disulfide bridges at positions 22-96 (V_H-V_L), 143-199 (C_H1-C_L), 256-316 (C_H2) and 362-420 (C_H3); light chain intrachain disulfide bridges at positions 22'-87' (V_H-V_L) and 136'-195' (C_H1-C_L); interchain heavy chain-heavy chain disulfide bridges at IgG2A isoform positions 218-218, 219-219, 222-222, and 225-225, at IgG2A/B isoform positions 218-130, 219-219, 222-222, and 225-

225, and at IgG2B isoform positions 219-130 (2), 222-222, and 225-225; and interchain heavy chain-light chain disulfide bridges at IgG2A isoform positions 130-213' (2), IgG2A/B isoform positions 218-213' and 130-213', and at IgG2B isoform positions 218-213' (2). The preparation and properties of utomilumab and its variants and fragments are described in U.S. Patent Nos. 8,821,867; 8,337,850; and 9,468,678, and International Patent Application Publication No. WO 2012/032433 A1, the disclosures of each of which are incorporated by reference herein. Preclinical characteristics of utomilumab are described in Fisher, *et al.*, *Cancer Immunolog. & Immunother.* 2012, *61*, 1721-33. Current clinical trials of utomilumab in a variety of hematological and solid tumor indications include U.S. National Institutes of Health clinicaltrials.gov identifiers NCT02444793, NCT01307267, NCT02315066, and NCT02554812.

[001031] In an embodiment, a 4-1BB agonist comprises a heavy chain given by SEQ ID NO:11 and a light chain given by SEQ ID NO:12. In an embodiment, a 4-1BB agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:11 and SEQ ID NO:12, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:11 and SEQ ID NO:12, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:11 and SEQ ID NO:12, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:11 and SEQ ID NO:12, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:11 and SEQ ID NO:12, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:11 and SEQ ID NO:12, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:11 and SEQ ID NO:12, respectively.

[001032] In an embodiment, the 4-1BB agonist comprises the heavy and light chain CDRs or variable regions (VRs) of utomilumab. In an embodiment, the 4-1BB agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:13, and the 4-1BB agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:14, and conservative amino acid substitutions thereof. In an embodiment, a 4-1BB agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:13 and SEQ ID NO:14, respectively. In an embodiment, a 4-1BB agonist comprises V_H

and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:13 and SEQ ID NO:14, respectively. In an embodiment, a 4-1BB agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:13 and SEQ ID NO:14, respectively. In an embodiment, a 4-1BB agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:13 and SEQ ID NO:14, respectively. In an embodiment, a 4-1BB agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:13 and SEQ ID NO:14, respectively. In an embodiment, a 4-1BB agonist comprises an scFv antibody comprising V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:13 and SEQ ID NO:13 and SEQ ID NO:14.

[001033] In an embodiment, a 4-1BB agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:15, SEQ ID NO:16, and SEQ ID NO:17, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:18, SEQ ID NO:19, and SEQ ID NO:20, respectively, and conservative amino acid substitutions thereof.

[001034] In an embodiment, the 4-1BB agonist is a 4-1BB agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to utomilumab. In an embodiment, the biosimilar monoclonal antibody comprises an 4-1BB antibody comprising an amino acid sequence which has at least 97% sequence identity, e.g., 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is utomilumab. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a 4-1BB agonist antibody authorized or submitted for authorization, wherein the 4-1BB agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is utomilumab. The 4-1BB agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological

product, wherein the reference medicinal product or reference biological product is utomilumab. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is utomilumab.

TABLE 23. Amino acid sequences for 4-1BB agonist antibodies related to utomilumab.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:11	EVQLVQSGAE VKKPGESLRI SCKGSGYSFS TYWISWVRQM PGKGLEWMGK IYPGDSYTNY	60
heavy chain for	SPSFQGQVTI SADKSISTAY LQWSSLKASD TAMYYCARGY GIFDYWGQGT LVTVSSASTK	120
utomilumab	GPSVFPLAPC SRSTSESTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS	180
	LSSVVTVPSS NFGTQTYTCN VDHKPSNTKV DKTVERKCCV ECPPCPAPPV AGPSVFLFPP	240
	KPKDTLMISR TPEVTCVVVD VSHEDPEVQF NWYVDGVEVH NAKTKPREEQ FNSTFRVVSV	300
	LTVVHQDWLN GKEYKCKVSN KGLPAPIEKT ISKTKGQPRE PQVYTLPPSR EEMTKNQVSL	360
	TCLVKGFYPS DIAVEWESNG QPENNYKTTP PMLDSDGSFF LYSKLTVDKS RWQQGNVFSC	420
	SVMHEALHNH YTQKSLSLSP G	441
SEQ ID NO:12	SYELTQPPSV SVSPGQTASI TCSGDNIGDQ YAHWYQQKPG QSPVLVIYQD KNRPSGIPER	60
light chain for	FSGSNSGNTA TLTISGTQAM DEADYYCATY TGFGSLAVFG GGTKLTVLGQ PKAAPSVTLF	120
utomilumab	PPSSEELQAN KATLVCLISD FYPGAVTVAW KADSSPVKAG VETTTPSKQS NNKYAASSYL	180
	SLTPEQWKSH RSYSCQVTHE GSTVEKTVAP TECS	214
SEQ ID NO:13	EVQLVQSGAE VKKPGESLRI SCKGSGYSFS TYWISWVRQM PGKGLEWMG KIYPGDSYTN	60
heavy chain	YSPSFQGQVT ISADKSISTA YLQWSSLKAS DTAMYYCARG YGIFDYWGQ GTLVTVSS	118
variable region		
for utomilumab		
SEQ ID NO:14	SYELTOPPSV SVSPGOTASI TCSGDNIGDO YAHWYQQKPG QSPVLVIYQD KNRPSGIPER	60
light chain	FSGSNSGNTA TLTISGTQAM DEADYYCATY TGFGSLAVFG GGTKLTVL	108
variable region		
for utomilumab		
SEQ ID NO:15	STYWIS	6
heavy chain CDR1		
for utomilumab		
SEO ID NO:16	KIYPGDSYTN YSPSFOG	17
heavy chain CDR2	~	
for utomilumab		
SEQ ID NO:17	RGYGIFDY	8
heavy chain CDR3		
for utomilumab		
SEO ID NO:18	SGDNIGDOYA H	11
light chain CDR1	~	
for utomilumab		
SEO ID NO:19	ODKNRPS	7
light chain CDR2		•
for utomilumab		
SEO ID NO:20	ATYTGFGSLA V	11
light chain CDR3		
for utomilumab		

[001035] In a preferred embodiment, the 4-1BB agonist is the monoclonal antibody urelumab, also known as BMS-663513 and 20H4.9.h4a, or a fragment, derivative, variant, or biosimilar thereof. Urelumab is available from Bristol-Myers Squibb, Inc., and Creative Biolabs, Inc. Urelumab is an immunoglobulin G4-kappa, anti-[Homo sapiens TNFRSF9 (tumor necrosis factor receptor superfamily member 9, 4-1BB, T cell antigen ILA, CD137)], Homo sapiens (fully human) monoclonal antibody. The amino acid sequences of urelumab are set forth in Table EE. Urelumab comprises N-glycosylation sites at positions 298 (and 298''); heavy chain intrachain disulfide bridges at positions 22-95 (V_H-V_L), 148-204 (C_H1-C_L), 262-322

(C_H2) and 368-426 (C_H3) (and at positions 22"-95", 148"-204", 262"-322", and 368"-426"); light chain intrachain disulfide bridges at positions 23'-88' (V_H-V_L) and 136'-196' (C_H1-C_L) (and at positions 23"'-88"' and 136"'-196"'); interchain heavy chain-heavy chain disulfide bridges at positions 227-227" and 230-230"; and interchain heavy chain-light chain disulfide bridges at 135-216' and 135"-216"'. The preparation and properties of urelumab and its variants and fragments are described in U.S. Patent Nos. 7,288,638 and 8,962,804, the disclosures of which are incorporated by reference herein. The preclinical and clinical characteristics of urelumab are described in Segal, *et al.*, *Clin. Cancer Res.* **2016**, *available at* http://dx.doi.org/ 10.1158/1078-0432.CCR-16-1272. Current clinical trials of urelumab in a variety of hematological and solid tumor indications include U.S. National Institutes of Health clinicaltrials.gov identifiers NCT01775631, NCT02110082, NCT02253992, and NCT01471210.

[001036] In an embodiment, a 4-1BB agonist comprises a heavy chain given by SEQ ID NO:21 and a light chain given by SEQ ID NO:22. In an embodiment, a 4-1BB agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively. In an embodiment, a 4-1BB agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively.

[001037] In an embodiment, the 4-1BB agonist comprises the heavy and light chain CDRs or variable regions (VRs) of urelumab. In an embodiment, the 4-1BB agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:23, and the 4-1BB agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:24, and conservative amino acid substitutions thereof. In an embodiment, a 4-1BB agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID

NO:23 and SEQ ID NO:24, respectively. In an embodiment, a 4-1BB agonist comprises $V_{\rm H}$ and $V_{\rm L}$ regions that are each at least 98% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively. In an embodiment, a 4-1BB agonist comprises $V_{\rm H}$ and $V_{\rm L}$ regions that are each at least 97% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively. In an embodiment, a 4-1BB agonist comprises $V_{\rm H}$ and $V_{\rm L}$ regions that are each at least 96% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively. In an embodiment, a 4-1BB agonist comprises $V_{\rm H}$ and $V_{\rm L}$ regions that are each at least 95% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively. In an embodiment, a 4-1BB agonist comprises an scFv antibody comprising $V_{\rm H}$ and $V_{\rm L}$ regions that are each at least 99% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:23 and SEQ ID NO:24.

[001038] In an embodiment, a 4-1BB agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:25, SEQ ID NO:26, and SEQ ID NO:27, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:28, SEQ ID NO:29, and SEQ ID NO:30, respectively, and conservative amino acid substitutions thereof.

[001039] In an embodiment, the 4-1BB agonist is a 4-1BB agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to urelumab. In an embodiment, the biosimilar monoclonal antibody comprises an 4-1BB antibody comprising an amino acid sequence which has at least 97% sequence identity, e.g., 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is urelumab. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a 4-1BB agonist antibody authorized or submitted for authorization, wherein the 4-1BB agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is urelumab. The 4-1BB agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or

different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is urelumab. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is urelumab.

TABLE 24: Amino acid sequences for 4-1BB agonist antibodies related to urelumab.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:21	QVQLQQWGAG LLKPSETLSL TCAVYGGSFS GYYWSWIRQS PEKGLEWIGE INHGGYVTYN	60
heavy chain for	PSLESRVTIS VDTSKNQFSL KLSSVTAADT AVYYCARDYG PGNYDWYFDL WGRGTLVTVS	120
urelumab	SASTKGPSVF PLAPCSRSTS ESTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS	180
	SGLYSLSSVV TVPSSSLGTK TYTCNVDHKP SNTKVDKRVE SKYGPPCPPC PAPEFLGGPS	240
	VFLFPPKPKD TLMISRTPEV TCVVVDVSQE DPEVQFNWYV DGVEVHNAKT KPREEQFNST	300
	YRVVSVLTVL HQDWLNGKEY KCKVSNKGLP SSIEKTISKA KGQPREPQVY TLPPSQEEMT	360
	KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSR LTVDKSRWQE	420
	GNVFSCSVMH EALHNHYTQK SLSLSLGK	448
SEQ ID NO:22	EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD ASNRATGIPA	60
light chain for	RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPPALTF CGGTKVEIKR TVAAPSVFIF	120
urelumab	PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYSLSST	180
	LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC	216
SEQ ID NO:23	MKHLWFFLLL VAAPRWVLSQ VQLQQWGAGL LKPSETLSLT CAVYGGSFSG YYWSWIRQSP	60
variable heavy	EKGLEWIGEI NHGGYVTYNP SLESRVTISV DTSKNQFSLK LSSVTAADTA VYYCARDYGP	120
chain for		
urelumab		
SEQ ID NO:24	MEAPAQLLFL LLLWLPDTTG EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP	60
variable light	GQAPRLLIYD ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ	110
chain for		
urelumab		
SEQ ID NO:25	GYYWS	5
heavy chain CDR1		
for urelumab		
SEQ ID NO:26	EINHGGYVTY NPSLES	16
heavy chain CDR2		
for urelumab		
SEQ ID NO:27	DYGPGNYDWY FDL	13
heavy chain CDR3		
for urelumab		
SEQ ID NO:28	RASOSVSSYL A	11
light chain CDR1		
for urelumab		
SEO ID NO:29	DASNRAT	7
light chain CDR2		•
for urelumab		
SEO ID NO:30	OORSDWPPAL T	11
light chain CDR3	Z Z a room a a a a a a a a a a a a a a a a a a	
for urelumab		

[001040] In an embodiment, the 4-1BB agonist is selected from the group consisting of 1D8, 3Elor, 4B4 (BioLegend 309809), H4-1BB-M127 (BD Pharmingen 552532), BBK2 (Thermo Fisher MS621PABX), 145501 (Leinco Technologies B591), the antibody produced by cell line deposited as ATCC No. HB-11248 and disclosed in U.S. Patent No. 6,974,863, 5F4 (BioLegend 31 1503), C65-485 (BD Pharmingen 559446), antibodies disclosed in U.S. Patent Application Publication No. US 2005/0095244, antibodies disclosed in U.S. Patent No. 7,288,638 (such as 20H4.9-IgGl (BMS-663031)), antibodies disclosed in U.S. Patent No. 6,887,673 (such as 4E9 or BMS-554271), antibodies disclosed in U.S. Patent No. 7,214,493,

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antibodies disclosed in U.S. Patent No. 6,303,121, antibodies disclosed in U.S. Patent No. 6,569,997, antibodies disclosed in U.S. Patent No. 6,905,685 (such as 4E9 or BMS-554271), antibodies disclosed in U.S. Patent No. 6,362,325 (such as 1D8 or BMS-469492; 3H3 or BMS-469497; or 3El), antibodies disclosed in U.S. Patent No. 6,974,863 (such as 53A2); antibodies disclosed in U.S. Patent No. 6,210,669 (such as 1D8, 3B8, or 3El), antibodies described in U.S. Patent No. 5,928,893, antibodies disclosed in U.S. Patent No. 6,303,121, antibodies disclosed in U.S. Patent No. 6,569,997, antibodies disclosed in International Patent Application Publication Nos. WO 2012/177788, WO 2015/119923, and WO 2010/042433, and fragments, derivatives, conjugates, variants, or biosimilars thereof, wherein the disclosure of each of the foregoing patents or patent application publications is incorporated by reference here.

[001041] In an embodiment, the 4-1BB agonist is a 4-1BB agonistic fusion protein described in International Patent Application Publication Nos. WO 2008/025516 A1, WO 2009/007120 A1, WO 2010/003766 A1, WO 2010/010051 A1, and WO 2010/078966 A1; U.S. Patent Application Publication Nos. US 2011/0027218 A1, US 2015/0126709 A1, US 2011/0111494 A1, US 2015/0110734 A1, and US 2015/0126710 A1; and U.S. Patent Nos. 9,359,420, 9,340,599, 8,921,519, and 8,450,460, the disclosures of which are incorporated by reference herein.

[001042] In an embodiment, the 4-1BB agonist is a 4-1BB agonistic fusion protein as depicted in Structure I-A (C-terminal Fc-antibody fragment fusion protein) or Structure I-B (N-terminal Fc-antibody fragment fusion protein), or a fragment, derivative, conjugate, variant, or biosimilar thereof (See, Figure 50). In structures I-A and I-B, the cylinders refer to individual polypeptide binding domains. Structures I-A and I-B comprise three linearlylinked TNFRSF binding domains derived from e.g., 4-1BBL (4-1BB ligand, CD137 ligand (CD137L), or tumor necrosis factor superfamily member 9 (TNFSF9)) or an antibody that binds 4-1BB, which fold to form a trivalent protein, which is then linked to a second triavelent protein through IgG1-Fc (including C_H3 and C_H2 domains) is then used to link two of the trivalent proteins together through disulfide bonds (small elongated ovals), stabilizing the structure and providing an agonists capable of bringing together the intracellular signaling domains of the six receptors and signaling proteins to form a signaling complex. The TNFRSF binding domains denoted as cylinders may be scFv domains comprising, e.g., a V_H and a V_L chain connected by a linker that may comprise hydrophilic residues and Gly and Ser sequences for flexibility, as well as Glu and Lys for solubility. Any scFv domain design may

be used, such as those described in de Marco, *Microbial Cell Factories*, **2011**, *10*, 44; Ahmad, *et al.*, *Clin. & Dev. Immunol.* **2012**, 980250; Monnier, *et al.*, *Antibodies*, **2013**, *2*, 193-208; or in references incorporated elsewhere herein. Fusion protein structures of this form are described in U.S. Patent Nos. 9,359,420, 9,340,599, 8,921,519, and 8,450,460, the disclosures of which are incorporated by reference herein.

[001043] Amino acid sequences for the other polypeptide domains of structure I-A are given in Table 9. The Fc domain preferably comprises a complete constant domain (amino acids 17-230 of SEQ ID NO:31) the complete hinge domain (amino acids 1-16 of SEQ ID NO:31) or a portion of the hinge domain (*e.g.*, amino acids 4-16 of SEQ ID NO:31). Preferred linkers for connecting a C-terminal Fc-antibody may be selected from the embodiments given in SEQ ID NO:32 to SEQ ID NO:41, including linkers suitable for fusion of additional polypeptides.

TABLE 25: Amino acid sequences for TNFRSF agonist fusion proteins, including 4-1BB agonist fusion proteins, with C-terminal Fc-antibody fragment fusion protein design (structure I-A).

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:31	KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW	60
Fc domain	YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS	120
	KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV	180
	LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK	230
SEQ ID NO:32 linker	GGPGSSKSCD KTHTCPPCPA PE	22
SEQ ID NO:33 linker	GGSGSSKSCD KTHTCPPCPA PE	22
SEQ ID NO:34 linker	GGPGSSSSS SKSCDKTHTC PPCPAPE	27
SEQ ID NO:35 linker	GGSGSSSSS SKSCDKTHTC PPCPAPE	27
SEQ ID NO:36 linker	GGPGSSSSS SSSKSCDKTH TCPPCPAPE	29
SEQ ID NO:37 linker	GGSGSSSSS SSSKSCDKTH TCPPCPAPE	29
SEQ ID NO:38 linker	GGPGSSGSGS SDKTHTCPPC PAPE	24
SEQ ID NO:39 linker	GGPGSSGSGS DKTHTCPPCP APE	23
SEQ ID NO:40 linker	GGPSSSGSDK THTCPPCPAP E	21
SEQ ID NO:41 linker	GGSSSSSSS GSDKTHTCPP CPAPE	25

[001044] Amino acid sequences for the other polypeptide domains of structure I-B are given in Table 10. If an Fc antibody fragment is fused to the N-terminus of an TNRFSF fusion protein as in structure I-B, the sequence of the Fc module is preferably that shown in SEQ ID NO:42, and the linker sequences are preferably selected from those embodiments set forth in SED ID NO:43 to SEQ ID NO:45.

TABLE 26: Amino acid sequences for TNFRSF agonist fusion proteins, including 4-1BB agonist fusion proteins, with N-terminal Fc-antibody fragment fusion protein design (structure I-B).

Identifier	Sequence (One-Letter Amino Acid Symbols)						
SEQ ID NO:42	METDTLLLWV LLLWVPAGNG DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT	60					
Fc domain	CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK	120					
	CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE	180					
	WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS	240					
	LSLSPG	246					
SEQ ID NO:43	SGSGSGSGS S	11					
linker							
SEQ ID NO:44	SSSSSGSGS GS	12					
linker							
SEQ ID NO:45	SSSSSGSGS GSGSGS	16					
linker							

[001045] In an embodiment, a 4-1BB agonist fusion protein according to structures I-A or I-B comprises one or more 4-1BB binding domains selected from the group consisting of a variable heavy chain and variable light chain of utomilumab, a variable heavy chain and variable light chain of utomilumab, a variable heavy chain and variable light chain of utomilumab, a variable heavy chain and variable light chain selected from the variable heavy chains and variable light chains described in Table 10, any combination of a variable heavy chain and variable light chain of the foregoing, and fragments, derivatives, conjugates, variants, and biosimilars thereof.

[001046] In an embodiment, a 4-1BB agonist fusion protein according to structures I-A or I-B comprises one or more 4-1BB binding domains comprising a 4-1BBL sequence. In an embodiment, a 4-1BB agonist fusion protein according to structures I-A or I-B comprises one or more 4-1BB binding domains comprising a sequence according to SEQ ID NO:46. In an embodiment, a 4-1BB agonist fusion protein according to structures I-A or I-B comprises one or more 4-1BB binding domains comprising a soluble 4-1BBL sequence. In an embodiment, a 4-1BB agonist fusion protein according to structures I-A or I-B comprises one or more 4-1BB binding domains comprising a sequence according to SEQ ID NO:47.

[001047] In an embodiment, a 4-1BB agonist fusion protein according to structures I-A or I-B comprises one or more 4-1BB binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:13 and SEQ ID NO:14, respectively, wherein the V_H and V_L domains are connected by a linker. In an embodiment, a 4-1BB agonist fusion protein according to structures I-A or I-B comprises one or more 4-1BB binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively, wherein the V_H and V_L domains are connected by a linker. In an

embodiment, a 4-1BB agonist fusion protein according to structures I-A or I-B comprises one or more 4-1BB binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the V_H and V_L sequences given in Table 11, wherein the V_H and V_L domains are connected by a linker.

TABLE 27: Additional polypeptide domains useful as 4-1BB binding domains in fusion proteins or as scFv 4-1BB agonist antibodies.

Identifier	S	equence (One-	Letter Ami	ino Acid Sy	ymbols)	
SEQ ID NO:46	MEYASDASLD PEAPW	PPAPR ARACRVLPWA	LVAGLLLLL	LAAACAVFLA	CPWAVSGARA	60
4-1BBL	SPGSAASPRL REGPE	LSPDD PAGLLDLRQG	MFAQLVAQNV	LLIDGPLSWY	SDPGLAGVSL	120
	TGGLSYKEDT KELVV	AKAGV YYVFFQLELF	RVVAGEGSGS	VSLALHLQPL	RSAAGAAALA	180
	LTVDLPPASS EARNS	AFGFQ GRLLHLSAGQ	RLGVHLHTEA	RARHAWQLTQ	GATVLGLFRV	240
	TPEIPAGLPS PRSE					254
SEQ ID NO:47	LRQGMFAQLV AQNVL	LIDGP LSWYSDPGLA	GVSLTGGLSY	KEDTKELVVA	KAGVYYVFFQ	60
4-1BBL soluble	LELRRVVAGE GSGSV	SLALH LQPLRSAAGA	AALALTVDLP	PASSEARNSA	FGFQGRLLHL	120
domain	SAGQRLGVHL HTEAR	ARHAW QLTQGATVLG	: LFRVTPEIPA	GLPSPRSE		168
SEQ ID NO:48	QVQLQQPGAE LVKPG	ASVKL SCKASGYTFS	SYWMHWVKQR	PGQVLEWIGE	INPGNGHTNY	60
variable heavy	NEKFKSKATL TVDKS	SSTAY MQLSSLTSED	SAVYYCARSF	TTARGFAYWG	QGTLVTVS	118
chain for 4B4-1-						
1 version 1						
SEQ ID NO:49	DIVMTQSPAT QSVTP	GDRVS LSCRASQTIS	DYLHWYQQKS	HESPRLLIKY	ASQSISGIPS	60
variable light	RFSGSGSGSD FTLSI	ISVEP EDVGVYYCQI	GHSFPPTFGG	GTKLEIK		107
chain for 4B4-1-						
1 version 1						
SEQ ID NO:50	QVQLQQPGAE LVKPG		~	~		60
variable heavy	NEKFKSKATL TVDKS	SSTAY MQLSSLTSEI	SAVYYCARSF	TTARGFAYWG	QGTLVTVSA	119
chain for 4B4-1-						
1 version 2						
SEQ ID NO:51	DIVMTQSPAT QSVTP	~	~ ~		ASQSISGIPS	60
variable light	RFSGSGSGSD FTLSI	ISVEP EDVGVYYCQI	GHSFPPTFGG	GTKLEIKR		108
chain for 4B4-1-						
1 version 2						
SEQ ID NO:52	MDWTWRILFL VAAAT		~		~	60
variable heavy	GKGLEWVADI KNDGS	TNYA PSLTNRFTIS	RDNAKNSLYL	QMNSLRAEDT	AVYYCARELT	120
chain for H39E3-						
2						
SEQ ID NO:53	MEAPAQLLFL LLLWL	-		-	-	60
variable light	WYQQKPGQPP KLLIY	ASTR QSGVPDRFSG	SGSGTDFTLT	ISSLQAEDVA		110
chain for H39E3-						
2						

[001048] In an embodiment, the 4-1BB agonist is a 4-1BB agonistic single-chain fusion polypeptide comprising (i) a first soluble 4-1BB binding domain, (ii) a first peptide linker, (iii) a second soluble 4-1BB binding domain, (iv) a second peptide linker, and (v) a third soluble 4-1BB binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, and wherein the additional domain is a Fab or Fc fragment domain. In an embodiment, the 4-1BB agonist is a 4-1BB agonistic single-chain fusion polypeptide comprising (i) a first soluble 4-1BB binding domain, (ii) a first peptide linker, (iii) a second soluble 4-1BB binding domain, (iv) a second peptide linker, and (v) a third soluble 4-1BB binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, wherein the additional domain is a Fab or Fc fragment domain, wherein each of the soluble 4-1BB domains lacks a stalk region (which contributes to trimerisation and provides a

certain distance to the cell membrane, but is not part of the 4-1BB binding domain) and the first and the second peptide linkers independently have a length of 3-8 amino acids.

[001049] In an embodiment, the 4-1BB agonist is a 4-1BB agonistic single-chain fusion polypeptide comprising (i) a first soluble tumor necrosis factor (TNF) superfamily cytokine domain, (ii) a first peptide linker, (iii) a second soluble TNF superfamily cytokine domain, (iv) a second peptide linker, and (v) a third soluble TNF superfamily cytokine domain, wherein each of the soluble TNF superfamily cytokine domains lacks a stalk region and the first and the second peptide linkers independently have a length of 3-8 amino acids, and wherein each TNF superfamily cytokine domain is a 4-1BB binding domain.

[001050] In an embodiment, the 4-1BB agonist is a 4-1BB agonistic scFv antibody comprising any of the foregoing V_H domains linked to any of the foregoing V_L domains.

[001051] In an embodiment, the 4-1BB agonist is BPS Bioscience 4-1BB agonist antibody catalog no. 79097-2, commercially available from BPS Bioscience, San Diego, CA, USA. In an embodiment, the 4-1BB agonist is Creative Biolabs 4-1BB agonist antibody catalog no. MOM-18179, commercially available from Creative Biolabs, Shirley, NY, USA.

3. OX40 (CD134) AGONISTS

[001052] In an embodiment, the TNFRSF agonist is an OX40 (CD134) agonist. The OX40 agonist may be any OX40 binding molecule known in the art. The OX40 binding molecule may be a monoclonal antibody or fusion protein capable of binding to human or mammalian OX40. The OX40 agonists or OX40 binding molecules may comprise an immunoglobulin heavy chain of any isotype (e.g., IgG, IgE, IgM, IgD, IgA, and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. The OX40 agonist or OX40 binding molecule may have both a heavy and a light chain. As used herein, the term binding molecule also includes antibodies (including full length antibodies), monoclonal antibodies (including full length monoclonal antibodies), polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), human, humanized or chimeric antibodies, and antibody fragments, e.g., Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, epitope-binding fragments of any of the above, and engineered forms of antibodies, e.g., scFv molecules, that bind to OX40. In an embodiment, the OX40 agonist is an antigen binding protein that is a fully human antibody. In an embodiment, the OX40 agonist is an antigen binding protein that is a humanized antibody. In some embodiments, OX40 agonists for use in the presently disclosed methods and compositions include anti-

OX40 antibodies, human anti-OX40 antibodies, mouse anti-OX40 antibodies, mammalian anti-OX40 antibodies, monoclonal anti-OX40 antibodies, polyclonal anti-OX40 antibodies, chimeric anti-OX40 antibodies, anti-OX40 adnectins, anti-OX40 domain antibodies, single chain anti-OX40 fragments, heavy chain anti-OX40 fragments, light chain anti-OX40 fragments, anti-OX40 fusion proteins, and fragments, derivatives, conjugates, variants, or biosimilars thereof. In a preferred embodiment, the OX40 agonist is an agonistic, anti-OX40 humanized or fully human monoclonal antibody (*i.e.*, an antibody derived from a single cell line).

[001053] In a preferred embodiment, the OX40 agonist or OX40 binding molecule may also be a fusion protein. OX40 fusion proteins comprising an Fc domain fused to OX40L are described, for example, in Sadun, *et al.*, *J. Immunother*. 2009, *182*, 1481-89. In a preferred embodiment, a multimeric OX40 agonist, such as a trimeric or hexameric OX40 agonist (with three or six ligand binding domains), may induce superior receptor (OX40L) clustering and internal cellular signaling complex formation compared to an agonistic monoclonal antibody, which typically possesses two ligand binding domains. Trimeric (trivalent) or hexameric (or hexavalent) or greater fusion proteins comprising three TNFRSF binding domains and IgG1-Fc and optionally further linking two or more of these fusion proteins are described, *e.g.*, in Gieffers, *et al.*, *Mol. Cancer Therapeutics* 2013, *12*, 2735-47.

[001054] Agonistic OX40 antibodies and fusion proteins are known to induce strong immune responses. Curti, *et al.*, *Cancer Res.* 2013, 73, 7189-98. In a preferred embodiment, the OX40 agonist is a monoclonal antibody or fusion protein that binds specifically to OX40 antigen in a manner sufficient to reduce toxicity. In some embodiments, the OX40 agonist is an agonistic OX40 monoclonal antibody or fusion protein that abrogates antibody-dependent cellular toxicity (ADCC), for example NK cell cytotoxicity. In some embodiments, the OX40 agonist is an agonistic OX40 monoclonal antibody or fusion protein that abrogates antibody-dependent cell phagocytosis (ADCP). In some embodiments, the OX40 agonist is an agonistic OX40 monoclonal antibody or fusion protein that abrogates complement-dependent cytotoxicity (CDC). In some embodiments, the OX40 agonist is an agonistic OX40 monoclonal antibody or fusion protein which abrogates Fc region functionality.

[001055] In some embodiments, the OX40 agonists are characterized by binding to human OX40 (SEQ ID NO:54) with high affinity and agonistic activity. In an embodiment, the OX40 agonist is a binding molecule that binds to human OX40 (SEQ ID NO:54). In an embodiment, the OX40 agonist is a binding molecule that binds to murine OX40 (SEQ ID

NO:55). The amino acid sequences of OX40 antigen to which an OX40 agonist or binding molecule binds are summarized in Table 12.

TABLE 28: Amino acid sequences of OX40 antigens.

Identifier	Sequence (One-Letter Amino Acid Symbols)						
SEQ ID NO:54	MCVGARRLGR GPCAALLLLG LGLSTVTGLH CVGDTYPSND RCCHECRPGN GMVSRCSRSQ	60					
human OX40	NTVCRPCGPG FYNDVVSSKP CKPCTWCNLR SGSERKQLCT ATQDTVCRCR AGTQPLDSYK	120					
(Homo sapiens)	PGVDCAPCPP GHFSPGDNQA CKPWTNCTLA GKHTLQPASN SSDAICEDRD PPATQPQETQ	180					
	GPPARPITVQ PTEAWPRTSQ GPSTRPVEVP GGRAVAAILG LGLVLGLLGP LAILLALYLL	240					
	RRDQRLPPDA HKPPGGGSFR TPIQEEQADA HSTLAKI	277					
SEQ ID NO:55	MYVWVQQPTA LLLLGLTLGV TARRLNCVKH TYPSGHKCCR ECQPGHGMVS RCDHTRDTLC	60					
murine OX40	HPCETGFYNE AVNYDTCKQC TQCNHRSGSE LKQNCTPTQD TVCRCRPGTQ PRQDSGYKLG	120					
(Mus musculus)	VDCVPCPPGH FSPGNNQACK PWTNCTLSGK QTRHPASDSL DAVCEDRSLL ATLLWETQRP	180					
	TFRPTTVQST TVWPRTSELP SPPTLVTPEG PAFAVLLGLG LGLLAPLTVL LALYLLRKAW	240					
	RLPNTPKPCW GNSFRTPIQE EHTDAHFTLA KI	272					

[001056] In some embodiments, the compositions, processes and methods described include a OX40 agonist that binds human or murine OX40 with a K_D of about 100 pM or lower, binds human or murine OX40 with a K_D of about 90 pM or lower, binds human or murine OX40 with a K_D of about 80 pM or lower, binds human or murine OX40 with a K_D of about 70 pM or lower, binds human or murine OX40 with a K_D of about 60 pM or lower, binds human or murine OX40 with a K_D of about 40 pM or lower, or binds human or murine OX40 with a K_D of about 30 pM or lower.

[001057] In some embodiments, the compositions, processes and methods described include a OX40 agonist that binds to human or murine OX40 with a k_{assoc} of about 7.5×10^5 1/M·s or faster, binds to human or murine OX40 with a k_{assoc} of about 7.5×10^5 1/M·s or faster, binds to human or murine OX40 with a k_{assoc} of about 8×10^5 1/M·s or faster, binds to human or murine OX40 with a k_{assoc} of about 8.5×10^5 1/M·s or faster, binds to human or murine OX40 with a k_{assoc} of about 9×10^5 1/M·s or faster, binds to human or murine OX40 with a k_{assoc} of about 9.5×10^5 1/M·s or faster, or binds to human or murine OX40 with a k_{assoc} of about 1×10^6 1/M·s or faster.

[001058] In some embodiments, the compositions, processes and methods described include a OX40 agonist that binds to human or murine OX40 with a k_{dissoc} of about 2×10^{-5} 1/s or slower, binds to human or murine OX40 with a k_{dissoc} of about 2.1×10^{-5} 1/s or slower, binds to human or murine OX40 with a k_{dissoc} of about 2.2×10^{-5} 1/s or slower, binds to human or murine OX40 with a k_{dissoc} of about 2.3×10^{-5} 1/s or slower, binds to human or murine OX40 with a k_{dissoc} of about 2.4×10^{-5} 1/s or slower, binds to human or murine OX40 with a k_{dissoc} of about 2.5×10^{-5} 1/s or slower, binds to human or murine OX40 with a k_{dissoc} of about 2.6×10^{-5} 1/s or slower or binds to human or murine OX40 with a k_{dissoc} of about 2.7×10^{-5} 1/s or slower, binds to human or murine OX40 with a k_{dissoc} of about 2.7×10^{-5} 1/s or slower, binds

to human or murine OX40 with a k_{dissoc} of about 2.9×10^{-5} 1/s or slower, or binds to human or murine OX40 with a k_{dissoc} of about 3×10^{-5} 1/s or slower.

[001059] In some embodiments, the compositions, processes and methods described include OX40 agonist that binds to human or murine OX40 with an IC₅₀ of about 10 nM or lower, binds to human or murine OX40 with an IC₅₀ of about 9 nM or lower, binds to human or murine OX40 with an IC₅₀ of about 8 nM or lower, binds to human or murine OX40 with an IC₅₀ of about 6 nM or lower, binds to human or murine OX40 with an IC₅₀ of about 6 nM or lower, binds to human or murine OX40 with an IC₅₀ of about 5 nM or lower, binds to human or murine OX40 with an IC₅₀ of about 3 nM or lower, binds to human or murine OX40 with an IC₅₀ of about 2 nM or lower, or binds to human or murine OX40 with an IC₅₀ of about 1 nM or lower.

[001060] In some embodiments, the OX40 agonist is tavolixizumab, also known as MEDI0562 or MEDI-0562. Tavolixizumab is available from the MedImmune subsidiary of AstraZeneca, Inc. Tavolixizumab is immunoglobulin G1-kappa, anti-[Homo sapiens TNFRSF4 (tumor necrosis factor receptor (TNFR) superfamily member 4, OX40, CD134)], humanized and chimeric monoclonal antibody. The amino acid sequences of tavolixizumab are set forth in Table 13. Tavolixizumab comprises N-glycosylation sites at positions 301 and 301'', with fucosylated complex bi-antennary CHO-type glycans; heavy chain intrachain disulfide bridges at positions 22-95 (V_H-V_L), 148-204 (C_H1-C_L), 265-325 (C_H2) and 371-429 (C_H3) (and at positions 22''-95'', 148''-204'', 265''-325'', and 371''-429''); light chain intrachain disulfide bridges at positions 23'-88' (V_H-V_L) and 134'-194' (C_H1-C_L) (and at positions 23'''-88''' and 134'''-194'''); interchain heavy chain-heavy chain disulfide bridges at positions 230-230'' and 233-233''; and interchain heavy chain-light chain disulfide bridges at 224-214' and 224''-214'''. Current clinical trials of tavolixizumab in a variety of solid tumor indications include U.S. National Institutes of Health clinicaltrials.gov identifiers NCT02318394 and NCT02705482.

[001061] In an embodiment, a OX40 agonist comprises a heavy chain given by SEQ ID NO:56 and a light chain given by SEQ ID NO:57. In an embodiment, a OX40 agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:56 and SEQ ID NO:57, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:56 and SEQ ID NO:57, respectively. In an embodiment, a OX40 agonist

comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:56 and SEQ ID NO:57, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:56 and SEQ ID NO:57, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:56 and SEQ ID NO:57, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:56 and SEQ ID NO:57, respectively.

[001062] In an embodiment, the OX40 agonist comprises the heavy and light chain CDRs or variable regions (VRs) of tavolixizumab. In an embodiment, the OX40 agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:58, and the OX40 agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:59, and conservative amino acid substitutions thereof. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:58 and SEQ ID NO:59, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:58 and SEQ ID NO:59, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:58 and SEQ ID NO:59, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:58 and SEQ ID NO:59, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:58 and SEQ ID NO:59, respectively. In an embodiment, an OX40 agonist comprises an scFv antibody comprising V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:58 and SEQ ID NO:59.

[001063] In an embodiment, a OX40 agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:60, SEQ ID NO:61, and SEQ ID NO:62, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, respectively, and conservative amino acid substitutions thereof.

[001064] In an embodiment, the OX40 agonist is a OX40 agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to tavolixizumab. In an embodiment, the biosimilar monoclonal antibody comprises an OX40 antibody comprising

an amino acid sequence which has at least 97% sequence identity, e.g., 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is tavolixizumab. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a OX40 agonist antibody authorized or submitted for authorization, wherein the OX40 agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is tavolixizumab. The OX40 agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is tavolixizumab. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is tavolixizumab.

TABLE 29: Amino acid sequences for OX40 agonist antibodies related to tavolixizumab.

Identifier		Seque	nce (One-l	Letter Ami	ino Acid S	ymbols)	
SEQ ID NO:56	QVQLQESGPG I	LVKPSQTLSL	TCAVYGGSFS	SGYWNWIRKH	PGKGLEYIGY	ISYNGITYHN	60
heavy chain for	PSLKSRITIN I	RDTSKNQYSL	QLNSVTPEDT	AVYYCARYKY	DYDGGHAMDY	WGQGTLVTVS	120
tavolixizumab	SASTKGPSVF	PLAPSSKSTS	GGTAALGCLV	KDYFPEPVTV	SWNSGALTSG	VHTFPAVLQS	180
	SGLYSLSSVV	TVPSSSLGTQ	TYICNVNHKP	SNTKVDKRVE	PKSCDKTHTC	PPCPAPELLG	240
	GPSVFLFPPK 1	PKDTLMISRT	PEVTCVVVDV	SHEDPEVKFN	WYVDGVEVHN	AKTKPREEQY	300
	NSTYRVVSVL T	TVLHQDWLNG	KEYKCKVSNK	ALPAPIEKTI	SKAKGQPREP	QVYTLPPSRE	360
	EMTKNQVSLT (CLVKGFYPSD	IAVEWESNGQ	PENNYKTTPP	VLDSDGSFFL	YSKLTVDKSR	420
	WQQGNVFSCS V	VMHEALHNHY	TQKSLSLSPG	K			451
SEQ ID NO:57	DIQMTQSPSS I	LSASVGDRVT	ITCRASQDIS	NYLNWYQQKP	GKAPKLLIYY	TSKLHSGVPS	60
light chain for	RFSGSGSGTD	YTLTISSLQP	EDFATYYCQQ	GSALPWTFGQ	GTKVEIKRTV	AAPSVFIFPP	120
tavolixizumab	SDEQLKSGTA :	SVVCLLNNFY	PREAKVQWKV	DNALQSGNSQ	ESVTEQDSKD	STYSLSSTLT	180
	LSKADYEKHK V	VYACEVTHQG	LSSPVTKSFN	RGEC			214
SEQ ID NO:58	QVQLQESGPG I	LVKPSQTLSL	TCAVYGGSFS	SGYWNWIRKH	PGKGLEYIGY	ISYNGITYHN	60
heavy chain	PSLKSRITIN 1	RDTSKNQYSL	QLNSVTPEDT	AVYYCARYKY	DYDGGHAMDY	WGQGTLVT	118
variable region							
for							
tavolixizumab							
SEQ ID NO:59	DIQMTQSPSS 1	LSASVGDRVT	ITCRASQDIS	NYLNWYQQKP	GKAPKLLIYY	TSKLHSGVPS	60
light chain	RFSGSGSGTD	YTLTISSLQP	EDFATYYCQQ	GSALPWTFGQ	GTKVEIKR		108
variable region							
for							
tavolixizumab							

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SEQ ID NO:60	GSFSSGYWN	9
heavy chain CDR1		
for		
tavolixizumab		
SEQ ID NO:61	YIGYISYNGI TYH	13
heavy chain CDR2		
for		
tavolixizumab		
SEQ ID NO:62	RYKYDYDGGH AMDY	14
heavy chain CDR3		
for		
tavolixizumab		
SEQ ID NO:63	QDISNYLN	8
light chain CDR1		
for		
tavolixizumab		
SEQ ID NO:64	LLIYYTSKLH S	11
light chain CDR2		
for		
tavolixizumab		
SEQ ID NO:65	QQGSALPW	8
light chain CDR3		
for		
tavolixizumab		

[001065] In some embodiments, the OX40 agonist is 11D4, which is a fully human antibody available from Pfizer, Inc. The preparation and properties of 11D4 are described in U.S. Patent Nos. 7,960,515; 8,236,930; and 9,028,824, the disclosures of which are incorporated by reference herein. The amino acid sequences of 11D4 are set forth in Table 14.

[001066] In an embodiment, a OX40 agonist comprises a heavy chain given by SEQ ID NO:66 and a light chain given by SEQ ID NO:67. In an embodiment, a OX40 agonist comprises heavy and light chains having the sequences shown in SEQ ID NO:66 and SEQ ID NO:67, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:66 and SEQ ID NO:67, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:66 and SEQ ID NO:67, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:66 and SEQ ID NO:67, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:66 and SEQ ID NO:67, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:66 and SEQ ID NO:67, respectively.

[001067] In an embodiment, the OX40 agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 11D4. In an embodiment, the OX40 agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:68, and the OX40 agonist light

chain variable region (V_L) comprises the sequence shown in SEQ ID NO:69, and conservative amino acid substitutions thereof. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:68 and SEQ ID NO:69, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:68 and SEQ ID NO:69, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:68 and SEQ ID NO:69, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:68 and SEQ ID NO:69, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:68 and SEQ ID NO:69, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:68 and SEQ ID NO:69, respectively.

[001068] In an embodiment, a OX40 agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:70, SEQ ID NO:71, and SEQ ID NO:72, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:73, SEQ ID NO:74, and SEQ ID NO:75, respectively, and conservative amino acid substitutions thereof.

[001069] In an embodiment, the OX40 agonist is a OX40 agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to 11D4. In an embodiment, the biosimilar monoclonal antibody comprises an OX40 antibody comprising an amino acid sequence which has at least 97% sequence identity, e.g., 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 11D4. In some embodiments, the one or more posttranslational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a OX40 agonist antibody authorized or submitted for authorization, wherein the OX40 agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 11D4. The OX40 agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or

more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 11D4. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 11D4.

TABLE 30: Amino acid sequences for OX40 agonist antibodies related to 11D4.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:66	EVQLVESGGG LVQPGGSLRL SCAASGFTFS SYSMNWVRQA PGKGLEWVSY ISSSSSTIDY	60
heavy chain for	ADSVKGRFTI SRDNAKNSLY LQMNSLRDED TAVYYCARES GWYLFDYWGQ GTLVTVSSAS	120
11D4	TKGPSVFPLA PCSRSTSEST AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL	180
	YSLSSVVTVP SSNFGTQTYT CNVDHKPSNT KVDKTVERKC CVECPPCPAP PVAGPSVFLF	240
	PPKPKDTLMI SRTPEVTCVV VDVSHEDPEV QFNWYVDGVE VHNAKTKPRE EQFNSTFRVV	300
	SVLTVVHQDW LNGKEYKCKV SNKGLPAPIE KTISKTKGQP REPQVYTLPP SREEMTKNQV	360
	SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPMLDSDGS FFLYSKLTVD KSRWQQGNVF	420
	SCSVMHEALH NHYTQKSLSL SPGK	444
SEQ ID NO:67	DIQMTQSPSS LSASVGDRVT ITCRASQGIS SWLAWYQQKP EKAPKSLIYA ASSLQSGVPS	60
light chain for	RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YNSYPPTFGG GTKVEIKRTV AAPSVFIFPP	120
11D4	SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT	180
	LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	214
SEQ ID NO:68	EVQLVESGGG LVQPGGSLRL SCAASGFTFS SYSMNWVRQA PGKGLEWVSY ISSSSSTIDY	60
heavy chain	ADSVKGRFTI SRDNAKNSLY LQMNSLRDED TAVYYCARES GWYLFDYWGQ GTLVTVSS	118
variable region		
for 11D4		
SEQ ID NO:69	DIQMTQSPSS LSASVGDRVT ITCRASQGIS SWLAWYQQKP EKAPKSLIYA ASSLQSGVPS	60
light chain	RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YNSYPPTFGG GTKVEIK	107
variable region		
for 11D4		
SEQ ID NO:70	SYSMN	5
heavy chain CDR1		
for 11D4		
SEQ ID NO:71	YISSSSTID YADSVKG	17
heavy chain CDR2		
for 11D4		
SEQ ID NO:72	ESGWYLFDY	9
heavy chain CDR3		
for 11D4		
SEQ ID NO:73	RASQGISSWL A	11
light chain CDR1		
for 11D4		
SEQ ID NO:74	AASSLQS	7
light chain CDR2		
for 11D4		
SEQ ID NO:75	QQYNSYPPT	9
light chain CDR3		
for 11D4		

[001070] In some embodiments, the OX40 agonist is 18D8, which is a fully human antibody available from Pfizer, Inc. The preparation and properties of 18D8 are described in U.S. Patent Nos. 7,960,515; 8,236,930; and 9,028,824, the disclosures of which are incorporated by reference herein. The amino acid sequences of 18D8 are set forth in Table 15.

[001071] In an embodiment, a OX40 agonist comprises a heavy chain given by SEQ ID NO:76 and a light chain given by SEQ ID NO:77. In an embodiment, a OX40 agonist

comprises heavy and light chains having the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively. In an embodiment, a OX40 agonist comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:76 and SEQ ID NO:77, respectively.

[001072] In an embodiment, the OX40 agonist comprises the heavy and light chain CDRs or variable regions (VRs) of 18D8. In an embodiment, the OX40 agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:78, and the OX40 agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:79, and conservative amino acid substitutions thereof. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:78 and SEQ ID NO:79, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:78 and SEQ ID NO:79, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:78 and SEQ ID NO:79, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:78 and SEQ ID NO:79, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:78 and SEQ ID NO:79, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:78 and SEQ ID NO:79, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:78 and

[001073] In an embodiment, a OX40 agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:80, SEQ ID NO:81, and SEQ ID NO:82, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:83, SEQ ID NO:84, and SEQ ID NO:85, respectively, and conservative amino acid substitutions thereof.

[001074] In an embodiment, the OX40 agonist is a OX40 agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to 18D8. In an embodiment, the biosimilar monoclonal antibody comprises an OX40 antibody comprising an amino acid sequence which has at least 97% sequence identity, e.g., 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 18D8. In some embodiments, the one or more posttranslational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a OX40 agonist antibody authorized or submitted for authorization, wherein the OX40 agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 18D8. The OX40 agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 18D8. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is 18D8.

TABLE 31: Amino acid sequences for OX40 agonist antibodies related to 18D8.

Identifier	Sequence (One-Letter Amino Acid Syr	mbols)	
1 dentilier	Sequence (one Letter rimino richa syr	1110015)	
SEQ ID NO:76	EVQLVESGGG LVQPGRSLRL SCAASGFTFD DYAMHWVRQA PGKGLEWVSG I	SWNSGSIGY	60
heavy chain for	ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TALYYCAKDQ STADYYFYYG M	1DVWGQGTTV	120
18D8	TVSSASTKGP SVFPLAPCSR STSESTAALG CLVKDYFPEP VTVSWNSGAL T	rsgvhtfpav	180
	LQSSGLYSLS SVVTVPSSNF GTQTYTCNVD HKPSNTKVDK TVERKCCVEC E	PPCPAPPVAG	240
	PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVQFNW YVDGVEVHNA F	KTKPREEQFN	300
	STFRVVSVLT VVHQDWLNGK EYKCKVSNKG LPAPIEKTIS KTKGQPREPQ \	/YTLPPSREE	360
	MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPM LDSDGSFFLY S	SKLTVDKSRW	420
	QQGNVFSCSV MHEALHNHYT QKSLSLSPGK		450
SEQ ID NO:77	EIVVTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD A	ASNRATGIPA	60
light chain for	RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPTFGQG TKVEIKRTVA F	APSVFIFPPS	120
18D8	DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS T	FYSLSSTLTL	180
	SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC		213
SEQ ID NO:78	EVQLVESGGG LVQPGRSLRL SCAASGFTFD DYAMHWVRQA PGKGLEWVSG I	SWNSGSIGY	60
heavy chain	ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TALYYCAKDQ STADYYFYYG N	1DVWGQGTTV	120
variable region	TVSS		124
for 18D8			
SEQ ID NO:79	EIVVTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD A	ASNRATGIPA	60
light chain	RFSGSGSGTD FTLTISSLEP EDFAVYYCOO RSNWPTFGOG TKVEIK		106

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	,	
variable region		
for 18D8		
SEQ ID NO:80	DYAMH	5
heavy chain CDR1		
for 18D8		
SEQ ID NO:81	GISWNSGSIG YADSVKG	17
heavy chain CDR2		
for 18D8		
SEQ ID NO:82	DQSTADYYFY YGMDV	15
heavy chain CDR3		
for 18D8		
SEQ ID NO:83	RASQSVSSYL A	11
light chain CDR1		
for 18D8		
SEQ ID NO:84	DASNRAT	7
light chain CDR2		
for 18D8		
SEQ ID NO:85	QQRSNWPT	8
light chain CDR3		
for 18D8		

[001075] In some embodiments, the OX40 agonist is Hu119-122, which is a humanized antibody available from GlaxoSmithKline plc. The preparation and properties of Hu119-122 are described in U.S. Patent Nos. 9,006,399 and 9,163,085, and in International Patent Publication No. WO 2012/027328, the disclosures of which are incorporated by reference herein. The amino acid sequences of Hu119-122 are set forth in Table 16.

[001076] In an embodiment, the OX40 agonist comprises the heavy and light chain CDRs or variable regions (VRs) of Hu119-122. In an embodiment, the OX40 agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:86, and the OX40 agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:87, and conservative amino acid substitutions thereof. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:86 and SEQ ID NO:87, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:86 and SEQ ID NO:87, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:86 and SEQ ID NO:87, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:86 and SEQ ID NO:87, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:86 and SEQ ID NO:87, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:86 and SEQ ID NO:87, respectively.

[001077] In an embodiment, a OX40 agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:88, SEQ ID NO:89, and SEQ ID NO:90, respectively, and conservative amino acid substitutions thereof, and light chain

CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:91, SEQ ID NO:92, and SEQ ID NO:93, respectively, and conservative amino acid substitutions thereof.

[001078] In an embodiment, the OX40 agonist is a OX40 agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to Hu119-122. In an embodiment, the biosimilar monoclonal antibody comprises an OX40 antibody comprising an amino acid sequence which has at least 97% sequence identity, e.g., 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is Hu119-122. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a OX40 agonist antibody authorized or submitted for authorization, wherein the OX40 agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is Hu119-122. The OX40 agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is Hull9-122. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is Hull9-122.

TABLE 32: Amino acid sequences for OX40 agonist antibodies related to Hu119-122.

Identifier	Sequence (One-Letter Amino Acid Symbols)						
SEQ ID NO:86	EVQLVESGGG LVQPGGSLRL SCAASEYEFP SHDMSWVRQA PGKGLELVAA INSDGGSTY	Y 60					
heavy chain	PDTMERRFTI SRDNAKNSLY LQMNSLRAED TAVYYCARHY DDYYAWFAYW GQGTMVTVS	SS 120					
variable region							
for Hull9-122							
SEQ ID NO:87	EIVLTQSPAT LSLSPGERAT LSCRASKSVS TSGYSYMHWY QQKPGQAPRL LIYLASNLE	ES 60					
light chain	GVPARFSGSG SGTDFTLTIS SLEPEDFAVY YCQHSRELPL TFGGGTKVEI K	111					
variable region							
for Hull9-122							
SEQ ID NO:88	SHDMS	5					
heavy chain CDRl							
for Hull9-122							

GEO ED NO-00	ATMODOGOGOV VDDOMED	1 7
SEQ ID NO:89	AINSDGGSTY YPDTMER	1 /
heavy chain CDR2		
for Hull9-122		
SEQ ID NO:90	HYDDYYAWFA Y	11
heavy chain CDR3		
for Hu119-122		
SEQ ID NO:91	RASKSVSTSG YSYMH	15
light chain CDR1		
for Hull9-122		
SEQ ID NO:92	LASNLES	7
light chain CDR2		
for Hu119-122		
SEQ ID NO:93	QHSRELPLT	9
light chain CDR3		
for Hull9-122		

[001079] In some embodiments, the OX40 agonist is Hu106-222, which is a humanized antibody available from GlaxoSmithKline plc. The preparation and properties of Hu106-222 are described in U.S. Patent Nos. 9,006,399 and 9,163,085, and in International Patent Publication No. WO 2012/027328, the disclosures of which are incorporated by reference herein. The amino acid sequences of Hu106-222 are set forth in Table 17.

[001080] In an embodiment, the OX40 agonist comprises the heavy and light chain CDRs or variable regions (VRs) of Hu106-222. In an embodiment, the OX40 agonist heavy chain variable region (V_H) comprises the sequence shown in SEQ ID NO:94, and the OX40 agonist light chain variable region (V_L) comprises the sequence shown in SEQ ID NO:95, and conservative amino acid substitutions thereof. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:94 and SEQ ID NO:95, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:94 and SEQ ID NO:95, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:94 and SEQ ID NO:95, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:94 and SEQ ID NO:95, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:94 and SEQ ID NO:95, respectively. In an embodiment, a OX40 agonist comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:94 and SEQ ID NO:95, respectively.

[001081] In an embodiment, a OX40 agonist comprises heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:96, SEQ ID NO:97, and SEQ ID NO:98, respectively, and conservative amino acid substitutions thereof, and light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:99, SEQ ID NO:100, and SEQ ID NO:101, respectively, and conservative amino acid substitutions thereof.

[001082] In an embodiment, the OX40 agonist is a OX40 agonist biosimilar monoclonal antibody approved by drug regulatory authorities with reference to Hu106-222. In an embodiment, the biosimilar monoclonal antibody comprises an OX40 antibody comprising an amino acid sequence which has at least 97% sequence identity, e.g., 97%, 98%, 99% or 100% sequence identity, to the amino acid sequence of a reference medicinal product or reference biological product and which comprises one or more post-translational modifications as compared to the reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is Hu106-222. In some embodiments, the one or more post-translational modifications are selected from one or more of: glycosylation, oxidation, deamidation, and truncation. In some embodiments, the biosimilar is a OX40 agonist antibody authorized or submitted for authorization, wherein the OX40 agonist antibody is provided in a formulation which differs from the formulations of a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is Hu106-222. The OX40 agonist antibody may be authorized by a drug regulatory authority such as the U.S. FDA and/or the European Union's EMA. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is Hu106-222. In some embodiments, the biosimilar is provided as a composition which further comprises one or more excipients, wherein the one or more excipients are the same or different to the excipients comprised in a reference medicinal product or reference biological product, wherein the reference medicinal product or reference biological product is Hu106-222.

TABLE 33: Amino acid sequences for OX40 agonist antibodies related to Hu106-222.

Identifier	Sequence (One-Letter Amino Acid Symbols)	
SEQ ID NO:94	QVQLVQSGSE LKKPGASVKV SCKASGYTFT DYSMHWVRQA PGQGLKWMGW INTETGEPTY	60
heavy chain	ADDFKGRFVF SLDTSVSTAY LQISSLKAED TAVYYCANPY YDYVSYYAMD YWGQGTTVTV	120
variable region for Hu106-222	SS	122
SEQ ID NO:95	DIQMTQSPSS LSASVGDRVT ITCKASQDVS TAVAWYQQKP GKAPKLLIYS ASYLYTGVPS	60
light chain	RFSGSGSGTD FTFTISSLQP EDIATYYCQQ HYSTPRTFGQ GTKLEIK	107
variable region		
for Hu106-222		
SEQ ID NO:96	DYSMH	5
heavy chain CDR1		
for Hu106-222		
SEQ ID NO:97	WINTETGEPT YADDFKG	17
heavy chain CDR2		
for Hu106-222		

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SEQ ID NO:98	PYYDYVSYYA MDY	13
heavy chain CDR3		
for Hu106-222		
SEQ ID NO:99	KASQDVSTAV A	11
light chain CDR1		
for Hu106-222		
SEQ ID NO:100	SASYLYT	7
light chain CDR2		
for Hu106-222		
SEQ ID NO:101	QQHYSTPRT	9
light chain CDR3		
for Hu106-222		

[001083] In some embodiments, the OX40 agonist antibody is MEDI6469 (also referred to as 9B12). MEDI6469 is a murine monoclonal antibody. Weinberg, et al., J. Immunother. 2006, 29, 575-585. In some embodiments the OX40 agonist is an antibody produced by the 9B12 hybridoma, deposited with Biovest Inc. (Malvern, MA, USA), as described in Weinberg, et al., J. Immunother. 2006, 29, 575-585, the disclosure of which is hereby incorporated by reference in its entirety. In some embodiments, the antibody comprises the CDR sequences of MEDI6469. In some embodiments, the antibody comprises a heavy chain variable region sequence and/or a light chain variable region sequence of MEDI6469.

[001084] In an embodiment, the OX40 agonist is L106 BD (Pharmingen Product #340420). In some embodiments, the OX40 agonist comprises the CDRs of antibody L106 (BD Pharmingen Product #340420). In some embodiments, the OX40 agonist comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody L106 (BD Pharmingen Product #340420). In an embodiment, the OX40 agonist is ACT35 (Santa Cruz Biotechnology, Catalog #20073). In some embodiments, the OX40 agonist comprises the CDRs of antibody ACT35 (Santa Cruz Biotechnology, Catalog #20073). In some embodiments, the OX40 agonist comprises a heavy chain variable region sequence and/or a light chain variable region sequence of antibody ACT35 (Santa Cruz Biotechnology, Catalog #20073). In an embodiment, the OX40 agonist is the murine monoclonal antibody anti-mCD134/mOX40 (clone OX86), commercially available from InVivoMAb, BioXcell Inc, West Lebanon, NH.

[001085] In an embodiment, the OX40 agonist is selected from the OX40 agonists described in International Patent Application Publication Nos. WO 95/12673, WO 95/21925, WO 2006/121810, WO 2012/027328, WO 2013/028231, WO 2013/038191, and WO 2014/148895; European Patent Application EP 0672141; U.S. Patent Application Publication Nos. US 2010/136030, US 2014/377284, US 2015/190506, and US 2015/132288 (including clones 20E5 and 12H3); and U.S. Patent Nos. 7,504,101, 7,550,140, 7,622,444, 7,696,175,

7,960,515, 7,961,515, 8,133,983, 9,006,399, and 9,163,085, the disclosure of each of which is incorporated herein by reference in its entirety.

[001086] In an embodiment, the OX40 agonist is an OX40 agonistic fusion protein as depicted in Structure I-A (C-terminal Fc-antibody fragment fusion protein) or Structure I-B (N-terminal Fc-antibody fragment fusion protein), or a fragment, derivative, conjugate, variant, or biosimilar thereof. The properties of structures I-A and I-B are described above and in U.S. Patent Nos. 9,359,420, 9,340,599, 8,921,519, and 8,450,460, the disclosures of which are incorporated by reference herein. Amino acid sequences for the polypeptide domains of structure I-A are given in Table 9. The Fc domain preferably comprises a complete constant domain (amino acids 17-230 of SEQ ID NO:31) the complete hinge domain (amino acids 1-16 of SEQ ID NO:31) or a portion of the hinge domain (e.g., amino acids 4-16 of SEQ ID NO:31). Preferred linkers for connecting a C-terminal Fc-antibody may be selected from the embodiments given in SEQ ID NO:32 to SEQ ID NO:41, including linkers suitable for fusion of additional polypeptides. Likewise, amino acid sequences for the polypeptide domains of structure I-B are given in Table 10. If an Fc antibody fragment is fused to the N-terminus of an TNRFSF fusion protein as in structure I-B, the sequence of the Fc module is preferably that shown in SEQ ID NO:42, and the linker sequences are preferably selected from those embodiments set forth in SED ID NO:43 to SEQ ID NO:45.

[001087] In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains selected from the group consisting of a variable heavy chain and variable light chain of tavolixizumab, a variable heavy chain and variable light chain of 11D4, a variable heavy chain and variable light chain of 18D8, a variable heavy chain and variable light chain of Hu119-122, a variable heavy chain and variable light chain of Hu106-222, a variable heavy chain and variable light chain selected from the variable heavy chains and variable light chains described in Table 17, any combination of a variable heavy chain and variable light chain of the foregoing, and fragments, derivatives, conjugates, variants, and biosimilars thereof.

[001088] In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains comprising an OX40L sequence. In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains comprising a sequence according to SEQ ID NO:102. In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains comprising a soluble OX40L sequence. In an

embodiment, a OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains comprising a sequence according to SEQ ID NO:103. In an embodiment, a OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains comprising a sequence according to SEQ ID NO:104.

[001089] In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:58 and SEQ ID NO:59, respectively, wherein the V_H and V_L domains are connected by a linker. In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:68 and SEQ ID NO:69, respectively, wherein the V_H and V_L domains are connected by a linker. In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:78 and SEQ ID NO:79, respectively, wherein the V_H and V_L domains are connected by a linker. In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:86 and SEQ ID NO:87, respectively, wherein the V_H and V_L domains are connected by a linker. In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:94 and SEQ ID NO:95, respectively, wherein the V_H and V_L domains are connected by a linker. In an embodiment, an OX40 agonist fusion protein according to structures I-A or I-B comprises one or more OX40 binding domains that is a scFv domain comprising V_H and V_L regions that are each at least 95% identical to the V_H and V_L sequences given in Table 14, wherein the V_H and V_L domains are connected by a linker.

TABLE 34: Additional polypeptide domains useful as OX40 binding domains in fusion proteins (e.g., structures I-A and I-B) or as scFv OX40 agonist antibodies.

Identifier	Sequence (One-Letter Amino Acid Symbols)						
SEQ ID NO:102	MERVQPLEEN VGNAARPRFE RNKLLLVASV IQGLGLLLCF TYICLHFSAL QVSHRYPRIQ	60					
OX40L	SIKVQFTEYK KEKGFILTSQ KEDEIMKVQN NSVIINCDGF YLISLKGYFS QEVNISLHYQ	120					
	KDEEPLFQLK KVRSVNSLMV ASLTYKDKVY LNVTTDNTSL DDFHVNGGEL ILIHQNPGEF	180					
	CVL	183					

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SEQ ID NO:103							
	SHRYPRIOSI	KVOFTEYKKE	KGFILTSOKE	DEIMKVQNNS	VIINCDGFYL	ISLKGYFSOE	60
OX40L soluble				LTYKDKVYLN			120
domain	IHONPGEFCV		TO VIOLITY AD	LIINDIVILIN	VIIDNIBEDD	INVIOUDELLE	131
	7-						
SEQ ID NO:104				MKVQNNSVII			60
OX40L soluble	SLHYQKDEEP	LFQLKKVRSV	NSLMVASLTY	KDKVYLNVTT	DNTSLDDFHV	NGGELILIHQ	120
domain	NPGEFCVL						128
(alternative)							
	DIATIDAGG	THODGGGTDI	aaaaaa	MATERIAL POR	DOMOT DEPLOY	Tagagggggyyy	<i>C</i> 0
SEQ ID NO:105				NYTMNWVRQA			60
variable heavy	ADSVKGRFTI	SRDNSKNTLY	LQMNSLRAED	TAVYYCAKDR	YSQVHYALDY	WGQGTLVTVS	120
chain for 008							
SEQ ID NO:106	DIVMTOSPDS	T.PVTPGFPAS	TSCRSSOSLL	HSNGYNYLDW	YLOKAGOSPO	LLTYLGSNRA	60
variable light				YYCQQYYNHP		ELITEODMIAI	108
_	SGVPDRFSGS	GSGTDFTLKI	SKVEAEDVGV	TICQQIINHP	TTFGQGTK		100
chain for 008							
SEQ ID NO:107	EVQLVESGGG	VVQPGRSLRL	SCAASGFTFS	DYTMNWVRQA	PGKGLEWVSS	ISGGSTYYAD	60
variable heavy	SRKGRFTISR	DNSKNTLYLO	MNNLRAEDTA	VYYCARDRYF	ROONAFDYWG	OGTLVTVSSA	120
chain for 011		E				2	
	DELBAMOGRA	I DI III DA CIDA C	TAGDAGOATI	HONOLOUITEL	VII OIZA GOGDO	T T TWI COMPA	60
SEQ ID NO:108	_			HSNGYNYLDW		LLIYLGSNRA	60
variable light	SGVPDRFSGS	GSGTDFTLKI	SRVEAEDVGV	YYCQQYYNHP	TTFGQGTK		108
chain for 011							
SEO ID NO:109	EVOLVESGGG	LVOPRGSLRL	SCAASGETES	SYAMNWVRQA	PGKGLEWVAV	TSYDGSNKYY	60
variable heavy				TAVYYCAKDR			120
4	ADSVIGRETT	DUDUNITI	TÖLMƏTVAED	IAVIICANDN	IIIDENADDI	MGGGITATAD	120
chain for 021							
SEQ ID NO:110				HSNGYNYLDW		LLIYLGSNRA	60
variable light	SGVPDRFSGS	GSGTDFTLKI	SRVEAEDVGV	YYCQQYKSNP	PTFGQGTK		108
chain for 021							
SEO ID NO:111	EMOTABECCC	TAMBCCCTDT	GCV CGCEUEG	CAVMHPD DO	DCKCI DIMICA	тспссспуул	60
~				SYAMHWVRQA			
variable heavy	DSVMGRFTIS	RDNSKNTLYL	QMNSLRAEDT	AVYYCARYDN	VMGLYWFDYW	GQGTLVTVSS	120
chain for 023							
SEQ ID NO:112	EIVLTOSPAT	LSLSPGERAT	LSCRASOSVS	SYLAWYOOKP	GOAPRLLIYD	ASNRATGIPA	60
variable light			-	RSNWPPAFGG	-		108
chain for 023	1 KI BOBOBOI B	TILLIDDELL	DDIAVITOQQ	TOWITHIOU	OIIIVEIIII		100
SEQ ID NO:113	EVQLQQSGPE	LVKPGASVKM	SCKASGYTFT	SYVMHWVKQK	PGQGLEWIGY	INPYNDGTKY	60
heavy chain	NEKFKGKATL	TSDKSSSTAY	MELSSLTSED	SAVYYCANYY	GSSLSMDYWG	QGTSVTVSS	119
variable region							
SEQ ID NO:114	ртомполисс	TENETCODIM	TGCDAGODTG	NYLNWYOOKP	DOTURETTAN	терт не <i>су</i> ре	60
_			-			LINDGILINGI	
light chain	RESGSGSGTD	YSLTISNLEQ	EDIATYFCQQ	GNTLPWTFGG	GTKLEIKR		108
variable region							
SEQ ID NO:115	EVQLQQSGPE	LVKPGASVKI	SCKTSGYTFK	DYTMHWVKQS	HGKSLEWIGG	IYPNNGGSTY	60
heavy chain	NONFKDKATI	TVDKSSSTAY	MEERSLISED	SAVYYCARMG	YHGPHLDFDV	WGAGTTVTVS	120
variable region	P						121
	-					3.00031100	
SEQ ID NO:116	_			AAVAWYQQKP		ASTRHTGVPD	60
		FTLTTSNVOS	EDLTDYFCOO	YINYPLTFGG	GTKLEIKR		108
light chain	RFTGGGSGTD	1111101100					
light chain variable region	RFTGGGSGTD	11111111119					
variable region		-		DYSMHWVKOA	PGKGLKWMGW	TNTETGEPTY	60
variable region SEQ ID NO:117	QIQLVQSGPE	LKKPGETVKI	SCKASGYTFT	DYSMHWVKQA			60
variable region SEQ ID NO:117 heavy chain	QIQLVQSGPE ADDFKGRFAF	LKKPGETVKI	SCKASGYTFT	DYSMHWVKQA TATYFCANPY			120
variable region SEQ ID NO:117 heavy chain variable region	QIQLVQSGPE	LKKPGETVKI	SCKASGYTFT				
variable region SEQ ID NO:117 heavy chain	QIQLVQSGPE ADDFKGRFAF	LKKPGETVKI	SCKASGYTFT				120
variable region SEQ ID NO:117 heavy chain variable region	QIQLVQSGPE ADDFKGRFAF	LKKPGETVKI	SCKASGYTFT				120
variable region SEQ ID NO:117 heavy chain variable region of humanized antibody	QIQLVQSGPE ADDFKGRFAF SS	LKKPGETVKI SLETSASTAY	SCKASGYTFT LQINNLKNED	TATYFCANPY	YDYVSYY AM D	YWGHGTSVTV	120
variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118	QIQLVQSGPE ADDFKGRFAF SS	LKKPGETVKI SLETSASTAY LKKPGASVKV	SCKASGYTFT LQINNLKNED SCKASGYTFT	TATYFCAN PY DYSMHWVRQA	YDYVSYYAMD PGQGLKWMGW	YWGHGTSVTV	120 122 60
variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118 heavy chain	QIQLVQSGPE ADDFKGRFAF SS QVQLVQSGSE ADDFKGRFVF	LKKPGETVKI SLETSASTAY LKKPGASVKV	SCKASGYTFT LQINNLKNED SCKASGYTFT	TATYFCANPY	YDYVSYYAMD PGQGLKWMGW	YWGHGTSVTV	120 122 60 120
variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118 heavy chain variable region	QIQLVQSGPE ADDFKGRFAF SS	LKKPGETVKI SLETSASTAY LKKPGASVKV	SCKASGYTFT LQINNLKNED SCKASGYTFT	TATYFCAN PY DYSMHWVRQA	YDYVSYYAMD PGQGLKWMGW	YWGHGTSVTV	120 122 60
variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118 heavy chain variable region of humanized	QIQLVQSGPE ADDFKGRFAF SS QVQLVQSGSE ADDFKGRFVF	LKKPGETVKI SLETSASTAY LKKPGASVKV	SCKASGYTFT LQINNLKNED SCKASGYTFT	TATYFCAN PY DYSMHWVRQA	YDYVSYYAMD PGQGLKWMGW	YWGHGTSVTV	120 122 60 120
variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118 heavy chain variable region	QIQLVQSGPE ADDFKGRFAF SS QVQLVQSGSE ADDFKGRFVF SS	LKKPGETVKI SLETSASTAY LKKPGASVKV SLDTSVSTAY	SCKASGYTFT LQINNLKNED SCKASGYTFT LQISSLKAED	TATYFCANPY DYSMHWVRQA TAVYYCANPY	YDYVSYYAMD PGQGLKWMGW YDYVSYYAMD	YWGHGTSVTV INTETGEPTY YWGQGTTVTV	120 122 60 120
variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118 heavy chain variable region of humanized	QIQLVQSGPE ADDFKGRFAF SS QVQLVQSGSE ADDFKGRFVF SS	LKKPGETVKI SLETSASTAY LKKPGASVKV SLDTSVSTAY	SCKASGYTFT LQINNLKNED SCKASGYTFT LQISSLKAED	TATYFCAN PY DYSMHWVRQA	YDYVSYYAMD PGQGLKWMGW YDYVSYYAMD	YWGHGTSVTV INTETGEPTY YWGQGTTVTV	120 122 60 120
variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118 heavy chain variable region of humanized antibody SEQ ID NO:119	QIQLVQSGPE ADDFKGRFAF SS QVQLVQSGSE ADDFKGRFVF SS	LKKPGETVKI SLETSASTAY LKKPGASVKV SLDTSVSTAY	SCKASGYTFT LQINNLKNED SCKASGYTFT LQISSLKAED	TATYFCANPY DYSMHWVRQA TAVYYCANPY TAVAWYQQKP	YDYVSYYAMD PGQGLKWMGW YDYVSYYAMD GQSPKLLIYS	YWGHGTSVTV INTETGEPTY YWGQGTTVTV	120 122 60 120 122
variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118 heavy chain variable region of humanized antibody SEQ ID NO:119 light chain	QIQLVQSGPE ADDFKGRFAF SS QVQLVQSGSE ADDFKGRFVF SS	LKKPGETVKI SLETSASTAY LKKPGASVKV SLDTSVSTAY	SCKASGYTFT LQINNLKNED SCKASGYTFT LQISSLKAED	TATYFCANPY DYSMHWVRQA TAVYYCANPY	YDYVSYYAMD PGQGLKWMGW YDYVSYYAMD GQSPKLLIYS	YWGHGTSVTV INTETGEPTY YWGQGTTVTV	120 122 60 120 122
variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118 heavy chain variable region of humanized antibody SEQ ID NO:119 light chain variable region	QIQLVQSGPE ADDFKGRFAF SS QVQLVQSGSE ADDFKGRFVF SS	LKKPGETVKI SLETSASTAY LKKPGASVKV SLDTSVSTAY	SCKASGYTFT LQINNLKNED SCKASGYTFT LQISSLKAED	TATYFCANPY DYSMHWVRQA TAVYYCANPY TAVAWYQQKP	YDYVSYYAMD PGQGLKWMGW YDYVSYYAMD GQSPKLLIYS	YWGHGTSVTV INTETGEPTY YWGQGTTVTV	120 122 60 120 122
variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118 heavy chain variable region of humanized antibody SEQ ID NO:119 light chain variable region of humanized	QIQLVQSGPE ADDFKGRFAF SS QVQLVQSGSE ADDFKGRFVF SS	LKKPGETVKI SLETSASTAY LKKPGASVKV SLDTSVSTAY	SCKASGYTFT LQINNLKNED SCKASGYTFT LQISSLKAED	TATYFCANPY DYSMHWVRQA TAVYYCANPY TAVAWYQQKP	YDYVSYYAMD PGQGLKWMGW YDYVSYYAMD GQSPKLLIYS	YWGHGTSVTV INTETGEPTY YWGQGTTVTV	120 122 60 120 122
variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118 heavy chain variable region of humanized antibody SEQ ID NO:119 light chain variable region	QIQLVQSGPE ADDFKGRFAF SS QVQLVQSGSE ADDFKGRFVF SS	LKKPGETVKI SLETSASTAY LKKPGASVKV SLDTSVSTAY	SCKASGYTFT LQINNLKNED SCKASGYTFT LQISSLKAED	TATYFCANPY DYSMHWVRQA TAVYYCANPY TAVAWYQQKP	YDYVSYYAMD PGQGLKWMGW YDYVSYYAMD GQSPKLLIYS	YWGHGTSVTV INTETGEPTY YWGQGTTVTV	120 122 60 120 122
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variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118 heavy chain variable region of humanized antibody SEQ ID NO:119 light chain variable region of humanized antibody SEQ ID NO:120	QIQLVQSGPE ADDFKGRFAF SS QVQLVQSGSE ADDFKGRFVF SS DIVMTQSHKF RFTGSGSGTD	LKKPGETVKI SLETSASTAY LKKPGASVKV SLDTSVSTAY MSTSVRDRVS FTFTISSVQA	SCKASGYTFT LQINNLKNED SCKASGYTFT LQISSLKAED ITCKASQDVS EDLAVYYCQQ	TATYFCANPY DYSMHWVRQA TAVYYCANPY TAVAWYQQKP HYSTPRTFGG	YDYVSYYAMD PGQGLKWMGW YDYVSYYAMD GQSPKLLIYS GTKLEIK GQSPKLLIYS	YWGHGTSVTV INTETGEPTY YWGQGTTVTV ASYLYTGVPD	120 122 60 120 122 60 107
variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118 heavy chain variable region of humanized antibody SEQ ID NO:119 light chain variable region of humanized antibody SEQ ID NO:120 light chain	QIQLVQSGPE ADDFKGRFAF SS QVQLVQSGSE ADDFKGRFVF SS DIVMTQSHKF RFTGSGSGTD	LKKPGETVKI SLETSASTAY LKKPGASVKV SLDTSVSTAY MSTSVRDRVS FTFTISSVQA	SCKASGYTFT LQINNLKNED SCKASGYTFT LQISSLKAED ITCKASQDVS EDLAVYYCQQ	TATYFCANPY DYSMHWVRQA TAVYYCANPY TAVAWYQQKP HYSTPRTFGG	YDYVSYYAMD PGQGLKWMGW YDYVSYYAMD GQSPKLLIYS GTKLEIK GQSPKLLIYS	YWGHGTSVTV INTETGEPTY YWGQGTTVTV ASYLYTGVPD	120 122 60 120 122 60 107
variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118 heavy chain variable region of humanized antibody SEQ ID NO:119 light chain variable region of humanized antibody SEQ ID NO:120 light chain variable region of humanized	QIQLVQSGPE ADDFKGRFAF SS QVQLVQSGSE ADDFKGRFVF SS DIVMTQSHKF RFTGSGSGTD	LKKPGETVKI SLETSASTAY LKKPGASVKV SLDTSVSTAY MSTSVRDRVS FTFTISSVQA	SCKASGYTFT LQINNLKNED SCKASGYTFT LQISSLKAED ITCKASQDVS EDLAVYYCQQ	TATYFCANPY DYSMHWVRQA TAVYYCANPY TAVAWYQQKP HYSTPRTFGG	YDYVSYYAMD PGQGLKWMGW YDYVSYYAMD GQSPKLLIYS GTKLEIK GQSPKLLIYS	YWGHGTSVTV INTETGEPTY YWGQGTTVTV ASYLYTGVPD	120 122 60 120 122 60 107
variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118 heavy chain variable region of humanized antibody SEQ ID NO:119 light chain variable region of humanized antibody SEQ ID NO:120 light chain variable region of humanized antibody	QIQLVQSGPE ADDFKGRFAF SS QVQLVQSGSE ADDFKGRFVF SS DIVMTQSHKF RFTGSGSGTD	LKKPGETVKI SLETSASTAY LKKPGASVKV SLDTSVSTAY MSTSVRDRVS FTFTISSVQA	SCKASGYTFT LQINNLKNED SCKASGYTFT LQISSLKAED ITCKASQDVS EDLAVYYCQQ	TATYFCANPY DYSMHWVRQA TAVYYCANPY TAVAWYQQKP HYSTPRTFGG	YDYVSYYAMD PGQGLKWMGW YDYVSYYAMD GQSPKLLIYS GTKLEIK GQSPKLLIYS	YWGHGTSVTV INTETGEPTY YWGQGTTVTV ASYLYTGVPD	120 122 60 120 122 60 107
variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118 heavy chain variable region of humanized antibody SEQ ID NO:119 light chain variable region of humanized antibody SEQ ID NO:120 light chain variable region of humanized	QIQLVQSGPE ADDFKGRFAF SS QVQLVQSGSE ADDFKGRFVF SS DIVMTQSHKF RFTGSGSGTD DIVMTQSHKF	LKKPGETVKI SLETSASTAY LKKPGASVKV SLDTSVSTAY MSTSVRDRVS FTFTISSVQA	SCKASGYTFT LQINNLKNED SCKASGYTFT LQISSLKAED ITCKASQDVS EDLAVYYCQQ ITCKASQDVS EDLAVYYCQQ	TATYFCANPY DYSMHWVRQA TAVYYCANPY TAVAWYQQKP HYSTPRTFGG TAVAWYQQKP HYSTPRTFGG	PGQGLKWMGW YDYVSYYAMD GQSPKLLIYS GTKLEIK GQSPKLLIYS GTKLEIK	YWGHGTSVTV INTETGEPTY YWGQGTTVTV ASYLYTGVPD ASYLYTGVPD	120 122 60 120 122 60 107
variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118 heavy chain variable region of humanized antibody SEQ ID NO:119 light chain variable region of humanized antibody SEQ ID NO:120 light chain variable region of humanized antibody	QIQLVQSGPE ADDFKGRFAF SS QVQLVQSGSE ADDFKGRFVF SS DIVMTQSHKF RFTGSGSGTD DIVMTQSHKF	LKKPGETVKI SLETSASTAY LKKPGASVKV SLDTSVSTAY MSTSVRDRVS FTFTISSVQA	SCKASGYTFT LQINNLKNED SCKASGYTFT LQISSLKAED ITCKASQDVS EDLAVYYCQQ ITCKASQDVS EDLAVYYCQQ	TATYFCANPY DYSMHWVRQA TAVYYCANPY TAVAWYQQKP HYSTPRTFGG	PGQGLKWMGW YDYVSYYAMD GQSPKLLIYS GTKLEIK GQSPKLLIYS GTKLEIK	YWGHGTSVTV INTETGEPTY YWGQGTTVTV ASYLYTGVPD ASYLYTGVPD	120 122 60 120 122 60 107
variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118 heavy chain variable region of humanized antibody SEQ ID NO:119 light chain variable region of humanized antibody SEQ ID NO:120 light chain variable region of humanized antibody SEQ ID NO:120 light chain variable region of humanized antibody SEQ ID NO:121	QIQLVQSGPE ADDFKGRFAF SS QVQLVQSGSE ADDFKGRFVF SS DIVMTQSHKF RFTGSGSGTD DIVMTQSHKF RFTGSGSGTD	LKKPGETVKI SLETSASTAY LKKPGASVKV SLDTSVSTAY MSTSVRDRVS FTFTISSVQA MSTSVRDRVS FTFTISSVQA LVQPGESLKL	SCKASGYTFT LQINNLKNED SCKASGYTFT LQISSLKAED ITCKASQDVS EDLAVYYCQQ ITCKASQDVS EDLAVYYCQQ SCESNEYEFP	TATYFCANPY DYSMHWVRQA TAVYYCANPY TAVAWYQQKP HYSTPRTFGG TAVAWYQQKP HYSTPRTFGG SHDMSWVRKT	YDYVSYYAMD PGQGLKWMGW YDYVSYYAMD GQSPKLLIYS GTKLEIK GQSPKLLIYS GTKLEIK PEKRLELVAA	YWGHGTSVTV INTETGEPTY YWGQGTTVTV ASYLYTGVPD ASYLYTGVPD INSDGGSTYY	60 122 60 122 60 107
variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118 heavy chain variable region of humanized antibody SEQ ID NO:119 light chain variable region of humanized antibody SEQ ID NO:120 light chain variable region of humanized antibody SEQ ID NO:120 light chain variable region of humanized antibody SEQ ID NO:121 heavy chain	QIQLVQSGPE ADDFKGRFAF SS QVQLVQSGSE ADDFKGRFVF SS DIVMTQSHKF RFTGSGSGTD DIVMTQSHKF RFTGSGSGTD	LKKPGETVKI SLETSASTAY LKKPGASVKV SLDTSVSTAY MSTSVRDRVS FTFTISSVQA MSTSVRDRVS FTFTISSVQA LVQPGESLKL	SCKASGYTFT LQINNLKNED SCKASGYTFT LQISSLKAED ITCKASQDVS EDLAVYYCQQ ITCKASQDVS EDLAVYYCQQ SCESNEYEFP	TATYFCANPY DYSMHWVRQA TAVYYCANPY TAVAWYQQKP HYSTPRTFGG TAVAWYQQKP HYSTPRTFGG SHDMSWVRKT	YDYVSYYAMD PGQGLKWMGW YDYVSYYAMD GQSPKLLIYS GTKLEIK GQSPKLLIYS GTKLEIK PEKRLELVAA	YWGHGTSVTV INTETGEPTY YWGQGTTVTV ASYLYTGVPD ASYLYTGVPD	60 122 60 122 60 107
variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118 heavy chain variable region of humanized antibody SEQ ID NO:119 light chain variable region of humanized antibody SEQ ID NO:120 light chain variable region of humanized antibody SEQ ID NO:120 light chain variable region of humanized antibody SEQ ID NO:121 heavy chain variable region variable region	QIQLVQSGPE ADDFKGRFAF SS QVQLVQSGSE ADDFKGRFVF SS DIVMTQSHKF RFTGSGSGTD DIVMTQSHKF RFTGSGSGTD	LKKPGETVKI SLETSASTAY LKKPGASVKV SLDTSVSTAY MSTSVRDRVS FTFTISSVQA MSTSVRDRVS FTFTISSVQA LVQPGESLKL	SCKASGYTFT LQINNLKNED SCKASGYTFT LQISSLKAED ITCKASQDVS EDLAVYYCQQ ITCKASQDVS EDLAVYYCQQ SCESNEYEFP	TATYFCANPY DYSMHWVRQA TAVYYCANPY TAVAWYQQKP HYSTPRTFGG TAVAWYQQKP HYSTPRTFGG SHDMSWVRKT	YDYVSYYAMD PGQGLKWMGW YDYVSYYAMD GQSPKLLIYS GTKLEIK GQSPKLLIYS GTKLEIK PEKRLELVAA	YWGHGTSVTV INTETGEPTY YWGQGTTVTV ASYLYTGVPD ASYLYTGVPD INSDGGSTYY	60 122 60 120 122 60 107
variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118 heavy chain variable region of humanized antibody SEQ ID NO:119 light chain variable region of humanized antibody SEQ ID NO:120 light chain variable region of humanized antibody SEQ ID NO:120 light chain variable region of humanized antibody SEQ ID NO:121 heavy chain variable region of humanized	QIQLVQSGPE ADDFKGRFAF SS QVQLVQSGSE ADDFKGRFVF SS DIVMTQSHKF RFTGSGSGTD DIVMTQSHKF RFTGSGSGTD	LKKPGETVKI SLETSASTAY LKKPGASVKV SLDTSVSTAY MSTSVRDRVS FTFTISSVQA MSTSVRDRVS FTFTISSVQA LVQPGESLKL	SCKASGYTFT LQINNLKNED SCKASGYTFT LQISSLKAED ITCKASQDVS EDLAVYYCQQ ITCKASQDVS EDLAVYYCQQ SCESNEYEFP	TATYFCANPY DYSMHWVRQA TAVYYCANPY TAVAWYQQKP HYSTPRTFGG TAVAWYQQKP HYSTPRTFGG SHDMSWVRKT	YDYVSYYAMD PGQGLKWMGW YDYVSYYAMD GQSPKLLIYS GTKLEIK GQSPKLLIYS GTKLEIK PEKRLELVAA	YWGHGTSVTV INTETGEPTY YWGQGTTVTV ASYLYTGVPD ASYLYTGVPD INSDGGSTYY	60 122 60 120 122 60 107
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variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118 heavy chain variable region of humanized antibody SEQ ID NO:119 light chain variable region of humanized antibody SEQ ID NO:120 light chain variable region of humanized antibody SEQ ID NO:120 light chain variable region of humanized antibody SEQ ID NO:121 heavy chain variable region of humanized	QIQLVQSGPE ADDFKGRFAF SS QVQLVQSGSE ADDFKGRFVF SS DIVMTQSHKF RFTGSGSGTD DIVMTQSHKF RFTGSGSGTD	LKKPGETVKI SLETSASTAY LKKPGASVKV SLDTSVSTAY MSTSVRDRVS FTFTISSVQA MSTSVRDRVS FTFTISSVQA LVQPGESLKL SRDNTKKTLY	SCKASGYTFT LQINNLKNED SCKASGYTFT LQISSLKAED ITCKASQDVS EDLAVYYCQQ ITCKASQDVS EDLAVYYCQQ SCESNEYEFP LQMSSLRSED	TATYFCANPY DYSMHWVRQA TAVYYCANPY TAVAWYQQKP HYSTPRTFGG TAVAWYQQKP HYSTPRTFGG SHDMSWVRKT	PGQGLKWMGW YDYVSYYAMD GQSPKLLIYS GTKLEIK GQSPKLLIYS GTKLEIK	YWGHGTSVTV INTETGEPTY YWGQGTTVTV ASYLYTGVPD ASYLYTGVPD INSDGGSTYY GQGTLVTVSA	60 122 60 122 60 107
variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118 heavy chain variable region of humanized antibody SEQ ID NO:119 light chain variable region of humanized antibody SEQ ID NO:120 light chain variable region of humanized antibody SEQ ID NO:121 heavy chain variable region of humanized antibody SEQ ID NO:121 heavy chain variable region of humanized antibody SEQ ID NO:122	QIQLVQSGPE ADDFKGRFAF SS QVQLVQSGSE ADDFKGRFVF SS DIVMTQSHKF RFTGSGSGTD DIVMTQSHKF RFTGSGSGTD EVQLVESGGG PDTMERRFII	LKKPGETVKI SLETSASTAY LKKPGASVKV SLDTSVSTAY MSTSVRDRVS FTFTISSVQA MSTSVRDRVS FTFTISSVQA LVQPGESLKL SRDNTKKTLY	SCKASGYTFT LQINNLKNED SCKASGYTFT LQISSLKAED ITCKASQDVS EDLAVYYCQQ ITCKASQDVS EDLAVYYCQQ SCESNEYEFP LQMSSLRSED SCAASEYEFP	TATYFCANPY DYSMHWVRQA TAVYYCANPY TAVAWYQQKP HYSTPRTFGG TAVAWYQQKP HYSTPRTFGG SHDMSWVRKT TALYYCARHY SHDMSWVRQA	PGQGLKWMGW YDYVSYYAMD GQSPKLLIYS GTKLEIK GQSPKLLIYS GTKLEIK PEKRLELVAA DDYYAWFAYW	YWGHGTSVTV INTETGEPTY YWGQGTTVTV ASYLYTGVPD ASYLYTGVPD INSDGGSTYY GQGTLVTVSA INSDGGSTYY	60 122 60 120 122 60 107
variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118 heavy chain variable region of humanized antibody SEQ ID NO:119 light chain variable region of humanized antibody SEQ ID NO:120 light chain variable region of humanized antibody SEQ ID NO:120 light chain variable region of humanized antibody SEQ ID NO:121 heavy chain variable region of humanized antibody SEQ ID NO:122 heavy chain SEQ ID NO:122 heavy chain	QIQLVQSGPE ADDFKGRFAF SS QVQLVQSGSE ADDFKGRFVF SS DIVMTQSHKF RFTGSGSGTD DIVMTQSHKF RFTGSGSGTD EVQLVESGGG PDTMERRFII	LKKPGETVKI SLETSASTAY LKKPGASVKV SLDTSVSTAY MSTSVRDRVS FTFTISSVQA MSTSVRDRVS FTFTISSVQA LVQPGESLKL SRDNTKKTLY	SCKASGYTFT LQINNLKNED SCKASGYTFT LQISSLKAED ITCKASQDVS EDLAVYYCQQ ITCKASQDVS EDLAVYYCQQ SCESNEYEFP LQMSSLRSED SCAASEYEFP	TATYFCANPY DYSMHWVRQA TAVYYCANPY TAVAWYQQKP HYSTPRTFGG TAVAWYQQKP HYSTPRTFGG SHDMSWVRKT TALYYCARHY	PGQGLKWMGW YDYVSYYAMD GQSPKLLIYS GTKLEIK GQSPKLLIYS GTKLEIK PEKRLELVAA DDYYAWFAYW	YWGHGTSVTV INTETGEPTY YWGQGTTVTV ASYLYTGVPD ASYLYTGVPD INSDGGSTYY GQGTLVTVSA INSDGGSTYY	120 122 60 120 122 60 107
variable region SEQ ID NO:117 heavy chain variable region of humanized antibody SEQ ID NO:118 heavy chain variable region of humanized antibody SEQ ID NO:119 light chain variable region of humanized antibody SEQ ID NO:120 light chain variable region of humanized antibody SEQ ID NO:121 heavy chain variable region of humanized antibody SEQ ID NO:121 heavy chain variable region of humanized antibody SEQ ID NO:122 heavy chain variable region of humanized antibody SEQ ID NO:122 heavy chain variable region	QIQLVQSGPE ADDFKGRFAF SS QVQLVQSGSE ADDFKGRFVF SS DIVMTQSHKF RFTGSGSGTD DIVMTQSHKF RFTGSGSGTD EVQLVESGGG PDTMERRFII	LKKPGETVKI SLETSASTAY LKKPGASVKV SLDTSVSTAY MSTSVRDRVS FTFTISSVQA MSTSVRDRVS FTFTISSVQA LVQPGESLKL SRDNTKKTLY	SCKASGYTFT LQINNLKNED SCKASGYTFT LQISSLKAED ITCKASQDVS EDLAVYYCQQ ITCKASQDVS EDLAVYYCQQ SCESNEYEFP LQMSSLRSED SCAASEYEFP	TATYFCANPY DYSMHWVRQA TAVYYCANPY TAVAWYQQKP HYSTPRTFGG TAVAWYQQKP HYSTPRTFGG SHDMSWVRKT TALYYCARHY SHDMSWVRQA	PGQGLKWMGW YDYVSYYAMD GQSPKLLIYS GTKLEIK GQSPKLLIYS GTKLEIK PEKRLELVAA DDYYAWFAYW	YWGHGTSVTV INTETGEPTY YWGQGTTVTV ASYLYTGVPD ASYLYTGVPD INSDGGSTYY GQGTLVTVSA INSDGGSTYY	60 122 60 120 122 60 107
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variable region of humanized antibody							
SEQ ID NO:124	EIVLTQSPAT	LSLSPGERAT	LSCRASKSVS	TSGYSYMHWY	QQKPGQAPRL	LIYLASNLES	60
light chain	GVPARFSGSG	SGTDFTLTIS	SLEPEDFAVY	YCQHSRELPL	TFGGGTKVEI	K	111
variable region							
of humanized							
antibody							
SEQ ID NO:125	MYLGLNYVFI	VFLLNGVQSE	VKLEESGGGL	VQPGGSMKLS	CAASGFTFSD	AWMDWVRQSP	60
heavy chain	EKGLEWVAEI	RSKANNHATY	YAESVNGRFT	ISRDDSKSSV	YLQMNSLRAE	DTGIYYCTWG	120
variable region	EVFYFDYWGQ	GTTLTVSS					138
SEQ ID NO:126	MRPSIQFLGL	LLFWLHGAQC	DIQMTQSPSS	LSASLGGKVT	ITCKSSQDIN	KYIAWYQHKP	60
light chain	GKGPRLLIHY	TSTLQPGIPS	RFSGSGSGRD	YSFSISNLEP	EDIATYYCLQ	YDNLLTFGAG	120
variable region	TKLELK						126

[001090] In an embodiment, the OX40 agonist is a OX40 agonistic single-chain fusion polypeptide comprising (i) a first soluble OX40 binding domain, (ii) a first peptide linker, (iii) a second soluble OX40 binding domain, (iv) a second peptide linker, and (v) a third soluble OX40 binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, and wherein the additional domain is a Fab or Fc fragment domain. In an embodiment, the OX40 agonist is a OX40 agonistic single-chain fusion polypeptide comprising (i) a first soluble OX40 binding domain, (ii) a first peptide linker, (iii) a second soluble OX40 binding domain, (iv) a second peptide linker, and (v) a third soluble OX40 binding domain, further comprising an additional domain at the N-terminal and/or C-terminal end, wherein the additional domain is a Fab or Fc fragment domain wherein each of the soluble OX40 binding domains lacks a stalk region (which contributes to trimerisation and provides a certain distance to the cell membrane, but is not part of the OX40 binding domain) and the first and the second peptide linkers independently have a length of 3-8 amino acids.

[001091] In an embodiment, the OX40 agonist is an OX40 agonistic single-chain fusion polypeptide comprising (i) a first soluble tumor necrosis factor (TNF) superfamily cytokine domain, (ii) a first peptide linker, (iii) a second soluble TNF superfamily cytokine domain, (iv) a second peptide linker, and (v) a third soluble TNF superfamily cytokine domain, wherein each of the soluble TNF superfamily cytokine domains lacks a stalk region and the first and the second peptide linkers independently have a length of 3-8 amino acids, and wherein the TNF superfamily cytokine domain is an OX40 binding domain.

[001092] In some embodiments, the OX40 agonist is MEDI6383. MEDI6383 is an OX40 agonistic fusion protein and can be prepared as described in U.S. Patent No. 6,312,700, the disclosure of which is incorporated by reference herein.

[001093] In an embodiment, the OX40 agonist is an OX40 agonistic scFv antibody comprising any of the foregoing V_H domains linked to any of the foregoing V_L domains.

[001094] In an embodiment, the OX40 agonist is Creative Biolabs OX40 agonist monoclonal antibody MOM-18455, commercially available from Creative Biolabs, Inc., Shirley, NY, USA.

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[001095] In an embodiment, the OX40 agonist is OX40 agonistic antibody clone Ber-ACT35 commercially available from BioLegend, Inc., San Diego, CA, USA.

I. Optional Cell Viability Analyses

[001096] Optionally, a cell viability assay can be performed after the priming first expansion (sometimes referred to as the initial bulk expansion), using standard assays known in the art. Thus, in certain embodiments, the method comprises performing a cell viability assay subsequent to the priming first expansion. For example, a trypan blue exclusion assay can be done on a sample of the bulk TILs, which selectively labels dead cells and allows a viability assessment. Other assays for use in testing viability can include but are not limited to the Alamar blue assay; and the MTT assay.

1. Cell Counts, Viability, Flow Cytometry

[001097] In some embodiments, cell counts and/or viability are measured. The expression of markers such as but not limited CD3, CD4, CD8, and CD56, as well as any other disclosed or described herein, can be measured by flow cytometry with antibodies, for example but not limited to those commercially available from BD Bio-sciences (BD Biosciences, San Jose, CA) using a FACSCanto[™] flow cytometer (BD Biosciences). The cells can be counted manually using a disposable c-chip hemocytometer (VWR, Batavia, IL) and viability can be assessed using any method known in the art, including but not limited to trypan blue staining. The cell viability can also be assayed based on USSN 15/863,634, incorporated by reference herein in its entirety. Cell viability can also be assayed based on U.S. Patent Publication No. 2018/0280436 or International Patent Publication No. WO/2018/081473, both of which are incorporate herein in their entireties for all purposes.

[001098] In some cases, the bulk TIL population can be cryopreserved immediately, using the protocols discussed below. Alternatively, the bulk TIL population can be subjected to REP and then cryopreserved as discussed below. Similarly, in the case where genetically modified TILs will be used in therapy, the bulk or REP TIL populations can be subjected to genetic modifications for suitable treatments.

2. Cell Cultures

[001099] In an embodiment, a method for expanding TILs, including those discussed above as well as exemplified in Figure 8, in particular, e.g., Figure 8B and/or Figure 8C, may include using about 5,000 mL to about 25,000 mL of cell medium, about 5,000 mL to about 10,000 mL of cell medium, or about 5,800 mL to about 8,700 mL of cell medium. In some embodiments, the media is a serum free medium. In some embodiments, the media in the priming first expansion is serum free. In some embodiments, the media in the second expansion is serum free. In some embodiments, the media in the priming first expansion and the second expansion (also referred to as rapid second expansion) are both serum free. In an embodiment, expanding the number of TILs uses no more than one type of cell culture medium. Any suitable cell culture medium may be used, e.g., AIM-V cell medium (Lglutamine, 50 µM streptomycin sulfate, and 10 µM gentamicin sulfate) cell culture medium (Invitrogen, Carlsbad CA). In this regard, the inventive methods advantageously reduce the amount of medium and the number of types of medium required to expand the number of TIL. In an embodiment, expanding the number of TIL may comprise feeding the cells no more frequently than every third or fourth day. Expanding the number of cells in a gas permeable container simplifies the procedures necessary to expand the number of cells by reducing the feeding frequency necessary to expand the cells.

[001100] In an embodiment, the cell culture medium in the first and/or second gas permeable container is unfiltered. The use of unfiltered cell medium may simplify the procedures necessary to expand the number of cells. In an embodiment, the cell medium in the first and/or second gas permeable container lacks beta-mercaptoethanol (BME).

[001101] In an embodiment, the duration of the method comprising obtaining a tumor tissue sample from the mammal; culturing the tumor tissue sample in a first gas permeable container containing cell medium including IL-2, 1X antigen-presenting feeder cells, and OKT-3 for a duration of about 1 to 8 days, *e.g.*, about 7 days as a priming first expansion, or about 8 days as a priming first expansion; transferring the TILs to a second gas permeable container and expanding the number of TILs in the second gas permeable container containing cell medium including IL-2, 2X antigen-presenting feeder cells, and OKT-3 for a duration of about 7 to 9 days, *e.g.*, about 7 days, about 8 days, or about 9 days.

[001102] In an embodiment, the duration of the method comprising obtaining a tumor tissue sample from the mammal; culturing the tumor tissue sample in a first gas permeable

container containing cell medium including IL-2, 1X antigen-presenting feeder cells, and OKT-3 for a duration of about 1 to 7 days, *e.g.*, about 7 days as a priming first expansion; transferring the TILs to a second gas permeable container and expanding the number of TILs in the second gas permeable container containing cell medium including IL-2, 2X antigen-presenting feeder cells, and OKT-3 for a duration of about 7 to 9 days, *e.g.*, about 7 days, about 8 days, or about 9 days.

[001103] In an embodiment, the duration of the method comprising obtaining a tumor tissue sample from the mammal; culturing the tumor tissue sample in a first gas permeable container containing cell medium including IL-2, 1X antigen-presenting feeder cells, and OKT-3 for a duration of about 1 to 7 days, *e.g.*, about 7 days as a priming first expansion; transferring the TILs to a second gas permeable container and expanding the number of TILs in the second gas permeable container containing cell medium including IL-2, 2X antigen-presenting feeder cells, and OKT-3 for a duration of about 7 to 10 days, *e.g.*, about 7 days, about 8 days, about 9 days or about 10 days.

[001104] In an embodiment, TILs are expanded in gas-permeable containers. Gas-permeable containers have been used to expand TILs using PBMCs using methods, compositions, and devices known in the art, including those described in U.S. Patent Application Publication No. 2005/0106717 A1, the disclosures of which are incorporated herein by reference. In an embodiment, TILs are expanded in gas-permeable bags. In an embodiment, TILs are expanded using a cell expansion system that expands TILs in gas permeable bags, such as the Xuri Cell Expansion System W25 (GE Healthcare). In an embodiment, TILs are expanded using a cell expansion system that expands TILs in gas permeable bags, such as the WAVE Bioreactor System, also known as the Xuri Cell Expansion System W5 (GE Healthcare). In an embodiment, the cell expansion system includes a gas permeable cell bag with a volume selected from the group consisting of about 100 mL, about 200 mL, about 300 mL, about 400 mL, about 500 mL, about 600 mL, about 700 mL, about 800 mL, about 900 mL, about 1 L, about 2 L, about 3 L, about 4 L, about 5 L, about 6 L, about 7 L, about 8 L, about 9 L, and about 10 L.

[001105] In an embodiment, TILs can be expanded in G-Rex flasks (commercially available from Wilson Wolf Manufacturing). Such embodiments allow for cell populations to expand from about 5×10^5 cells/cm² to between 10×10^6 and 30×10^6 cells/cm². In an embodiment this is without feeding. In an embodiment, this is without feeding so long as medium resides at a height of about 10 cm in the G-Rex flask. In an embodiment this is without feeding but

with the addition of one or more cytokines. In an embodiment, the cytokine can be added as a bolus without any need to mix the cytokine with the medium. Such containers, devices, and methods are known in the art and have been used to expand TILs, and include those described in U.S. Patent Application Publication No. US 2014/0377739A1, International Publication No. WO 2014/210036 A1, U.S. Patent Application Publication No. us 2013/0115617 A1, International Publication No. WO 2013/188427 A1, U.S. Patent Application Publication No. US 2011/0136228 A1, U.S. Patent No. US 8,809,050 B2, International publication No. WO 2011/072088 A2, U.S. Patent Application Publication Publication No. US 2016/0208216 A1, U.S. Patent Application Publication No. US 2012/0244133 A1, International Publication No. WO 2012/129201 A1, U.S. Patent Application Publication No. US 2013/0102075 A1, U.S. Patent No. US 8,956,860 B2, International Publication No. WO 2013/173835 A1, U.S. Patent Application Publication No. US 2015/0175966 A1, the

disclosures of which are incorporated herein by reference. Such processes are also described

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J. Optional Genetic Engineering of TILs

in Jin et al., J. Immunotherapy, 2012, 35:283-292.

[001106] In some embodiments, the expanded TILs of the present invention are further manipulated before, during, or after an expansion step, including during closed, sterile manufacturing processes, each as provided herein, in order to alter protein expression in a transient manner. In some embodiments, the transiently altered protein expression is due to transient gene editing. In some embodiments, the expanded TILs of the present invention are treated with transcription factors (TFs) and/or other molecules capable of transiently altering protein expression in the TILs. In some embodiments, the TFs and/or other molecules that are capable of transiently altering protein expression provide for altered expression of tumor antigens and/or an alteration in the number of tumor antigen-specific T cells in a population of TILs.

[001107] In certain embodiments, the method comprises genetically editing a population of TILs. In certain embodiments, the method comprises genetically editing the first population of TILs, the second population of TILs and/or the third population of TILs.

[001108] In some embodiments, the present invention includes genetic editing through nucleotide insertion, such as through ribonucleic acid (RNA) insertion, including insertion of messenger RNA (mRNA) or small (or short) interfering RNA (siRNA), into a population of TILs for promotion of the expression of one or more proteins or inhibition of the expression

of one or more proteins, as well as simultaneous combinations of both promotion of one set of proteins with inhibition of another set of proteins.

[001109] In some embodiments, the expanded TILs of the present invention undergo transient alteration of protein expression. In some embodiments, the transient alteration of protein expression occurs in the bulk TIL population prior to first expansion, including, for example in the TIL population obtained from for example, Step A as indicated in Figure 8 (particularly Figure 8B and/or Figure 8C). In some embodiments, the transient alteration of protein expression occurs during the first expansion, including, for example in the TIL population expanded in for example, Step B as indicated in Figure 8 (for example Figure 8B and/or Figure 8C). In some embodiments, the transient alteration of protein expression occurs after the first expansion, including, for example in the TIL population in transition between the first and second expansion (e.g. the second population of TILs as described herein), the TIL population obtained from for example, Step B and included in Step C as indicated in Figure 8. In some embodiments, the transient alteration of protein expression occurs in the bulk TIL population prior to second expansion, including, for example in the TIL population obtained from for example, Step C and prior to its expansion in Step D as indicated in Figure 8. In some embodiments, the transient alteration of protein expression occurs during the second expansion, including, for example in the TIL population expanded in for example, Step D as indicated in Figure 8 (e.g. the third population of TILs). In some embodiments, the transient alteration of protein expression occurs after the second expansion, including, for example in the TIL population obtained from the expansion in for example, Step D as indicated in Figure 8.

[001110] In an embodiment, a method of transiently altering protein expression in a population of TILs includes the step of electroporation. Electroporation methods are known in the art and are described, *e.g.*, in Tsong, *Biophys. J.* 1991, *60*, 297-306, and U.S. Patent Application Publication No. 2014/0227237 A1, the disclosures of each of which are incorporated by reference herein. In an embodiment, a method of transiently altering protein expression in population of TILs includes the step of calcium phosphate transfection. Calcium phosphate transfection methods (calcium phosphate DNA precipitation, cell surface coating, and endocytosis) are known in the art and are described in Graham and van der Eb, *Virology* 1973, *52*, 456-467; Wigler, *et al.*, *Proc. Natl. Acad. Sci.* 1979, *76*, 1373-1376; and Chen and Okayarea, *Mol. Cell. Biol.* 1987, *7*, 2745-2752; and in U.S. Patent No. 5,593,875, the disclosures of each of which are incorporated by reference herein. In an embodiment, a

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method of transiently altering protein expression in a population of TILs includes the step of liposomal transfection. Liposomal transfection methods, such as methods that employ a 1:1 (w/w) liposome formulation of the cationic lipid *N*-[1-(2,3-dioleyloxy)propyl]-*n*,*n*,*n*-trimethylammonium chloride (DOTMA) and dioleoyl phophotidylethanolamine (DOPE) in filtered water, are known in the art and are described in Rose, *et al.*, *Biotechniques* **1991**, *10*, 520-525 and Felgner, *et al.*, *Proc. Natl. Acad. Sci. USA*, **1987**, *84*, 7413-7417 and in U.S. Patent Nos. 5,279,833; 5,908,635; 6,056,938; 6,110,490; 6,534,484; and 7,687,070, the disclosures of each of which are incorporated by reference herein. In an embodiment, a method of transiently altering protein expression in a population of TILs includes the step of transfection using methods described in U.S. Patent Nos. 5,766,902; 6,025,337; 6,410,517; 6,475,994; and 7,189,705; the disclosures of each of which are incorporated by reference herein.

[001111] In some embodiments, transient alteration of protein expression results in an increase in Stem Memory T cells (TSCMs). TSCMs are early progenitors of antigenexperienced central memory T cells. TSCMs generally display the long-term survival, selfrenewal, and multipotency abilities that define stem cells, and are generally desirable for the generation of effective TIL products. TSCM have shown enhanced anti-tumor activity compared with other T cell subsets in mouse models of adoptive cell transfer (Gattinoni et al. Nat Med 2009, 2011; Gattinoni, Nature Rev. Cancer, 2012; Cieri et al. Blood 2013). In some embodiments, transient alteration of protein expression results in a TIL population with a composition comprising a high proportion of TSCM. In some embodiments, transient alteration of protein expression results in an at least 5%, at least 10%, at least 10%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% increase in TSCM percentage. In some embodiments, transient alteration of protein expression results in an at least a 1-fold, 2-fold, 3-fold, 4-fold, 5-fold, or 10-fold increase in TSCMs in the TIL population. In some embodiments, transient alteration of protein expression results in a TIL population with at least at least 5%, at least 10%, at least 10%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% TSCMs. In some embodiments, transient alteration of protein expression results in a therapeutic TIL population with at least at least 5%, at least 10%, at least 10%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 95% TSCMs.

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[001112] In some embodiments, transient alteration of protein expression results in rejuvenation of antigen-experienced T-cells. In some embodiments, rejuvenation includes, for example, increased proliferation, increased T-cell activation, and/or increased antigen recognition.

[001113] In some embodiments, transient alteration of protein expression alters the expression in a large fraction of the T-cells in order to preserve the tumor-derived TCR repertoire. In some embodiments, transient alteration of protein expression does not alter the tumor-derived TCR repertoire. In some embodiments, transient alteration of protein expression maintains the tumor-derived TCR repertoire.

[001114] In some embodiments, transient alteration of protein results in altered expression of a particular gene. In some embodiments, the transient alteration of protein expression targets a gene including but not limited to PD-1 (also referred to as PDCD1 or CC279), TGFBR2, CCR4/5, CBLB (CBL-B), CISH, CCRs (chimeric co-stimulatory receptors), IL-2, IL-12, IL-15, IL-21, NOTCH 1/2 ICD, TIM3, LAG3, TIGIT, TGFβ, CCR2, CCR4, CCR5, CXCR1, CXCR2, CSCR3, CCL2 (MCP-1), CCL3 (MIP-1α), CCL4 (MIP1-β), CCL5 (RANTES), CXCL1/CXCL8, CCL22, CCL17, CXCL1/CXCL8, VHL, CD44, PIK3CD, SOCS1, and/or cAMP protein kinase A (PKA). In some embodiments, the transient alteration of protein expression targets a gene selected from the group consisting of PD-1, TGFBR2, CCR4/5, CBLB (CBL-B), CISH, CCRs (chimeric co-stimulatory receptors), IL-2, IL-12, IL-15, IL-21, NOTCH 1/2 ICD, TIM3, LAG3, TIGIT, TGFβ, CCR2, CCR4, CCR5, CXCR1, CXCR2, CSCR3, CCL2 (MCP-1), CCL3 (MIP-1α), CCL4 (MIP1-β), CCL5 (RANTES), CXCL1/CXCL8, CCL22, CCL17, CXCL1/CXCL8, VHL, CD44, PIK3CD, SOCS1, and/or cAMP protein kinase A (PKA). In some embodiments, the transient alteration of protein expression targets PD-1. In some embodiments, the transient alteration of protein expression targets TGFBR2. In some embodiments, the transient alteration of protein expression targets CCR4/5. In some embodiments, the transient alteration of protein expression targets CBLB. In some embodiments, the transient alteration of protein expression targets CISH. In some embodiments, the transient alteration of protein expression targets CCRs (chimeric costimulatory receptors). In some embodiments, the transient alteration of protein expression targets IL-2. In some embodiments, the transient alteration of protein expression targets IL-12. In some embodiments, the transient alteration of protein expression targets IL-15. In

some embodiments, the transient alteration of protein expression targets IL-21. In some embodiments, the transient alteration of protein expression targets NOTCH 1/2 ICD. In some embodiments, the transient alteration of protein expression targets TIM3. In some embodiments, the transient alteration of protein expression targets LAG3. In some embodiments, the transient alteration of protein expression targets TIGIT. In some embodiments, the transient alteration of protein expression targets TGFB. In some embodiments, the transient alteration of protein expression targets CCR1. In some embodiments, the transient alteration of protein expression targets CCR2. In some embodiments, the transient alteration of protein expression targets CCR4. In some embodiments, the transient alteration of protein expression targets CCR5. In some embodiments, the transient alteration of protein expression targets CXCR1. In some embodiments, the transient alteration of protein expression targets CXCR2. In some embodiments, the transient alteration of protein expression targets CSCR3. In some embodiments, the transient alteration of protein expression targets CCL2 (MCP-1). In some embodiments, the transient alteration of protein expression targets CCL3 (MIP-1α). In some embodiments, the transient alteration of protein expression targets CCL4 (MIP1-β). In some embodiments, the transient alteration of protein expression targets CCL5 (RANTES). In some embodiments, the transient alteration of protein expression targets CXCL1. In some embodiments, the transient alteration of protein expression targets CXCL8. In some embodiments, the transient alteration of protein expression targets CCL22. In some embodiments, the transient alteration of protein expression targets CCL17. In some embodiments, the transient alteration of protein expression targets VHL. In some embodiments, the transient alteration of protein expression targets CD44. In some embodiments, the transient alteration of protein expression targets PIK3CD. In some embodiments, the transient alteration of protein expression targets SOCS1. In some embodiments, the transient alteration of protein expression targets cAMP protein kinase A (PKA).

[001115] In some embodiments, the transient alteration of protein expression results in increased and/or overexpression of a chemokine receptor. In some embodiments, the chemokine receptor that is overexpressed by transient protein expression includes a receptor with a ligand that includes but is not limited to CCL2 (MCP-1), CCL3 (MIP-1α), CCL4 (MIP1-β), CCL5 (RANTES), CXCL1, CXCL8, CCL22, and/or CCL17.

[001116] In some embodiments, the transient alteration of protein expression results in a decrease and/or reduced expression of PD-1, CTLA-4, TIM-3, LAG-3, TIGIT, TGFβR2, and/or TGFβ (including resulting in, for example, TGFβ pathway blockade). In some embodiments, the transient alteration of protein expression results in a decrease and/or reduced expression of CBLB (CBL-B). In some embodiments, the transient alteration of protein expression results in a decrease and/or reduced expression of CISH.

[001117] In some embodiments, the transient alteration of protein expression results in increased and/or overexpression of chemokine receptors in order to, for example, improve TIL trafficking or movement to the tumor site. In some embodiments, the transient alteration of protein expression results in increased and/or overexpression of a CCR (chimeric costimulatory receptor). In some embodiments, the transient alteration of protein expression results in increased and/or overexpression of a chemokine receptor selected from the group consisting of CCR1, CCR2, CCR4, CCR5, CXCR1, CXCR2, and/or CSCR3.

[001118] In some embodiments, the transient alteration of protein expression results in increased and/or overexpression of an interleukin. In some embodiments, the transient alteration of protein expression results in increased and/or overexpression of an interleukin selected from the group consisting of IL-2, IL-12, IL-15, and/or IL-21.

[001119] In some embodiments, the transient alteration of protein expression results in increased and/or overexpression of NOTCH 1/2 ICD. In some embodiments, the transient alteration of protein expression results in increased and/or overexpression of VHL. In some embodiments, the transient alteration of protein expression results in increased and/or overexpression of CD44. In some embodiments, the transient alteration of protein expression results in increased and/or overexpression of PIK3CD. In some embodiments, the transient alteration of protein expression results in increased and/or overexpression of SOCS1,

[001120] In some embodiments, the transient alteration of protein expression results in decreased and/or reduced expression of cAMP protein kinase A (PKA).

[001121] In some embodiments, the transient alteration of protein expression results in decreased and/or reduced expression of a molecule selected from the group consisting of PD-1, LAG3, TIM3, CTLA-4, TIGIT, CISH, TGFβR2, PKA, CBLB, BAFF (BR3), and combinations thereof. In some embodiments, the transient alteration of protein expression results in decreased and/or reduced expression of two molecules selected from the group consisting of PD-1, LAG3, TIM3, CTLA-4, TIGIT, CISH, TGFβR2, PKA, CBLB, BAFF

(BR3), and combinations thereof. In some embodiments, the transient alteration of protein expression results in decreased and/or reduced expression of PD-1 and one molecule selected from the group consisting of LAG3, TIM3, CTLA-4, TIGIT, CISH, TGFβR2, PKA, CBLB, BAFF (BR3), and combinations thereof. In some embodiments, the transient alteration of protein expression results in decreased and/or reduced expression of PD-1, LAG-3, CISH, CBLB, TIM3, and combinations thereof. In some embodiments, the transient alteration of protein expression results in decreased and/or reduced expression of PD-1 and one of LAG3, CISH, CBLB, TIM3, and combinations thereof. In some embodiments, the transient alteration of protein expression results in decreased and/or reduced expression of PD-1 and LAG3. In some embodiments, the transient alteration of protein expression results in decreased and/or reduced expression of PD-1 and CISH. In some embodiments, the transient alteration of protein expression results in decreased and/or reduced expression of PD-1 and CBLB. In some embodiments, the transient alteration of protein expression results in decreased and/or reduced expression of LAG3 and CISH. In some embodiments, the transient alteration of protein expression results in decreased and/or reduced expression of LAG3 and CBLB. In some embodiments, the transient alteration of protein expression results in decreased and/or reduced expression of CISH and CBLB. In some embodiments, the transient alteration of protein expression results in decreased and/or reduced expression of TIM3 and PD-1. In some embodiments, the transient alteration of protein expression results in decreased and/or reduced expression of TIM3 and LAG3. In some embodiments, the transient alteration of protein expression results in decreased and/or reduced expression of TIM3 and CISH. In some embodiments, the transient alteration of protein expression results in decreased and/or reduced expression of TIM3 and CBLB.

[001122] In some embodiments, an adhesion molecule selected from the group consisting of CCR2, CCR4, CCR5, CXCR2, CXCR3, CX3CR1, and combinations thereof, is inserted by a gammaretroviral or lentiviral method into the first population of TILs, second population of TILs, or harvested population of TILs (*e.g.*, the expression of the adhesion molecule is increased).

[001123] In some embodiments, the transient alteration of protein expression results in decreased and/or reduced expression of a molecule selected from the group consisting of PD-1, LAG3, TIM3, CTLA-4, TIGIT, CISH, TGFβR2, PKA, CBLB, BAFF (BR3), and combinations thereof, and increased and/or enhanced expression of CCR2, CCR4, CCR5, CXCR2, CXCR3, CX3CR1, and combinations thereof. In some embodiments, the transient

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alteration of protein expression results in decreased and/or reduced expression of a molecule selected from the group consisting of PD-1, LAG3, TIM3, CISH, CBLB, and combinations thereof, and increased and/or enhanced expression of CCR2, CCR4, CCR5, CXCR2, CXCR3, CX3CR1, and combinations thereof.

[001124] In some embodiments, there is a reduction in expression of about 5%, about 10%, about 10%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95%. In some embodiments, there is a reduction in expression of at least about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95%. In some embodiments, there is a reduction in expression of at least about 75%, about 80%, about 85%, about 90%, or about 95%. In some embodiments, there is a reduction in expression of at least about 80%, about 85%, about 90%, or about 95%. In some embodiments, there is a reduction in expression of at least about 85%, about 90%, or about 95%. In some embodiments, there is a reduction in expression of at least about 80%. In some embodiments, there is a reduction in expression of at least about 85%, In some embodiments, there is a reduction in expression of at least about 90%. In some embodiments, there is a reduction in expression of at least about 95%. In some embodiments, there is a reduction in expression of at least about 99%.

[001125] In some embodiments, there is an increase in expression of about 5%, about 10%, about 10%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95%. In some embodiments, there is an increase in expression of at least about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95%. In some embodiments, there is an increase in expression of at least about 75%, about 80%, about 85%, about 90%, or about 95%. In some embodiments, there is an increase in expression of at least about 80%, about 85%, about 90%, or about 95%. In some embodiments, there is an increase in expression of at least about 85%, about 90%, or about 95%. In some embodiments, there is an increase in expression of at least about 80%. In some embodiments, there is an increase in expression of at least about 85%, In some embodiments, there is an increase in expression of at least about 90%. In some embodiments, there is an increase in expression of at least about 95%. In some embodiments, there is an increase in expression of at least about 99%.

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[001126] In some embodiments, transient alteration of protein expression is induced by treatment of the TILs with transcription factors (TFs) and/or other molecules capable of transiently altering protein expression in the TILs. In some embodiments, the SQZ vectorfree microfluidic platform is employed for intracellular delivery of the transcription factors (TFs) and/or other molecules capable of transiently altering protein expression. Such methods demonstrating the ability to deliver proteins, including transcription factors, to a variety of primary human cells, including T cells (Sharei et al. PNAS 2013, as well as Sharei et al. PLOS ONE 2015 and Greisbeck et al. J. Immunology vol. 195, 2015) have been described; see, for example, International Patent Publications WO 2013/059343A1, WO 2017/008063A1, and WO 2017/123663A1, all of which are incorporated by reference herein in their entireties. Such methods as described in International Patent Publications WO 2013/059343A1, WO 2017/008063A1, and WO 2017/123663A1 can be employed with the present invention in order to expose a population of TILs to transcription factors (TFs) and/or other molecules capable of inducing transient protein expression, wherein said TFs and/or other molecules capable of inducing transient protein expression provide for increased expression of tumor antigens and/or an increase in the number of tumor antigen-specific T cells in the population of TILs, thus resulting in reprogramming of the TIL population and an increase in the rapeutic efficacy of the reprogrammed TIL population as compared to a nonreprogrammed TIL population. In some embodiments, the reprogramming results in an increased subpopulation of effector T cells and/or central memory T cells relative to the starting or prior population (i.e., prior to reprogramming) population of TILs, as described herein.

[001127] In some embodiments, the transcription factor (TF) includes but is not limited to TCF-1, NOTCH 1/2 ICD, and/or MYB. In some embodiments, the transcription factor (TF) is TCF-1. In some embodiments, the transcription factor (TF) is NOTCH 1/2 ICD. In some embodiments, the transcription factor (TF) is MYB. In some embodiments, the transcription factor (TF) is administered with induced pluripotent stem cell culture (iPSC), such as the commercially available KNOCKOUT Serum Replacement (Gibco/ThermoFisher), to induce additional TIL reprogramming. In some embodiments, the transcription factor (TF) is administered with an iPSC cocktail to induce additional TIL reprogramming. In some embodiments, the transcription factor (TF) is administered without an iPSC cocktail. In some embodiments, reprogramming results in an increase in the percentage of TSCMs. In some embodiments, reprogramming results in an increase in the percentage of TSCMs by about

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5%, about 10%, about 10%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95% TSCMs.

[001128] In some embodiments, a method of transient altering protein expression, as described above, may be combined with a method of genetically modifying a population of TILs includes the step of stable incorporation of genes for production of one or more proteins. In certain embodiments, the method comprises a step of genetically modifying a population of TILs. In certain embodiments, the method comprises genetically modifying the first population of TILs, the second population of TILs and/or the third population of TILs. In an embodiment, a method of genetically modifying a population of TILs includes the step of retroviral transduction. In an embodiment, a method of genetically modifying a population of TILs includes the step of lentiviral transduction. Lentiviral transduction systems are known in the art and are described, e.g., in Levine, et al., Proc. Nat'l Acad. Sci. 2006, 103, 17372-77; Zufferey, et al., Nat. Biotechnol. 1997, 15, 871-75; Dull, et al., J. Virology 1998, 72, 8463-71, and U.S. Patent No. 6,627,442, the disclosures of each of which are incorporated by reference herein. In an embodiment, a method of genetically modifying a population of TILs includes the step of gamma-retroviral transduction. Gamma-retroviral transduction systems are known in the art and are described, e.g., Cepko and Pear, Cur. Prot. Mol. Biol. 1996, 9.9.1-9.9.16, the disclosure of which is incorporated by reference herein. In an embodiment, a method of genetically modifying a population of TILs includes the step of transposonmediated gene transfer. Transposon-mediated gene transfer systems are known in the art and include systems wherein the transposase is provided as DNA expression vector or as an expressible RNA or a protein such that long-term expression of the transposase does not occur in the transgenic cells, for example, a transposase provided as an mRNA (e.g., an mRNA comprising a cap and poly-A tail). Suitable transposon-mediated gene transfer systems, including the salmonid-type Tel-like transposase (SB or Sleeping Beauty transposase), such as SB10, SB11, and SB100x, and engineered enzymes with increased enzymatic activity, are described in, e.g., Hackett, et al., Mol. Therapy 2010, 18, 674-83 and U.S. Patent No. 6,489,458, the disclosures of each of which are incorporated by reference herein.

[001129] In some embodiments, transient alteration of protein expression is a reduction in expression induced by self-delivering RNA interference (sdRNA), which is a chemicallysynthesized asymmetric siRNA duplex with a high percentage of 2'-OH substitutions

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(typically fluorine or -OCH₃) which comprises a 20-nucleotide antisense (guide) strand and a 13 to 15 base sense (passenger) strand conjugated to cholesterol at its 3' end using a tetraethylenglycol (TEG) linker. In some embodiments, the method comprises transient alteration of protein expression in a population of TILs, comprising the use of self-delivering RNA interference (sdRNA), which is a chemically-synthesized asymmetric siRNA duplex with a high percentage of 2'-OH substitutions (typically fluorine or -OCH₃) which comprises a 20-nucleotide antisense (guide) strand and a 13 to 15 base sense (passenger) strand conjugated to cholesterol at its 3' end using a tetraethylenglycol (TEG) linker. Methods of using sdRNA have been described in Khvorova and Watts, Nat. Biotechnol. 2017, 35, 238-248; Byrne, et al., J. Ocul. Pharmacol. Ther. 2013, 29, 855-864; and Ligtenberg, et al., Mol. Therapy, 2018, in press, the disclosures of which are incorporated by reference herein. In an embodiment, delivery of sdRNA to a TIL population is accomplished without use of electroporation, SQZ, or other methods, instead using a 1 to 3 day period in which a TIL population is exposed to sdRNA at a concentration of 1 µM/10,000 TILs in medium. In certain embodiments, the method comprises delivery sdRNA to a TILs population comprising exposing the TILs population to sdRNA at a concentration of 1 µM/10,000 TILs in medium for a period of between 1 to 3 days. In an embodiment, delivery of sdRNA to a TIL population is accomplished using a 1 to 3 day period in which a TIL population is exposed to sdRNA at a concentration of 10 µM/10,000 TILs in medium. In an embodiment, delivery of sdRNA to a TIL population is accomplished using a 1 to 3 day period in which a TIL population is exposed to sdRNA at a concentration of 50 μM/10,000 TILs in medium. In an embodiment, delivery of sdRNA to a TIL population is accomplished using a 1 to 3 day period in which a TIL population is exposed to sdRNA at a concentration of between 0.1 μM/10,000 TILs and 50 μM/10,000 TILs in medium. In an embodiment, delivery of sdRNA to a TIL population is accomplished using a 1 to 3 day period in which a TIL population is exposed to sdRNA at a concentration of between 0.1 μ M/10,000 TILs and 50 μ M/10,000 TILs in medium, wherein the exposure to sdRNA is performed two, three, four, or five times by addition of fresh sdRNA to the media. Other suitable processes are described, for example, in U.S. Patent Application Publication No. US 2011/0039914 A1, US 2013/0131141 A1, and US 2013/0131142 A1, and U.S. Patent No. 9,080,171, the disclosures of which are incorporated by reference herein.

[001130] In some embodiments, sdRNA is inserted into a population of TILs during manufacturing. In some embodiments, the sdRNA encodes RNA that interferes with

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

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JUMBO APPLICATIONS/PATENTS

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WHAT IS CLAIMED IS:

- 1. A method of treating non-small cell lung carcinoma (NSCLC) with a population of tumor infiltrating lymphocytes (TILs) comprising the steps of:
 - (a) obtaining and/or receiving a first population of TILs from surgical resection, needle biopsy, core biopsy, small biopsy, or other means for obtaining a sample that contains a mixture of tumor and TIL cells from a NSCLC tumor in a patient;
 - (c) contacting the tumor fragments with a first cell culture medium;
 - (d) performing an initial expansion of the first population of TILs in the first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2;
 - (e) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), and optionally irradiated allogeneic peripheral blood mononuclear cells (PBMCs); and wherein the rapid expansion is performed over a period of 14 days or less;
 - (f) harvesting the third population of TILs; and
 - (g) administering a therapeutically effective portion of the third population of TILs to a patient with the NSCLC;

wherein the NSCLC is refractory to treatment with an anti-PD-1 antibody.

- 2. The method of Claim 1, wherein the obtaing the first population of TILs comprises a multilesional sampling method.
- 3. The method of Claim 1, wherein the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 and/or anti-PD-L2 antibody.
- 4. The method of Claim 1, wherein the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.
- 5. The method of Claim 1, wherein the refractory NSCLC has been treated with a chemotherapeutic agent.

- 6. The method of Claim 1, wherein the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has been previously treated a chemotherapeutic agent.
- 7. The method of Claim 1, wherein the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has been previously treated a chemotherapeutic agent.
- 8. The method of Claims 5 to 7, wherein the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.
- 9. The method of Claim 1, wherein the refractory NSCLC has low expression of PD-L1.
- 10. The method of Claim 1, wherein the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has low expression of PD-L1.
- 11. The method of Claim 1, wherein the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has low expression of PD-L1.
- 12. The method of Claim 1, wherein the refractory NSCLC has been treated with a chemotherapeutic agent and has low expression of PD-L1.
- 13. The method of Claim 1, wherein the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent and has low expression of PD-L1
- 14. The method of Claim 1, wherein the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has bulky disease at baseline.
- 15. The method of Claim 1, wherein the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has bulky disease at baseline.
- 16. The method of Claim 1, wherein the refractory NSCLC has been treated with a chemotherapeutic agent and has bulky disease at baseline.
- 17. The method of Claim 1, wherein the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent and has bulky disease at baseline.
- 18. The method of Claims 14 to 17, wherein bulky disease is indicated where the maximal tumor diameter is greater than 7 cm measured in either the transverse or coronal plane

- or swollen lymph nodes with a short-axis diameter of 20 mm or greater.
- 19. The method of Claim 1, wherein the refractory NSCLC is refractory to at least two prior systemic treatment courses, not including neo-adjuvant or adjuvant therapies.
- 20. The method of Claim 1, wherein the refractory NSCLC is refractory to an anti-PD-1 or an anti-PD-L1 antibody is selected from the group consisting of nivolumab, pembrolizumab, JS001, TSR-042, pidilizumab, BGB-A317, SHR-1210, REGN2810, MDX-1106, PDR001, anti-PD-1 from clone: RMP1-14, an anti-PD-1 antibodies disclosed in U.S. Patent No. 8,008,449, durvalumab, atezolizumab, avelumab, and fragments, derivatives, variants, as well as biosimilars thereof.
- 21. The method of Claim 1, wherein the refractory NSCLC is refractory to pembrolizumab or a biosimilar thereof.
- 22. The method of Claim 1, wherein the refractory NSCLC is refractory to nivolumab or a biosimilar thereof.
- 23. The method of Claim 1, wherein the refractory NSCLC is refractory to an anti-CLTA-4 antibody, such as ipilimumab or a biosimilar thereof.
- 24. The method of Claim 1, wherein the refractory NSCLC is refractory to an anti-CLTA-4 antibody, such as ipilimumab or a biosimilar thereof and pembrolizumab or a biosimilar thereof.
- 25. The method of Claim 1, wherein the refractory NSCLC is refractory to an anti-CLTA-4 antibody, such as ipilimumab or a biosimilar thereof and nivolumab or a biosimilar thereof.
- 26. The method of Claim 1, wherein the refractory NSCLC is refractory to durvalumab or a biosimilar thereof.
- 27. The method of Claim 1, wherein the refractory NSCLC is refractory to atezolizumab or a biosimilar thereof.
- 28. The method of Claim 1, wherein the refractory NSCLC is refractory to avelumab or a biosimilar thereof.
- 29. The method of any one of Claims 1 to 28, wherein the initial expansion is performed over a period of 21 days or less.
- 30. The method of any one of Claims 1 to 29, wherein the initial expansion is performed over

- a period of 14 days or less.
- 31. The method of any one of Claims 1 to 30, wherein the IL-2 is present at an initial concentration of between 1000 IU/mL and 6000 IU/mL in the first cell culture medium.
- 32. The method of any one of Claims 1 to 31, wherein the IL-2 is present at an initial concentration of between 1000 IU/mL and 6000 IU/mL and the OKT-3 antibody is present at an initial concentration of about 30 ng/mL in the second cell culture medium.
- 33. The method of any one of Claims 1 to 32, wherein the initial expansion is performed using a gas permeable container.
- 34. The method of any one of Claims 1 to 33, wherein the rapid expansion is performed using a gas permeable container.
- 35. The method of any one of Claims 1 to 34, wherein the first cell culture medium further comprises a cytokine selected from the group consisting of IL-4, IL-7, IL-15, IL-21, and combinations thereof.
- 36. The method of any one of Claims 1 to 35, wherein the second cell culture medium further comprises a cytokine selected from the group consisting of IL-4, IL-7, IL-15, IL-21, and combinations thereof.
- 37. The method of any one of Claims 1 to 36, further comprising the step of treating the patient with a non-myeloablative lymphodepletion regimen prior to administering the third population of TILs to the patient.
- 38. The method of Claim 37, wherein the non-myeloablative lymphodepletion regimen comprises the steps of administration of cyclophosphamide at a dose of 60 mg/m²/day for two days followed by administration of fludarabine at a dose of 25 mg/m²/day for five days.
- 39. The method of any one of Claims 1 to 38, further comprising the step of treating the patient with an IL-2 regimen starting on the day after administration of the third population of TILs to the patient.
- 40. The method of Claim 39, wherein the IL-2 regimen is a high-dose IL-2 regimen comprising 600,000 or 720,000 IU/kg of aldesleukin, or a biosimilar or variant thereof, administered as a 15-minute bolus intravenous infusion every eight hours until tolerance.
- 41. A method of treating non-small cell lung carcinoma (NSCLC) with a population of tumor

infiltrating lymphocytes (TILs) comprising the steps of:

- (a) resecting a tumor from a patient, the tumor comprising a first population of TILs;
- (b) fragmenting the tumor into tumor fragments;
- (c) contacting the tumor fragments with a first cell culture medium;
- (d) performing an initial expansion of the first population of TILs in the first cell culture medium to obtain a second population of TILs, wherein the second population of TILs is at least 5-fold greater in number than the first population of TILs, wherein the first cell culture medium comprises IL-2;
- (e) performing a rapid expansion of the second population of TILs in a second cell culture medium to obtain a third population of TILs, wherein the third population of TILs is at least 50-fold greater in number than the second population of TILs after 7 days from the start of the rapid expansion; wherein the second cell culture medium comprises IL-2, OKT-3 (anti-CD3 antibody), and optionally irradiated allogeneic peripheral blood mononuclear cells (PBMCs); and wherein the rapid expansion is performed over a period of 14 days or less;
- (f) harvesting the third population of TILs; and
- (g) administering a therapeutically effective portion of the third population of TILs to a patient with the NSCLC;

wherein the NSCLC is refractory to treatment with an anti-PD-1 antibody.

- 42. The method of Claim 41, wherein the tumor is resected from one or more tumor cites.
- 43. The method of Claim 41, wherein the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 and/or anti-PD-L2 antibody.
- 44. The method of Claim 41, wherein the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.
- 45. The method of Claim 41, wherein the refractory NSCLC has been treated with a chemotherapeutic agent.
- 46. The method of Claim 41, wherein the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has been previously treated a chemotherapeutic agent.

47. The method of Claim 41, wherein the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has been previously treated a chemotherapeutic agent.

- 48. The method of Claims 45 to 47, wherein the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.
- 49. The method of Claim 41, wherein the refractory NSCLC has low expression of PD-L1.
- 50. The method of Claim 41, wherein the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has low expression of PD-L1.
- 51. The method of Claim 41, wherein the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has low expression of PD-L1.
- 52. The method of Claim 41, wherein the refractory NSCLC has been treated with a chemotherapeutic agent and has low expression of PD-L1.
- 53. The method of Claim 41, wherein the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent and has low expression of PD-L1.
- 54. The method of Claim 41, wherein the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has bulky disease at baseline.
- 55. The method of Claim 41, wherein the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has bulky disease at baseline.
- 56. The method of Claim 41, wherein the refractory NSCLC has been treated with a chemotherapeutic agent and has bulky disease at baseline.
- 57. The method of Claim 41, wherein the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent and has bulky disease at baseline.
- 58. The method of Claims 54 to 57, wherein said bulky disease is indicated where the maximal tumor diameter is greater than 7 cm measured in either the transverse or coronal plane or swollen lymph nodes with a short-axis diameter of 20 mm or greater.
- 59. The method of Claim 41, wherein the refractory NSCLC is refractory to at least two prior systemic treatment courses, not including neo-adjuvant or adjuvant therapies.

- 60. The method of Claim 41, wherein the refractory NSCLC is refractory to an anti-PD-1 or an anti-PD-L1 antibody is selected from the group consisting of nivolumab, pembrolizumab, JS001, TSR-042, pidilizumab, BGB-A317, SHR-1210, REGN2810, MDX-1106, PDR001, anti-PD-1 from clone: RMP1-14, an anti-PD-1 antibodies disclosed in U.S. Patent No. 8,008,449, durvalumab, atezolizumab, avelumab, and fragments, derivatives, variants, as well as biosimilars thereof.
- 61. The method of Claim 41, wherein the refractory NSCLC is refractory to pembrolizumab or a biosimilar thereof.
- 62. The method of Claim 41, wherein the refractory NSCLC is refractory to nivolumab or a biosimilar thereof.
- 63. The method of Claim 41, wherein the refractory NSCLC is refractory to an anti-CLTA-4 antibody, such as ipilimumab or a biosimilar thereof.
- 64. The method of Claim 41, wherein the refractory NSCLC is refractory to an anti-CLTA-4 antibody, such as ipilimumab or a biosimilar thereof and pembrolizumab or a biosimilar thereof.
- 65. The method of Claim 41, wherein the refractory NSCLC is refractory to an anti-CLTA-4 antibody, such as ipilimumab or a biosimilar thereof and nivolumab or a biosimilar thereof.
- 66. The method of Claim 41, wherein the refractory NSCLC is refractory to durvalumab or a biosimilar thereof.
- 67. The method of Claim 41, wherein the refractory NSCLC is refractory to atezolizumab or a biosimilar thereof.
- 68. The method of Claim 41, wherein the refractory NSCLC is refractory to avelumab or a biosimilar thereof.
- 69. The method of any one of Claims 41 to 68, wherein the initial expansion is performed over a period of 21 days or less.
- 70. The method of any one of Claims 41 to 69, wherein the initial expansion is performed over a period of 14 days or less.
- 71. The method of any one of Claims 41 to 70, wherein the IL-2 is present at an initial concentration of between 1000 IU/mL and 6000 IU/mL in the first cell culture medium.

72. The method of any one of Claims 41 to 71, wherein the IL-2 is present at an initial concentration of between 1000 IU/mL and 6000 IU/mL and the OKT-3 antibody is present at an initial concentration of about 30 ng/mL in the second cell culture medium.

- 73. The method of any one of Claims 41 to 72, wherein the initial expansion is performed using a gas permeable container.
- 74. The method of any one of Claims 41 to 73, wherein the rapid expansion is performed using a gas permeable container.
- 75. The method of any one of Claims 41 to 74, wherein the first cell culture medium further comprises a cytokine selected from the group consisting of IL-4, IL-7, IL-15, IL-21, and combinations thereof.
- 76. The method of any one of Claims 41 to 75, wherein the second cell culture medium further comprises a cytokine selected from the group consisting of IL-4, IL-7, IL-15, IL-21, and combinations thereof.
- 77. The method of any one of Claims 41 to 76, further comprising the step of treating the patient with a non-myeloablative lymphodepletion regimen prior to administering the third population of TILs to the patient.
- 78. The method of Claim 77, wherein the non-myeloablative lymphodepletion regimen comprises the steps of administration of cyclophosphamide at a dose of 60 mg/m²/day for two days followed by administration of fludarabine at a dose of 25 mg/m²/day for five days.
- 79. The method of any one of Claims 41 to 78, further comprising the step of treating the patient with an IL-2 regimen starting on the day after administration of the third population of TILs to the patient.
- 80. The method of Claim 79, wherein the IL-2 regimen is a high-dose IL-2 regimen comprising 600,000 or 720,000 IU/kg of aldesleukin, or a biosimilar or variant thereof, administered as a 15-minute bolus intravenous infusion every eight hours until tolerance.
- 81. A method for treating a subject with non-small cell lung carcinoma (NSCLC), wherein the cancer is refractory to treatment with an anti-PD-1 antibody, the method comprising administering expanded tumor infiltrating lymphocytes (TILs) comprising:
 - (a) obtaining and/or receiving a first population of TILs from a tumor resected from a subject by processing a tumor sample obtained from the subject into multiple

tumor fragments;

- (b) adding the tumor fragments into a closed system;
- (c) performing a first expansion by culturing the first population of TILs in a cell culture medium comprising IL-2 to produce a second population of TILs, wherein the first expansion is performed in a closed container providing a first gaspermeable surface area, wherein the first expansion is performed for about 3-14 days to obtain the second population of TILs, wherein the second population of TILs is at least 50-fold greater in number than the first population of TILs, and wherein the transition from step (b) to step (c) occurs without opening the system;
- (d) performing a second expansion by supplementing the cell culture medium of the second population of TILs with additional IL-2, OKT-3, and antigen presenting cells (APCs), to produce a third population of TILs, wherein the second expansion is performed for about 7-14 days to obtain the third population of TILs, wherein the third population of TILs is a therapeutic population of TILs which comprises an increased subpopulation of effector T cells and/or central memory T cells relative to the second population of TILs, wherein the second expansion is performed in a closed container providing a second gas-permeable surface area, and wherein the transition from step (c) to step (d) occurs without opening the system;
- (e) harvesting therapeutic population of TILs obtained from step (d), wherein the transition from step (d) to step (e) occurs without opening the system; and
- (f) transferring the harvested TIL population from step (e) to an infusion bag, wherein the transfer from step (e) to (f) occurs without opening the system;
- (g) cryopreserving the infusion bag comprising the harvested TIL population from step (f) using a cryopreservation process; and
- (h) administering a therapeutically effective dosage of the third population of TILs from the infusion bag in step (g) to the subject.
- 82. The method of Claim 81, wherein the tumor sample is derived from a multilesional sampling method.
- 83. The method of Claim 81, wherein the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.
- 84. The method of Claim 81, wherein the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody.

- 85. The method of Claim 81, wherein the refractory NSCLC has been treated with a chemotherapeutic agent.
- 86. The method of Claim 81, wherein the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has been previously treated with a chemotherapeutic agent.
- 87. The method of Claim 81, wherein the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has been previously treated a chemotherapeutic agent.
- 88. The method of Claims 85 to 87, wherein the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent.
- 89. The method of Claim 81, wherein the refractory NSCLC has low expression of PD-L1.
- 90. The method of Claim 81, wherein the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has low expression of PD-L1.
- 91. The method of Claim 81, wherein the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has low expression of PD-L1.
- 92. The method of Claim 81, wherein the refractory NSCLC has been treated with a chemotherapeutic agent and has low expression of PD-L1.
- 93. The method of Claim 81, wherein the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent and has low expression of PD-L1
- 94. The method of Claim 81, wherein the refractory NSCLC has not been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has bulky disease at baseline.
- 95. The method of Claim 81, wherein the refractory NSCLC has been previously treated with an anti-PD-1 and/or anti-PD-L1 antibody and has bulky disease at baseline.
- 96. The method of Claim 81, wherein the refractory NSCLC has been treated with a chemotherapeutic agent and has bulky disease at baseline.
- 97. The method of Claim 81, wherein the refractory NSCLC has been treated with a chemotherapeutic agent but is not being currently treated with a chemotherapeutic agent and has bulky disease at baseline.

98. The method of Claims 94 to 97, wherein bulky disease is indicated where the maximal tumor diameter is greater than 7 cm measured in either the transverse or coronal plane or swollen lymph nodes with a short-axis diameter of 20 mm or greater.

- 99. The method of Claim 81, wherein the refractory NSCLC is refractory to at least two prior systemic treatment courses, not including neo-adjuvant or adjuvant therapies.
- or an anti-PD-L1 antibody is selected from the group consisting of nivolumab, pembrolizumab, JS001, TSR-042, pidilizumab, (BGB-A317, SHR-1210, REGN2810, MDX-1106, PDR001, anti-PD-1 from clone: RMP1-14, an anti-PD-1 antibodies disclosed in U.S. Patent No. 8,008,449, durvalumab, atezolizumab, avelumab, and fragments, derivatives, variants, as well as biosimilars thereof.
- 101. The method of Claim 81, wherein the refractory NSCLC is refractory to pembrolizumab or a biosimilar thereof.
- 102. The method of Claim 81, wherein the refractory NSCLC is refractory to nivolumab or a biosimilar thereof.
- 103. The method of Claim 81, wherein the refractory NSCLC is refractory to an anti-CLTA-4 antibody, such as ipilimumab or a biosimilar thereof.
- 104. The method of Claim 81, wherein the refractory NSCLC is refractory to an anti-CLTA-4 antibody, such as ipilimumab or a biosimilar thereof and pembrolizumab or a biosimilar thereof.
- 105. The method of Claim 81, wherein the refractory NSCLC is refractory to an anti-CLTA-4 antibody, such as ipilimumab or a biosimilar thereof and nivolumab or a biosimilar thereof.
- 106. The method of Claim 81, wherein the refractory NSCLC is refractory to durvalumab or a biosimilar thereof.
- 107. The method of Claim 81, wherein the refractory NSCLC is refractory to atezolizumab or a biosimilar thereof.
- 108. The method of Claim 81, wherein the refractory NSCLC is refractory to avelumab or a biosimilar thereof.
- 109. The method of any one of Claims 81 to 108, wherein the initial expansion is

- performed over a period of 21 days or less.
- 110. The method of any one of Claims 81 to 109, wherein the initial expansion is performed over a period of 14 days or less.
- 111. The method of any one of Claims 81 to 110, wherein the IL-2 is present at an initial concentration of between 1000 IU/mL and 6000 IU/mL in the first cell culture medium.
- 112. The method of any one of Claims 81 to 111, wherein the IL-2 is present at an initial concentration of between 1000 IU/mL and 6000 IU/mL and the OKT-3 antibody is present at an initial concentration of about 30 ng/mL in the second cell culture medium.
- 113. The method of any one of Claims 81 to 112, wherein the initial expansion is performed using a gas permeable container.
- 114. The method of any one of Claims 81 to 113, wherein the rapid expansion is performed using a gas permeable container.
- 115. The method of any one of Claims 81 to 114, wherein the first cell culture medium further comprises a cytokine selected from the group consisting of IL-4, IL-7, IL-15, IL-21, and combinations thereof.
- 116. The method of any one of Claims 81 to 115, wherein the second cell culture medium further comprises a cytokine selected from the group consisting of IL-4, IL-7, IL-15, IL-21, and combinations thereof.
- 117. The method of any one of Claims 81 to 116, further comprising the step of treating the patient with a non-myeloablative lymphodepletion regimen prior to administering the third population of TILs to the patient.
- 118. The method of Claim 117, wherein the non-myeloablative lymphodepletion regimen comprises the steps of administration of cyclophosphamide at a dose of 60 mg/m²/day for two days followed by administration of fludarabine at a dose of 25 mg/m²/day for five days.
- 119. The method of any one of Claims 81 to 118, further comprising the step of treating the patient with an IL-2 regimen starting on the day after administration of the third population of TILs to the patient.
- 120. The method of Claim 119, wherein the IL-2 regimen is a high-dose IL-2 regimen comprising 600,000 or 720,000 IU/kg of aldesleukin, or a biosimilar or variant thereof,

administered as a 15-minute bolus intravenous infusion every eight hours until tolerance.

- 121. The method according to any of the preceding Claims, wherein the NSCLC is refractory to a combination treatment or therapy comprising an anti-PD-1 and a chemotherapeutic agent.
- 122. The method of Claim 121, wherein the anti-PD-1 or the anti-PD-L1 antibody is selected from the group consisting of nivolumab, pembrolizumab, JS001, TSR-042, pidilizumab, (BGB-A317, SHR-1210, REGN2810, MDX-1106, PDR001, anti-PD-1 from clone: RMP1-14, an anti-PD-1 antibodies disclosed in U.S. Patent No. 8,008,449, durvalumab, atezolizumab, avelumab, and fragments, derivatives, variants, as well as biosimilars thereof.
- 123. The method according Claim 121, wherein the antiPD-1 is pembrolizumab.
- 124. The method according any one of Claims 121 to 123, wherein the chemotherapeutic agent is a platinum doublet chemotherapeutic agent(s).
- 125. The method according any one of Claims 121 to 123, wherein the platinum doublet therapy comprises:
 - i) a first chemotherapeutic agent selected from the group consisting of cisplatin and carboplatin,
 - ii) and a second chemotherapeutic agent selected from the group consisting of vinorelbine, gemcitabine and a taxane (including for example, paclitaxel, docetaxel or nab-paclitaxel).
- 126. The method according any one of Claims 121 to 125, wherein the chemotherapeutic agent(s) is in combination with pemetrexed.
- 127. The method according any one of Claims 121 to 126, wherein the NSCLC is refractory to a combination therapy comprising carboplatin, paclitaxel, pemetrexed, and cisplatin.
- 128. The method according any one of Claims 121 to 127, wherein the NSCLC is refractory to a combination therapy comprising carboplatin, paclitaxel, pemetrexed, cisplatin, nivolumab, and ipilimumab.

Figure 1

Process 2A: about 22 days from Steps A - E

1. <u>STEP A</u>

Obtain Patient Tumor Sample

2. <u>STEP B</u>

Fragmentation and First Expansion

3 days to 14 days

3. STEP C

First Expansion to Second Expansion Transition

No Storage and Closed System

4. <u>STEP D</u>

Second Expansion

IL-2, OKT-3, and antigen-presenting feeder cells

Closed System

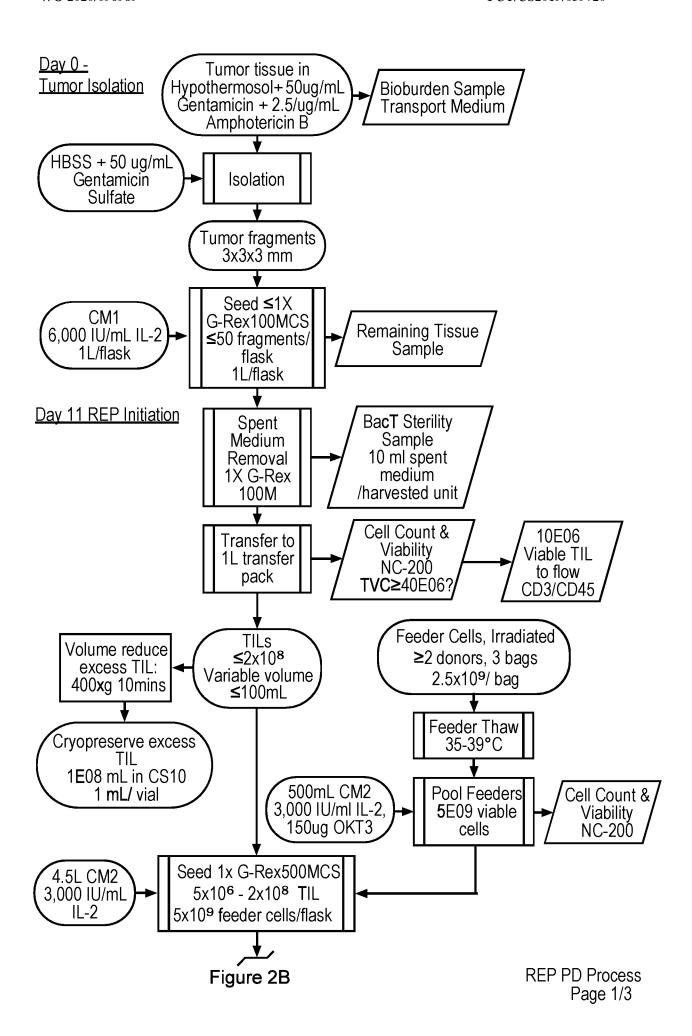
5. <u>STEP E</u>

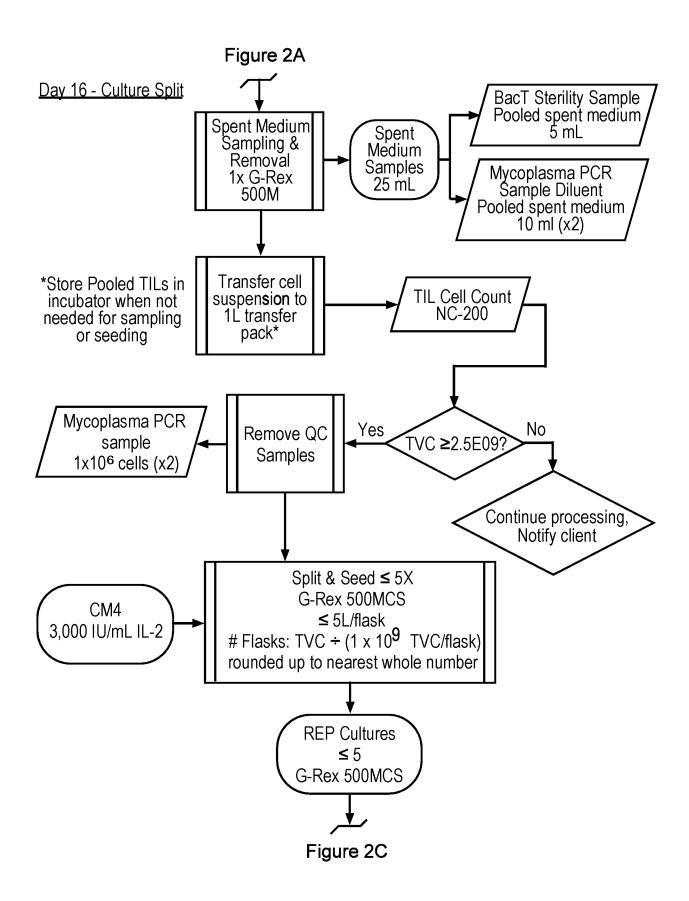
Harvest TILS from Step D

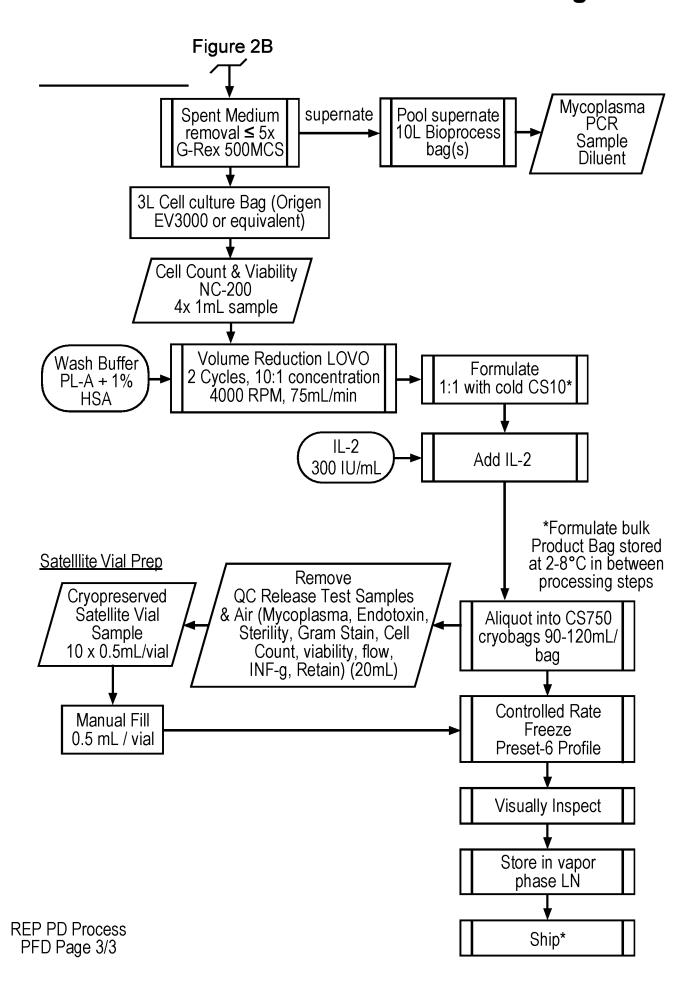
Closed System

6. STEP F

Final Formulation and/or Transfer to Infusion Bag (optionally cryopreserve)







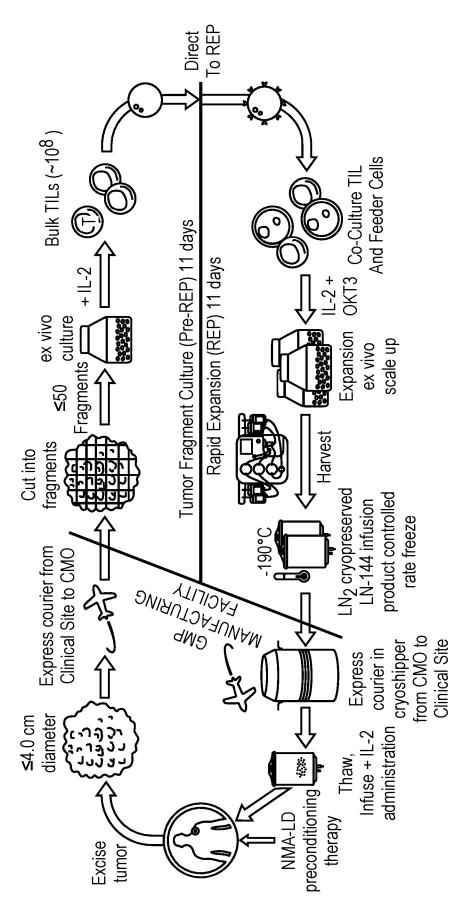


Figure 3

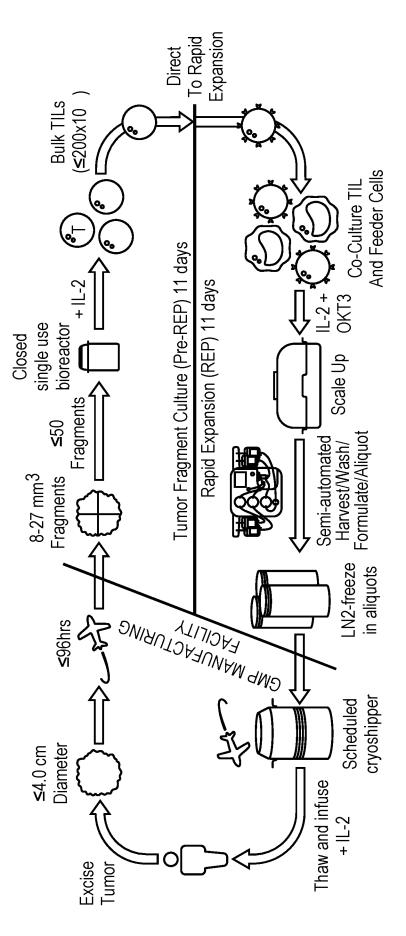


Figure 4

Figure 5

Process 1C: 43-55 Days for Steps A - E	Process 2A: about 22 days from Steps A - E	
1. <u>STEP A</u>	1. <u>STEP A</u>	
Obtain Patient Tumor Sample	Obtain Patient Tumor Sample	
2. <u>STEP B</u>	2. <u>STEP B</u>	
Fragmentation and First Expansion	Fragmentation and First Expansion	
11 days to 21 days	3 days to 14 days	
3. <u>STEP C</u>	3. <u>STEP C</u>	
First Expansion to Second Expansion Transition	First Expansion to Second Expansion Transition	
Optional Storage until Selection	No Storage and Closed System	
4. <u>STEP D</u>	4. <u>STEP D</u>	
Second Expansion	Second Expansion	
IL-2, OKT-3, antigen-presenting feeder cells	IL-2, OKT-3, and antigen-presenting feeder cells	
Optionally repeat one or more times	Closed System	
g syrian r	5. <u>STEP E</u>	
5. <u>STEP E</u>	Harvest TILS from Step D	
Harvest TILS from Step D	Closed System	
6. <u>STEP F</u>	6. <u>STEP F</u>	
Final Formulation and/or Transfer to Infusion	Final Formulation and/or Transfer to Infusion Bag	
Bag	(optionally cryopreserve)	

Figure 6

Process Step	Process 1C Embodiment	Process 2A Embodiment	Advantages
Pre-REP	 4 fragments per 10 GREX-10 flasks 11-21 day duration 	 40 fragments per 1 GREX-100M flask 11 day duration 	 Increased tumor fragments per flask Shortened culture time Reduced number of steps Amenable to closed system
Pre-REP to REP Transition	• Pre-REP TIL are frozen until phenotyped for selection then thawed to proceed to the REP (~day 30)	Pre-REP TIL directly move to REP on day 11	 Shortened pre-REP-to-REP process Reduced number of steps
	• REP requires >40×10 ⁶ TIL	 REP requires 25- 200×10⁶ TIL 	Eliminated phenotyping selectionAmenable to closed system
REP	 6 GREX-100M flasks on REP day 0 5×10⁶ TIL and 5×10⁸ PBMC feeders per flask on REP day 0 Split to 18-36 flasks on REP day 7 	 1 GREX-500M flask on day 11 25-200×10⁶ TIL and 5x10⁹ PBMC feeders on day 11 Split to ≤ 6 GREX- 500M flasks on day 16 	 Reduced number of steps Shorter REP duration Closed system transfer of TIL between flasks
	• 14 day duration	11 day duration TIL harvested via	 Closed system media exchanges Reduced number of steps
Harvest	TIL harvested via centrifugation	LOVO automated cell washing system'	 Automated cell washing Closed system Reduced loss of product during wash
Final Formulation	• Fresh product in Hypothermosol	 Cyropreserved product in PlasmaLyte-A + 1% HSA and CS10 stored in LN2 	Shipping flexibility
	Single infusion bagLimited shipping stability	Multiple aliquotsLonger shipping stability	Flexible patient schedulingMore timely release testing
Overall Estimated Process Time	• 43-55 days	• 22 days	Faster turnaround to patient

Figure 7



Frozen tumor (banked) /
Fresh tumor /
____ Core biopsy _____

Mechanical / enzymatic digest of tumor / core biopsy PD1 or other selection (optional)

Seed bioreactor to initiate Pre-REP. Culture media (serum containing or serum free) supplemented with IL-2, OKT3, 4-1BB, feeder cells or feeder alternatives

Media replacement to initiate REP.
Culture media (serum free or serum containing) supplemented with OKT3, OX40, feeder cells or feeder alternatives,

Scale up to larger, multiple bioreactors.
Culture media (serum free)
supplemented with IL-2

Harvest and cryopreserve in DMSO containing media with IL-2 Day 0: Tumor / biopsy prep

Day 0: Pre-REP Initiation

Day 5-8: REP initiation

Day 9 to 11: REP Scale Up

Day 12 to16: Harvest

Figure 8A

Process 2A: about 22 days from Steps A - E Process GEN 3: about 14-18 days from Steps A - E

STEP A

Obtain Patient Tumor Sample (optionally can be frozen before Step B)

STEP B

First Expansion (physical fragmentation to at least 40 fragments per container grown for about 3 days to 14 days with

media comprising IL-2)

STEP C

First Expansion to Second Expansion Transition (Step B TILs directly move to Step D, optionally on Step B day 11)

STEP D

Second Expansion

(TILs grown in growth media medium comprising closed container)

STEP E

Harvest TILS from Step D (TILs harvested via closed system)

STEP F

Final Formulation and/or Transfer to Infusion Bag (optionally cryopreserve)

STEP A

Obtain Patient Tumor Sample (optionally can be frozen before Step B)

STEP B

Priming First Expansion (physical fragmentation of up to 60 fragments per container grown for about 1 days to 7 days with media comprising IL-2, OKT-3, and antigenpresenting feeder cells)

STEP C

Priming First Expansion to Rapid Second Expansion Transition (Step B TILs directly move to Step D on day 7)

STEP D

Rapid Second Expansion

(TILs grown in growth media medium comprising IL-2, OKT-3, and antigen-presenting feeder cells in a IL-2, OKT-3, and 2X antigen-presenting feeder cells; Days 10-11 scale up and add additional IL-2)

STEP E

Harvest TILS from Step D

STEP F

Final Formulation and/or Transfer to Infusion Bag (optionally cryopreserve)

Figure 8B

Process GEN 3: about 14-18 days from Steps A - E

STEP A

Obtain Patient Tumor Sample (optionally can be frozen before Step B)

STEP B

Priming First Expansion

(physical fragmentation of up to 60 fragments per container grown for about 1 days to 7 days with media comprising IL-2, OKT-3, and antigen-presenting feeder cells)

STEP C

Priming First Expansion to Rapid Second Expansion Transition (Step B TILs directly move to Step D on day 7)

STEP D

Rapid Second Expansion

(TILs grown in growth media medium comprising IL-2, OKT-3, and 2X antigenpresenting feeder cells; Days 10-11 scale up and add additional IL-2)

STEP E

Harvest TILS from Step D

STEP F

Final Formulation and/or Transfer to Infusion Bag (optionally cryopreserve)

Figure 8C

Embodiment GEN 3.1 **Embodiment GEN 3.1 Embodiment GEN 3.0:** control: Test/F: about 14-18 days from Steps A - E about 14-18 days from Steps about 14-18 days from Steps A - E A - E

STEP A

Obtain Patient Tumor Sample (optionally can be frozen before Step B)

STEP B

Priming First Expansion (physical fragmentation of up to 60 fragments per container grown for about 1 days to 7/8 days with media comprising IL-2)

STEP C

Priming First Expansion to Rapid Second Expansion Transition (Step B TILs directly move to Step D on day 7/8)

STEP D

Rapid Second Expansion (TILs grown in growth media medium comprising IL-2, OKT-3, and antigen-presenting feeder cells; Days 10-11 scale up and add additional IL-2)

STEP E

Harvest TILS from Step D

STEP F

Final Formulation and/or Transfer to Infusion Bag (optionally cryopreserve)

before Step B)

STEP B

STEP A

(optionally can be frozen

Priming First Expansion (physical fragmentation of up to 60 fragments per container grown for about 1 days to 7/8 days with media comprising IL-2, and OKT-3)

STEP C

Priming First Expansion to Rapid Second Expansion Transition (Step B TILs directly move to (Step B TILs directly move to Step D on day 7/8)

STEP D

Rapid Second Expansion (TILs grown in growth media medium comprising IL-2, OKT-3, and 2X antigenpresenting feeder cells; Days 10-11 scale up and add additional IL-2)

STEP E

Harvest TILS from Step D

STEP F

Final Formulation and/or Transfer to Infusion Bag (optionally cryopreserve)

STEP A

Obtain Patient Tumor Sample Obtain Patient Tumor Sample (optionally can be frozen before Step B)

STEP B

Priming First Expansion (physical fragmentation of up to 60 fragments per container grown for about 1 days to 7/8 days with media comprising IL-2, OKT-3, and antigenpresenting feeder cells)

STEP C

Priming First Expansion to Rapid Second Expansion Transition Step D on day 7/8)

STEP D

Rapid Second Expansion (TILs grown in growth media medium comprising IL-2, OKT-3, and 2X antigenpresenting feeder cells; Days 10-11 scale up and add additional IL-2)

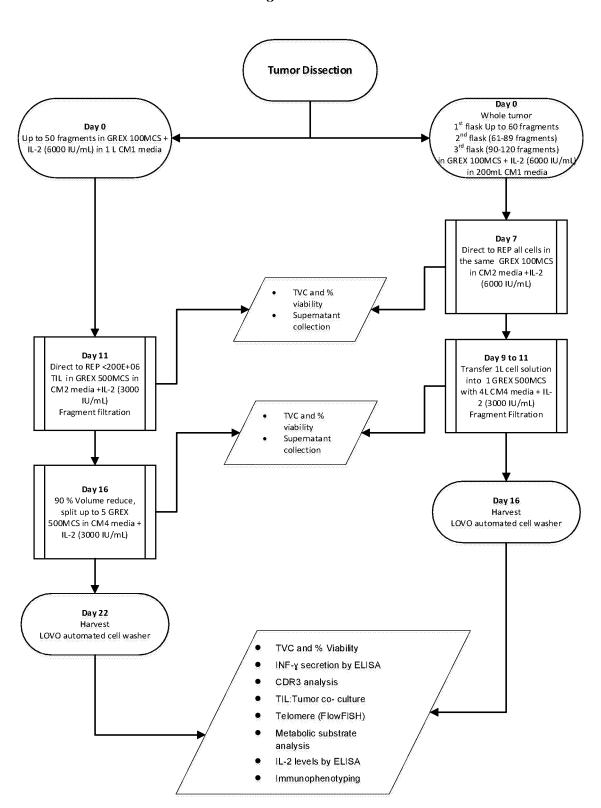
STEP E

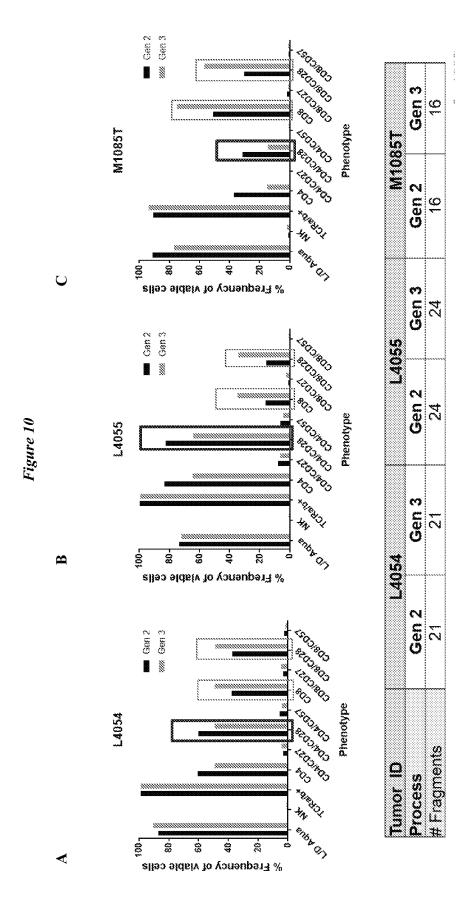
Harvest TILS from Step D

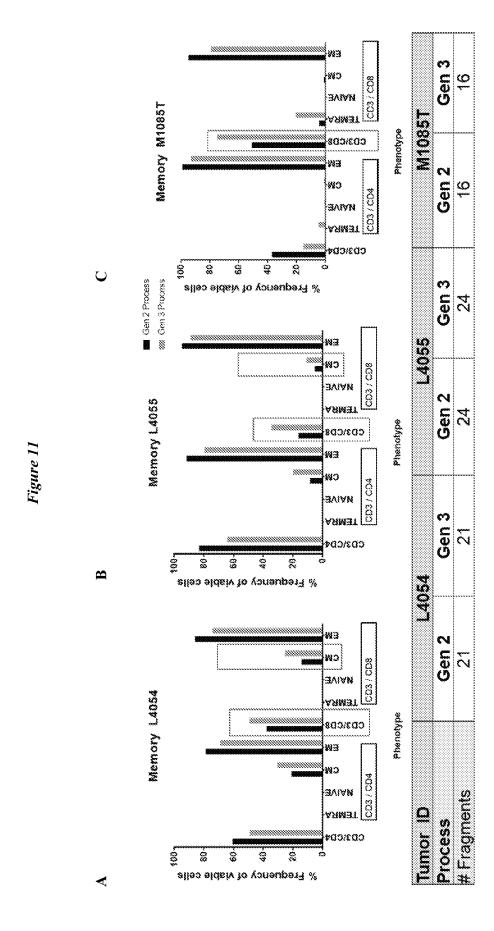
STEP F

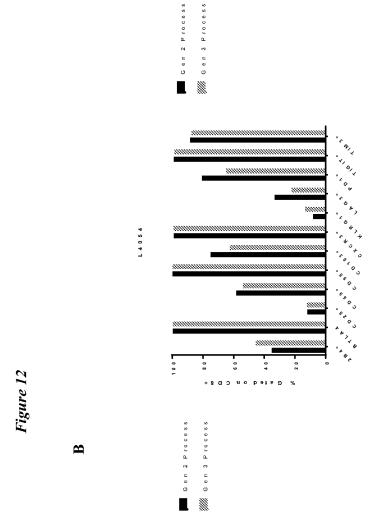
Final Formulation and/or Transfer to Infusion Bag (optionally cryopreserve)

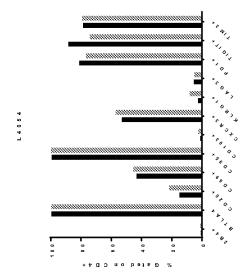
Figure 9



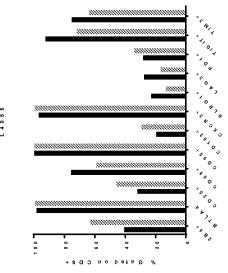








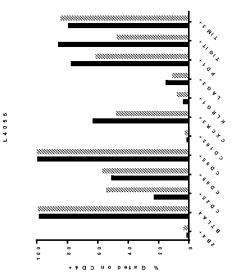


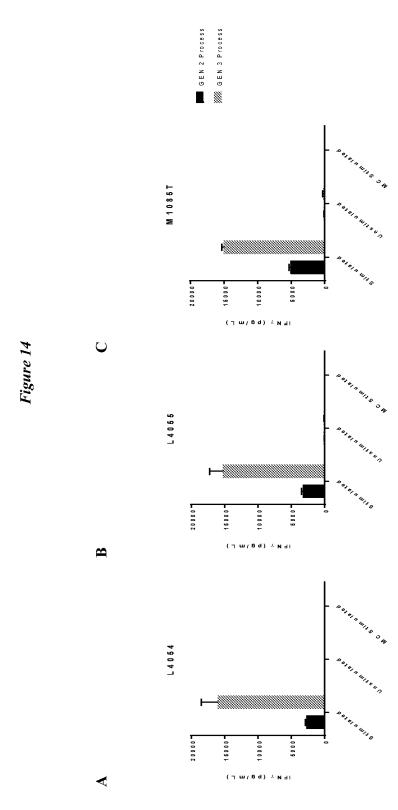


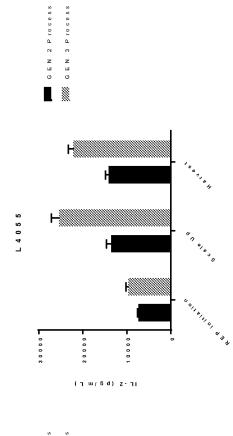


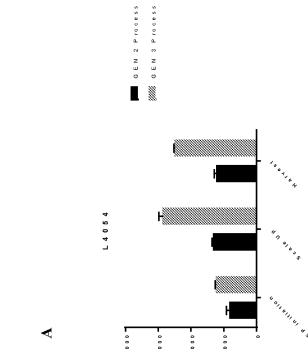
Gen 3 Process

Figure 13







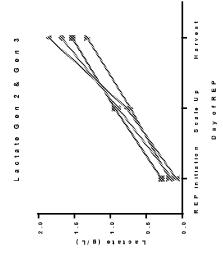


(J m / 6 d) Z - JI

Figure 15

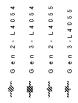
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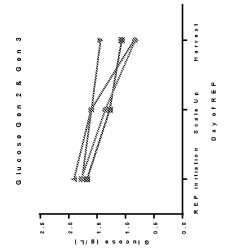




B

Figure 16

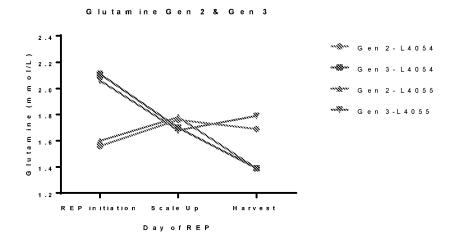




-

Figure 17

 \mathbf{A}



В

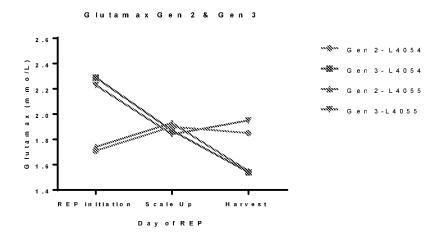
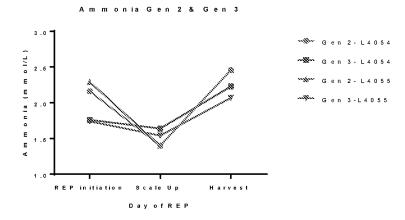
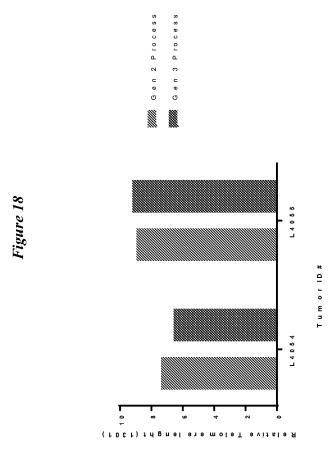


Figure 17

 \mathbf{C}





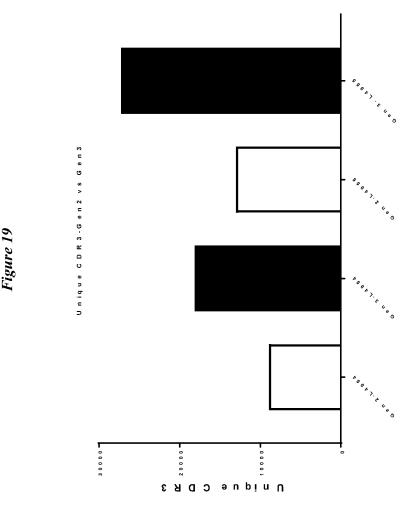
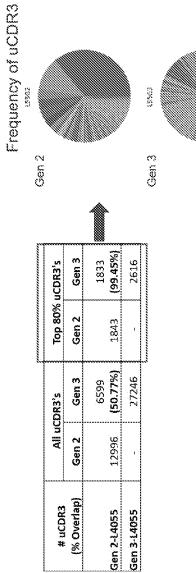


Figure 20

Frequency of uCDR3

(5453 15462 Gen 2 199 (97.07%) Gen 3 Top 80% uCDR3's Gen 2 205 (48.85%) Gen 3 18130 4355 All uCDR3's Gen 2 8915 (% Overlap) # uCDR3 Gen 2-L4054 Gen 3-L4054

199 sequences are shared between Gen 3 and Gen 2 final Gen 3 product, corresponding to 97.07% of top 80% of unique CDR3 sequences from Gen 2 shared with Gen 3 final product.



final product, corresponding to 99.45% of top 80% of unique CDR3 sequences from Gen 2 shared with Gen 3 final • 1833 sequences are shared between Gen 3 and Gen 2 product.

×

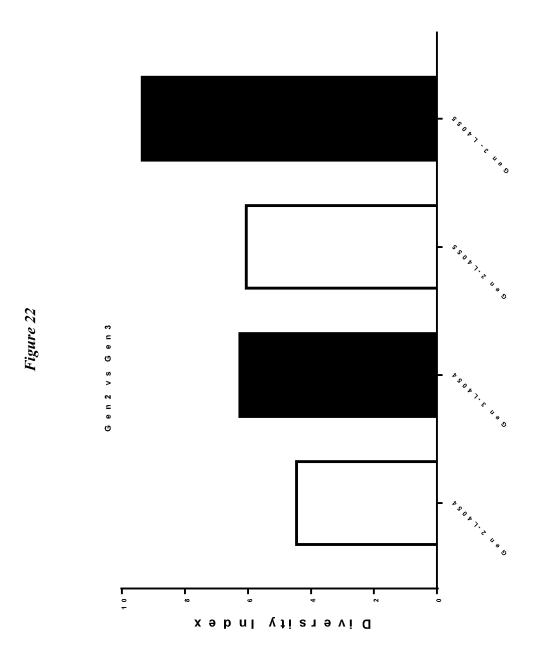


Figure 23 Cell counts Day 7-Gen 3 REP initiation

Volume (mL)		Count 1 (cells/mL)	Count 2 (cells/mL)	Count 3 (cells/mL)	Average (cells/mL)	Total Cells Average*Volume
	Total	2.46E+05	2.28E+05	2.31E+05	2.35E+05	4.42E+07
00	Live	2.37E+05	2.27E+05	2.26E+05	2.30E+05	4.32E+07
000	Dead	9.26E+03	7.03E+02	4.63E+03	4.86E+03	9.14E+05
	% Viability	96.20%	99.70%	98.00%	97.97%	
	Total	8.26E+04	8.00E+04	7.66E+04	7.97E+04	1.50E+07
0000	Live	7.60E+04	7.54E+04	6.89E+04	7.34E+04	1.38E+07
000	Dead	6.61E+03	4.63E+03	7.73E+03	6.32E+03	1.19E+06
	% Viability	92.00%	94.20%	89.90%	92.03%	
	Total	2.44E+04	4.20E+04	1.05E+04	2.56E+04	5.13E+06
C	Live	1.74E+04	2.80E+04	7.03E+03	1.75E+04	3.50E+06
7007	Dead	7.03E+03	1.40E+04	3.48E+03	8.17E+03	1.63E+06
	% Viability	71.20%	%02'99	%06:99	68.27%	

Figure 24
[0001] Cell counts Day 11-Gen 2 REP initiation and Gen 3 Scale Up

l n	Malama (m.1)		Count 1	Count 3	Count 2	Average	Total Cells
ID	Volume (mL)		(cells/mL)	(cells/mL)	(cells/mL)	(cells/mL)	Average*Volume
		Total	9.11E+05	1.01E+06	1.08E+06	1.00E+06	1.00E+09
Gen 3 #L4054	1000	Live	8.60E+05	9.34E+05	1.01E+06	9.35E+05	9.35E+08
First Round	1000	Dead	5.09E+04	7.49E+04	6.74E+04	6.44E+04	6.44E+07
		% Viability	94.40%	92.60%	93.70%	93.57%	
		Total	8.56E+05	9.04E+05	8.81E+05	8.80E+05	8.80E+08
Gen 3 #L4055	1000	Live	8.24E+05	8.67E+05	8.42E+05	8.44E+05	8.44E+08
Second Round	1000	Dead	3.17E+04	3.70E+04	3.87E+04	3.58E+04	3.58E+07
Second Round		% Viability	96.30%	95.90%	95.60%	95.93%	
Second Round		Total	2.32E+06	2.25E+06		2.29E+06	4.57E+08
Gen 3 #M1085T	200	Live	1.68E+06	1.57E+06		1.63E+06	3.25E+08
Gell 2 #IVITO021	200	Dead	6.41E+05	6.79E+05		6.60E+05	1.32E+08
		% Viability	72.40%	69.90%		71.15%	
		Total	1.08E+06	9.84E+05	1.00E+06	1.02E+06	1.45E+08
Gen 2 #L4054	142	Live	1.06E+06	9.71E+05	9.79E+05	1.00E+06	1.42E+08
First Round	142	Dead	2.05E+04	1.26E+04	2.12E+04	1.81E+04	2.57E+06
First Round		% Viability	98.10%	98.70%	97.90%	98.23%	
		Total	2.93E+05	3.05E+05	2.64E+05	2.87E+05	2.76E+07
Gen 2 #L4055	96	Live	2.88E+05	2.96E+05	2.55E+05	2.80E+05	2.68E+07
Second Round	30	Dead	4.72E+03	9.14E+03	8.26E+03	7.37E+03	7.08E+05
		% Viability	98.40%	97.00%	96.90%	97.43%	
		Total	9.10E+04	5.60E+04		7.35E+04	1.47E+07
Gen 2 #M1085T	200	Live	8.05E+04	4.21E+04		6.13E+04	1.23E+07
Gen 2 #M10851	200	Dead	1.04E+04	1.39E+04		1.22E+04	2.43E+06
		% Viability	88.50%	75.20%		81.85%	

Figure 25
[0002] Cell counts Day 16-Gen 2 Scale Up and Gen 3 Harvest

Total	ID	Volume (mL)		Count 1 (cells/mL)	Count 2 (cells/mL)	Count 3 (cells/mL)	Average (cells/mL)	Total Cells Average*Volume
Live			Total			, , ,		-
Dead								
Total Gas First Round First Round Page First Round Page First Round Page First Round Page		1243.1					***************************************	
Total 6.35E+07 6.07E+07 6.21E+07 2.05E+10	LOVO							
Live 5.72E+07 5.44E+07 5.58E+07 1.84E+10 Lovo Dead 6.35E+06 6.27E+06 6.31E+06 2.08E+09 Wibility 90.00% 89.70% 89.85% Lovo Second Round -pre LOVO Total 3.98E+05 3.08E+05 3.08E+05 Lovo Dead 5.85E+05 6.75E+05 6.30E+05 3.08E+05 Lovo Second Round -pre LOVO Total 3.31E+07 2.28E+07 3.08E+05 6.30E+05 6.51E+08 Lovo Wibility 93.80% 93.00% 93.00% 93.00% 93.70% 6.51E+08 Lovo Dead 5.85E+05 6.75E+05 6.30E+05 6.51E+08 Lovo Dead 4.56E+06 3.61E+06 4.12E+06 4.09E+06 1.35E+07 Lovo Dead 4.56E+06 3.61E+06 4.12E+06 4.09E+06 1.35E+09 Lovo Dead 4.56E+06 3.61E+06 4.12E+06 4.09E+06 1.35E+09 Lovo Dead 2.85E+07 2.46E+07 2.77E+07 2.66E+07 8.76E+09 Lovo Dead 4.56E+06 3.61E+06 4.12E+06 4.09E+06 1.35E+09 Lovo Dead 2.85E+05 3.30E+05 3.08E+05 1.28E+10 Lovo Dead 2.85E+05 3.30E+05 3.08E+05 1.28E+10 Lovo Dead 2.85E+05 3.30E+05 3.08E+05 1.28E+10 Lovo Dead 2.85E+05 3.30E+05 3.08E+05 1.28E+09 Lovo Dead 2.85E+05 3.30E+05 3.08E+05 1.28E+09 Lovo Dead 2.85E+05 3.30E+05 3.08E+05 1.28E+09 Lovo Dead 2.85E+05 3.30E+05 3.08E+05 1.54E+09 Lovo Dead 2.85E+05 3.30E+05 3.38E+05 1.54E+09 Lovo Dead 2.85E+05 3.30E+05 3.38E+05 1.54E+09 Lovo Dead 2.85E+05 3.30E+05 3.38E+05 3.38E+05 1.54E+09 Lovo Dead 2.85E+05 3.30E+05 3.38E+06 3.35E+06 3.35			· · · · · ·					2 05F+10
Dead 6.35E+06 6.27E+06 6.31E+06 2.08E+09	Gen 3 #L4054							
Total Second Round - protection Second Round - prote	First Round -post	330						
D	LOVO							2.002103
D								
Cells/mL ID	Maluma (mal)		Count 1	Count 2	Count 3	Average	Total Cells	
Second Round - pre LOVO	טו	volume (mL)		(cells/mL)	(cells/mL)	(cells/mL)	(cells/mL)	Average*Volume
Second Round - pre Lovo Dead 5.85E+05 6.30E+05 6.30E+05 6.51E+08	Com 3 #1 4055		Total	9.49E+06	1.05E+07		1.00E+07	1.03E+10
Dead 5.85E+05 6.75E+05 6.30E+05 6.51E+08 93.70% 93.80% 93.80% 93.80% 93.80% 93.80% 93.60% 93.70% 93.70% 93.80% 93.80% 93.60% 93.70% 93.70% 93.80% 93.60% 93.70% 93.70% 93.80% 93.60% 93.70% 93.70% 93.70% 93.60% 93.70% 93.60% 93.70% 93.60% 93.70% 93.60% 93.70% 93.60% 93.70% 93.60% 93.60% 93.60% 93.60% 93.70% 93.6		1022.6	Live	8.90E+06	9.79E+06		9.35E+06	9.65E+09
Second Round - post Second Round - post Second Round - post LoVO Second Round Sec	•	1032.6	Dead	5.85E+05	6.75E+05		6.30E+05	6.51E+08
Total 3.31E+07 2.82E+07 3.18E+07 3.07E+07 1.01E+10	LOVO		% Viability	93.80%	93.60%		93.70%	
Second Round - post Live 2.85£+07 2.46£+07 2.77£+07 2.66£+07 8.76£+09 Dead 4.56£+06 3.61£+06 4.12£+06 4.09£+06 1.35£+09 Wiability 86.20% 87.20% 87.10% 86.70% Second Round - post Round			3.31E+07	2.82E+07	3.18E+07	3.07E+07	1.01E+10	
LOVO			Live	2.85E+07	2.46E+07	2.77E+07	2.66E+07	8.76E+09
Notability 86.20% 87.20% 87.10% 86.70%	•	330	Dead	4.56E+06	3.61E+06	4.12E+06	4.09E+06	1.35E+09
Total Cells Count 1 Count 2 Count 3 Average Cells/mL) (cells/mL) (c	LOVO		% Viability	86.20%	87.20%	87.10%	86.70%	
Sond Live 1.97E+06 2.31E+06 2.14E+06 1.07E+10 Dead 2.85E+05 3.30E+05 3.08E+05 1.54E+09 W Viability 87.40% 87.50% 87.45% Sond Ry.45% Ry.45% Ry.45% Sond Ry.45% Ry.45% Ry.45% Ry.45% Sond Ry.45% Ry.45% Ry.45% Ry.45% Sond Ry.45% Ry.45%	ID	Volume (mL)		l I			_	Total Cells Average*Volume
Dead 2.85E+05 3.30E+05 3.08E+05 1.54E+09			Total	2.26E+06	2.64E+06		2.45E+06	1.23E+10
Dead 2.85E+05 3.30E+05 3.08E+05 1.54E+09	Gen 3 #M1085T	F000	Live	1.97E+06	2.31E+06		2.14E+06	1.07E+10
Total 6.27E+07 5.44E+07 5.86E+07 8.78E+09	pre-LOVO	5000	Dead	2.85E+05	3.30E+05		3.08E+05	1.54E+09
Live			% Viability	87.40%	87.50%		87.45%	
Dead 7.70E+06 6.96E+06 7.33E+06 1.10E+09	C 3 #NA100FT		Total	6.27E+07	5.44E+07		5.86E+07	8.78E+09
Dead 7.70E+06 6.96E+06 7.33E+06 1.10E+09 87.459 87.4		150	Live	5.50E+07	4.74E+07		5.12E+07	7.68E+09
Note		150	Dead	7.70E+06	6.96E+06		7.33E+06	1.10E+09
Cells/mL Cells/mL Cells/mL Cells/mL Cells/mL Cells/mL Cells/mL Average*Volume (mL)	addition		% Viability	87.70%	87.20%		87.45%	
Cells/mL Cells/mL Cells/mL Cells/mL Cells/mL Cells/mL Cells/mL Average*Volume (mL)		_		Count 1	Count 2	Count 3	Average	Total Cells
Total 3.53E+06 4.30E+06 3.92E+06 3.57E+09 First Round 913 Live 3.35E+06 4.00E+06 3.68E+06 3.36E+09 Dead 1.75E+05 3.03E+05 2.39E+05 2.18E+08 % Viability 95.00% 93.00% 94.00% Total 1.29E+07 1.36E+07 1.33E+07 3.87E+09 Live 1.16E+07 1.23E+07 1.20E+07 3.49E+09 Dead 1.27E+06 1.23E+06 1.25E+06 3.65E+08 % Viability 90.10% 90.90% 90.50% Total 6.75E+06 6.98E+06 6.87E+06 2.53E+09 Live 5.22E+06 5.58E+06 5.40E+06 1.99E+09	ID	Volume (mL)					_	Average*Volume
Gen 2 #L4054 First Round 913 Live 3.35E+06 4.00E+06 3.68E+06 3.36E+09 Dead 1.75E+05 3.03E+05 2.39E+05 2.18E+08 % Viability 95.00% 93.00% 94.00% For 2 #L4055 Second Round 292 Live 1.29E+07 1.36E+07 1.23E+07 3.49E+09 Dead 1.27E+06 1.23E+06 1.25E+06 3.65E+08 % Viability 90.10% 90.90% 90.50% Total 6.75E+06 6.98E+06 6.87E+06 2.53E+09 Live 5.22E+06 5.58E+06 5.40E+06 1.99E+09			Total					
First Round Dead 1.75E+05 3.03E+05 2.39E+05 2.18E+08 % Viability 95.00% 93.00% 94.00% Total 1.29E+07 1.36E+07 1.33E+07 3.87E+09 Live 1.16E+07 1.23E+07 1.20E+07 3.49E+09 Dead 1.27E+06 1.23E+06 1.25E+06 3.65E+08 % Viability 90.10% 90.90% Total 6.75E+06 6.98E+06 6.87E+06 2.53E+09 Live 5.22E+06 5.58E+06 5.40E+06 1.99E+09	Gen 2 #L4054							
% Viability 95.00% 93.00% 94.00%		913						
Total 1.29E+07 1.36E+07 1.33E+07 3.87E+09 Second Round Live 1.16E+07 1.23E+07 1.20E+07 3.49E+09 Dead 1.27E+06 1.23E+06 1.25E+06 3.65E+08 % Viability 90.10% 90.90% 90.50% Total 6.75E+06 6.98E+06 6.87E+06 2.53E+09 Live 5.22E+06 5.58E+06 5.40E+06 1.99E+09								2.252.50
Gen 2 #L4055 Second Round Live 1.16E+07 1.23E+07 1.20E+07 3.49E+09 Dead 1.27E+06 1.23E+06 1.25E+06 3.65E+08 % Viability 90.10% 90.90% 90.50% Total 6.75E+06 6.98E+06 6.87E+06 2.53E+09 Live 5.22E+06 5.58E+06 5.40E+06 1.99E+09			· · · · · ·					3.87F+09
Dead 1.27E+06 1.23E+06 1.25E+06 3.65E+08 % Viability 90.10% 90.90% 90.50% Total 6.75E+06 6.98E+06 6.87E+06 2.53E+09 Live 5.22E+06 5.58E+06 5.40E+06 1.99E+09								
% Viability 90.10% 90.90% 90.50% Total 6.75E+06 6.98E+06 6.87E+06 2.53E+09 Live 5.22E+06 5.58E+06 5.40E+06 1.99E+09	Gen 2 #I 4055		IVA				1.202.0/	J. 1JL 10J
Total 6.75E+06 6.98E+06 6.87E+06 2.53E+09 Live 5.22E+06 5.58E+06 5.40E+06 1.99E+09		292					1 25F±06	3 65F±08
Gen 2 #M1085T 369 Live 5.22E+06 5.58E+06 5.40E+06 1.99E+09		292	Dead	1.27E+06	1.23E+06			3.65E+08
Gen 2 #M1085T 369		292	Dead % Viability	1.27E+06 90.10%	1.23E+06 90.90%		90.50%	
		292	Dead % Viability Total	1.27E+06 90.10% 6.75E+06	1.23E+06 90.90% 6.98E+06		90.50% 6.87E+06	2.53E+09
% Viability 77.20% 79.90% 78.55%	Second Round		Dead % Viability Total Live	1.27E+06 90.10% 6.75E+06 5.22E+06	1.23E+06 90.90% 6.98E+06 5.58E+06		90.50% 6.87E+06 5.40E+06	2.53E+09 1.99E+09

Figure 26
[0003] Cell counts Day 22-Gen 2 Harvest

ID	Volume (mL)		Count 1 (cells/mL)	Count 2 (cells/mL)	Count 3 (cells/mL)	Average (cells/mL)	Total Cells Average*Volume
0 0 111 405 4		Total	3.55E+07	4.12E+07	4.03E+07	3.90E+07	5.40E+10
Gen 2 #L4054	1385.7	Live	3.26E+07	3.73E+07	3.67E+07	3.55E+07	4.92E+10
First Round -pre LOVO	1385.7	Dead	2.93E+06	3.87E+06	3.59E+06	3.46E+06	4.80E+09
LOVO		% Viability	91.70%	90.60%	91.10%	91.13%	
Con 2 #1 40F4		Total	1.70E+08	1.79E+08	1.68E+08	1.72E+08	5.69E+10
Gen 2 #L4054 First Round -post	330	Live	1.49E+08	1.58E+08	1.48E+08	1.52E+08	5.01E+10
LOVO	550	Dead	2.16E+07	2.04E+07	2.00E+07	2.07E+07	6.82E+09
LOVO		% Viability	87.30%	88.60%	88.10%	87.95%	
ID	Volume (mL)		Count 1 (cells/mL)	Count 2 (cells/mL)	Count 3 (cells/mL)	Average (cells/mL)	Total Cells Average*Volume
Gen 2 #L4055		Total	3.15E+07	2.51E+07	2.97E+07	2.88E+07	5.66E+10
First Round -pre	1968.2	Live	2.89E+07	2.25E+07	2.72E+07	2.62E+07	5.16E+10
LOVO	1900.2	Dead	2.57E+06	2.61E+06	2.52E+06	2.57E+06	5.05E+09
LOVO		% Viability	91.80%	89.60%	91.50%	90.97%	
Gen 2 #L4055		Total	2.33E+08	1.89E+08	1.53E+08	1.92E+08	6.33E+10
First Round -post	330	Live	2.03E+08	1.66E+08	1.33E+08	1.67E+08	5.52E+10
LOVO	330	Dead	3.00E+07	2.24E+07	1.94E+07	2.39E+07	7.90E+09
LOVO		% Viability	87.10%	88.10%	87.30%	87.50%	
ID	Volume (mL)		Count 1 (cells/mL)	Count 2 (cells/mL)	Count 3 (cells/mL)	Average (cells/mL)	Total Cells Average*Volume
		Total				#DIV/0!	#DIV/0!
Gen 2 #M1085T-pre	N1 / A	Live				#DIV/0!	#DIV/0!
LOVO	N/A	Dead				#DIV/0!	*#DIV/0!
		% Viability				#DIV/0!	
C 2 #1 44 00FT		Total	8.51E+07	9.05E+07		8.78E+07	1.32E+10
Gen 2 #M1085T -	150	Live	7.33E+07	7.79E+07		7.56E+07	1.13E+10
post LOVO pre CS10 addition	150	Dead	1.18E+07	1.26E+07		1.22E+07	1.83E+09
addition		% Viability	86.10%	86.10%		86.10%	

For L4054 Gen 2, post LOVO count was extrapolated to 4 flasks, because was the total number of the study. 1 flask was contaminated, and the extrapolation was done for total = 6.67E+10

Figure 27

2.0 3							
S1/S2/All/11 ve/CD14- /TCR4D/CD3- 4/Q8- CD62L- BV421-A-, CD45RA- AF700-A- Freq. of Parent (%)	EM	88 88	91.6	69.2	79.7	49.1	
\$1/\$2/All/lu ve/CD14- /TCRab/CD 4/Q7: CD62- BV421-A+ CD45RA- AF700-A- Freq. of Parent (%)	Σ. O	21.1	m ∞	30.7	20.1	16.4	
1/52/Aliju 51/52/Aliju 51/52/A	NATVE	0.032	0.014	0.049	0.072	23.1	
\$1/\$2/All/U1 we/CD14	TEMRA	0,056	0.036	0.059	0.12	11.4	
	Ξ	96.3	97.4	97.5	92.5	46.9	
1/82/AII/UI 51/52/AII/UI 51/52/AII/UI 51/52/AII/UI ve/CD14- ve/CD1	S	3.37	2.39	2.29	7.12	16.2	
1.452/All/Ll: 51/52/All/Ll: ve/CD14- Ve	NAÏVE	0.073	0.047	0.059	0.18	36.1	
\$1/52/All/U \$1/52	TEMRA	0.25	0.16	0.2	0.25	0.91	
Secretarion second ACCRETCE ACCRETCE Free around Ref		et es et	8T-9	4.02	PO.	2 m C	
SECTION SEC		8	0.34	0.18	0.26	0.041	
SACKARABID		 	82.6	88.9	54	40.4	
Section substantitions of the section of the sectio		KS eri	3	¢Ω ≅	527	155 157 157	
### 1972/46/10 \$152/46/10 \$152/		9 G9	83.1	T og	54.8	17.70	
1/52/Altri verCD14 7/Exeb] ven sfindi ven sfindi		67: 861 67:	C 55	60 60 60	566	6.08	
verCD14 KD191 KD191 en. drod F		œ.	c	1,725-03	0,018	12 17 18	
A STATE WHAT STATE WHEN STATE WHAT STATE WAS A STATE OF S		0.56	0.12	£6.0	0.44	13.5	
ritzanii. ectiisi. Fen of F		177E-03	c	o	2.56E-03	F03	
STATE AND STATE AND STATE STAT		2.58	60 60 86	196	72.1	e e er	ie graph
***	******	st.fcs	nd.fcs	st.fcs	nd.fcs	C.fcs	area was include to make the graph TCRab+ are = CD3+
		A1 gen2 1st.fcs	2 gen 2 21	A3 gen3 1st.fcs	4 gen3 21	A5 PBMC.fcs	ea was include to m TCRab+ are ≃ CD3+

51/52/All/Li ve/CD14- /TCRgd /Teq. of null (%)	***************************************	0	0	0	0	0		
51/52/All/Live/C 51/52/	ĒM	85.9	94.7	74.4	89.1	44.3		
σ ζυζ	8	14.1	5.24	25.5	10.6	6.23		
S1/S2/All/Live /CD14- /TCRab/CD8/ Q6:CD62L BV421-A+, CD4SRA- AF700-A+ Freq. of Parent (%)	NAÏVE	9.37E-03	0.014	0.017	0.044	27.1		
S1/S2/All/bve/C D14 TTCRah/CD8/Q5 CD62L-B4921 A -, CD4SRA- AF700-A + Freq. of Parent (%)	TEMRA	0.033	0.071	7.70.0	0.29	22.3		
\$1/52/All/Live/C \$1/52/	EM	95.7	95.2	96.8	89.5	48		
\$1/52/All/Li ve/CD14- · /TCRab/CD 8/Q3: CCR7- PE-A+, CD45RA- AF700-A Freq. of Parent (%)	CM	4.24	4.76	3.11	10.2	3.02		
\$1/\$2/All/Live/CD14	NAÏVE	0	0.014	6.97E-03	0.13	40.9		
S1/S2/All/Live/CD1 4-/TCRab/CD8/Q1: CCR7-PE-A- , CD4SRA-AF700-A+ I Freq. of Parent (%)	TEMRA	0.028	0.042	0.056	0.18	8.05		
1/24/Alfu S1/23/Alfu S1/34/Alfu S		231	0.17	1.53	n O	EG CS		
SYSZANJU SYS		0 40 C	6.67	971	1,57	6,75		
U. ST/SZ/AU/U ve/Did ve/Did //CD28† III Peq of not		en (en	15.8	48 년	¥	27.4		
S/S/AH/U ve/CO14 TCRA/CO S/CO27 F-Fec. of hulfl (%)		3.25	1.08	4,83	2.46	8.52		
SLyszykutt werchist //Tenbuck B Freq. or multifall		G LE	16.1	49.2	χ. 20 30	29.6		

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GEN 3-Day 16-Harvest GEN 2-D22-Harvest	
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	CD3+	CD4+ 2B4+	2B4+	BTLA+	CD103+	CD25+	CD69+	CD95+	CXCR3+	KLRG1+	LAG3+	PD1+	TIGIT+	TIM3+	
Gen 2-L4054				0.61	.50		14.80	43.20	99.40				81.20	88.40	78.60
Gen 3-L4054				1.1	.50	2.28	21.70	45.40	99.70	56.90	8.06	5.07	76.70	74.10	79.30
Gen 2-L4055				1.61			23.10	51.10	99.80				77.60	86.00	79.50
Gen 3- L4055				3.57			54.40	57.00	06.66				61.40	47.50	84.60
									CD8						
Gen 2-L4054		CD8+	2B4+	BTLA4+	CD103+	CD25+	CD95+	+69CO	CXCR3+	KLRG1+	LAG3+	PD1+	TIGIT+	TIM3+	
Gen 3-L4054				35.20		74.90	11.80	99.80	58.30				80.60	99.10	88.30
Gen 2-L4055				45.50	9.60	62.40	12.10	06.66	54.00	99.30	13.40	22.10	64.90	98.50	87.50
Gen 3- L4055				40.60	8.20	9.50	32.00	99.70	75.50				28.10	92.30	75.10
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Figure 30

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				Til. Geo	Til. Geo	Til. Gen	TIL (50)	76 OH	74 Geo	MC-	MC-	MC							
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		3000	1550				Yes	let.	189	3	3	3	Cont/Dil						
				Td. Geo	TiL Geo	TiL: Gen	Tit. Con	7 L 300	74, 500	MC-	MC-	мс							
	200	2465	2100	2 etimologed	2 stimulated	2 silicobileit	Commun	Costicopi	Orestacous	Stimulate d xG2	Stimulate d xG2	Stimulate d xG2	Well ID						
			608	9	g.	ş		1164	194	9	9	9	Cont/Dil						
				TiL Geo	TiL Geo	TiL Gen	Tit. See	3.6 365	Th. Ser	MC-	MC-	MC-							
	200	260	200	Setimulated	atimudated	alimulated	Stockholis	Cherimati	Charmon	Unstimula ted xG2	Unstimula ted xG2	Unstimula ted xG2	Well ID						
			100	27	27	27				3	3	3	Cont/Dil				: :		
				T/L-GHA	TiL Gen	TIL Gen	Fit. Gen	TO Get	Title Ger	MC-	MC-	M¢-		:					
8	23004	2,023	2000	Stimuleted	stinadeted	shoulated	(Appellerate	Utermote	Chermon	Unstimula ted xG2	Unstimula ted xG2	Unstimula ted xG2	Well ID						
	100	128	128	81	81	81				9	9	9	Conc/Dil		ļ	ļ	ļ		
				T/L. Gen	TAL: Gen	TIL Gen	Til. Sen	Tit. Gen	T.L. Gen	MC-	MC-	MC-							
	6166	e3356	eaps	stimulated	3- stimulated	3 sticrulated	decembe	Linstinudo	Linstinulo	Stimulate d xG3	Stimulate d xG3	Stirrufate d xG3	Well ID				: :		
			1026	3	3	3	ied.	ien	1266	3	3	3	Conc/Dil						
				Til. Gen	TiL-Gen	TIL Gen	TIL Sen	TIL TOOK	TIL Gib	MC-	MC-	MC-							
	9756	espe	erpe	3 stimulated:	3. Stirrolated	3 sterulated	chestando	Linstinado	Linstinulo	Stimulate d xG3	Stimulate d xG3	Stimulate d xG3	Well ID						
				9	9	9	160	100	184	9	9	9	Cont/Dil						
				Til, Gen	Tit. Gen	TIL Gen	Til Gen	TL Geo	Til Geo	MC-	MC-	MC-							
	9101	STEV	8107	2- stimulated	2- stirculated	2- sterulated	Unstriule	Unstinuda	Unstinula	Unstimula ted xG3	Unstimula ted xG3	Unstimula ted xG3	Well ID						
	12.5	et a	100	27	27	27	16Q	led 37	16d 37	3	3	3	Cont/Dil						
				T≀L Gen	TiL Gen	TIL Gen	TIL Gen	TL Geo	71. Geo	MC-	MC	MC-							
- 44	200	2702	arce.	2 stimolated	2 stircobiled	2- sterolated	Costimula	Unstiroota	Uris Freebi	Unstimula tert xG3	Unstimula ted xG3	Unstimula fed xG3	Well ID						
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22.6																			
22.6 22.6																			
22 6 22 6	******		2336		2.184	123481	0.117	0.116	0.117	0.105	0.108	0.102	450	Gen 2-Stimulated+TIL 1:3	1 2890.216	2084.946	3055.126	Average 2676.76267	Average 2757.81
22 6 22 6	2 05	12.00 20.00	2 300 2006	1 212	2 184 C 048	1 2051	0.117 0.041	0.116 0.043	0.117 0.041	30 0.105 0.041	0.108 0.043	0.102 0.041	450 570	Gen 2-Stimulated+TIL 1:3 Gen 2-Stimulated+TIL 1:9	2967.887	2084.946 2117.46	3072.942	2676.76267 2719.42967	Average 2757.81
22 6 22 6	******	8:05 1002:343	8:05 1004.079	963.405	0.048 2.199	\$ 051 1018.375	0.041 0.076	0.043 0.074	0.041 0.076	0.041 0.064	0.043 0.065	0.041 0.06	450 570 Deta [Concentratio	Gen 2-Stimulated+TIL 1:9 Gen 2-Stimulated+TIL 1:27	2967.887 2952.028	2117.46 2128.412	3072.942 3035.11	2676.76267 2719.42967 2705.18333	Average 2757.81
22.6 22.6	994.773			963.405 2890.216	0:048 2:038 694.982 2084.946	0.051 1018.375 3055.126	0.041 0.076 1.825 5.474	0.043 0.074 1.421 4.262	0.041 0.076 1.952 5.855	0.041 0.064 <0.000 <0.000	0.043 0.065 <0.000 <0.000	0.041 0.06 <0.000 <0.000	1	Gen 2-Stirrulated+TIL 1:9 Gen 2-Stirrulated+TIL 1:27 Gen 2-Stirrulated+TIL 1:81	2967.887 2952.028	2117.46 2128.412	3072.942	2676.76267 2719.42967 2705.18333 2929.867	
22.6 22.6	188	£ 35 £ 35 1002.343 1.884 £ 646	2 004 2 05 1 004 079 1 008 2 046		0.048 2.839 694.982		0.041 0.076 1.825	0.043 0.074 1.421	0.041 0.076 1.952	0.041 0.064 <0.000	0.043 0.065 <0.000	0.041 0.06 <0.000	Delta (Concentratio ni	Gen 2-Stimulated+TIL 1:9 Gen 2-Stimulated+TIL 1:27	2967.887 2952.028 3261.251 ?????	2117.46 3 2128.412 2361.138 77777	3072.942 3035.11	2676.76267 2719.42967 2705.18333	Average 2757.81 #DIV/0! 16089.32
22.6 22.6	8 d5 994.773 1.688 0.046 1.612	1.884 0.046 1.808	1 868 0 046 1 604	2890.216 1.181 0.048 1.136	G 048 2 138 694 982 2084 946 0 047 G 853	3055.126 1.212 0.045	0.041 0.076 1.825 5.474 0.107 0.042 0.066	0.043 0.074 1.421 4.262 0.107 0.041 0.066	0.041 0.076 1.952 5.855 0.108 0.042 0.067	0.041 0.064 <0.000 <0.000 0.106 0.043 0.062	0.043 0.065 <0.000 <0.000 0.105 0.042 0.063	0.041 0.06 <0.000 <0.000 0.102 0.042 0.061	Delta (Concentratio ni	Gen 2-Stirmulated+TiL 1.9 Gen 2-Stirmulated+TiL 1.27 Gen 2-Stirmulated+TiL 1.81 Gen 3-Stirmulated+TiL 1.3 Gen 3-Stirmulated+TiL 1.9 Gen 3-Stirmulated+TiL 1.27	2967.887 2952.028 3261.251 2777? 13273.546 16947.994	2117.46 3 2128.412 2361.138 77777 5 >13500.00 1 16962.84	3072.942 3035.11 3167.212 227777 13340.37 17161.47	2676.76267 2719.42967 2705.18333 2929.867 #DIV/0! 13306.9575 17024.1	#DIV/0!
22.6 22.6	994.773 1.688 0.046	1.884 0.046	1 902 0 046	2890.216 1.181 0.045 1.136 329.765	0.048 3.137 694.982 2084.946 0.9 0.047 0.653 235.273	3055.126 1.319 0.045 1.17 341.438	0.041 0.076 1.825 5.474 0.107 0.042 0.066 <0.000	0.043 0.074 1.421 4.262 0.107 0.041 0.066 <0.000	0:041 0:076 1.952 5.855 0:108 0:042 0:067 <0.000	0.041 0.064 <0.000 <0.000 0.106 0.042 0.062 <0.000	0.043 0.065 <0.000 <0.000 0.105 0.042 0.063 <0.000	0.041 0.06 <0.000 <0.000 0.102 0.042 0.061 <0.000	Dets [Concentratio n] xdii factor 460 570	Gen 2-Stirmulated+TiL 1-9 Gen 2-Stirmulated+TiL 1-27 Gen 2-Stirmulated+TiL 1-81 Gen 3-Stirmulated+TiL 1-3 Gen 3-Stirmulated+TiL 1-9	2967.887 2952.028 3261.251 2777? 13273.546 16947.994	2117.46 3 2128.412 2361.138 77777 5 >13500.00 1 16962.84	3072.942 3035.11 3167.212 77777 13340.37	2676.76267 2719.42967 2705.18333 2929.867 #DIV/0! 13306.9575 17024.1	#DIV/0!
22.6 22.6	994.773 1.688 0.046 1.612 499.866	1.854 0.046 1.808 497.826	1.88 0.046 1.604 496.528	2890.216 1.181 0.048 1.136 329.765 2967.887 0.494	0.048 2.19 694.982 2084.946 0.9 0.047 0.853 235.273 2117.46 0.391	3055.126 1.3358 0.045 1.37 341.438 3072.942 0.505	0.041 0.076 1.825 5.474 0.107 0.042 0.066 <0.000 0.106	0.043 0.074 1.421 4.262 0.107 0.041 0.066 <0.000 <0.000	0.041 0.076 1.952 5.855 0.108 0.042 0.067 <0.000 0.107	0.041 0.064 <0.000 <0.000 0.106 0.043 0.062 <0.000 <0.000	0.043 0.065 <0.000 0.105 0.042 0.063 <0.000 <0.000	0.041 0.06 <0.000 <0.000 0.102 0.042 0.061 <0.000 <0.000	Dets [Concentratio n] xdii factor 460 570	Gen 2 Stirrulated+TIL 1 9 Gen 2 Stirrulated+TIL 1 27 Gen 2 Stirrulated+TIL 1 21 Gen 3 Stirrulated+TIL 1 3 Gen 3 Stirrulated+TIL 1 3 Gen 3 Stirrulated+TIL 1 9 Gen 3 Stirrulated+TIL 1 27 Gen 3 Stirrulated+TIL 1 27 Gen 3 Stirrulated+TIL 1 81	2967.887 2952.028 3261.251 77777 13273.546 16947.994 17571.427	2117.46 3 2128.412 2361.138 77777 5 >13500.00 1 16962.84 1 18246.77	3072.942 3035.11 3167.212 77777 13340.37 17161.47 17992.49	2676.76267 2719.42967 2705.18333 2929.867 #DIV/01 13306.9575 17024.1 17936.8973	#DIV/0!
22.6 22.6	994.773 1.688 0.046 1.612 499.866	1.654 0.046 1.606 497.826	t:mb 0.046 1:804 496.528	2890.216 1.181 0.045 1.136 329.765 2967.887	0.048 2.19 694.982 2084.946 0.9 0.047 0.653 235.273 2117.46	3055.126 1.335 0.045 1.37 341.438 3072.942	0.041 0.076 1.825 5.474 0.107 0.042 0.066 <0.000	0.043 0.074 1.421 4.262 0.107 0.041 0.066 <0.000	0.041 0.076 1.952 5.855 0.108 0.042 0.067 <0.000	0.041 0.064 <0.000 <0.000 0.106 0.043 0.062 <0.000	0.043 0.065 <0.000 <0.000 0.105 0.042 0.063 <0.000	0.041 0.06 <0.000 <0.000 0.102 0.042 0.061 <0.000	Dets [Concentratio n] xdi factor 450 570 Dets [Concentratio n] xdi factor	Gen 2 Stirrulated + Til. 1 9 Gen 2 Stirrulated + Til. 1 127 Gen 2 Stirrulated + Til. 1 181 Gen 3 Stirrulated + Til. 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	2967.887 2952.028 3261.251 7777? 13273.546 16947.994 17571.427	2117.46 3 2128.412 2361.138 77777 5 >13500.00 1 16962.84 1 18246.77 4.262 <0.000	3072.942 3035.11 3167.212 77777 13340.37 17161.47	2676.76267 2719.42967 2705.18333 2929.867 #DIV/0! 13306.9575 17024.1 17936.8973	#DIV/0! 16089.32
22.6 22.6	994.773 994.773 1.688 0.346 1.612 499.866 0.952 0.944	1.854 0.646 1.608 497.826 0.966 5.048	1.92 0.046 1.604 496.528 5.54 5.043	2890.216 1.181 0.048 1.136 329.765 2967.887 0.494 0.042 0.452 109.334	0.048 694.982 2084.946 0.9 0.047 0.653 235.273 2117.46 0.391 0.042 0.248 78.83	3055.126 1:338 0.045 1:37 341.438 3072.942 0.505 0.043 0.463 112.411	0.041 0.076 1.825 5.474 0.107 0.042 0.060 <0.000 0.106 0.041 0.065 <0.000	0.043 0.074 1.421 4.262 0.107 0.041 0.066 <0.000 <0.000 0.107 0.042 0.065 <0.000	0.041 0.076 1.952 5.855 0.108 0.042 0.067 <0.000 <0.000 0.107 0.042 0.065 <0.000	0.041 0.064 <0.000 <0.000 0.106 0.043 0.062 <0.000 <0.000 0.107 0.043 0.063 <0.000	0.043 0.065 <0.000 0.105 0.042 0.063 <0.000 <0.000 0.105 0.042 0.063 <0.000	0.041 0.06 <0.000 0.102 0.042 0.061 <0.000 <0.000 0.103 0.042 0.062 <0.000	Octa (Concentration) (I) xdf factor 450 970 Deta (Concentration) (Concentration) xdf factor 450 570 Deta (Concentration) (Concentration) (Concentration)	Gen 2 Stirrulated + Til. 1 9 Gen 2 Stirrulated + Til. 1 127 Gen 2 Stirrulated + Til. 1 181 Gen 3 Stirrulated + Til. 1 13 Gen 3 Stirrulated + Til. 1 13 Gen 3 Stirrulated + Til. 1 19 Gen 2 Stirrulated + Til. 1 181 Gen 2 - Unstirrulated + Til. 1 181 Gen 2 - Unstirrulated + Til. 1 181 Gen 2 - Unstirrulated + Til. 1 19	2967.887 2952.028 3261.251 77777 13273.546 16947.994 17571.427 5.474	2117.46 3 2128.412 2361.138 77777 5 >13500.00 16962.84 18246.77 4.262 <0.000 <0.000	3072.942 3035.11 3167.212 77777 13340.37 17161.47 17992.49 5.855 <0.000	2676.76267 2719.42967 2705.18333 2929.867 #DIV/01 13306.9575 17024.1 17936.8973 5.197 #DIV/01	#DIV/0! 16089.32
22.6 22.6	994 773 1 688 6 646 1 353 499 866 0 552 6 044 6 868 253 244 0 549	1.884 0.046 1.908 497.826 0.966 0.048 0.919 256.8	\$ 988 0.046 1.904 496.528 0.54 0.043 0.898 249.399	2890.216 1.181 0.045 3.136 329.765 2967.887 0.494 0.042 0.482 109.334 2952.028 0.258	694, 982 2084, 946 0.96 0.947 0.647 0.653 235, 273 2117, 46 0.391 0.042 0.248 78, 83 2128, 412 0.218	3055.126 3.33% 5.045 341.438 3072.942 0.505 0.043 0.462 112.411 3035.11 0.259	0.041 0.076 1.825 5.474 0.107 0.042 0.066 <0.000 0.106 0.041 0.065 <0.000 <0.000 0.000 0.000 0.000	0.043 0.074 1.421 4.262 0.107 0.041 0.066 <0.000 0.107 0.042 0.065 <0.000 0.000 0.000 0.000	0.041 0.076 1.952 5.855 0.108 0.042 0.067 <0.000 0.107 0.042 0.062 0.062 0.060 0.000	0.041 0.064 <0.000 0.106 0.062 <0.000 0.107 0.043 0.062 <0.000 0.107 0.043 0.000 <0.000 0.111	0.043 0.065 <0.000 0.000 0.105 0.042 0.063 <0.000 0.105 0.042 0.063 0.000 0.105	0.041 0.06 <0.000 0.000 0.102 0.042 0.061 <0.000 0.103 0.42 0.062 0.062 0.000 0.000 0.000 0.000	Deta Concentratio	Gen 2-Stirrulated+TIL 1-9 Gen 2-Stirrulated+TIL 1-8 Gen 3-Stirrulated+TIL 1-81 Gen 3-Stirrulated+TIL 1-8 Gen 3-Stirrulated+TIL 1-8 Gen 3-Stirrulated+TIL 1-9 Gen 3-Stirrulated+TIL 1-81 Gen 2-Unstirrulated+TIL 1-81 Gen 2-Unstirrulated 1-9 Gen 2-Unstirrulated 1-8 Gen 2-Unstirrulated 1-8 Gen 2-Unstirrulated 1-8 Gen 2-Unstirrulated 1-8	2967.887 2952.028 3261.251 77777 13273.546 16947.994 17571.427 5.474 <0.000 <0.000	2117.46 3 2128.412 2361.138 77777 > 13500.00 16962.84 18246.77 4.262 <0.000 <0.000	3072.942 3035.11 3167.212 77777 13340.37 17161.47 17992.49 5.855 <0.000 <0.000 <0.000	2676, 76267 2719, 42967 2705, 18333 2929, 867 #DIV/0! 13306, 9575 17024, 1 17936, 8973 5, 197 #DIV/0! #DIV/0! #DIV/0! 2, 25133333	#DIV/0! 16089.32
22 6 22 6	994.773 3.658 6.046 3.533 499.866 0.552 5.044 6.808 253.244 0.542 0.544	1.8854 0.646 1.806 497.826 0.986 0.948 0.919 256.8 0.541	1.88 2.046 1.804 496.528 0.54 0.643 2.49.399 0.542 0.043	2890.216 1:181 0:045 1:136 329.765 2967.887 0.494 0.042 0.482 109.334 2952.028 0.258 0.042	694,982 2084,946 2,5 0,247 0,653 235,273 2117,46 0,391 0,042 0,248 78,83 2128,412 0,218 0,041	3055.126 1.318 0.045 1.37 341.438 3072.942 0.505 0.043 112.411 3035.11 0.259 0.047	0.041 0.076 1.825 5.474 0.107 0.042 0.066 <0.000 0.106 0.041 0.065 <0.000 0.000 0.000 0.000 0.000 0.000 0.000	0.043 0.074 1.421 4.262 0.107 0.041 0.066 <0.000 0.107 0.042 0.065 <0.000 0.101 0.000	0.041 0.076 1.952 5.855 0.108 0.042 0.067 <0.000 <0.000 0.107 0.042 0.065 <0.000 <0.000 0.103 0.043	0.041 0.064 <0.000 0.106 0.043 0.062 <0.000 <0.000 0.107 3.943 0.063 <0.000 <0.000 0.111	0.043 0.065 <0.000 0.105 0.042 0.063 <0.000 <0.000 0.105 0.042 0.063 <0.000 0.003 <0.000 0.105 0.042 0.063 <0.000 0.000	0.041 0.06 <0.000 0.102 0.042 0.061 <0.000 0.103 0.103 0.042 0.062 <0.000 <0.000 0.103 0.042 0.062 <0.000 0.103 0.042 0.062	Deta IConcentrato XxII factor Add Add Add Add Add Add Add Add Add Ad	Gen 2-Stimulated+TiL 1-9 Gen 2-Stimulated+TiL 1-8 Gen 2-Stimulated+TiL 1-81 Gen 3-Stimulated+TiL 1-3 Gen 3-Stimulated+TiL 1-3 Gen 3-Stimulated+TiL 1-9 Gen 3-Stimulated+TiL 1-8 Gen 2-Unstimulated+TiL 1-81 Gen 2-Unstimulated+TiL 1-8 Gen 2-Unstimulated 1-9 Gen 2-Unstimulated 1-81 Gen 3-Unstimulated 1-81 Gen 3-Unstimulated 1-81 Gen 3-Unstimulated 1-8	2967.887 2952.028 3261.251 77727 13273.546 16947.994 17571.427 5.474 <0.000 <0.000 <0.000	2117.46 2128.412 2361.138 77777 >>13500.00 16962.84 18246.77 4.262 <0.000 <0.000 <0.000	3072.942 3035.11 3167.212 77777 13340.37 17161.47 17992.49 5.855 <0.000 <0.000 <0.000	2676, 76267 2719, 42967 2705, 18333 29,29, 867 #DIV/0! 13306, 9575 17024, 1 17936, 8973 #DIV/0! #DIV/0! #DIV/0! 2,25133333 10,304	#DIV/0! 16089-32 5-20
22 6 22 6	994 773 1 688 6 646 1 353 499 866 0 552 6 044 6 868 253 244 0 549	1.884 0.046 1.908 497.826 0.966 0.048 0.919 256.8	\$ 988 0.046 1.904 496.528 0.54 0.043 0.898 249.399	2890.216 1.181 0.045 3.136 329.765 2967.887 0.494 0.042 0.482 109.334 2952.028 0.258	694, 982 2084, 946 0.96 0.947 0.647 0.653 235, 273 2117, 46 0.391 0.042 0.248 78, 83 2128, 412 0.218	3055.126 3.33% 5.045 341.438 3072.942 0.505 0.043 0.462 112.411 3035.11 0.259	0.041 0.076 1.825 5.474 0.107 0.042 0.066 <0.000 0.106 0.041 0.065 <0.000 <0.000 0.000 0.000 0.000	0.043 0.074 1.421 4.262 0.107 0.041 0.066 <0.000 0.107 0.042 0.065 <0.000 0.000 0.000 0.000	0.041 0.076 1.952 5.855 0.108 0.042 0.067 <0.000 0.107 0.042 0.062 0.062 0.060 0.000	0.041 0.064 <0.000 0.106 0.062 <0.000 0.107 0.043 0.062 <0.000 0.107 0.043 0.000 <0.000 0.111	0.043 0.065 <0.000 0.000 0.105 0.042 0.063 <0.000 0.105 0.042 0.063 0.000 0.105	0.041 0.06 <0.000 0.000 0.102 0.042 0.061 <0.000 0.103 0.42 0.062 0.062 0.000 0.000 0.000 0.000	Deta Concentratio	Gen 2-Stimulated+TiL 1-9 Gen 2-Stimulated+TiL 1-8 Gen 2-Stimulated+TiL 1-81 Gen 3-Stimulated+TiL 1-8 Gen 3-Stimulated+TiL 1-3 Gen 3-Stimulated+TiL 1-9 Gen 3-Stimulated+TiL 1-9 Gen 3-Stimulated+TiL 1-81 Gen 2-Unstimulated 1-9 Gen 2-Unstimulated 1-9 Gen 2-Unstimulated 1-9 Gen 2-Unstimulated 1-9 Gen 3-Unstimulated 1-81 Gen 3-Unstimulated 1-81 Gen 3-Unstimulated 1-9 Gen 3-Unstimulated 1-27	2967.887 2952.026 3261.251 77777 13273.546 16947.994 17571.427 <0.000 <0.000 <0.000 3.436 10.304 30.236	2117.46 2128.412 2361.138 77777 >13500.00 16962.84 18246.77 4.262 <0.000 <0.000 <0.000 0.000 <0.000	3072.942 3035.11 3167.212 7???? 13340.37 17161.47 17992.49 5.855 -0.000 <0.000 <0.000 <0.000	2676, 76267 2719, 42967 2719, 42967 2705, 18333 2929, 867 #DIV/01 13306, 9575 17024, 1 17936, 8973 #DIV/01 #DIV/01 #DIV/01 #DIV/01 225, 133333 10, 304 30, 9135	#DIV/0! 16089-32 5-20
22 6 22 6	\$45 \$45 \$45 \$45 \$498 \$4986 \$4986 \$4986 \$4986 \$44 \$4986 \$44 \$4986 \$44 \$4986 \$44 \$4986 \$44 \$4986 \$44 \$4986 \$44 \$4986 \$44 \$4986 \$4966 \$4966 \$4966 \$4966 \$4966 \$4966 \$	1.884 0.046 1.808 497.826 0.988 0.948 0.948 0.958.8 0.581 0.044 0.448 0.498 123.174	1 88 0 046 1 804 496.528 9 54 0 043 0 949 0 043 0 499 123.508	2890.216 1.185 0.048 329.765 2967.887 0.494 0.0482 109.334 2952.028 0.258 0.0216 40.262 3261.251	GOAR 654 982 2084 946 0.9 0.947 0.95 225 273 2117 46 0.348 78.83 2128.412 0.218 0.041 0.176 29.15 236 138	3055 126 3312 0 045 341 438 3072 942 0 505 0 043 0 483 112 411 3035 11 0 259 0 647 0 212 3 9 101 3167 212	0.041 0.076 1.825 5.474 0.107 0.062 <0.000 0.065 <0.000 0.065 <0.000 0.102 0.041 0.065 <0.000 0.102 0.041 0.065	0.043 0.074 1.421 4.262 0.107 0.041 0.066 <0.000 0.107 0.042 0.065 <0.000 <0.000 <1.000 0.101 0.042 0.052 <0.000 <0.000	0.041 0.076 1.952 5.855 0.108 0.042 0.067 <0.000 0.107 0.042 0.065 <0.000 0.103 0.042 0.061 0.001	0.041 0.064 <0.000 0.108 0.062 0.000 <0.000 0.107 0.043 0.063 0.063 0.000 <0.000 0.111 0.000 0.111	0.043 0.065 0.000 0.105 0.042 0.063 <0.000 0.105 0.042 0.063 <0.000 0.102 0.063 0.002 0.002 0.002 0.000	0.041 0.06 <0.000 0.102 0.042 0.061 <0.000 0.103 0.042 0.062 <0.000 0.101 0.057 <0.000 0.101 0.057	Deta IConcentrato XxII factor Add Add Add Add Add Add Add Add Add Ad	Gen 2-Stirrulated +TIL 1:9 Gen 2-Stirrulated +TIL 1:27 Gen 2-Stirrulated +TIL 1:31 Gen 3-Stirrulated +TIL 1:31 Gen 3-Stirrulated +TIL 1:31 Gen 3-Stirrulated +TIL 1:31 Gen 3-Stirrulated +TIL 1:31 Gen 2-Stirrulated +TIL 1:31 Gen 2-Unstirrulated 1:3 Gen 2-Unstirrulated 1:3 Gen 2-Unstirrulated 1:37 Gen 2-Unstirrulated 1:37 Gen 2-Unstirrulated 1:37 Gen 3-Unstirrulated 1:37	2967.887 2952.028 3261.251 77777 13273.546 16947.994 17571.427 <0.000 <0.000 <0.000 3.436 10.304 30.235 9.644	2117.46 2128.412 2361.138 77777 >13500.00 16962.84 18246.77 4.262 <0.000 <0.000 <0.000 0.854 <0.000 40.000 40.000 40.000	3072.942 3035.11 3167.212 77??? 13340.37 17161.47 17992.49 5.855 <0.000 <0.000 0.000 2.465 <0.000 31.588 92.74	EFTS FEGET 2719 42967 2719 42967 2719 42967 2719 42967 2719 4719 2719 2719 2719 2719 2719 2719 2719 2	#DIV/0! 16089-32 5-20
22 6 22 8	994 773 3.688 0.048 1.693 499.866 0.552 0.044 0.808 253.244 0.548 0.044 0.505 125.458	1:884 2:949 1:808 497.826 0.986 0.948 2:948 2:948 2:948 0.044 0.498 123.174 0.332 0.042	2.98 2.946 1.803 496.528 9.94 0.543 2.898 249.399 0.542 0.043 0.499 123.508 0.332 0.042	2890.216 5.185 0.048 329.765 2967.887 0.494 0.042 0.482 109.334 2952.028 0.258 0.216 40.262 3261.251 OVRFLW	GC48 654 982 2084 946 6.9 0.9 0.947 235 273 2117 46 0.391 0.042 0.248 0.248 0.218 0.041 0.176 29.15 236 1138 0VRFLW	3055 126 1.3319 0.045 341.438 3072.942 0.505 0.8463 112.411 3035.11 0.259 39.101 3167.212 0VRFLW	0.041 0.076 1.825 5.474 0.107 0.066 <0.000 0.041 0.065 <0.000 <0.000 0.102 0.000 0.102 0.000 0.102 0.000 0.102	0.043 0.074 1.421 4.262 0.107 0.041 0.066 <0.000 0.107 0.042 0.065 <0.000 <0.000 <0.000 <0.000 <0.000 0.101 0.042 0.059 <0.000 0.101 0.042 0.059 <0.000 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001	0.041 0.076 1.952 5.855 0.108 0.067 <0.000 0.107 0.042 0.065 <0.000 0.103 0.042 0.061 <0.000 0.103 0.042 0.061 <0.000	0.841 0.064 <0.000 <1.000 0.106 0.062 <0.000 <0.000 <0.000 0.107 0.063 <0.000 0.111 \$365 0.061 <0.000 <0.000 0.000 0.000 0.000 0.000 0.000 0.000	0.843 0.065 0.000 0.105 0.042 0.063 0.042 0.063 0.042 0.063 0.000 0.102 0.042 0.063 0.000 0.102 0.062 0.000	0.041 0.06 0.000 0.102 0.062 0.061 0.061 0.062 0.062 0.062 0.000 0.101 0.062 0.000 0.101 0.063 0.052 0.000 0.101 0.063 0.052 0.000 0.000 0.000 0.000	Contact Maria Concentration Assistance Assistance Concentration Assistance Assistanc	Gen 2-Stimulated+TiL 1-9 Gen 2-Stimulated+TiL 1-8 Gen 2-Stimulated+TiL 1-81 Gen 3-Stimulated+TiL 1-8 Gen 3-Stimulated+TiL 1-3 Gen 3-Stimulated+TiL 1-9 Gen 3-Stimulated+TiL 1-9 Gen 3-Stimulated+TiL 1-81 Gen 2-Unstimulated 1-9 Gen 2-Unstimulated 1-9 Gen 2-Unstimulated 1-9 Gen 2-Unstimulated 1-9 Gen 3-Unstimulated 1-81 Gen 3-Unstimulated 1-81 Gen 3-Unstimulated 1-9 Gen 3-Unstimulated 1-27	2967.887 2952.026 3261.251 77777 13273.546 16947.994 17571.427 <0.000 <0.000 <0.000 3.436 10.304 30.236	2117.46 2128.412 2361.138 77777 >13500.00 16962.84 18246.77 4.262 <0.000 <0.000 <0.000 0.000 <0.000	3072.942 3035.11 3167.212 7???? 13340.37 17161.47 17992.49 5.855 -0.000 <0.000 <0.000 <0.000	2676, 76267 2719, 42967 2719, 42967 2705, 18333 2929, 867 #DIV/01 13306, 9575 17024, 1 17936, 8973 #DIV/01 #DIV/01 #DIV/01 #DIV/01 225, 133333 10, 304 30, 9135	#DIV/0! 16089-32 5-20
22 6 22 6	994.773 1.688 (246 1.693) 1.698 (246 1.693) 499.866 0.952 (244 0.808 253.244 0.549 (0.549 0.945 1.25.458	3-884 0-948 1-808 497-826 0-986 0-986 0-988 2-98 0-541 0-048 123-174 0-332 0-042 0-29	1.88 2.048 1.804 496.528 9.54 0.649 249.399 0.542 0.043 0.043 0.459 123.508	2890.216 (£185) (£186) (£136) (299.765) 2997.887 (£494) (£142) (£	6048 694,982 2084,946 0,9 0,947 0,953 235,273 235,273 2117,46 0,391 0,042 0,248 78,83 2128,412 0,041 0,176 29,15 2361,138 0,041,0176 29,15 2361,138	3055 126 133 38 50 048 341 438 3072 942 0.505 0.505 0.463 112 411 0.259 0.259 0.212 39.101 3167.212 OVRFLW	0.041 0.076 1.825 5.474 0.107 0.042 0.066 <0.000 0.106 0.041 0.065 <0.000 0.102 0.000 0.000 0.102 0.000 0.102 0.000 0.102 0.000 0.102 0.000 0.102 0.000 0.102 0.0000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.0000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.00000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.	0.043 0.074 1.421 4.262 0.107 0.041 0.066 <0.000 0.107 0.042 0.065 <0.000 0.101 0.042 0.052 0.000 0.101 0.042 0.000 0.101 0.042 0.000 0.101 0.042 0.000	0.041 0.076 1.952 5.855 0.108 0.042 0.067 <0.000 0.107 0.042 0.065 <0.000 0.103 0.042 0.061 0.061 0.000 0.103 0.042 0.061 0.000	0.941 0.064 0.000 0.106 0.342 0.062 0.062 0.062 0.063 0.063 0.063 0.063 0.063 0.061 0.000 0.111 0.000 0.111 0.000 0.111 0.000 0.001 0.000 0.001	0.943 0.065 <0.000 <0.000 0.105 0.042 0.063 <0.000 0.105 0.042 0.063 <0.000 0.105 0.042 0.060 0.102 0.062 0.063 0.000 0.102 0.042 0.06	0.041 0.06 <0.000 <0.000 0.102 0.042 0.061 <0.000 <0.000 0.103 0.042 <0.000 <0.000 <0.000 0.101 0.043 0.057 <0.000 0.104 0.000 0.104 0.000 0.104 0.000 0.104 0.000 0.104 0.0000 0.00	Deta Concentratio Concentratio 400 570 Deta IConcentratio IConcentratio Concentratio 700 Deta 400 700 Deta Concentratio Concentratio Red 400 700 Deta Concentratio Red 400 700 Deta Concentratio Red Concentratio Red Concentratio	Gen 2-Stirrulated+TIL 1-9 Gen 2-Stirrulated+TIL 1-8 Gen 3-Stirrulated+TIL 1-81 Gen 3-Stirrulated+TIL 1-8 Gen 3-Stirrulated+TIL 1-8 Gen 3-Stirrulated+TIL 1-9 Gen 3-Stirrulated+TIL 1-8 Gen 2-Unstirrulated+TIL 1-81 Gen 3-Unstirrulated+TIL 1-81	2967.887 2952.028 3261.251 77777 13273.546 16947.994 17571.427 <.0.000 3.432 6.0000 3.432 10.300 3.0235 9.644 <0.000	2117.46 2128.412 2361.138 77777 >13500.00 186962.84 18246.77 4.262 <0.000 <0.000	3075.942 3035.11 3167.212 77.777 17.161.47 17.992.49 5.855 <0.000 <0.000 0.000 31.588 92.74 <0.000	EFIS 76267 2719 42967 2705 18333 2929 867 #DIV/O! 13306.9575 17024 1 17936.8973 #DIV/O! #DIV/O! 225133333 10.304 30.9135 35.4743333 #DIV/O!	#DIV/0! 16089-32 5-20
22.6	994 773 1888 2 G46 1893 499 866 2 0542 2 8 044 2 808 2 53 244 0 549 0 505 125 458 0 334 0 291 61 826	0.548 0.548 0.968 0.968 0.968 0.548 0.549 0.541 0.044 0.498 123.174 0.332 0.042 0.29 61.537	9.544 9.543 9.543 9.543 9.542 0.543 2.696 249.399 0.542 0.543 0.543 0.043 0.043 0.043 0.043 0.043 0.042 0.042 0.042 0.042	2890.216 5.185 0.048 329.765 2967.887 0.494 0.042 0.482 109.334 2952.028 0.258 0.216 40.262 3261.251 OVRFLW	GC48 654 982 2084 946 6.9 0.9 0.947 235 273 2117 46 0.391 0.042 0.248 0.248 0.218 0.041 0.176 29.15 236 1138 0VRFLW	3055 126 3339 5 0445 341.438 3072.942 0.505 0.8463 112.411 3035.11 0.259 39.101 3167.212 0VRFLW	0.041 0.074 1.825 5.474 0.107 0.042 0.066 <0.000 0.106 0.041 0.065 <0.000 0.102 0.041 0.065 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.001 0.045 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.001 0.045 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 0.0000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.0000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.0000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.0000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.0000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.0000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.0000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.0000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0	0.043 0.074 1.421 4.262 0.107 0.041 0.066 <0.000 0.107 0.065 <0.000 0.101 0.065 <0.000 0.101 0.042 0.059 <0.000 <0.000 0.101 0.062 0.000 <0.000 0.101 0.062 0.000	0.041 0.076 1.952 5.855 0.108 0.042 0.067 -0.000 0.107 0.045 -0.000 -0.000 0.103 0.042 0.061 -0.000 -0.000 0.103 0.042 0.061 -0.000 -0.000 0.103 0.042 0.061 -0.000 -0.000 0.000 -0.000 0.000 -0.0000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.0000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.0000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.0000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.0000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.0000 -0.000 -0	0.841 0.064 <0.000 <1.000 0.106 0.062 <0.000 <0.000 <0.000 0.107 0.063 <0.000 0.111 \$365 0.061 <0.000 <0.000 0.000 0.000 0.000 0.000 0.000 0.000	0.943 0.065 0.000 0.105 0.042 0.063 0.105 0.015 0.042 0.063 0.102 0.060 0.102 0.062 0.000 0.102 0.062 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000	0.041 0.06 <0.000 <0.000 0.102 0.042 0.061 <0.000 0.103 0.402 0.062 <0.000 <0.000 0.101 0.043 0.052 <0.000 <0.000 0.101 0.003 0.002 <0.000 <0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000	Contact Maria Concentration Assistance Assistance Concentration Assistance Assistanc	Gen 2 Stirrulated + Til. 1.9 Gen 2 Stirrulated + Til. 1.27 Gen 2 Stirrulated + Til. 1.18 Gen 3 Stirrulated + Til. 1.18 Gen 3 Stirrulated + Til. 1.19 Gen 3 Stirrulated + Til. 1.19 Gen 3 Stirrulated + Til. 1.19 Gen 2 Stirrulated + Til. 1.19 Gen 2 Unstirrulated + Til. 1.27 Gen 2 Unstirrulated + Til. 1.27 Gen 2 Unstirrulated + Til. 1.27 Gen 3 Unstirrulated + Til. 1.3 Gen 3 Unstirrulated + Til. 1.3 Gen 3 Unstirrulated + Til. 1.3 Gen 2 Unstirrulated + Til. 1.3 Gen 3 Unstirrulated + Til. 1.3 Gen	2967.887 2952.026 3261.251 77727 13273.546 1997.994 17571.427 5.474 <0.000 <0.000 3.432 10.304 30.236 9.644 <0.000	2117.46 2128.412 2361.138 77777 >13500.00 16962.84 18246.77 4.262 <0.000 <0.000 <0.000 4.030 <0.000 4.030 <0.000 <0.000 4.030 <0.000 <0.000	3072-942 3035-11 3035-11 3167-212 77777 13240-37 17161-47 17992-49 5.855 00.000 <0.000 2.465 0.000 31.588 92.74 <0.000	を守ってを2年7 2719 4299 7 2719 4299 7 2705 18333 2929 867 神DIV/01 13306 9575 17024 1 17936 8973 5 197 #DIV/01 #DIV/01 #DIV/01 225133333 10.304 30.9135 35.4743333 #DIV/01 #DIV/01 #DIV/01 #DIV/01 #DIV/01 #DIV/01 #DIV/01 #DIV/01 #DIV/01 #DIV/01 #DIV/01 #DIV/01 #DIV/01 #DIV/01 #DIV/01 #DIV/01	#DIV/0! 16089-32 5-20
22 6	994.773 1.688 (246 1.693) 1.698 (246 1.693) 499.866 0.952 (244 0.808 253.244 0.549 (0.549 0.945 1.25.458	3-884 0-948 1-808 497-826 0-986 0-986 0-988 2-98 0-541 0-048 123-174 0-332 0-042 0-29	1.88 2.048 1.804 496.528 9.54 0.649 249.399 0.542 0.043 0.043 0.459 123.508	2890.216 () (85) () 0.248 () 1340 329.765 2997.887 () 494 () 0.249 () 482 () 0.258 () 0.258 () 0.258 () 0.262 () 0.258 () 0.262 () 0.278 ()	GC48 654.982 2084.946 9.6 9.6 9.6 9.6 9.6 9.6 9.6 9.	3055 126 33338 0.048 341.438 3072.942 0.505 0.043 0.483 112.411 3035 11 0.259 8.047 0.212 3167.212 0.7777 77777	0.041 0.076 1.825 5.474 0.107 0.042 0.066 <0.000 <0.000 0.106 0.041 0.065 <0.000 <0.000 0.102 0.041 0.065 <0.000 0.112 0.041 0.065 <0.000 0.112 0.041 0.065 <0.000	0.043 0.074 1.421 4.262 0.107 0.041 0.066 <0.000 <0.000 0.107 0.042 0.055 <0.000 <0.000 0.101 0.045 0.059 <0.000 0.110 0.041 0.069 0.061 0.061	0.041 0.076 1.952 5.855 0.108 0.042 0.067 <0.000 <0.000 0.107 0.042 0.065 <0.000 <0.000 0.103 0.042 0.061 <0.000 0.103 0.042 0.061 <0.000 0.113 0.042 0.061 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.00000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.00000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.00000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.00000 0.00000 0.00000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.00	0.041 0.064 0.000 0.105 3.043 0.062 0.000 0.107 3.043 0.000 0.107 3.043 0.000 0.107 0.000 0.103 0.001 0.000 0.103 0.001 0.000 0.103 0.002 0.000	0.943 0.065 <0.000 <1.000 0.105 0.042 0.063 <0.000 <1.005 0.042 0.063 0.000 <0.000 0.102 0.063 <0.000 0.102 0.064 0.000 0.102 0.064 0.000 0.102 0.064 0.000 0.102 0.064 0.000 0.102 0.064	0.041 0.06 <0.000 0.102 0.042 0.061 <0.000 0.103 0.042 0.062 0.000 <0.000 0.101 0.057 <0.000 0.104 0.005 0.104 0.005 0.104 0.000 0.104 0.000 0.104 0.000 0.104 0.000 0.104 0.000 0.000 0.104 0.000 0.104 0.0000 0.0000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.000000	Contact Maria Concentration Assistance Assistance Concentration Assistance Assistanc	Gen 2 Stirrulated + Til. 1 : 9 Gen 2 Stirrulated + Til. 1 : 127 Gen 2 Stirrulated + Til. 1 : 13 Gen 3 - Stirrulated + Til. 1 : 13 Gen 3 - Stirrulated + Til. 1 : 13 Gen 3 - Stirrulated + Til. 1 : 14 Gen 3 - Stirrulated + Til. 1 : 127 Gen 3 - Stirrulated + Til. 1 : 127 Gen 3 - Stirrulated + Til. 1 : 181 Gen 2 - Unstirulated 1 : 13 Gen 2 - Unstirulated 1 : 13 Gen 3 - Unstirulated 1 : 14 Gen 3 - Unstirulated 1 : 19 Gen 3 - Unstirulated 1 : 19 Gen 3 - Unstirulated 1 : 13 Gen 3 - Unstirulated 1 : 13 Gen 3 - Unstirulated 1 : 13 Gen 2 - Unstirulated 1 : 13 Gen 3 - Unstirulated 1 : 13	2967.887 2952.026 3261.251 77777 13273.546 16947.99 17571.427 <0.000 <0.000 <0.000 3.436 10.304 20.236 9.644 <0.000 <0.000	2117.46 2 2128.412 2361.138 77777 >13500.00 16962.84 18246.77 4.262 <0.000 <0.000 <0.000 4.039 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000	3075-942 3035-11 3167-212 77777 13340-37 17161-47 17992-49 50.000 50.000 2.465 50.000 2.465 50.000 2.465 50.000 50.000 50.000 50.000 50.000 50.000 50.000	EFIS 76267 2719 42967 2705 18333 2929 867 #DIV/O! 13306.9575 17024 1 17936.8973 #DIV/O! #DIV/O! 225133333 10.304 30.9135 35.4743333 #DIV/O!	#DIV/0! 16089-32 5-20
22.6	994,773 \$698 9.048 9.953 9.944 9.868 253,244 0.544 0.505 0.605 0.605 0.605 0.605 0.605 0.605 0.605 0.605 0.605 0.605 0.605 0.605 0.602 0.602 0.602 0.602 0.602 0.602 0.603 0.603 0.605	0.986 0.986 0.986 0.986 0.986 0.986 0.988 0.981 0.541 0.044 0.488 123.174 0.332 0.042 0.29 61.537	2.648 2.646 1.804 496.528 9.54 0.043 0.698 249.399 0.542 0.043 0.439 123.508 0.332 0.042 0.042 0.024	2890.216 () (85) () 0.248 () 1340 329.765 299.7687 () 494 () 0.249 () 482 () 0.258 () 0.258 () 0.258 () 0.262 () 0.258 () 0.262 () 0.278 ()	GC48 654.982 2084.946 9.6 9.6 9.6 9.6 9.6 9.6 9.6 9.	3055 126 33338 0.048 341.438 3072.942 0.505 0.043 0.483 112.411 3035 11 0.259 8.047 0.212 3167.212 0.7777 77777	0.041 0.076 1.825 5.474 0.107 0.042 0.066 0.000 0.106 0.041 0.085 0.000 0.102 0.041 0.085 0.000 0.1102 0.041 0.085 0.000 0.114 0.085 0.000 0.114 0.085 0.000 0.114 0.085	0.043 0.074 1.421 4.262 0.107 0.041 0.066 <0.000 0.107 0.042 0.000 0.107 0.042 0.000 0.101 0.042 0.059 <0.000 0.101 0.042 0.059 0.065 0.065 0.065 0.065	0.041 0.076 1.952 5.855 0.108 0.042 0.067 0.000 0.107 0.042 0.065 0.000 0.103 0.042 0.061 0.000 0.113 0.042 0.022 0.022 0.022 0.022 0.023	0.041 0.064 -0.000 -0.000 0.106 0.062 -0.000 0.107 0.043 -0.000 -0.000 0.001 -0.000 0.001 -0.000 0.001 -0.000 0.001 -0.000 0.001 -0.000 0.001 -0.000 0.001 -0.000 0.001 -0.000 0.0000 0.00	0.043 0.065 0.000	0.041 0.06 0.000 0.000 0.002 0.042 0.081 0.000 0.103 0.042 0.082 0.082 0.000 0.101 0.000 0.101 0.000 0.104 0.000 0.104 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.00000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.00000 0.00000 0.00000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.00000 0.00000 0.0000 0.0000 0.0000 0.0000 0.0000 0.00000 0.0	Debt Concentration of the Conc	Gen 2 Stirrulated + Til. 1.9 Gen 2 Stirrulated + Til. 1.27 Gen 2 Stirrulated + Til. 1.18 Gen 3 Stirrulated + Til. 1.18 Gen 3 Stirrulated + Til. 1.19 Gen 3 Stirrulated + Til. 1.19 Gen 3 Stirrulated + Til. 1.19 Gen 2 Stirrulated + Til. 1.19 Gen 2 Unstirrulated + Til. 1.27 Gen 2 Unstirrulated + Til. 1.27 Gen 2 Unstirrulated + Til. 1.27 Gen 3 Unstirrulated + Til. 1.3 Gen 3 Unstirrulated + Til. 1.3 Gen 3 Unstirrulated + Til. 1.3 Gen 2 Unstirrulated + Til. 1.3 Gen 3 Unstirrulated + Til. 1.3 Gen	2967.887 2952.026 3261.251 77727 13273.546 1997.994 17571.427 5.474 <0.000 <0.000 3.432 10.304 30.236 9.644 <0.000	2117.46 2128.412 2361.138 77777 >13500.00 16962.84 18246.77 4.262 <0.000 <0.000 <0.000 4.030 <0.000 4.030 <0.000 <0.000 4.030 <0.000 <0.000	3072-942 3035-11 3035-11 3167-212 77777 13240-37 17161-47 17992-49 5.855 00.000 <0.000 2.465 0.000 31.588 92.74 <0.000	を呼らずを267 2719 42967 2705 18333 2929 867 #D1V/01 13306 9575 17024 1 17936 8873 5 1977 #D1V/01 #D1V/01 2 25133333 10.304 35 47743333 #D1V/01 #D1V/01 #D1V/01	#DIVIGI 16089-32 5-20 19-74
22.6	5-15 5-15 3-688 6-048 17533 459.866 0.552 0.544 0.569 0.	0.986 0.988 0.988 0.988 0.988 0.919 256.8 0.541 0.044 0.488 123.174 0.332 0.042 0.29 61.537	\$ 688 \$ 646 \$ 594 496 528 \$ 594 \$ 0.643 \$ 6898 249 399 \$ 542 \$ 0.043 \$ 0.459 123 508 \$ 0.332 \$ 0.242 \$ 0.29 \$ 61.594	2890.216 () (85) () 0.248 () 1340 329.765 299.7687 () 494 () 0.249 () 482 () 0.258 () 0.258 () 0.258 () 0.262 () 0.258 () 0.262 () 0.278 ()	GC48 654.982 2084.946 9.6 9.6 9.6 9.6 9.6 9.6 9.6 9.	3055 126 1333 141.438 341.438 3072.942 0.505 0.043 0.5463 112.411 3035.11 0.259 0.212 39.101 3167.212 0.VRFLW	0.041 0.076 1.825 5.474 0.107 0.096 0.000 <0.000 0.106 0.041 0.065 <0.000 0.102 0.41 0.065 <0.000 0.102 0.41 0.061 1.145 0.3435 0.114 0.041	0.043 0.074 1.421 1.426 0.107 0.041 0.066 0.000 0.107 0.042 0.000 0.101 0.042 0.000 0.101 0.041 0.069 0.285 0.080	0.041 0.076 1.952 5.855 0.108 0.042 0.067 0.000 0.107 0.042 0.065 0.000 0.103 0.042 0.061 0.000 0.00	0.041 0.064 <0.000 <0.000 0.106 0.062 0.000 0.107 0.003 0.003 0.003 0.000 0.111 0.000 0.101 0.000 0.101 0.000 0.101 0.000 0.000 0.101 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000	0.043 0.065 0.000 0.000 0.105 0.042 0.063 0.063 0.063 0.063 0.000 0.102 0.042 0.066 0.000 0.102 0.042 0.061 0.000 0.102 0.042 0.061 0.000 0.102 0.042 0.061 0.000 0.103 0.042 0.061 0.000 0.103 0.042	0.041 0.06 0.000 0.000 0.000 0.002 0.042 0.081 0.000 0.103 0.042 0.082 0.082 0.000 0.101 0.000 0.101 0.000 0.101 0.000 0.101 0.000 0.101 0.000 0.101 0.000 0.101 0.000 0.101 0.000 0.101 0.000 0.101 0.000 0.101 0.0000 0.000	Data Data Grandman M And Indoor A	Gen 2 Stirrulated + Til. 1 : 9 Gen 2 Stirrulated + Til. 1 : 127 Gen 2 Stirrulated + Til. 1 : 13 Gen 3 - Stirrulated + Til. 1 : 13 Gen 3 - Stirrulated + Til. 1 : 13 Gen 3 - Stirrulated + Til. 1 : 14 Gen 3 - Stirrulated + Til. 1 : 127 Gen 3 - Stirrulated + Til. 1 : 127 Gen 3 - Stirrulated + Til. 1 : 181 Gen 2 - Unstirulated 1 : 13 Gen 2 - Unstirulated 1 : 13 Gen 3 - Unstirulated 1 : 14 Gen 3 - Unstirulated 1 : 19 Gen 3 - Unstirulated 1 : 19 Gen 3 - Unstirulated 1 : 13 Gen 3 - Unstirulated 1 : 13 Gen 3 - Unstirulated 1 : 13 Gen 2 - Unstirulated 1 : 13 Gen 3 - Unstirulated 1 : 13	2967.887 2952.026 3261.251 77777 13273.546 16947.99 17571.427 <0.000 <0.000 <0.000 3.436 10.304 20.236 9.644 <0.000 <0.000	2117.46 2 2128.412 2361.138 77777 >13500.00 16962.84 18246.77 4.262 <0.000 <0.000 <0.000 4.039 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000	3075-942 3035-11 3167-212 77777 13340-37 17161-47 17992-49 50.000 50.000 2.465 50.000 2.465 50.000 2.465 50.000 50.000 50.000 50.000 50.000 50.000 50.000	を呼らずを267 2719 42967 2705 18333 2929 867 #D1V/01 13306 9575 17024 1 17936 8873 5 1977 #D1V/01 #D1V/01 2 25133333 10.304 35 47743333 #D1V/01 #D1V/01 #D1V/01	#DIVIGI 16089-32 5-20 19-74
22.6	994 773 1,668 9,048 1,653 499,866 0,552 0,044 0,862 253,244 0,545 0,044 0,545 0,044 0,406 125,458 0,305 0,305	1.884 0.646 1.808 497.626 0.988 0.948 0.948 0.948 0.948 0.488 0.488 0.488 0.488 0.488 0.49	\$ 688 6 646 1 904 496 528 0 943 0 943 0 949 0 942 0 942 0 942 0 123 508 0 123 508 0 123 508 0 124 6 1 594	2890.216 (F.185) (D.248) (E.134) (E.13	6048 694982 2084946 0.6 0.6 0.8 0.8 0.8 0.8 0.3 235273 2217746 0.341 0.042 0.248 0.248 0.241 0.041 0.176 29.15 2361138 0.9471.W	3055 126 1339 0.048 341438 341438 341438 3072 942 0.505 0.043 112 411 3035 11 0.259 0.212 0.212 0.212 77777 77777 77777 77777	0.041 0.078 1.825 5.474 0.062 0.060 <0.000 0.106 0.041 0.065 0.000 <0.000 0.106 0.001 0.001 0.001 0.001 0.001 1.006 0.000 0.102 0.001 0.001 1.006 0.000 1.102 0.001 1.006 0.000 0.102 0.001 1.006 0.000 0.102 0.001 0.00	0.043 0.074 1.421 4.262 0.107 0.041 0.066 <0.000 <0.000 0.107 0.042 0.065 0.000 0.101 0.042 0.059 0.000 0.101 0.069 0.000 0.11 0.069 0.265 0.854 0.104 0.063	0.041 0.076 1.952 5.855 0.042 0.067 <0.000 0.107 0.042 0.065 0.000 0.107 0.042 0.061 0.000 0.107 0.042 0.061 0.000 0.107 0.042 0.000 0.107 0.042 0.000	0.941 0.064 0.000 0.106 0.000 0.108 0.043 0.062 0.000 0.107 0.000 0.107 0.001 0.001 0.001 0.001 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000	0.043 0.065 0.000 0.105 0.042 0.060 0.105 0.042 0.063 0.000 0.105 0.042 0.063 0.000 0.102 0.062 0.060 0.102 0.060 0.102 0.061 0.060 0.102 0.061 0.060 0.000 0.102 0.062	0.041 0.06 <0.000 0.102 0.042 0.081 0.000 0.102 0.042 0.081 0.000 0.103 0.042 0.082 0.000 0.101 0.003 0.057 0.000 0.104 0.000 0.104 0.000 0.104 0.000 0.104 0.001 0.104 0.001 0.104 0.005 0.104 0.005 0.104 0.005 0.104 0.005 0.104 0.005 0.104 0.005 0.005 0.104 0.005 0.005 0.005	Data Data Grandman M And Indoor A	Gen 2 Stirrulated + Til. 1 : 9 Gen 2 Stirrulated + Til. 1 : 127 Gen 2 Stirrulated + Til. 1 : 13 Gen 3 - Stirrulated + Til. 1 : 13 Gen 3 - Stirrulated + Til. 1 : 13 Gen 3 - Stirrulated + Til. 1 : 14 Gen 3 - Stirrulated + Til. 1 : 127 Gen 3 - Stirrulated + Til. 1 : 127 Gen 3 - Stirrulated + Til. 1 : 181 Gen 2 - Unstirulated 1 : 13 Gen 2 - Unstirulated 1 : 13 Gen 3 - Unstirulated 1 : 14 Gen 3 - Unstirulated 1 : 19 Gen 3 - Unstirulated 1 : 19 Gen 3 - Unstirulated 1 : 13 Gen 3 - Unstirulated 1 : 13 Gen 3 - Unstirulated 1 : 13 Gen 2 - Unstirulated 1 : 13 Gen 3 - Unstirulated 1 : 13	2967.887 2952.026 3261.251 77777 13273.546 16947.99 17571.427 <0.000 <0.000 <0.000 3.436 10.304 20.236 9.644 <0.000 <0.000	2117.46 2 2128.412 2361.138 77777 >13500.00 16962.84 18246.77 4.262 <0.000 <0.000 <0.000 4.039 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000	3075-942 3035-11 3167-212 77777 13340-37 17161-47 17992-49 50.000 50.000 2.465 50.000 2.465 50.000 2.465 50.000 50.000 50.000 50.000 50.000 50.000 50.000	を呼らずを267 2719 42967 2705 18333 2929 867 #D1V/01 13306 9575 17024 1 17936 8873 5 1977 #D1V/01 #D1V/01 2 25133333 10.304 35 47743333 #D1V/01 #D1V/01 #D1V/01	#DIVIGI 16089-32 5-20 19-74
22.6	994 773 994 773 995 974 775 975 975 975 975 975 975 975 975 975	. 888 . 0 de . 0 de . 1 008 . 497 826 . 0 968 . 0 548 . 0 919 . 256 8 . 0 541 . 0 044 . 0 104 . 0 1	\$88 6.046 7.003 496.528 5.94 0.043 2.898 249.399 0.542 0.043 0.499 123.508 0.332 0.042 0.29 61.594 0.224 0.42 0.42 0.29 61.594	2890.216 5.181 5.181 5.181 5.181 5.184 5.184 5.186 5.2967.887 6.494 6.49	\$0.948 \$8.88 \$8.88 694, 982 2054, 946 6.9 0.947 205, 273 22117, 46 0.041 0.041 0.041 0.178 29.15 20218 0.041 0.178 29.15 2018 0.041 0.178 29.15 2018 0.041 0.178 29.15 2018 0.041 0.178 29.15 2018 0.041	3055 126 13348 3014 348 341 438 3072 842 0.505 0.505 0.463 112 411 3035 11 0.259 8.647 0.212 39.101 3167 212 0VRFLW	0.041 0.076 1.825 5.474 0.107 0.042 0.066 <0.000 0.106 0.041 0.065 <0.000 0.106 0.041 0.065 <0.000 0.102 0.041 0.08 0.000 0.102 0.041 0.08 0.000 1.102 0.041 0.08 0.000 1.102 0.041 0.08 0.000 0.102 0.041 0.08 0.000 0.102 0.041 0.08 0.000 0.102 0.041 0.08 0.000 0.102 0.041 0.08 0.000 0.102 0.041 0.08 0.000 0.102 0.041 0.08 0.000 0.102 0.041 0.08 0.000 0.102 0.001 0.000 0.114 0.041 0.041 0.041 0.041 0.041 0.05 0.000 0.114 0.041 0.041 0.041 0.041 0.041 0.041 0.05 0.000 0.114 0.041 0.041 0.041 0.041 0.041 0.041 0.041 0.05 0.000 0.114 0.041	0.043	0.041 0.076 1.952 5.855 0.108 0.042 0.067 <0.000 0.107 0.042 0.065 <0.000 0.103 0.042 0.061 <0.000 0.113 0.042 0.072 0.082 0.072 0.082 0.082 0.090 0.107 0.042 0.082 0.082 0.090 0.114	0.041	0.043 0.065 <0.000 0.105 0.042 0.063 0.000 0.105 0.042 0.063 0.063 0.063 0.060 0.102 0.063 0.063 0.060 0.102 0.061 0.062 0.061 0.062 0.061 0.062 0.061 0.062 0.061 0.062	0.041 0.08 <0.000 0.102 0.042 0.061 0.000 0.103 0.042 0.061 0.000 0.103 0.042 0.061 0.000 0.104 0.000 0.104 0.000 0.104 0.000 0.104 0.000 0.104 0.001 0.001 0.001 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000	Deba (Canner and a control of a	Gen 2-Stirrulated+TIL 1:9 Gen 2-Stirrulated+TIL 1:81 Gen 3-Stirrulated+TIL 1:81 Gen 3-Stirrulated+TIL 1:81 Gen 3-Stirrulated+TIL 1:9 Gen 3-Stirrulated+TIL 1:9 Gen 3-Stirrulated+TIL 1:9 Gen 2-Unstirrulated 1:127 Gen 2-Unstirrulated 1:3 Gen 2-Unstirrulated 1:3 Gen 2-Unstirrulated 1:3 Gen 2-Unstirrulated 1:27 Gen 2-Unstirrulated 1:27 Gen 2-Unstirrulated 1:27 Gen 3-Unstirrulated 1:3 Gen 3-Unstirrulated 1:3 Gen 3-Unstirrulated 1:3 Gen 3-Unstirrulated 1:9 Gen 3-Unstirrulated 1:9 Gen 3-Unstirrulated 1:9 Gen 3-Media Control Stirrulated 1:3 Gen 3-Media Control Stirrulated 1:3 Gen 3-Media Control Stirrulated 1:3 Gen 3-Media Control Stirrulated 1:9 Gen 3-Media Control Stirrulated 1:9 Gen 3-Media Control Stirrulated 1:9	2967.887 2952.025 3261.251 77727 13273.546 16947.99 1.7577.427 <0.000 <0.000 0.000 3.435 10.304 0.000 <0.000 <0.000	2117.46 2 2361.138 77777 > 13500.00 16962.84 18246.77 4.262 <0.000 <0.000 4.039 <0.000 4.039 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000	3072-942 3035-11 3167-212 77777 13340-37 17161-47 17992-49 <0.000 <0.000 <0.000 2.465 <0.000 2.465 <0.000 31.588 92.74 <0.000 <0.000	e7f9 7f2e7 27f9 42e97 27f9 42e97 27g7 4f2e7 27g7 4f2e7 1330e 9f75 17g24 1 17g36 8f73 5 197 #D1V/0! #D1V/0! #D1V/0! #D1V/0! #D1V/0! #D1V/0! #D1V/0! #D1V/0!	#DIVIGI 16089-32 5-20 19-74
22.6	994 773 (1989) 994 773 (1989) 994 773 (1989) 995 995 995 995 995 995 995 995 995 9	1884 2 946 2 946 1898 497 826 0 998 2 949 2 56.8 0 944 0 498 123.174 0 332 0 042 0 29 61.537 0 292 0 293 0 179 29.82	\$88 6:046 1:004 496 528 5:54 6:043 6:696 249,399 6:542 6:043 6:349 123,508 6:342 6:29 6:1,594 0:224 0:224 0:24 0:24 0:342 0:342 0:342 0:342 0:29 0:342 0:342 0:342 0:342 0:342 0:342 0:342 0:343 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	2890.216 \$1,181 \$1,181 \$1,245 \$1,141	\$046 \$888 \$888 \$654 982 2084 946 25 0.261 235 273 235 273 23117.46 0.391 0.248 7.248 7.248 7.248 7.248 7.279 7.2797 7.279	3055 126 1339 5044 331 341 438 3072 642 5 505 0 463 112 411 10 259 5 6047 0 212 39 101 3167 212 0 VFFW 77777 77777 77777 77777 77777 77777 7777	0.041	0.043	0,041 0,076 1,952 5,855 0,108 0,042 0,067 0,000 0,107 0,042 0,068 0,000 0,103 0,042 0,061 0,000	0.041	0.043 0.065 -0.000 -0.000 0.105 0.042 0.000 0.105 0.042 0.003 -0.000 0.105 0.042 0.003 0.000 0.102 0.000	0.041 0.061 0.068 0.060	Debt Concentration of the Conc	Gen 2 Stirrulated +TIL 1.9 Gen 2 Stirrulated +TIL 1.81 Gen 3 Stirrulated +TIL 1.81 Gen 3 Stirrulated +TIL 1.9 Gen 3 Stirrulated +TIL 1.81 Gen 2-Unstirrulated +TIL 1.81 Gen 2-Unstirrulated 1.9 Gen 2-Unstirrulated 1.9 Gen 2-Unstirrulated 1.9 Gen 3 Stirrulated 1.9	2967.887 2952.025 3261.251 77777 13273.546 15947.992 17571.427 <0.000 <0.000 <0.000 3.432 10.304 30.235 9.644 <0.000 <0.000	2117.46 3 2128.412 2361.138 77777 >13500.00 18962.84 18948.77 4.262 <0.000 <0.000 4.039 <0.000 4.039 <0.000 <0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000	3072-942 3035-11 3167-212 77777 13340-37 17161-47 17992-49 5.855 <0.000 <0.000 2.465 <0.000 31.588 92.74 <0.000 <0.000	erro Fozer 2719 42967 2705 1833 2719 42967 2705 18333 2719 4206 2875 17024 1 17306 9575 17024 1 17936 8973 10.204 20.9135 35.4743333 10.204 (申し)(1)(1)(1)(1)(1)(1)(1)(1)(1)(1)(1)(1)(1)	#D)V/0! 16099-32 5-20 19-74 0.00
22.6	994 773 994 773 995 974 775 975 975 975 975 975 975 975 975 975	. 888 . 0 de . 0 de . 1 008 . 497 826 . 0 968 . 0 548 . 0 919 . 256 8 . 0 541 . 0 044 . 0 104 . 0 1	\$88 6.046 7.003 496.528 5.94 0.043 2.898 249.399 0.542 0.043 0.499 123.508 0.332 0.042 0.29 61.594 0.224 0.42 0.42 0.29 61.594	2890 216 1 191 1 1	GO45 654 825 2004 946 6 4 825 2004 946 6 4 825 2004 946 6 4 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8	3055 126 133 26 3014 33 3017 242 2 5 506 2 504 3 112 411 3035 11 3035 11 304 21 30 101 3167 212 30 101 3167 212 3167	0.041	0.043	0.041	0.041	0.043	0.041	Deba (Canner and a control of a	Gen 2-Stirrulated+TIL 1:9 Gen 2-Stirrulated+TIL 1:81 Gen 3-Stirrulated+TIL 1:81 Gen 3-Stirrulated+TIL 1:81 Gen 3-Stirrulated+TIL 1:9 Gen 3-Stirrulated+TIL 1:9 Gen 3-Stirrulated+TIL 1:9 Gen 2-Unstirrulated 1:127 Gen 2-Unstirrulated 1:3 Gen 2-Unstirrulated 1:3 Gen 2-Unstirrulated 1:3 Gen 2-Unstirrulated 1:27 Gen 2-Unstirrulated 1:27 Gen 2-Unstirrulated 1:27 Gen 3-Unstirrulated 1:3 Gen 3-Unstirrulated 1:3 Gen 3-Unstirrulated 1:3 Gen 3-Unstirrulated 1:9 Gen 3-Unstirrulated 1:9 Gen 3-Unstirrulated 1:9 Gen 3-Media Control Stirrulated 1:3 Gen 3-Media Control Stirrulated 1:3 Gen 3-Media Control Stirrulated 1:3 Gen 3-Media Control Stirrulated 1:9 Gen 3-Media Control Stirrulated 1:9 Gen 3-Media Control Stirrulated 1:9	2967.887 2952.025 3261.251 77727 13273.546 16947.99 1.7577.427 <0.000 <0.000 0.000 3.435 10.304 0.000 <0.000 <0.000	2117.46 2 2361.138 77777 > 13500.00 16962.84 18246.77 4.262 <0.000 <0.000 4.039 <0.000 4.039 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000	3072-942 3035-11 3167-212 77777 13340-37 17161-47 17992-49 <0.000 <0.000 <0.000 2.465 <0.000 2.465 <0.000 31.588 92.74 <0.000 <0.000	e7f9 7f2e7 27f9 42e97 27f9 42e97 27g7 4f2e7 27g7 4f2e7 1330e 9f75 17g24 1 17g36 8f73 5 197 #D1V/0! #D1V/0! #D1V/0! #D1V/0! #D1V/0! #D1V/0! #D1V/0! #D1V/0!	#D)V/0! 16099-32 5-20 19-74 0.00
22.6	994 773 984 773 984 773 984 773 495 866 9949 99999 99	3884 0.04e 3.04e 3.04e 5.04e 5.04e 5.04e 5.04e 5.04e 123.174 0.332 0.22 0.22 0.26 0.29 0.29 0.29 0.29 0.29 0.29 0.29 0.29	0.042 0.049 0.049 0.043 0.043 0.043 0.043 0.043 0.043 0.043 0.043 0.042 0.042 0.042 0.042 0.042 0.042 0.042 0.042 0.043 0.042 0.042 0.043 0.042 0.042 0.043 0.042 0.042 0.043 0.042 0.043 0.043 0.042 0.043	2800.216 (101)	GO45 84 88 88 88 88 88 88 88 88 88 88 88 88	3055126 1 3398 1	0.041	0.043	0.041	0.041	0.043	0.041	Deba (Canner and a control of a	Gen 2-Stirrulated+TIL 1:9 Gen 3-Stirrulated+TIL 1:81 Gen 3-Stirrulated+TIL 1:81 Gen 3-Stirrulated+TIL 1:81 Gen 3-Stirrulated+TIL 1:9 Gen 3-Stirrulated+TIL 1:9 Gen 3-Stirrulated+TIL 1:9 Gen 2-Unstirrulated+TIL 1:81 Gen 2-Unstirrulated+1:9 Gen 2-Unstirrulated+1:3 Gen 2-Unstirrulated+1:3 Gen 2-Unstirrulated+1:3 Gen 3-Unstirrulated+1:3 Gen 3-Unstirrulated+1:4 Gen 3-Unstirrulated+1:9 Gen 3-Unstirrulated+1:9 Gen 3-Unstirrulated+1:9 Gen 3-Media Control Stirrulated+1:3 Gen 3-Media Control Stirrulated+1:9 Gen 3-Media Control Stirrulated+1:9 Gen 3-Media Control Stirrulated+1:9 Gen 3-Media Control Stirrulated+1:9 Gen 2-Media Control Stirrulated+1:9 Gen 2-Media Control Stirrulated+1:9 Gen 2-Media Control Stirrulated+1:9 Gen 2-Media Control Unstirrulated+1:9 Gen 2-Media Control Unstirrulated+1:9	2967.887 2952.025 3261.251 77727 13272.546 16947.994 17577.427 <0.000 <0.000 3.432 10.304 0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000	2 117.4 d 2 2 2 2 1 1 1 2 2 2 2 1 1 1 2 2 2 2 1 1 1 2 2 2 2 1 1 1 2 2 2 2 1 1 1 2 2 2 2 1 1 2 2 2 2 1 1 2 2 2 2 1 2	3072 942 3033 11 3167 212 77277 17461 47 17461 47 17461 47 17592 49 40 400 400 400 400 400 400 400 400 4	e7f9 7f2e7 27f9 42e97 27f9 42e97 27g7 4f2e7 27g7 4f2e7 1330e 9f75 17g24 1 17g36 8f73 5 197 #D1V/0! #D1V/0! #D1V/0! #D1V/0! #D1V/0! #D1V/0! #D1V/0! #D1V/0!	#D)V/0! 16099-32 5-20 19-74 0.00
22 6 22 6	984 773 984 773 984 773 985 984 495 686 989 98 989 98 9	8854 Supplemental	1. 684 0. 046 1. 690 1. 690	2800 216 (1/6) (1/	GC448	3055 126 333 343 343 343 344 328 3075 342 347 347 347 347 347 347 347 347 347 347	0.041	0.043	0.041	0.041	0.043	0.041	Deba (Canner and a control of a	Gen 2-Stirrulated+TIL 1:9 Gen 2-Stirrulated+TIL 1:81 Gen 3-Stirrulated+TIL 1:81 Gen 3-Stirrulated+TIL 1:81 Gen 3-Stirrulated+TIL 1:9 Gen 3-Stirrulated+TIL 1:9 Gen 3-Stirrulated+TIL 1:9 Gen 2-Unstirrulated 1:127 Gen 2-Unstirrulated 1:3 Gen 2-Unstirrulated 1:3 Gen 2-Unstirrulated 1:3 Gen 2-Unstirrulated 1:27 Gen 2-Unstirrulated 1:27 Gen 2-Unstirrulated 1:27 Gen 3-Unstirrulated 1:3 Gen 3-Unstirrulated 1:3 Gen 3-Unstirrulated 1:3 Gen 3-Unstirrulated 1:9 Gen 3-Unstirrulated 1:9 Gen 3-Unstirrulated 1:9 Gen 3-Media Control Stirrulated 1:3 Gen 3-Media Control Stirrulated 1:3 Gen 3-Media Control Stirrulated 1:3 Gen 3-Media Control Stirrulated 1:9 Gen 3-Media Control Stirrulated 1:9 Gen 3-Media Control Stirrulated 1:9	2967.887 2952.025 3261.251 77727 13272.546 16947.994 17577.427 <0.000 <0.000 3.432 10.304 0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000	2117.46 2 2361.138 77777 > 13500.00 16962.84 18246.77 4.262 <0.000 <0.000 4.039 <0.000 4.039 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000	3072-942 3035-11 3167-212 77777 13340-37 17161-47 17992-49 <0.000 <0.000 <0.000 2.465 <0.000 2.465 <0.000 31.588 92.74 <0.000 <0.000	e7f9 7f2e7 27f9 42e97 27f9 42e97 27g7 4f2e7 27g7 4f2e7 1330e 9f75 17g24 1 17g36 8f73 5 197 #D1V/0! #D1V/0! #D1V/0! #D1V/0! #D1V/0! #D1V/0! #D1V/0! #D1V/0!	#D)V/0! 16099-32 5-20 19-74 0.00
22.6	994 773 994 773 996 773 996 773 997 499 696 997 997 997 997 997 997 997	355 2 046 3 596 3 596 5 048 5 048 5 048 5 048 5 048 5 048 5 048 123 174 0 042 0 042 0 042 0 042 0 042 0 17 0 043 0 17 0 044 0 17 0 045 1 18 1 18	0.942 0.942 0.942 0.943	2800_216 0.048 0.048 228 785 226 787 0.042 228 785 0.042 0.044 0.042 0.044	GO45 8 64 892 2084 946 6 28 25 25 27 3 26 1 26 1 26 1 26 2 25 27 3 26 1 26 2 26 2 26 2 26 2 26 2 26 2 26	3055 126 305 1	0.041	0.043	0.041	0.041	0.043	0.041 0.000	Deba (Canner and a control of a	Gen 2-Stirrulated+TIL 1:9 Gen 3-Stirrulated+TIL 1:81 Gen 3-Stirrulated+TIL 1:81 Gen 3-Stirrulated+TIL 1:81 Gen 3-Stirrulated+TIL 1:9 Gen 3-Stirrulated+TIL 1:9 Gen 3-Stirrulated+TIL 1:9 Gen 2-Unstirrulated+TIL 1:81 Gen 2-Unstirrulated+1:9 Gen 2-Unstirrulated+1:3 Gen 2-Unstirrulated+1:3 Gen 2-Unstirrulated+1:3 Gen 3-Unstirrulated+1:3 Gen 3-Unstirrulated+1:4 Gen 3-Unstirrulated+1:9 Gen 3-Unstirrulated+1:9 Gen 3-Unstirrulated+1:9 Gen 3-Media Control Stirrulated+1:3 Gen 3-Media Control Stirrulated+1:9 Gen 3-Media Control Stirrulated+1:9 Gen 3-Media Control Stirrulated+1:9 Gen 3-Media Control Stirrulated+1:9 Gen 2-Media Control Stirrulated+1:9 Gen 2-Media Control Stirrulated+1:9 Gen 2-Media Control Stirrulated+1:9 Gen 2-Media Control Unstirrulated+1:9 Gen 2-Media Control Unstirrulated+1:9	2967.887 2952.025 3261.251 77727 13272.546 16947.994 17577.427 <0.000 <0.000 3.432 10.304 0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000	2 117.4 d 2 2 2 2 3 6 1 1 3 8 2 2 2 3 6 1 1 3 8 2 2 3 6 1 1 3 8 2 2 3 6 1 1 3 8 2 2 3 6 1 1 3 2 4 6 2 2 3 6 1 1 3 2 4 6 2 2 3 6 2 3	3072 942 3 3055,113 3167,212 77977 13340,375,1761,47 17992,49 40,000 40,000 40,000 40,000 40,000 40,000 40,000 40,000 40,000 40,000 40,000 40,000 40,000	e7f9 7f2e7 27f9 42e97 27f9 42e97 27g7 4f2e7 27g7 4f2e7 1330e 9f75 17g24 1 17g36 8f73 5 197 #D1V/0! #D1V/0! #D1V/0! #D1V/0! #D1V/0! #D1V/0! #D1V/0! #D1V/0!	#D)V/0! 16099-32 5-20 19-74 0.00
22.6	984 773 984 773 984 773 985 984 495 686 989 98 989 98 9	8854 Supplemental	1. 684 0. 046 1. 690 1. 690	2890.216 5.0 2890.216 5.0 1.65 1.	GC448	3055-126-3 341438 341438 341448 34148 341	0.041	0.043	0.041	0.041	0.043	0.041	Deba (Canner and a control of a	Gen 2-Stirrulated+TIL 1:9 Gen 3-Stirrulated+TIL 1:81 Gen 3-Stirrulated+TIL 1:81 Gen 3-Stirrulated+TIL 1:81 Gen 3-Stirrulated+TIL 1:9 Gen 3-Stirrulated+TIL 1:9 Gen 3-Stirrulated+TIL 1:9 Gen 2-Unstirrulated+TIL 1:81 Gen 2-Unstirrulated+1:9 Gen 2-Unstirrulated+1:3 Gen 2-Unstirrulated+1:3 Gen 2-Unstirrulated+1:3 Gen 3-Unstirrulated+1:3 Gen 3-Unstirrulated+1:4 Gen 3-Unstirrulated+1:9 Gen 3-Unstirrulated+1:9 Gen 3-Unstirrulated+1:9 Gen 3-Media Control Stirrulated+1:3 Gen 3-Media Control Stirrulated+1:9 Gen 3-Media Control Stirrulated+1:9 Gen 3-Media Control Stirrulated+1:9 Gen 3-Media Control Stirrulated+1:9 Gen 2-Media Control Stirrulated+1:9 Gen 2-Media Control Stirrulated+1:9 Gen 2-Media Control Stirrulated+1:9 Gen 2-Media Control Unstirrulated+1:9 Gen 2-Media Control Unstirrulated+1:9	2967.887 2952.025 3261.251 77727 13272.546 16947.994 17577.427 <0.000 <0.000 3.432 10.304 0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000	2 117.4 d 2 2 2 2 3 6 1 1 3 8 2 2 2 3 6 1 1 3 8 2 2 3 6 1 1 3 8 2 2 3 6 1 1 3 8 2 2 3 6 1 1 3 2 4 6 2 2 3 6 1 1 3 2 4 6 2 2 3 6 2 3	3072 942 3 3055,113 3167,212 77977 13340,375,1761,47 17992,49 40,000 40,000 40,000 40,000 40,000 40,000 40,000 40,000 40,000 40,000 40,000 40,000 40,000	e7f9 7f2e7 27f9 42e97 27f9 42e97 27g7 4f2e7 27g7 4f2e7 1330e 9f75 17g24 1 17g36 8f73 5 197 #D1V/0! #D1V/0! #D1V/0! #D1V/0! #D1V/0! #D1V/0! #D1V/0! #D1V/0!	#D)V/0! 16099-32 5-20 19-74 0.00

Figure 31

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				Title Gen	TH, Gen	TH, Gen	T.C. Seri	Tit. Den	T.C. (340)	MC-	MC-	MC-							
	2.00	2.00		stirouladed	stirouladed	stimulated	Charles	Chetitouls	Stemala	Stimulate d xG2	Stimulate d xG2	Stimulate d xG2	WellD						
	100	1,000	1000		3	3				3	3	3	Cont/Dil						
				TIL: GEN	TH. Gen	TH. Sen	25 396	20-100	20,000	MC-	MC-	MC-	WellD						
				stimulated	stimulated	simulated	Obstroom	Chetitoda	Coetenita	Stimulate d xG2	Stimulate d xG2	Stimulate d xG2	Wellio						
	200			9	9	9				9	9	9	Contribil	;					
				TIL: Gen	TR. Gen	TR. Gen				MC- Unstimula	MC- Unstimuta	MC- Unstimula	Well ID						
				silmilated	stimulated	silmületed	Chstroote	Chetrous	Coetonia	ted xG2	ted xG2	ted xG2							
	200			27	27	27		***	10000	3	3.	3	ConclDii						
	8704	81704	a100e	Tile Gen J	TA: Gen	Tit. Gen				MC Unstimula	MC- Unstimula	MC- Unstimula	Well ID						
				stimulated		silmidated	Act and a second	Acceptance	200-00000	ted xG2	ted xG2	ted xG2							
		112		TIL Gen	11L Gen	TIL Gen	TIL Gen	TL GE	TIL Get	MC-	MC-	MC-	ConclDii						
	8708	2102	2006	3	3	3	l in Shrinish	- Originalis	Gristimula	Stimulate	Stimulate	Stroulate	WellD						
				stimulated	stimulated	stimulated	led	ted	led	d xG3	d xG3	d xG3							
				TIL Gen	Til. Gen	TiL-Gen	TL Gen	TL Gen	T.L. Gest	MC	MC.	MC	Contibil						
	875/8	8156	91700	3-	3-	3-	Enstinada	uristimus Uristimus	Chistimula	Stimulate	Stimulate	Stimulate	Well ID						
				stimulated	stimulated	stimudated	160	ted	led	d xG3	d xG3	d xG3	ConstDi						
				TIL- Gen	TiL- Gen	TiL-Gen	70£ Gen	Til Gen	TIL Gen	MC-	MC-	MC-	e-effected	· * · · · · · · · · · · · · · · · · · · ·	· · · · · · · · · · · · · · · · · · ·		;	;	
				3	3 stimulated	3 stimulated	Linsimude	Lintsitirede	Constitute	Unstimula ted xG3	Unstimula ted xG3	Unstimula ted xG3	Well ID						
				27	-синыкиед 27	27		Hed gr	160	iou XGS	3	1GO XOS	Conc/Dil						
				TiL Gen	TiL- Gen	TiL-Gen	TIC Och	Tig. Swin	TIL See	MC	MC-	MC							
	6106	erpe	87728	3 chiroutatad	3- stimulated	3 stimulated	Linstinede	Linstinado	Checimula	Unstimula ted xG3	Unstimula ted xG3	Unstimula ted xG3	Well ID						
				81	81	81	iees Sis	Heid 24	Herd Sit	9	9	9	Conc/Dil						
22.9																			
22.9									:	1									
	:	:	:						:	:	:		_	:	:				
	1989	1966					0.128	0.126	0.132	0.11	0.111	0.107	450	Gen 2-Stimulated+TIL 1:3	3435.858	2933.14	2905.979	Average 3091.659	Average 3261.65
	1024	2.052	2.052	2,555	2 823	7 W W	0.128 0.041	0.126 0.041	0.132 0.042	0.11 0.042	0.111 0.041	0.107 0.042	450 570	Gen 2-Stimulated+TIL 1:3 Gen 2-Stimulated+TIL 1:9	3435.858 3676.262	3001.429		3091.659 3201.388333	3261.65
	0.024	995.223	0:052 20052 1003.493	0.059 1145.286	0.855 977.713	21.852 21.852 24.866							450 570 Delta (Concentratio			3001.429 3097.07	2926.474 2994.844	3091.659 3201.388333	3261.65
	<u> </u>			3435.858	2933.14	968.66 2905.979	0.041 0.087 2.922 8.766	0.041 0.085 2.418 7.254	0.042 0.09 3.712 11.136	0.042 0.069 <0.000 <0.000	0.041 0.069 <0.000 <0.000	0.042 0.065 <0.000 <0.000	Delta (Concentratio n) xdii factor	Gen 2-Stimulated+TIL 1:9 Gen 2-Stimulated+TIL 1:27 Gen 2-Stimulated+TIL 1:81	3676.262 3471.282	3001.429 3097.07	2926.474 2994.844	3091,659 3201,388333 3187,732 3565,818	3261.65
	1 866 0 047	4-838 0.046	1.668 0.047	3435.858 1,411 0.046	2933.14 3.139 0.045	968.66 2905.979 1.127 0.047	0.041 0.087 2.922 8.766 0.119 0.041	0.041 0.085 2.418 7.254 0.118 0.042	0.042 0.09 3.712 11.136 0.126 0.044	0.042 0.069 <0.000 <0.000 0.112 0.042	0.041 0.069 <0.000 <0.000 0.112 0.041	0.042 0.065 <0.000 <0.000 0.114 0.042	Delta (Concentratio n) xdi factor 450	Gen 2-Stimulated+TiL 1:9 Gen 2-Stimulated+TiL 1:27 Gen 2-Stimulated+TiL 1:81 Gen 3-Stimulated+TiL 1:3 Gen 3-Stimulated+TiL 1:9	3676.262 3471.282 3910.387 ????? 13183.826	3001.429 3097.07 3552.941 ????? 13421.925	2926.474 2994.844 3234.126 ????? 12822.143	3091.659 3201.388333 3187.732 3565.818 #DIV/0! 13142.63133	3261.65 #DIV/0!
	1.886	1.635 0.046 1.566	1.008 0.047 1.021	3435.858 1.411 0.046 1.268	2933.14 1.198 0.045 1.184	968.66 2905.979 1:177 0:047	0.041 0.087 2.922 8.766 0.119 0.041 0.078	0.041 0.085 2.418 7.254 0.118 0.042 0.076	0.042 0.09 3.712 11.136 0.126 0.044 0.082	0.042 0.069 <0.000 <0.000 0.112 0.042 0.07	0.041 0.069 <0.000 <0.000 0.112 0.041 0.07	0.042 0.065 <0.000 <0.000 0.114 0.042 0.072	Delta (Concentratio n) xdii factor	Gen 2-Stimulated+TiL 1:9 Gen 2-Stimulated+TiL 1:27 Gen 2-Stimulated+TiL 1:81 Gen 3-Stimulated+TiL 1:3 Gen 3-Stimulated+TiL 1:9 Gen 3-Stimulated+TiL 1:27	3676.262 3471.282 3910.387 ????? 13183.826 16231.22	3001.429 3097.07 3552.941 ????? 13421.925 16700.175	2926.474 2994.844 3234.126 ????? 12822.143 14586.268	3091.659 3201.388333 3187.732 3565.818 #DIV/0! 13142.63133 15839.221	3261.65 #DIV/0!
	6.886 0.047 1.622 503.563	1-838 0-646 1-869 491-203	1.668 0.047 1.624 503.336	3435.858 1.301 0.046 1.365 408.474 3676.262	2933.14 1:199 0:045 1:194 333.492 3001.429	968.66 2905.979 1:127 0:047 1:13 325.164 2926.474	0.041 0.087 2.922 8.766 0.119 0.041 0.078 0.931 8.383	0.041 0.085 2.418 7.254 0.118 0.042 0.076 0.531 4.779	0.042 0.09 3.712 11.136 0.126 0.044 0.082 1.786 16.076	0.042 0.069 <0.000 <0.000 0.112 0.042 0.07 <0.000	0.041 0.069 <0.000 <0.000 0.112 0.041 0.07 <0.000	0.042 0.065 <0.000 <0.000 0.114 0.042 0.072 <0.000	Delta (Concentratio ni xdi factor 450 570 Delta (Concentratio n) xdi factor	Gen 2-Simsdated +TIL 1, 9, Gen 2-Simsdated +TIL 1, 127 Gen 2-Stimsdated +TIL 1, 181 Gen 3-Stimsdated +TIL 1, 13 Gen 3-Stimsdated +TIL 1, 19 Gen 3-Stimsdated +TIL 1, 181 Gen 3-Stimsdated +TIL 1, 181	3676.262 3471.282 3910.387 ????? 13183.826 16231.22 17140.679	3001.429 3097.07 3552.941 ????? 13421.925 16700.175 17638.195	2926.474 2994.844 3234.126 ????? 12822.143 14586.268 16007.402	3091.659 3201.388333 3187.732 3565.818 #DIV/0! 13142.63133 15839.221 16928.75867	3261.65 #DIV/0!
\$	1-886 0.047 1-822	1.635 0.046 1.566	1.998 6.647 1.924 503.336 0.939 6.045	3435.858 4.444 9.046 4.268 408.474 3676.262 0.876 9.045	2933.14 1:199 0:045 1:194 333.492	968.66 2905.979 11.177 0.047 113 325.164 2926.474 0.518 0.045	0.041 0.087 2.922 8.766 0.119 0.041 0.078 0.931 8.383 0.115 0.041	0.041 0.085 2.418 7.254 0.118 0.042 0.076 0.531	0.042 0.09 3.712 11.136 0.126 0.044 0.082 1.786	0.042 0.069 <0.000 <0.000 0.112 0.042 0.07 <0.000 <0.000 0.111 0.041	0.041 0.069 <0.000 <0.000 0.112 0.041 0.07 <0.000	0.042 0.065 <0.000 <0.000 0.114 0.042 0.072 <0.000 <0.000 0.115 0.043	Detta (Concentratio et al. Concentratio et al.	Gen 2-Stimulated+TiL 1:9 Gen 2-Stimulated+TiL 1:27 Gen 2-Stimulated+TiL 1:81 Gen 3-Stimulated+TiL 1:3 Gen 3-Stimulated+TiL 1:9 Gen 3-Stimulated+TiL 1:27	3676.262 3471.262 3910.387 ????? 13183.826 16231.22 17140.676 8.766 8.363	3001.429 3097.07 3552.941 ????? 13421.925 16700.175 17638.195 7.254 4.779	2926.474 2994.844 3234.126 ????? 12822.143 14586.268 16007.402 11.136 16.076	3091 659 3201 388333 3187 732 3565 818 #DIV/01 13142 63133 15839 221 16928 75867 9,052 9,746	#DIV/0! 15303.54
8	6.888 0.047 1.822 503.563 0.974 0.045 0.928	- 1838 - 046 - 1886 - 491 203 - 0.987 - 0.043 - 0.914	1.888 0.047 1.824 503.336 0.939 0.045 0.7594	3435.858 4.441 6.046 4.268 408.474 3676.262 0.576 6.045 0.531	2933 14 1:139 0:045 1:154 333 492 3001 429 0:528 0:043 0:486	968.66 2905.979 1.177 0.047 3.13 325.164 2926.474 0.518 0.045 0.473	0.041 0.087 2.922 8.766 0.119 0.041 0.078 0.931 8.383 0.115 0.041 0.074	0.041 0.085 2.418 7.254 0.118 0.042 0.076 0.531 4.779 0.116 0.044 0.072	0.042 0.09 3.712 11.136 0.126 0.044 0.082 1.786 16.076 0.125 0.042 0.083	0.042 0.069 <0.000 <0.000 0.112 0.07 <0.000 <0.000 0.111 0.041 0.07	0.041 0.069 <0.000 <0.000 0.112 0.041 0.07 <0.000 <0.000 0.114 0.043 0.071	0.042 0.065 <0.000 <0.000 0.114 0.042 0.072 <0.000 <0.000 0.115 0.043 0.071	Deta (Concentratio n) xdi factor 450 570 Detta (Concentratio n) xdi factor 450 450 450 450	Gen 2. Stimulated +Til. 1.9 Gen 2. Stimulated +Til. 1.27 Gen 3. Stimulated +Til. 1.13 Gen 3. Stimulated +Til. 1.3 Gen 3. Stimulated +Til. 1.9 Gen 3. Stimulated +Til. 1.27 Gen 3. Stimulated +Til. 1.27 Gen 2. Unstimulated 1.3 Gen 2. Unstimulated 1.27 Gen 2. Unstimulated 1.27	3676.262 3471.282 3910.387 7???? 13183.826 16231.22 17140.676 8.766 8.383 5.632	3001.429 3097.07 3552.941 ????? 13421.925 16700.175 17638.195 7.254 4.779	2926.474 2994.844 3234.126 ????? 12822.143 14586.268 16007.402 11.136 16.076 53.672	3091 659 3201 388333 3187 732 3565 818 #DIV/01 13142 63133 15839 221 16928 75867 9.052 9.746 29.652	#DIV/0! 15303.54 27.10
8	0.947 6.822 503.563 0.974 0.045 0.928 256.406	1.838 2.046 1.888 491.203 0.987 2.042 0.914 251.388	1.988 g 047 1.921 503.336 0.939 0.045 0.294 244.654	3435 858 1.3(1) 0.046 1.268 408 474 3676 262 0.576 0.045 0.531 128 566 3471 282	2933.14 3:198 6:045 3:184 333.492 3001.429 0:\$28 0.043 0.486 114.706 3097.07	968.66 2905.979 1:177 0.047 3:13 325.164 2926.4774 0.518 0.045 0.473 110.92 2994.844	0.041 0.087 2.922 8.766 0.119 0.041 0.078 0.931 8.383 0.115 0.041 0.074 0.209	0.041 0.085 2.418 7.254 0.118 0.042 0.076 0.531 4.779 0.116 0.044 0.072 <0.000	0.042 0.09 3.712 11.136 0.126 0.044 0.082 1.786 16.076 0.125 0.042 0.083 1.988	0.042 0.069 <0.000 <0.000 0.112 0.042 0.07 <0.000 0.111 0.041 0.07 <0.000	0.041 0.069 <0.000 0.112 0.041 0.07 <0.000 <0.000 0.114 0.045 0.071 <0.000	0.042 0.065 <0.000 <0.000 0.114 0.042 0.072 <0.000 0.115 0.043 0.071 <0.000 <0.000	Delta (Concentratio (Concentratio 450 450 570 Oelta (Concentratio q) xdi factor 650 577 Oelta (Concentratio q) yxdi rator (Concentratio q) q, xdi factor	Gen 2. Stimulated +Til. 1.9 Gen 2. Stimulated +Til. 1.27 Gen 3. Stimulated +Til. 1.21 Gen 3. Stimulated +Til. 1.3 Gen 3. Stimulated +Til. 1.9 Gen 3. Stimulated +Til. 1.27 Gen 3. Stimulated +Til. 1.27 Gen 3. Stimulated +Til. 1.27 Gen 2. Unstimulated 1.3 Gen 2. Unstimulated 1.27 Gen 2. Unstimulated 1.28	3676,262 3471,282 3910,387 7???? 13183,826 16231,22 17140,676 8,393 5,632 <0.000	3001.429 3097.07 3552.941 ????? 13421.925 16700.175 17638.195 7.254 4.779 <0.000	2926.474 2994.844 3234.126 7???? 12822.143 14596.268 16007.402 11.136 16.076 53.672 59.939	3091 659 3201 388333 3187 732 3565 818 #DIVIOI 13142 63133 15939 221 16928 75867 9,052 9,746 29,652 59,939	#DIV/01 15303.54 27.10
3	6.888 0.047 1.822 503.563 0.974 0.045 0.928	- 1838 - 046 - 1886 - 491 203 - 0.987 - 0.043 - 0.914	1.888 0.047 1.824 503.336 0.939 0.045 0.7594	3435 858 4 441 0.046 1.268 408.474 3676 262 0.576 0.045 0.531 128.566	2933 14 3.138 0.045 3.134 333.492 3001.429 0.528 0.043 0.486 114.706	968.66 2905.979 1.177 6.047 1.13 325.164 2926.474 0.518 0.045 0.473 110.92	0.041 0.087 2.922 8.766 0.119 0.041 0.078 0.931 8.383 0.115 0.041 0.074 0.209	0.041 0.085 2.418 7.254 0.118 0.042 0.076 0.531 4.779 0.116 0.044 0.072 <0.000	0.042 0.09 3.712 11.136 0.126 0.044 0.082 1.786 16.076 0.125 0.042 0.083 1.988	0.042 0.069 <0.000 <0.000 0.112 0.07 <0.000 <0.000 0.111 0.041 0.07 <0.000	0.041 0.069 <0.000 <0.000 0.112 0.041 0.07 <0.000 <0.000 0.114 0.043 0.071 <0.000	0.042 0.065 <0.000 <0.000 0.114 0.042 <0.072 <0.000 <0.000 0.115 0.043 0.071 <0.000	Deta (Concentratio of validation) xell factor 469 570 Deta (Concentratio of validation) xell factor 469 459 570 Deta (Concentratio of validation) 570 Deta (Concentratio of validation)	Gen 2. Stimulated +Til. 1.9 Gen 2. Stimulated +Til. 1.27 Gen 3. Stimulated +Til. 1.13 Gen 3. Stimulated +Til. 1.3 Gen 3. Stimulated +Til. 1.9 Gen 3. Stimulated +Til. 1.27 Gen 3. Stimulated +Til. 1.27 Gen 2. Unstimulated 1.3 Gen 2. Unstimulated 1.27 Gen 2. Unstimulated 1.27	3676.262 3471.282 3910.387 7???? 13183.826 16231.22 17140.676 8.766 8.383 5.632	3001.429 3097.07 3552.941 ????? 13421.925 16700.175 17638.195 7.254 4.779 <0.000	2926.474 2994.844 3234.126 ????? 12822.143 14586.268 16007.402 11.136 16.076 53.672 59.939	3091 659 3201 388333 3187 732 3565 818 #DIV/01 13142 63133 15839 221 16928 75867 9.052 9.746 29.652	#DIV/01 15303.54 27.10
3	6.088 6.647 6.822 503.563 0.974 6.045 0.928 256.406 0.877 0.877	6.838 6.646 9.888 491.203 0.957 0.042 0.914 251.388 0.851 0.042 0.509	0.989 0.045 0.045 0.033 0.045 0.045 0.049 244.654 0.56 0.044 0.516	3435.858 0.341 0.046 0.368 408.474 3676.262 0.976 0.045 0.531 128.566 3471.282 0.301 0.042 0.259	2933 14 3.199 0.045 3.194 333 492 3001 429 0.928 0.043 0.486 114.706 3097.07 0.266 0.043 0.243	968.66 2905.979 11:127 0.047 13:13 325.164 2926.474 0.518 0.045 0.045 0.0473 110.92 2994.844 0.27 0.041	0.041 0.087 2.922 8.766 0.119 0.041 0.078 0.931 8.383 0.115 0.041 0.074 0.209 5.632 0.115 0.042	0.041 0.085 2.418 7.254 0.118 0.042 0.076 0.531 4.779 0.116 0.044 0.072 <0.000 <0.000 0.11 0.043 0.067	0.042 0.09 3.712 11.136 0.126 0.044 0.082 1.786 16.076 0.125 0.042 0.083 1.988 53.672 0.042 0.077	0.042 0.069 <0.000 0.112 0.042 0.07 <0.000 <0.000 0.111 0.041 0.07 <0.000 <0.000 0.111 0.07 <0.000 0.000 0.000 0.000 0.000	0.041 0.069 <0.000 0.112 0.041 0.07 <0.000 <0.000 0.114 0.943 0.071 <0.000 <0.000 0.112 0.001 0.000	0.042 0.065 <0.000 <0.000 0.114 0.042 0.072 <0.000 0.115 0.043 0.071 <0.000 <0.000 0.110 0.000	Deta Concentrate	Sen 2. Stimulated +TL 1.9 Sen 2. Stimulated +TL 1.27 Gen 2. Stimulated +TL 1.81 Gen 3. Stimulated +TL 1.81 Gen 3. Stimulated +TL 1.9 Gen 3. Stimulated +TL 1.9 Gen 3. Stimulated +TL 1.19 Gen 3. Stimulated +TL 1.19 Gen 2. Unstimulated 1.19 Gen 2. Unstimulated 1.19 Gen 2. Unstimulated 1.19 Gen 3. Unstimulated 1.19 Gen 3. Unstimulated 1.27 Gen 3. Unstimulated 1.30 Gen 3. Unstimulated 1.30 Gen 3. Ge	3676.262 3471.282 3910.387 77777 13183.826 16231.22 17140.676 8.362 5.632 <0.000 19.738 13.876 0.172	3001.429 3097.07 3552.941 ????? 13421.925 16700.175 17638.195 7.254 4.779 <0.000 0.000 13.255 31.096 <0.000	2926.474 2994.844 3234.126 77777 12822.143 14596.268 16007.402 11.136 16.076 53.672 59.939 20.614 19.718 33.321	2091 659 3201 388333 3187 732 3565 818 #DIV/01 13142 63133 15839 221 16928 75867 9 746 29 652 59 939 17 869 21 563 16 7465	#DIV/0! 15303.54 27.10
8	0.974 0.945 0.945 0.945 0.924 256.406 0.877 0.944	1.838 2.046 1.886 491.203 0.957 2.042 0.914 251.388 0.851 0.042	1.988 0.047 1.981 503.336 0.939 0.045 0.294 244.654	3435.858 (.31) 0.046 1.368 408.474 3676.262 0.976 0.045 0.531 128.566 3471.282 0.301 0.042	2933 14 1 198 0 045 1 198 333 492 3001 429 0 928 0 043 0 486 114 706 3097 07 0 286 0 043	968.66 2905.979 1:197 6:047 3:13 325.164 2926.474 0.518 0.045 0.473 110.92 2994.844 0.27 0.041	0.041 0.087 2.922 8.766 0.119 0.041 0.078 0.931 8.383 0.115 0.041 0.074 0.209 5.632 0.115	0.041 0.085 2.418 7.254 0.118 0.042 0.076 0.531 4.779 0.116 0.044 0.072 <0.000 <0.000 0.111 0.043	0.042 0.09 3.712 11.136 0.126 0.044 0.082 1.786 16.076 0.125 0.042 0.083 1.988 53.672 0.119	0.042 0.069 <0.000 0.010 0.012 0.042 0.07 <0.000 <0.000 0.111 0.07 <0.000 <0.000 <0.000 0.000 0.000 0.000	0.041 0.069 <0.000 0.112 0.041 0.07 <0.000 <0.000 0.114 0.071 <0.000 0.114 0.000 <0.000 0.000 0.000	0.042 0.065 <0.000 0.114 0.042 0.072 <0.000 <0.000 0.115 0.043 0.071 <0.000 <0.000	Debts	Gen 2. Stimulated +Ti. 1. 9. Gen 2. Stimulated +Ti. 1. 127 Gen 2. Stimulated +Ti. 1. 137 Gen 3. Stimulated +Ti. 1. 13 Gen 3. Stimulated +Ti. 1. 13 Gen 3. Stimulated +Ti. 1. 19 Gen 3. Stimulated +Ti. 1. 127 Gen 3. Stimulated +Ti. 1. 127 Gen 3. Stimulated +Ti. 1. 131 Gen 2. Lustimulated 1. 19 Gen 2. Lustimulated 1. 127 Gen 2. Lustimulated 1. 13 Gen 3. Lustimulated 1. 13	3676.262 3471.282 3910.387 77777 13183.826 16231.22 17140.676 8.362 5.632 <0.000 19.738 13.876 0.172	3001.429 3097.07 3552.941 ????? 13421.925 16700.175 17638.195 7.254 4.779 <0.000 0.000 13.255 31.096	2926.474 2994.844 3234.126 77777 12822.143 14596.268 16007.402 11.136 16.076 53.672 59.939 20.614 19.718 33.321	3091 659 3201 388333 3187,732 3565.818 #DIV/01 13142.63133 15939.221 16928.75867 9,052 9,746 29,652 59,939 17,869 21,563	#DIV/0! 15303.54 27.10
3	5:886 5:047 5:03.563 5:03.563 5:03.563 5:03.563 5:09.29 256.406 0:577 5:044 0:533 129.057	\$2.046 \$3.046 \$3.046 \$491.203 \$0.042 \$0.944 \$251.388 \$0.851 \$0.042 \$0.909 \$121.737	0.589 0.042 0.524 503.336 0.589 0.045 0.2894 244.654 0.56 0.044 0.516 123.877	3435.858 	2933.14 3.189 6.045 3.184 333.492 3001.429 0.928 0.043 0.486 114.706 3097.07 0.264 0.043 0.243 43.863	968.66 2905.979 11.172 0.047 3.13 325.164 2926.474 0.045 0.473 110.92 2994.844 0.27 0.041 0.229 3.9.927 3.9.927	0.041 0.087 2.922 8.766 0.119 0.041 0.078 0.931 8.383 0.115 0.041 0.074 0.209 5.632 0.115 0.042 0.073 <0.000	0.041 0.085 2.418 7.254 0.118 0.042 0.076 0.531 4.779 0.116 0.044 0.072 <0.000 0.110 0.043 0.067 <0.000 0.135	0.042 0.09 3.712 11.136 0.126 0.044 0.082 1.786 16.076 0.125 0.083 1.988 53.672 0.119 0.042 0.077 0.77	0.042 0.069 0.000 0.000 0.012 0.07 0.000 0.07 0.001 0.07 0.000 0.07 0.000 0.00	0.041 0.069 <0.000 0.112 0.041 0.07 <0.000 0.114 0.07 <0.000 <0.000 <0.000 0.114 0.071 <0.000 <0.000 0.0000 0.000	0.042 0.065 <0.000 0.114 0.042 0.072 <0.000 0.115 0.071 <0.000 <0.000 0.115 0.042 0.068 <0.000 0.068 <0.000	Dotta Governments rel saya file factor 440 570 Dotta Concentratio 19 19 100 100 100 100 100 100 100 100 1	Sen 2. Stimulated +TL 1.9	3676,262 3471,282 34910,387 77777 13183,826 16231,22 177140,676 8,362 5,632 <0.000 19,736 13,876 0,177 77,18	3001.429 3097.07 3352.941 ????? 13421.925 16700.175 17638.195, 7,254 4,779 <0.000, 0.000, 13,255 31,096 <0.000, 171,968	2926 474 2994 844 2994 844 3224 126 27777 12822 143 14586 268 16007 402 11 136 16 076 53.672 59.939 20.614 19.718 33.321 101.73 <0.000	3091 (598 3201 (3893 3187 732 3565 818 \$DIVIOI 13142-839 15039 221 16928 75967 9.052 9.746 26.652 59.939 17.869 21.563 16.7465 116.9593333 #DIVIOI #	#DIV/0! 15303.54 27.10
	0.886 0.047 0.047 0.045 0.045 0.045 0.044 0.044 0.053 12.053 12.053 0.061 0.042 0.041	3.888 2.d46 5.886 491.203 0.357 2.042 5.914 251.388 0.851 0.042 0.509 121.737 0.35 0.042 0.309	1.868 C.047 1.897 503.336 0.859 0.048 0.294 244.654 0.56 0.044 0.516 123.877 0.346 0.042 0.304	3435 858 3411 2 046 3 246 3 246 3 246 3 247 3 27 3 27 3 27 3 27 3 27 3 27 3 27 3 2	2933.14 3.198 0.045 3.194 333.492 0.528 0.043 0.486 114.706 3097.07 0.286 0.043 43.863 3552.941 0.VRFLW	968.66 2905.979 14.102 3.0047 3.103 325.164 2926.474 0.518 0.445 0.479 110.92 2994.844 0.27 0.041 0.299 3.294.126 0.WRFLW	0.041 0.087 2.922 8.766 0.119 0.041 0.078 0.931 8.383 0.115 0.041 0.074 0.209 5.632 0.115 0.042 0.073 0.000 <0.000 0.143 0.041 0.102	0.041 0.085 2.418 7.254 0.118 0.042 0.076 0.531 4.779 0.116 0.072 <0.000 0.11 0.043 0.067 <0.000 <0.000 0.135 0.042 0.002	0.042 0.09 3.712 11.136 0.126 0.082 1.786 16.076 0.125 0.042 0.083 1.988 53.672 0.119 0.042 0.077 0.74 59.939 0.145 0.043	0.042 0.069 0.000 0.000 0.012 0.042 0.07 0.000 0.111 0.041 0.07 0.000 0.000 0.111 0.02 0.000 0.111 0.02 0.000 0.000 0.111 0.042 0.000 0.00	0.041 0.069 <0.000 0.112 0.041 0.07 <0.000 0.114 0.543 0.071 <0.000 <0.000 0.114 0.000 0.000 0.114 0.000 0.000 0.112 0.041 0.07	0.042 0.065 0.000 0.114 0.042 0.072 0.072 0.000 0.115 0.043 0.071 0.000 0.11 0.042 0.068 0.000 0.11 0.068	Doris Concentrato al serior Association Concentrato Co	Gen 2. Stimulated +TL 1.9 Gen 2. Stimulated +TL 1.27 Gen 2. Stimulated +TL 1.21 Gen 3. Stimulated +TL 1.31 Gen 3. Stimulated +TL 1.31 Gen 3. Stimulated +TL 1.32 Gen 3. Stimulated +TL 1.37 Gen 3. Stimulated +TL 1.37 Gen 3. Stimulated +TL 1.31 Gen 2. Unstimulated 1.32 Gen 2. Unstimulated 1.32 Gen 3. Unstimulated 1.34 Gen 3. Unstimulated 1.34	3676.262 3471.282 3910.387 72727 13183.826 16231.22 17140.675 8.786 8.382 5.632 <0.000 19.738 13.876 0.172 77.16	3001.429 3097.07 3352.941 ????? 13421.925 16700.175 17638.195, 7,254 4,779 <0.000, 0.000, 13,255 31,096 <0.000, 171,968	2926 474 294 844 3224 126 2227 2822 143 14586 268 16007 402 11 126 55 672 59 939 20 614 19 718 33 321 101 73	3991 659 3201 388333 3187 732 3565 818 \$DIV/01 13142,63133 15839,221 16928,75967 9,052 9,746 29,652 59,939 17,869 21,563 16,7465 116,9593333	#DIV/01 15303.54
	0.974 0.948 50.974 0.928 256.406 0.877 0.944 0.533 129.057	\$388 \$.046 \$890 491.203 0.387 \$.042 251.388 0.851 0.042 0.509 121.737	3.868 C.047 T.824 503.336 0.939 0.045 0.894 244.654 0.56 0.044 0.519 123.877	3435.858 3431. 9.046. 1.266. 1.266. 1.266. 1.266. 1.266. 1.276. 1.28.566. 3471.282. 0.301. 0.042. 0.259. 48.276. 3910.387.	2933.14 3.198 0.045 3.194 333.492 3001.429 0.528 0.043 0.486 114.706 3097.07 0.286 0.043 0.243 43.863 3552.941	968.66 2905.979 11.177 3.133 325.164 2926.474 0.518 0.045 0.479 110.92 2994.844 0.27 0.27 0.29 39.927 3234.126 0.VRFLW	0.041 0.087 2.922 8.766 0.119 0.041 0.078 0.931 8.383 0.115 0.041 0.209 5.632 0.115 0.042 0.073 <0.000 0.143 0.041 0.074 0.000 0.143 0.041 0.000 0.143 0.041 0.014 0.000 0.041 0.000 0.041 0.000 0.041 0.000 0.041 0.000 0.041 0.000 0.041 0.000 0.041 0.000 0.041 0.000 0.041 0.000 0.041 0.000 0.041 0.0000 0.0000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.0	0.041 0.085 2.418 7.254 0.118 0.042 0.076 0.531 4.779 0.116 0.044 0.072 <0.000 0.11 0.043 0.067 <0.000 0.135 0.042 0.093 4.418	0.042 0.09 3.712 11.136 0.126 0.042 1.786 16.076 0.125 0.042 0.083 1.988 53.672 0.119 0.042 0.077 0.77 0.74 0.042 0.077 0.042 0.077 0.042 0.042 0.043	0.042 0.069 <0.000 0.112 0.07 <0.000 <1.007 <0.000 0.111 0.07 <0.000 0.111 0.041 0.064 0.000 <0.000 0.111 0.042 0.000 <0.000 0.111 0.042 0.000 <0.000 0.0000 0.0000 0.0	0.041 0.069 <0.000 <0.000 0.112 0.041 0.07 <0.000 0.114 0.043 0.071 <0.000 0.114 0.000 0.111 0.000 0.112 0.000 0.112 0.000	0.042 0.065 -0.000 -0.000 -0.114 0.042 0.072 -0.0000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.0000 -0.000 -0.00000 -0.0000 -0.0000 -0.0000 -0.0000 -0.0000 -0.0000 -0.0000 -0.0	Octal Concentrato al antificación al antificac	Sen 2. Stimulated +TL 1.9	3676,262 3471,282 34910,387 77777 13183,826 16231,22 177140,676 8,362 5,632 <0.000 19,736 13,876 0,177 77,18	3001.429 3097.07 3352.941 ????? 13421.925 16700.175 17638.195, 7,254 4,779 <0.000, 0.000, 13,255 31,096 <0.000, 171,968	2926 474 2994 844 2994 844 3224 126 27777 12822 143 14586 268 16007 402 11 136 16 076 53.672 59.939 20.614 19.718 33.321 101.73 <0.000	3091 (598 3201 (3893 3187 732 3565 818 \$DIVIOI 13142-839 15039 221 16928 75967 9.052 9.746 26.652 59.939 17.869 21.563 16.7465 116.9593333 #DIVIOI #	#DIV/01 15303.54
	50.866 6.647 6.632 503.563 0.645 0.645 2.56.406 0.577 0.644 0.533 129.057 0.361 0.442 0.319 65.323	2.548 2.646 2.646 2.666 491.203 0.957 2.642 2.51.388 0.851 0.042 0.509 121.737 0.35 0.35 0.35 0.309 62.395	0.042 0.042 0.042 0.042 0.030 0.045 0.045 0.046 0.046 0.056 0.046 0.056 0.046 0.056 0.046 0.056 0.046 0.056 0.046 0.056	3435 858 3431: 6 046 5 266 408 474 3676 262 0 .576 0 .531 128 566 3471 225 0 .301 0 .042 0 .259 48 .276 3910 .387 OVRFLW	2933.14 3:138 6:045 3:134 333.492 3001.429 0:043 0:043 0:243 43.863 3552.641 OVEFLW	968.66 2905.979 11.172 0.0047 3.03 325.164 2926.474 0.51b 0.045 0.473 110.92 2994.844 0.27 0.041 0.229 39.927 3234.126 0.04FLW	0.041 0.087 2.922 8.766 0.119 0.041 0.078 0.931 0.115 0.041 0.074 0.209 5.632 0.115 0.042 0.073 0.000 0.113 0.000 0.1143 0.000 0.1143 0.002 0.003 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.003 0.002 0.003 0.004 0.002 0.004	0.041 0.085 2.418 7.254 0.118 0.042 0.076 0.531 4.779 0.116 0.044 0.072 <0.000 <0.000 0.111 0.043 0.067 <0.000 <0.000 0.135 0.002 0.003 4.418 13.255 0.144	0.042 0.09 3.712 11.136 0.126 0.044 0.082 1.766 0.125 0.042 0.083 1.988 53.672 0.119 0.042 0.077 0.74 59.939 0.145 0.046 0.103 6.871 0.042	0.042 0.069 <0.000 <0.000 0.012 0.042 0.07 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.0000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.00000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.00000 <0.00000 <0.00000 <0.00000 <0.00000 <0.00000 <0.00000 <0.00000 <0.00000 <0.00000 <0.000000 <0.00000 <0.00000 <0.000000 <0.000000 <0.00000000	0.041 0.069 <0.000 0.112 0.041 0.07 <0.000 0.114 0.07 <0.000 0.114 0.000 <0.000 <0.000 <112 0.041 0.07 <0.000 <112 0.041 0.07 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 0.112 0.043 0.043 0.071 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.00000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.00000 <0.00000 <0.0000 <0.00000 <0.00000 <0.00000 <0.00000 <0.00000 <0.00000 <0.00000 <0.00000 <0.00000 <0.00000 <0.00000 <0.000000 <0.00000 <0.00000 <0.000000 <0.000000 <0.0000000 <0.00000000	0.042 0.065 0.000 0.114 0.042 0.072 0.000 0.115 0.043 0.071 0.000 0.000 0.110 0.068 0.000 0.110 0.068 0.000	Dotal Concentratio III III III III III III III III III I	Gen 2. 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	0.886 0.947 0.928 503.563 0.974 0.948 0.929 256.406 0.577 0.944 0.533 129.057 0.361 0.042 0.319 65.323	2 546 2 546 2 546 2 546 3 886 491 203 0 857 2 542 0 994 2 251 388 0 851 0 342 0 509 121 737 0 35 0 342 0 309 62 395	0.589 0.045 0.045 0.045 0.045 0.045 0.044 0.516 123.877 0.346 0.042 0.304 0.042 0.304	3435 858 3431: 6 046 5 266 408 474 3676 262 0 .576 0 .531 128 566 3471 225 0 .301 0 .042 0 .259 48 .276 3910 .387 OVRFLW	2933.14 3:138 6:045 3:134 333.492 3001.429 0:043 0:043 0:243 43.863 3552.641 OVEFLW	968.66 205.979 11.122 0.047 31/33 325.164 2026.474 0.518 0.045 0.479 110.92 2994.844 0.29 30.927 3234.126 0.VEFLW	0.041 0.087 2.922 8.766 0.119 0.041 0.078 0.931 8.383 0.115 0.041 0.209 5.632 0.115 0.042 0.073 0.000 0.000 0.143 0.000 0.143 0.000 0.143 0.000 0.000 0.143 0.000 0.143 0.000 0.000 0.143 0.0000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.00000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.	0.041 0.085 2.418 7.254 0.118 0.042 0.076 0.531 4.779 0.116 0.042 0.000 0.000 0.11 0.043 0.067 <0.000 <0.000 0.134 0.067 <0.000 0.134 0.0634	0.042 0.09 3.712 11.136 0.125 0.044 0.082 1.786 16.076 0.125 0.042 0.083 1.988 53.672 0.042 0.074 59.939 0.145 0.042 0.074 0.042 0.074 0.042 0.074 0.042 0.042 0.043 0.043 0.043 0.044 0.042 0.042 0.042 0.042 0.042 0.043 0.044 0.042 0.043 0.043 0.043 0.043 0.043 0.043 0.043 0.044 0.043 0.044 0.045 0.0	0.042 0.069 <0.000 0.112 0.042 0.07 <0.000 0.111 0.07 <0.000 0.111 0.042 0.000 0.111 0.042 0.000 0.115 0.000 0.115 0.000	0.041 0.069 <0.000 0.112 0.041 0.07 <0.000 <0.000 0.114 0.071 <0.000 0.114 0.071 <0.000 0.011 0.071 <0.000 0.011 0.001 0.011 0.0000 0.0000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.00000 0.00000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.00000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.00000 0.00000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.00000 0.00000 0.0	0.042 0.065 -0.000 -0.000 0.114 0.042 0.072 -0.000 -0.115 0.047 -0.0000 -0.000 -0.00000 -0.00000 -0.	Dotal Governmental rel Avid Indoor	Gen 2. Stimulated +TL, 1.9 Gen 2. Stimulated +TL, 1.7 Gen 3. Stimulated +TL, 1.81 Gen 3. Stimulated +TL, 1.7 Gen 3. Stimulated +TL, 1.81 Gen 2. Unstimulated 1.9 Gen 2. Unstimulated 1.9 Gen 2. Unstimulated 1.81 Gen 3. Unstimulated 1.81 Gen 3. Unstimulated 1.9 Gen 3. Unstimulated 1.9 Gen 3. Unstimulated 1.9 Gen 3. Unstimulated 1.61	3976_292 3471_282	3091.07 3552.941 77777 3352.941 77777 13421.925 16700.175 17638.195	2926.474 2994.844 3234.126 27777 12822.143 41596.266 16007.402 11.136 16.076 53.672 59.939 20.614 19.718 33.321 101.73 <0.000	3091 (595 3201) (3953) 3201 (3953) 3201 (3953) 3187 732 3565 818 \$\text{PDIVIOL}\$ (13)142 (63)33 (1509 22) (16028 7596) 29 746 29 (552 559) 99 17 869 21 563 16 7465 116 9593333 #DIVIOL #DIVI	#DIV/01 15303.54 27.10 43.28
4	\$ 886 \$ 647 \$ 832 \$ 503.563 \$ 503.563 \$ 503.563 \$ 503.563 \$ 256.406 \$ 577 \$ 644 \$ 0.503 \$ 129.057 \$ 0.042 \$ 0.319 \$ 65.323 \$ 0.237 \$ 0.042	251 388 0.357 2.042 251 388 0.857 2.042 251 388 0.856 0.042 0.509 121 737 0.35 0.042 0.309 62 395 0.233 0.043	0.589 0.045 0.045 0.045 0.045 0.045 244.654 0.516 123.877 0.346 0.042 0.304 0.0239 0.042	3435 858 3411 6 046 3 266 3 267 408 474 408 474 408 474 408 474 50 76 262 0 376 0 481 0 259 48 276 3910 387 0 VPFLW 77777 77777	2933 14 3:158 0:045 3:154 333 492 0:01 429 0:528 0:043 0:436 114.706 3097.07 0:226 0:043 0:243 43.863 3552 641 0VRFLW ????? ?????	968.66 2005.979 31.122 0.047 31.33 325.164 2926.474 0.518 0.045 0.472 0.041 0.229 39.927 3234.126 0.VRFLW	0.041 0.087 2.922 8.766 0.119 0.041 0.078 0.931 8.383 0.115 0.041 0.074 0.204 0.204 0.073 <0.000 0.143 0.041 0.102 6.579 19.738 0.122 0.193 0.193 0.000 0.143 0.041 0.193 0.193 0.0193 0.0193 0.0193 0.000 0.000 0.0000 0.00000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.00000 0	0.041 0.085 2.418 7.254 0.118 0.042 0.076 0.531 4.779 0.116 0.043 0.072 4.0072 4.0000 6.000 6.111 0.043 0.067 6.000 6.135 0.044 0.000 6.135 0.042 0.000 6.135 0.042 0.003 6.144 0.023 6.144 0.023 6.144 0.023 0.043	0.042 0.09 3.712 11.136 0.125 0.044 0.082 1.786 16.076 0.125 0.042 0.083 1.988 53.672 0.119 0.042 0.077 0.77 0.74 0.103 0.103 0.104 0.103 0.104 0.103 0.104 0.103 0.104 0.103 0.104 0.103 0.104 0.103 0.104	0.042 0.069 <0.000 <0.000 0.012 0.042 0.07 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 0.0000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.0000 0.000 0.00	0.041 0.069 0.000 0.000 0.112 0.041 0.07 0.000 0.114 0.07 0.000 0.	0.042 0.065 -0.000 -0.000 0.114 0.042 0.072 -0.000 -0.115 0.043 0.071 -0.000 -0.000 -0.110 0.043 -0.000 0.111 0.042 -0.000 0.111 0.042 -0.000 0.111 0.042 -0.000 0.0000 0.00000 0.0000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.000000	Dotal Concentratio rel sel factor Josephan Josep	Gen 2. Stimulated +TL 1. 9 Gen 2. Stimulated +TL 1. 27 Gen 2. Stimulated +TL 1. 13 Gen 3. Stimulated +TL 1. 13 Gen 3. Stimulated +TL 1. 19 Gen 3. Stimulated +TL 1. 19 Gen 3. Stimulated +TL 1. 19 Gen 3. Stimulated +TL 1. 127 Gen 3. Stimulated +TL 1. 121 Gen 2. Unstimulated 1. 19 Gen 2. Unstimulated 1. 19 Gen 2. Unstimulated 1. 19 Gen 3. Unstimulated 1. 27 Gen 3. Unstimulated 1. 27 Gen 3. Unstimulated 1. 29 Gen 3. Media Control Stimulated 1. 3 Gen 2. Media Control Stimulated 1. 3 Gen 3. Media Control Stimulated 1. 3	3976_292 3471_282	3091.07 3552.941 77777 3352.941 77777 13421.925 16700.175 17638.195	2926 474 2994 844 3234 126 27777 12822 143 14596 268 16007 402 11,136 16,076 53,672 59,939 20,614 19,718 33,321 101,73 <0,000 <0,000	3091 (598 3201) 3093 33 3187 732 3321 3983 33 3187 732 3365 818 30 50 50 50 50 50 50 50 50 50 50 50 50 50	#DIV/01 15303.54 27.10 43.28
	0.044 0.047 0.048 0.048 0.048 0.0926 256.406 0.577 0.044 0.533 129.057 0.042 0.319 65.323	\$ 888 \$ 046 \$ 806 \$ 491 203 \$ 0442 \$ 0.954 \$ 2.914 \$ 251 388 \$ 0.851 \$ 0.042 \$ 0.509 \$ 121 737 \$ 0.35 \$ 0.042 \$ 0.309 \$ 62 395 \$ 0.043 \$ 0.043 \$ 0.19	3.888 6.047 3.891 503.336 0.995 0.695 2.894 244.654 0.56 0.044 0.516 123.877 0.346 0.042 0.304 61.049	3435 858 3411 2 046 3 298 408 474 3676 262 0 376 2 045 0 327 0 327 0 327 0 327 0 327 0 327 0 327 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	293.14 3:198 0:045 3:194 333.492 0:528 0:528 0:528 0:439 0:43 0:243 0:243 0:243 0:243 10:486 0:486 0:497 0:2777 10:2777 1491.325 1491.325	968.66 2005.979 11.127 0.047 3.13 325.164 2026.474 0.0518 0.045 0.479 110.92 2994.844 0.27 3.927	0.041 0.087 2.922 8.766 0.119 0.041 0.078 0.931 8.383 0.115 0.041 0.074 0.074 0.074 0.079 5.632 0.115 0.041 0.073 0.115 0.041 0.073 0.115 0.041 0.074 0.029 0.042 0.073 0.045 0.045 0.046 0.	0.041 0.085 2.418 7.254 0.118 0.042 0.076 0.531 4.779 0.116 0.044 0.072 0.000 0.11 0.043 0.067 0.000 0.135 0.044 0.072 0.000 0.144 0.072 0.000 0.145 0.043 0.067	0.042 0.09 3.712 11.136 0.042 0.044 0.082 1.786 16.076 0.125 0.042 0.083 1.988 53.672 0.119 0.042 0.077 0.145 0.042 0.013 0.013 0.014 0.01	0.042 0.069 <0.000 <0.000 0.012 0.07 <0.000 0.111 0.07 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.00000 <0.0000 <0.0000 <0.0000 <0.0000 <0.00000 <0.00000 <0.00000 <0.00000 <0.00000 <0.00000 <0.00000 <0.00000 <0.00000 <0.00000 <0.000000 <0.000000 <0.00000000	0.041 0.069 <0.000 <0.000 0.112 0.041 0.07 <0.000 0.114 0.041 0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.0000 <0.00000 <0.0000 <0.0000 <0.0000 <0.00000 <0.00000 <0.00000 <0.0000 <0.00000 <0.00000 <0.00000 <0.00000 <0.00000 <0.00000 <0.00000 <0.000000 <0.000000 <0.00000000	0.042 0.065 <0.000 0.114 0.042 0.072 <0.000 0.115 0.043 0.071 <0.000 <0.000 <0.000 0.115 0.042 0.0000 0.0000 0.0000 0.00000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.00000 0.0000 0.00000 0.00000 0.00000 0.00000 0.00000 0.00000 0.000000	Dotal Concentratio III III III III III III III III III I	Gen 2. 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	0.84 0.94 0.94 0.94 0.94 0.94 0.94 0.94 0.9	\$38 5.046 \$2.046 \$3.000 \$3	1.568 0.047 503.336 0.3595 0.048 0.556 0.044 0.3516 1.23.877 0.346 61.049 0.197 31.253 0.193 0.1	3435 858 3 404 3 505 4 08 474 408 474 408 474 408 474 408 474 408 474 408 474 408 474 408 474 408 474 408 474 408 478	2933 He	988 86 2905 978 11:127 0:047 3:25:164 2026 474 0:188 0:045 0:045 0:047 0:27 0:041 0:29 39:927 7:277 7:	0.041	0.041 7.254 0.118 0.042 0.076 0.551 4.778 0.072 0.000 0.072 0.000 0.072 0.000 0.013 0.042 0.000 0.033 0.043 0.043 0.043 0.043 0.043 0.053 0.044 0.000 0.053 0.044 0.000 0.053 0.044 0.000 0.053 0.044 0.000 0.053 0.044 0.000 0.053 0.044 0.000 0.053 0.044 0.000 0.053 0.044 0.000 0.053 0.044 0.000 0.053 0.044 0.000 0.053 0.053 0.053 0.053 0.053 0.053 0.053 0.053 0.053 0.053 0.053 0.053 0.053 0.053 0.053	0.042 0.000	0.042	0.041	0.042	Detail Concentration of the Co	Gen 2-Stimulated +TL 1.9 Gen 2-Stimulated +TL 1.27 Gen 2-Stimulated +TL 1.27 Gen 2-Stimulated +TL 1.27 Gen 3-Stimulated +TL 1.27 Gen 2-Unstimulated 1.3 Gen 2-Unstimulated 1.9 Gen 2-Unstimulated 1.9 Gen 3-Unstimulated 1.3 Gen 3-Media Control Stimulated 1.3 Gen 2-Media Control Unstimulated 1.3 Gen 2-Media Control Unstimulated 1.3 Gen 2-Media Control Unstimulated 1.3	3976.292 347.1282 3910.387 322.3910.387 322.3910.387 3910.387 3910.387 3910.391 3	3091.07 3552.941 7777 3552.941 7777 17932.1925 16700.175 17932.195 √ 0.00 13.255 √ 0.000 171.988 √ 0.000 √ 0.000 √ 0.000 √ 0.000 √ 0.000 √ 0.000 ✓ 0.000	2926 474 2994 844 3234.126 77777 12822.143 41596.268 16007.402 11.136 16.076 53.672 59.939 20.614 19.718 33.321 101.73 <0.000 <0.000 <0.000 <0.000 <0.000 <0.000	3091 (598 3201) 3093 33 3187 732 3321 3983 33 3187 732 3365 818 30 50 50 50 50 50 50 50 50 50 50 50 50 50	#DIV/01. 15303.54
3	0.042 0.047 503.563 0.974 0.948 0.926 256.406 0.577 0.043 0.533 129.057 0.042 0.319 65.323 0.042 0.042 0.198 30.739 0.182 0.182 0.182 0.182 0.182 0.182 0.182 0.182 0.182 0.182 0.182 0.182 0.183 0.182 0.182 0.182 0.183 0	0.985 0.042 0.042 0.042 0.042 0.042 0.042 0.042 0.042 0.042 0.05 0.042 0.000 0.042 0.000 0.042 0.000 0.042 0.000 0.042 0.000 0.042 0.000 0.042 0.042 0.000 0.042 0	0.550 0.046 0.045 0.046 0.046 0.046 0.046 0.046 0.046 0.046 0.042 0.047 0.046 0.047	2.438.692.604.604.604.604.604.604.604.604.604.604	2933 14 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	988.66 988.66 988.67 10.127 10.127 10.137 10	0.041	0.041 7 254 0.058 2.418 0.042 0.042 0.072 0.531 0.772 0.116 0.042 0.072 0.072 0.072 0.072 0.072 0.073 0.073 0.073 0.073 0.073 0.073 0.073 0.073 0.073 0.073 0.073 0.073 0.073 0.073 0.088 0.116 0.088 0.116 0.088 0.117 0.088 0.118 0.088 0.119 0.089 0.073 0.093 0.119 0.089	0.042 0.000	0.042	0.041	0.042 0.000 0.011 0.041 0.000	Dotal Concentratio In	Sein 2. Stimulated +TL. 1.9 Gen 2. Stimulated +TL. 1.27 Gen 3. Stimulated +TL. 1.81 Gen 3. Stimulated +TL. 1.81 Gen 3. Stimulated +TL. 1.19 Gen 2. Unstimulated 1.3 Gen 2. Unstimulated 1.9 Gen 2. Unstimulated 1.9 Gen 3. Unstimulated 1.9 Gen 3. Unstimulated 1.9 Gen 3. Unstimulated 1.9 Gen 3. Stimulated 1.81 Gen 3. Stimulated 1.83 Gen 3. Media Control Stimulated 1.3 Gen 3. Media Control Stimulated 1.3 Gen 3. Media Control Stimulated 1.9 Gen 2. Media Control Stimulated 1.9 Gen 2. Media Control Stimulated 1.9	3976.292 341.282 3910.397 2928 3910.397 2928 3910.397 3910.39	3091.07 3552.941 7777 3552.941 7777 15421.925 16700.175 17638.195 -7.254 4.779 <0.000 13.255 <0.000 171.968 <0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000	2926 474 2994 844 3234.126 2797 12822.143 14596.268 16.007.402 11.136 16.076 53.672 20.614 19.718 33.321 101.73 <0.000 <0.000 <0.000	3091 (598 3201) 3093 33 3187 732 3321 3983 33 3187 732 3365 818 30 50 50 50 50 50 50 50 50 50 50 50 50 50	#DIV/01. 15303.54
5	\$60,504 \$60,504 \$60,504 \$60,504 \$60,604 \$60	\$388.00 one \$1,000 one	3,550 3,047 3,550 3,500	3.438.882 0.016 3.9995 0.016 3.9995 0.017 0.017 0.0591 1.28.566 0.471 282 0.0591 1.28.566 0.471 282 0.0791 1.28.566 0.471 282 0.0791 1.28.566 0.017 0.017 1.28.566 0.017 0.017 1.28.566 0.017 1.28.566 0.017 1.28.566 0.017 1.28.566 0.017 1.28.566 0.017 1.28.566 0.017 0.017 0.017 1.28.566 0.017	2933 14 2 3 3 3 492 3 6 1 4 3 6 6 1 5 2 5 6 7 6 7 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7	986 66 20 20 5 7 9 1 1 2 2 2 2 2 2 4 4 2 4 2 2 2 2 4 4 4 5 2 4 2 2 2 4 4 4 5 2 4 4 4 5 2 4 4 4 6 2 4 4 4 5 2 4 4 4 6 2 4 4 4 5 2 4 4 4 6 2 4 4 4 5 2 4 4 6 2 4 4 4 5 2 4 4 6 2 4 4 4 5 2 4 4 5 4 4 6 2 4 4 4 5 4 6 2 4 4 4 6 2 4 4 6 2 4 4 6 2 4 4 6 2 4 4 6 2 4 4 6 2 4 4 6 2 4 4 6 2 4 4 6 2 4 4 6 2 4 4 6 2 4 4 6 2 4 4 6 2 4 4 6 2 4 4 6 2 4 4 6 2 4 4 6 2 4 4 6 2 4 4 6 2 4 6 2 4 6 2 4 4 6 2 4 6	0.041	0.041	0.042 0.082 1.786 0.092 0.082 1.786 0.082 1.786 0.082 1.786 0.082 1.786 0.082 1.786 0.082 1.786 0.082 0.083 0.082 0.083 0.082 0.083 0.082 0.083 0.082 0.083 0.082 0.083 0.082 0.083 0.082 0.083 0.082 0.084 0.083 0.082 0.084 0.083 0.082 0.084 0.083	0.042	0.041	0.042	Doris Concentrato al anticol a	Gen 2. Stimulated +TL, 1.9 Gen 2. Stimulated +TL, 1.27 Gen 3. Stimulated +TL, 1.23 Gen 3. Stimulated +TL, 1.13 Gen 3. Stimulated +TL, 1.19 Gen 3. Stimulated +TL, 1.19 Gen 3. Stimulated +TL, 1.19 Gen 3. Stimulated +TL, 1.27 Gen 3. Stimulated +TL, 1.21 Gen 2. Unstimulated 1.3 Gen 2. Unstimulated 1.27 Gen 3. Unstimulated 1.27 Gen 3. Unstimulated 1.27 Gen 3. Unstimulated 1.27 Gen 3. Unstimulated 1.3 Gen 3. Unstimulated 1.3 Gen 3. Unstimulated 1.3 Gen 3. Unstimulated 1.3 Gen 3. Media Control Stimulated 1.3 Gen 3. Media Control Unstimulated 1.3 Gen 2. Media Control Unstimulated 1.3 Gen 3. Media Control Unstimulated 1.3	Serie 262 341 282 341 282 341 282 341 282 341 282 341 282 341 282 341 282 341	3091.07 3552.941 7777 3552.941 7777 15421.925 16700.175 17638.195 -7.254 4.779 <0.000 13.255 <0.000 171.968 <0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000	2926 474 2994 844 3234.126 2994 844 3234.126 2994 844 3234.126 2917 12822.143 14566.268 16007.402 11.136 16.076 53.672 59.939 20.614 19.718 33.321 101.73 <0.000 <0.000 <0.000 <0.000 <<0.000 <<0.000	3091 (598 3201) 3093 33 3187 732 3321 3983 33 3187 732 3365 818 30 50 50 50 50 50 50 50 50 50 50 50 50 50	#DIV/01. 15303.54
1	0.042 0.047 503.563 0.974 0.948 0.926 256.406 0.577 0.043 0.533 129.057 0.042 0.319 65.323 0.042 0.042 0.198 30.739 0.182 0.182 0.182 0.182 0.182 0.182 0.182 0.182 0.182 0.182 0.182 0.182 0.183 0.182 0.182 0.182 0.183 0	0.985 0.042 0.042 0.042 0.042 0.042 0.042 0.042 0.042 0.042 0.05 0.042 0.000 0.042 0.000 0.042 0.000 0.042 0.000 0.042 0.000 0.042 0.000 0.042 0.042 0.000 0.042 0	0.550 0.046 0.045 0.046 0.046 0.046 0.046 0.046 0.046 0.042 0.042 0.047	2.438.692.604.604.604.604.604.604.604.604.604.604	2033 14 2 3 3 3 4 9 2 3 5 1 1 4 7 0 6 3 1 1 4 7 0 6 3 1 1 4 7 0 6 3 1 1 4 7 0 6 3 1 1 4 7 0 6 3 1 1 4 7 0 6 3 1 1 4 7 0 6 3 1 1 4 7 0 6 3 1 1 4 7 0 6 3 1 1 4 7 0 6 3 1 1 4 7 0 6 3 1 1 4 7 0 6 3 1 1 4 7 0 6 3 1 1 4 7 0 6 3 1 1 4 7 0 6 3 1 1 4 7 0 6 3 1 1 4 7 0 6 3 1 1 4 7 0 6 3 1 1 4 7 0 6 3 1 1 4 7 0 7 0 7 0 7 0 7 0 7 0 7 0 7 0 7 0 7	886 66 20 20 20 20 20 20 20 20 20 20 20 20 20	0.041	0.041 7 254 0.058 2.418 0.042 0.042 0.072 0.072 0.531 4.779 0.116 0.042 0.072 0.072 0.072 0.072 0.073 0.073 0.074 0.075 0.073 0.073 0.073 0.073 0.073 0.073 0.073 0.073 0.073 0.073 0.088 0.116 0.088 0.116 0.088 0.117 0.088 0.118 0.088 0.119 0.089 0.073 0.093 0.119 0.089	0.042 0.000	0.042	0.041	0.042 0.000 0.011 0.041 0.000	Cortine Consentration In Inc. Consentration	Gen 2. Stimulated +TL, 1.9 Gen 2. Stimulated +TL, 1.27 Gen 3. Stimulated +TL, 1.27 Gen 3. Stimulated +TL, 1.13 Gen 3. Stimulated +TL, 1.19 Gen 3. Stimulated +TL, 1.19 Gen 3. Stimulated +TL, 1.19 Gen 3. Stimulated +TL, 1.27 Gen 3. Stimulated +TL, 1.21 Gen 2. Unstimulated 1.3 Gen 2. Unstimulated 1.27 Gen 3. Unstimulated 1.27 Gen 3. Unstimulated 1.27 Gen 3. Unstimulated 1.27 Gen 3. Unstimulated 1.3 Gen 3. Unstimulated 1.3 Gen 3. Unstimulated 1.3 Gen 3. Unstimulated 1.3 Gen 3. Media Control Stimulated 1.3 Gen 3. Media Control Unstimulated 1.3 Gen 2. Media Control Unstimulated 1.3 Gen 3. Media Control Unstimulated 1.3	Serie 262 341 282 341 282 341 282 341 282 341 282 341 282 341 282 341 282 341	3091.07 3552.941 7777 3552.941 7777 15421.925 16700.175 17638.195 -7.254 4.779 <0.000 13.255 <0.000 171.968 <0.000 -0.000 -0.000 -0.000 -0.000 -0.000 -0.000	2926 474 2994 844 3234.126 2994 844 3234.126 2994 844 3234.126 2917 12822.143 14566.268 16007.402 11.136 16.076 53.672 59.939 20.614 19.718 33.321 101.73 <0.000 <0.000 <0.000 <0.000 <<0.000 <<0.000	3091 (598 3201) 3093 33 3187 732 3321 3983 33 3187 732 3365 818 30 50 50 50 50 50 50 50 50 50 50 50 50 50	#DIV/01. 15303.54

Figure 32

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	11000	1666	1666	BEAD) TH.	BEAD: TIL	BEAG+TOL	24- 01C	2A-M€	SA-MC	2A: Unstimulated	Unstimblished	Linshmolated	Well ID	:			- 1	
***************************************	(1900)	11000011	1300	2	3	3		3				3	Co no/Dil					
	(Adda)	1140411	No.	24-	24	24	28-600	2A-MC	2A-MC	26. Chatimulated	2A-	24	Wellin	:	:		:	
****** * *****				BEAR TK	BEAR-TIL	BEAD-FIL					Distribulated:	Unstimulated	St.		4			
-	**************************************		*****	35	74.	761			***************************************		74.	74.	3		:		- :	
	VISSON!	163641	11000	BEAD TO	BEAD HIL	BEAD-TH.	24 MC	2AM2	24-MC	24 kinstruktion	Grehmadated	Cristinglister	Well ID	:	:		:	
	1100011			27	27	27	27	27	27	27	27	27	Cono/Dil	:				
				2A-	2A	24-	ZAMC	SAME	SA-MC	ZA-Cyristim (Isba)	24	24	WALID					
- SSSS				BEAD TR	BRAC: UL	BRAGRA					Continuent	Linstmotided						
***************************************	WW.	777	111/4/11	394	26	24	91 28-	83 284) At	21	81	51	Cond/Dil					
	1/2009/	12000	18885	BEAD TH	EEAC TIL	EEAS-TIL	Distinutated:	Licefortulated	: 26-Unatinolated	25.860	26-MC	26-MC	Well ID	i .			1	
- B000000000000000000000000000000000000			1168611		1 3	3	3		4	9		9	Cono/Dil	:	:			
				26	28	29	29	28	28-Chahirulatik	200-600	26-MC	26-MC	Well ID	:				
- Marie - Mari				BEAD TO	BEADERIC	BEAD+ DE	Chetimulated:	Linshroubled.	. Are consultant				M		A			
	11362	1190911	11300	9	9	9	9	9	9	9	9	9	Cond/Dil					
	(NAME)	1996	15000	READ TO	BRAC-TIL	READ-DIG	Continuisted	Unstignalebad	2B-Dostinblated	2B-MC	2B-MC	ZB-MC	Well ID		1			
	THE STATE OF			27	DECRUT OF	BE THE CO.	AND DESCRIPTION OF THE PARTY OF	Orean mean	97	97	0.7	0.7	Si Canordii		1			
	MILLION IN			20	28	26	26	26	1				3	:	:		1	
B	MANAGE		(Helle)	HEAD) TH	BEAD TH	BEAGGIL	Dosimulated:	Unetichatetel	28-Gristimulated	25:860	S8-MC	28-MC	Well ID		1			
	IIIIIII)			- 61	81	81	St	84	84	61	81	81	Cond/Dil					
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24.1	<u> </u>			·	÷			.										
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300000000000000000000000000000000000000	8000000	30002000	100000000	\$6000000000000000000000000000000000000		988888888888		300000000000000000000000000000000000000	S 4000000000000000000000000000000000000			800000000000000000000000000000000000000	3	2A-beads+TIL 1:3	1		#DIV/0!	
	VANNA.	THE STATE OF THE S	CONTRACT OF THE PARTY OF THE PA	Manager			0.079	0.079	0.081	0.18	0.198	0.191	450	2A-beads+TIL 1:9	4656.178		49 4919.92	7 5124.412
	0.948	0.049	EKO E	0.062	0.052	0.052	0.042	0.042	9.043	0.042	0.043	0.042	570	:2A-beads+TIL 1:27	4916,763	5266.064 5189.9	55: 5124.26	1
	Manuel .	((8)488))	UKKHI)	HIIIKIIII	HIIIHHIII	HIHAHIII	0.037	0.037	0.037	0.138	0.156	0.149	De ta	2A-beads+TIL 1:81	5249.956	5464.506 5272.6	86 5329.04	9
	951.995	1012.581	1035.454	1479.442	>1500.000	>1500.000	0.379	0.287	0.472	37.604	44.509	41.927	n)					
	1			4438.326	>4500.000	>4500.000	1.137	0.861	1.417	112.812	133.527	125.78	xdifactor :	2B-beads+TIL 1:3	:77777	77777 77777	#DIV/0!	
	1,221	122	1,352	1.286	1.361	1,352	0.077	0.077	0.077	0,109	0.115	0.114	450	2B-beads+TIL 1:9	1		#DIV/0	
	0.546	0.046	5.048	0.046	0.047	0.047	0.042 0.035	0.033	0.042 0.035	0.042	0.043 0.072	0.042	De ta	2B-beads+TIL 1:27 2B-beads+TIL 1:81	15284.891	13019.2 16306.8 13205.761 16467.2	87: 14870.3 37: 15253.2	
- 10000 5 0000	496,244	3000	511.027	0.2180		300000000000000000000000000000000000000	<0.000	<0.000	<0.000	0,067 10,74		0.072	(Concentratio	2B-Deads+IIL I.61	10000.04	13203.761 10467.2	31 10200.2	1
	495.244	495.812	511.027	517.353	563,806	558.817					12.637	12.564	n)		1			
	0.677	0.661	0.661	4656.178 -0.531	5074.253 0.563	5029.349 0.555	<0.000 0.075	<0.000 0.074	<0.000 0.075	96.66 9.087	113.737 0.096	113.077 0.091	xdifactor	2A-Unstimulated 1:3	112.812 96.66		78: 124.039 77: 107.824	
	0.043	0.944	5 044	0.031	0.045	0.043	0.042	0.042	0.042	0.087	0.045	0.042	570	2A-Unstimulated 1:27	76.848		74: 107.55	2
	0.634	0.637	2.637	0.488	0.616	2.511	0.033	0.032	0.033	0.045	0.05	0.049	De ta	;2A-Unstimulated 1:81	71.65		87; 90.0796	
	245.876	247.384	247,428	182.102	195.039	192.221	<0.000	< 0.000	< 0.000	2.846	4.883	4.221	(Concentratio		:			
	3			4916.763	5266.064	5189.955	<0.000	<0.000	<0.000	76.848	131.834	113.974	xdifactor	2B-Unstimulated 1:3	317.235	324.939 224.7	65: 288.979	7 236 1614
100000000000000000000000000000000000000	0.406	0.495	5.437	0.251	0.257	0.25	0.075	0.075	0.077	0.082	0.081	0.064	450	2B-Unstimulated 1:9	285.917		37: 266.16	
	0.044	0.043	0.044	0.044	0.043	0.042	0.042	0.043	0.043	0.944	0.042	0.844	570	2B-Unstimulated 1:27	205.324	161.226 93.4	86 153.338	7:
	0.363	0.362	9.363	0.207	0.214	0.208	0.033	0.032	0.035	0.039	0.039	0.04	De ta	2B-Unstimulated 1:81				
B0000000000000000000000000000000000000	128.798	128.379	128.798	64.814	67.463	65.095	<0.000	< 0.000	<0.000	0.885	1.014	1.438	(Concentratio		1			
	3			5249.956	5464.506	5272.686	<0.000	< 0.000	<0.000	71.65	82.102	116.487	xdifactor	:2A-Media Control 1:3	1.137	0.861 1.4	17: 1.13833	3 1.138778
	0.244	0.241	0.241	OVRFLW	OVRFLW	OVRFLW	0.35	0.356	0.275	0.078	0.079	0.079	H50	2A-Media Control 1:9			į	
10000000000000000000000000000000000000	0.042	0.042	0.042	?????	?????	?????	0.043 0.307	0.043 0.314	0.043 0.232	0.042 0.036	0.042 0.037	0.043 0.036	De ta	:2A-Media Control 1:27 2A-Media Control 1:81				
	62.572	61.493	61.533	22222	22222	22222	105,745	108,313	74.922	0.079	0.318	<0.000	(Concentratio		÷			
B33333333	3	31,463		22222	22222	77777	317.235	324.939	224.765	0.237	0.953	<0.000	n] xdifactor	20 Madia Control 1:2		0.052 <0.000		6 4 47405
***********	0.166	0.165	0.161	<i>IIIIIIIIIII</i>	anii ilia	MANAGERITA	0.165	324.939 0.17	0.146	0.237	0.953	<0.000 0.078	Asn .	2B-Media Control 1:3 2B-Media Control 1:9	: 0.237 : 0.457	0.953 < 0.000 4 25 < 0.000	2.353	5: 1.47425 5:
B0000000000000000000000000000000000000	0.042	0.043	0.043		0.050	100000	0.043	0.042	8 045	0.042	0.042	0.042	570	2B-Media Control 1:27		1.20 -0.000	: 2.555	7
	0.124	0.122	0.119	IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII	HAHAIIR	KINARATIK	0.123	0.128	0.101	0.036	0.037	0.035	De ta	2B-Media Control 1:81				
10000000000000000000000000000000000000	31.999	31.384	30.079	>1500.000	1346.731	>1500.000	31.769	33.579	23.374	0.051	0.472	<0.000	[Concentratio		:			
	1			>13500.000	12120.579	>13500.000	285.917	302.211	210.37	0.457	4.25	<0.000	xd i factor		:			
	0.122	0.119	0.117	3:371	1.184	1.446	0.102	0.097	0.092	0.072	0.072	0.07	450					
100000000000000000000000000000000000000	0.043	0.042	0.043	0.062	0.048	0.062	0.043	0.044	0.046	0.043	0.046	0.043	570					
100000000000000000000000000000000000000	0.076	0.076	0.074	000000000000000000000000000000000000000	00000000	1.596	0.058	0.054	0.046	0.029	0.028	0.027	De ta	:	:		1	
100000000000000000000000000000000000000	14.956	14.181	13.334	566.107	482.193	603.959	7.605	5.971	3.462	<0.000	<0.000	<0.000	n1 :		1		-	
	1	ļ	ļ	15284.891	13019.2	16306.887	205.324	161.226	93.466	<0.000	<0.000	<0.000	xdifactor :		:		1	
	0.077	0.084 0.042	0.077 0.042	0.572	0.469 0.945	9.583 0.046	0.098	0,082 0,043	0.086 0.043	0.074 0.043	0.073 0.043	0.07 0.043	450					
PROFESSION OF THE PROFESSION O	0.042	0.042	0.042	0.526	0.045	9.537	0.049 0.05	0.043	0.043	0.043	0.043	0.043	De ta		·			
B0000000000000000000000000000000000000	<0.000	2.136	0.023	198.6	163,034	203.299	4.534	0.756	2.305	<0.000	<0.000	<0.000	(Concentratio				· · · · · · · · ·	
B0000000000000000000000000000000000000	-0.000		23	16086.64	13205.761	16467.237	367.254	61.271	186.666	<0.000	<0.000	<0.000	[0]					

Figure 33

500000000000000	201200000000000000000000000000000000000	000000000000000000000000000000000000000	100000000000000000000000000000000000000	Processors and the second	100000000000000000000000000000000000000	10000020000	100000000000000000000000000000000000000	£00002000	200000000000000000000000000000000000000	50500000000000000000000000000000000000		 ,					;		
	MILLIN	minn.	minin	G603-D7	Sen 3.07	Gen 3:07	Gen 3-D7	Gen 3-D7	Gen 3-D7			 							
	1600		Messell 1	19T FR#	157 RUN		2ND RUN	2ND RUN	2ND RUN	Wel									
	1/2000	112000	1120003			Gen 2	Gen 2	Gen 3	Geo 2	Con	nc/Dil	 							
	(executive	September 1	Netter 1	Qeb 2 Q11		DILIGI	D11:2ND	D11 2ND		Wei	SI D								
**************************************				19T RUN	RUN	FAN	RUN	RUN	RUN										
	11600	1,1000	111000							Con	nc/Dil	 							
	(cook			G693-D16	Gen3 Dig ist	Gen.V Cis. Ist	Gen 3 D16 2ND	Gen 3- D16 2ND	Gen S D16 2ND	Wei	41D								
				ISTRUN	RUN	PUN	RUN	RUN	RUN										
	1188811	11200	111000							Con	nc/Dil	 							
				Gen 2 DIT		Gen 2 £11 (61)	Gen 2 D11 2ND	Gen 2 D11 2ND	Geo.2 D11.2ND	Wei	#ID								
- ESSENCE				19T FUN	RUN	FORM	RUN	RUN	RUN								- 1		
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				G69 2 D16	Gen.2	Gen.V	GenZ	Gen 2	Gen 2	Wei	!								
- 1000 4 000	(Heart)	11444	114464	ISTRUN	DIE IST RUN	CHE IST	C16 2ND RUN	C16 2NC	D16 2ND RUN	Vos	HID :								
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	Western)	(INTERNAL	(Lease)	19T RUN	DZZ (ST RUN	DZZ IST FORE	D22.2ND RUN	D22 2ND RUN	D22 2ND RUN	Wel	:								
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	MAH	(HHHH)		0.218	0.22	0.215	0.187	0.187	0.184	450	0	Dilution Factor=100			,				
					The second of														
			0.061	0.042	0.042	0.043	0.044	0.043	38888333	570		 	Deading		Dandina	Danellon	Dankan	Danmon	
					0.042	0.043 0.172	0.143	0.043	0.133	570 Det		 	Reading A				Reading B*100		Average
	1970.541	2046.905	1987.758	0.042						Det			Α	Reading B	С	A *100	B*100	C*100	Average
	1970.541 005	2046.905	1987.758	0.042 0.175	0.177	0:172	0.143	0.145	0.133	Det	ta oncentratio	Gen 3 Rep initiation 1st run Gen 3 Scale up 1st run		Reading B 126.082	С	A *100		C*100	12409.1
	8 Q85 3 G47	1.281 0.049	1 276 £ 517	0.042 0.179 124.53 0.415 0.043	0.177 126.082 0.412 0.042	0.172 121.662 0.435 0.042	0.143 99.302 0.384 0.043	0 145 100 904 0 382 0 944	0.133 92.083 0.356 0.044	Det (Coi	ta oncentratio	 Gen 3 Rep initiation 1st run	A 124.530	Reading B 126.082 280.328	C 121.662	A *100 12453.0	B*100 12608.2 28032.8	C*100 12166.2	12409.1 28752.7
	1 Q65 0.047 1.048	1.281 0.048 1.234	0.047 0.047 1.000	0.042 0.175 124.53 0.415 0.043 0.372	0 177 126 082 0 413 0 042 0 269	0.172 121.662 0.435 0.042 0.393	0.143 99.302 0.394 0.043 0.351	0 145 100.904 0.392 0.944 0.348	0.133 92.083 0.356 0.044 0.312	Det	ta oncentratio D	 Gen 3 Rep initiation 1st run Gen 3 Scale up 1st run Gen 3 Harvest 1st run	A 124.530 282.400 252.774	Reading B 126.082 280.328 247.768	121.662 299.854 250.557	A*100 12453.0 28240.0	B*100 12608.2 28032.8	C*180 12166.2 28985.4	12409.1 28752.7 25036.6
	8.095 9.649 8.048 877.734	1.281 0.048 1.234 1.051.728	1.276 2.317 1.228 1047.027	0.042 0.178 124.53 0.419 0.043 0.372 282.4	0.177 126.082 0.413 0.042 0.369 280.328	0.172 121.662 0.435 0.042 0.383 299.854	0.143 99.302 0.384 0.043 0.351 264.954	0.145 100.904 0.393 0.944 0.346 262.893	0.133 92.083 0.356 0.944 0.312 233.453		ta oncentratio 0 0 ta oncentratio	 Gen 3 Rep initiation 1st run Gen 3 Scale up 1st run Gen 3 Harvest 1st run Gen 2 Rep initiation 1st run	A 124.530 282.400 252.774 79.199	Reading B 126.082 280.328 247.768 77.702	C 121.662 299.854 250.557 93.523	A*100 12453.0 28240.0 25277.4 7819.9	B*100 12608.2 28032.8 24776.8 7770.2	C*100 12166.2 28985.4 28085.7 8352.3	12409.1 28752.7 25036.6 8347.5
	1 Q95 0.049 1.048 877.734 0.683	1.281 0.048 1.284 1051.728 0.682	1 276 2 047 1 228 1047 027 5 68	Q 043 Q 179 124.53 Q 415 C 043 Q 372 282.4 C 378	0.177 126.082 0.413 0.042 0.269 280.328 0.372	0.173 121.662 0.435 0.042 0.393 299.854 0.378	0.143 99.302 0.384 0.042 0.351 264.954 0.358	0.145 100.904 0.382 0.944 0.348 262.893 0.328	0.133 92.083 0.356 0.944 0.312 233.453 0.33		ta D D ta D ta	 Gen 3 Rep initiation 1st run Gen 3 Scale up 1st run Gen 3 Harvest 1st run Gen 2 Rep initiation 1st run Gen 2 Scale up 1st run	A 124.530 282.400 252.774 79.199 136.754	Reading B 126.082 280.328 247.768 77.702 131.526	C 121.662 299.854 250.557 93.523 131.682	A*100 12453.0 28240.0 25277.4 7819.8 13675.4	8*100 12608.2 28032.8 24776.8 7770.2 12152.6	C*100 12166.2 28985.4 25065.7 8352.3 12168.2	12409 1 28752 7 25036 6 8347 5 13332 1
	8 QR5 8 GR7 8 948 877.734 8 683 0 045	1.281 0.048 1.294 1.051.728 0.682 0.044	1.276 9.087 4.238 1047.027 5.68 0.044	9.042 9.179 124.53 9.419 0.043 9.372 282.4 0.378 9.043	0.177 126.082 0.413 0.042 0.369 280.328 0.372 0.043	0.173 121.662 0.435 0.042 0.393 299.854 0.378 0.043	0.143 99.302 0.384 0.043 0.351 264.954 0.388 0.043	0.145 100.904 0.389 0.944 0.348 262.893 0.328 0.043	0.133 92.083 0.356 0.044 0.312 233.453 0.33 0.43		ta uncentratio u ta necentratio	 Gen 3 Rep initiation 1st run Gen 3 Scale up 1st run Gen 3 Harvest 1st run Gen 2 Rep initiation 1st run	A 124.530 282.400 252.774 79.199	Reading B 126.082 280.328 247.768 77.702 131.526	C 121.662 299.854 250.557 93.523 131.682	A*100 12453.0 28240.0 25277.4 7819.8 13675.4	B*100 12608.2 28032.8 24776.8 7770.2	C*100 12166.2 28985.4 25065.7 8352.3 12168.2	12409 1 28752 7 25036 6 8347 5 13332 1
	1 Q95 0.049 1.048 877.734 0.683	1.281 0.048 1.284 1051.728 0.682	1 276 2 047 1 228 1047 027 5 68	Q 043 Q 179 124.53 Q 415 C 043 Q 372 282.4 C 378	0.177 126.082 0.413 0.042 0.269 280.328 0.372	0.173 121.662 0.435 0.042 0.393 299.854 0.378	0.143 99.302 0.384 0.042 0.351 264.954 0.358	0.145 100.904 0.382 0.944 0.348 262.893 0.328	0.133 92.083 0.356 0.944 0.312 233.453 0.33		ta D D ta nocentratio D ta nocentratio	 Gen 3 Rep initiation 1st run Gen 3 Scale up 1st run Gen 3 Harvest 1st run Gen 2 Rep initiation 1st run Gen 2 Scale up 1st run	A 124.530 282.400 252.774 79.199 136.754	Reading B 126.082 280.328 247.768 77.702 131.526	C 121.662 299.854 250.557 93.523 131.682	A*100 12453.0 28240.0 25277.4 7819.8 13675.4	8*100 12608.2 28032.8 24776.8 7770.2 12152.6	C*100 12166.2 28985.4 25065.7 8352.3 12168.2	12409 1 28752 7 25036 6 8347 5 13332 1
	3.085 0.049 3.048 877.734 0.663 0.045 0.638 510.008	1.28 0.048 1.234 1.051.728 0.682 0.044 0.639 510.619	0.047 0.278 1047.027 5.88 0.044 0.637 508.261 0.382	9.042 9.179 124.53 9.445 6.043 9.372 282.4 0.378 0.042 0.396 252.774 0.162	0.177 126.082 0.413 0.042 0.269 280.328 0.372 0.043 0.33	0.173 121.662 0.435 0.042 0.393 299.854 0.378 0.043 0.333	0.143 99.302 0.384 0.043 0.356 264.954 0.358 0.043 0.313	0.145 100.904 0.389 0.944 0.348 262.893 0.338 0.043 0.295 219.211	0 133 92 083 0 356 0 944 0 312 233 453 0 043 0 287 212 888 0 149		ta D D La D Concentratio	Gen 3 Rep initiation 1st run Gen 3 Scale up 1st run Gen 3 Harvest 1st run Gen 2 Rep initiation 1st run Gen 2 Scale up 1st run	A 124.530 282.400 252.774 79.199 136.754 117.564	Reading B 126.082 280.328 247.768 77.702 131.526	C 121.662 299.854 250.557 93.523 131.682	A*100 12453 0 28240 0 25277 4 7819 9 13675 4 11756 4	8*100 12608 2 28032 8 24776 8 7770 2 12152 6 13012 5	C*100 12166.2 29985.4 29085.7 9352.3 12168.2 12189.5	12409.1 28752.7 25036.6 8347.5 13332.1 12319.5
	3.085 0.047 3.948 877.734 0.663 0.045 0.648 510.008 0.37 0.043	2.048 3.28 1051.728 2.682 0.044 3.638 510.619 0.38 0.045	0.047.027 6.88 0.044 5.88 0.044 5.637 508.261 0.382 0.943	0.042 0.178 124.53 0.415 0.043 0.372 282.4 0.378 0.043 0.336 252.774 0.162 0.048	0.177 126.082 0.413 0.042 0.369 280.328 0.372 0.043 0.33 247.768 0.156 0.042	0.173 121.662 0.435 0.042 0.393 299.854 0.378 0.043 0.043 250.557 0.177 0.042	0.143 99.302 0.384 0.042 0.361 264.954 0.398 0.043 0.313 233.943 0.155 0.043	0 145 100.904 9 382 0 944 0 348 262.893 0 398 0 398 0 295 219.211 0 15	0.133 92.083 0.356 0.044 0.312 233.453 0.33 0.287 212.888 0.149 0.043	Details (Co. 1) (Co. 1	ta oncentratio D Ta oncentratio D ta oncentratio D ta oncentratio	Gen 3 Rep initiation 1st run Gen 3 Scale up 1st run Gen 3 Harvest 1st run Gen 2 Rep Initiation 1st run Gen 2 Scale up 1st run Gen 3 Rep Initiation 2nd run Gen 3 Rep Initiation 2nd run	A 124.530 282.400 252.774 79.199 136.754 117.564 99.302 264.954	Reading B 126.082 280.328 247.768 77.702 131.526 130.125 100.904 262.893	C 121.662 299.854 250.557 93.523 131.682 121.895 92.083 233.453	A*100 12453 0 28240 0 25277 4 7619 9 13675 4 11756 4 9930 2 26495 4	#*100 12608 2 28032 8 24776 8 7770 2 12152 6 13012 5 10090 4 26289 3	C*100 12166.2 28985.4 28088.7 8352.3 12168.2 12189.5 9208.3 23345.3	12409.1 28752.7 25036.6 8347.5 13332.1 12319.5 9743.0 25376.7
5	3.085 0.047 0.048 877.734 0.663 0.045 0.638 510.008 0.37 0.043 0.328	1.281 2.548 3.253 1051.728 2.682 0.044 3.639 510.619 2.38 0.045 0.335	1, 276 2, 047 1, 228 1047, 027 5, 88 0, 044 9, 637 508, 261 0, 382 0, 943 9, 338	0.042 0.179 124.53 0.415 0.043 0.372 282.4 0.278 0.043 0.396 252.774 0.046 0.116	0.177 126.082 0.413 0.042 0.269 280.328 0.372 0.643 0.33 247.768 0.156 0.042 0.144	0.173 121.662 0.435 0.042 0.385 299.854 0.043 5.333 250.557 0.177 0.042 0.195	0.143 99.302 5.384 9.043 6.385 264.954 0.388 0.043 0.313 233.943 0.155 0.943 0.112	0 145 100 904 0 389 0 044 0 346 262 893 0 228 0 043 0 295 219 211 0 15 9 344 0 106	0 133 92.083 0.356 9.944 0.312 233.453 0.33 0.043 0.287 212.888 0.149 0.043 0.106	Details (Control of the Control of t	ta oncentratio D Ta oncentratio D ta oncentratio D ta oncentratio	Gen 3 Rep initiation 1st run Gen 3 Scale up 1st run Gen 3 Harvest 1st run Gen 2 Rep initiation 1st run Gen 2 Scale up 1st run Gen 2 Harvest 1st run Gen 3 Rep initiation 2nd run	A 124.530 282.400 252.774 79.199 136.754 117.564	Reading B 126.082 280.328 247.768 77.702 131.526 130.125	C 121.662 299.854 250.557 93.523 131.682 121.895	A*100 12453 0 28240 0 25277 4 7619 9 13675 4 11756 4 9930 2 26495 4	#*100 12608 2 28032 8 24776 8 7770 2 12152 6 13012 5 10090 4 26289 3	C*100 12166.2 28985.4 28088.7 8352.3 12168.2 12189.5 9208.3 23345.3	12409.1 28752.7 25036.6 8347.5 13332.1 12319.5 9743.0 25376.7
	3.085 0.042 3.048 877.734 0.683 0.045 0.638 510.008 0.37 0.32 0.32 0.32 0.32 0.32 0.32 0.32	1.28 .2 048 .234 1051.728 .2 682 .0 044 .3 638 .510.619 .2 38 .3 045 .9 335 .252.035	0.000 0.000	0.042 0.173 124.53 0.415 0.043 0.372 282.4 0.236 0.236 252.774 0.162 0.116 79.199	0.177 126.082 0.413 0.042 0.266 280.328 0.372 0.043 0.93 247.768 0.156 0.042 0.114 77.702	0.172 121.662 0.435 0.035 0.035 299.854 0.043 0.043 0.043 250.557 0.172 0.042 0.135 93.523	0.143 99.302 0.384 0.043 0.255 264.954 0.358 0.043 0.313 233.943 0.112 76.431	0.145 100.904 0.383 0.944 262.893 0.238 0.043 0.295 219.211 0.15 0.344 0.106 71.588	0.133 92.083 0.356 0.044 0.312 233.453 0.32 0.043 0.287 212.888 0.149 0.649 0.106 71.737	Det (1) (2) (3) (4) (4) (4) (4) (4) (4) (4) (4) (4) (4	ta Oncentratio ta noncentratio ta noncentratio ta noncentratio	Gen 3 Rep initiation 1st run Gen 3 Scale up 1st run Gen 2 Rep initiation 1st run Gen 2 Scale up 1st run Gen 3 Scale up 1st run Gen 3 Harvest 1st run Gen 3 Rep initiation 2nd run Gen 3 Scale up 2nd run Gen 3 Tenrest 2nd run	A 124,530 282,400 252,774 79,199 136,754 117,564 99,302 264,954 233,943	Reading B 126.082 280.328 247.768 77.702 131.526 130.125 100.904 262.893 219.211	C 121.662 299.854 250.557 93.523 131.682 121.895 92.083 233.453 212.888	A*100 12453.0 28240.0 25277.4 7819.6 13675.4 11756.4	12608.2 28032.8 24776.8 7770.2 12152.8 13012.5 10090.4 26289.3 21921.1	2100 12166.2 29985.4 25085.7 8352.3 12168.2 12189.5 9208.3 23345.3 21288.8	12409.1 28752.7 25036.6 8347.5 13332.1 12319.5 9743.0 25376.7 22201.4
	3.085 0.382 3.548 877.734 0.682 0.045 0.045 510.008 0.37 0.432 0.328 246.046	0.048 0.048 0.051.728 0.682 0.044 0.638 510.619 0.38 0.045 0.335 252.035	1047.027 6.88 0.044 6.637 508.261 0.382 0.043 9.338 254.91	2.042 2.179 124.53 0.415 0.043 2.824 0.278 0.043 0.278 0.043 0.278 0.042 0.276 0.162 0.046 0.116 79.199	0 177 126 082 0 413 0 042 0 289 280 328 0 372 0 033 247 768 0 156 0 042 0 114 77 702	0 173 121.662 5.435 0.042 0.293 299.854 0.043 0.043 250.557 0.177 0.042 0.135 9.3523 0.228	0.143 99.302 0.384 0.043 0.386 0.386 0.043 0.313 233.943 0.155 0.043 0.112 76.431	0.145 100.904 0.383 0.944 0.346 262.893 0.285 0.043 0.295 219.211 0.15 0.106 71.588	0.133 92.083 0.356 0.0244 0.312 233.453 0.33 0.0287 212.888 0.149 0.049 0.106 71.737	Det 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	ta noncentratio ta noncentratio ta noncentratio ta ta noncentratio ta ta noncentratio	Gen 3 Rep initiation 1st run Gen 3 Scale up 1st run Gen 3 Scale up 1st run Gen 2 Rep initiation 1st run Gen 2 Scale up 1st run Gen 3 Harvest 1st run Gen 3 Scale up 2st run Gen 3 Harvest 2nd run Gen 3 Harvest 2nd run	A 124.530 282.400 252.774 79.199 136.754 117.564 99.302 264.954 233.943	Reading B 126.082 280.328 247.768 77.702 131.526 130.125 100.904 262.893 219.211 71.588	C 121.662 299.854 250.557 93.523 131.682 121.895 92.083 233.453 212.888	A*100 12453.0 28240.0 25277.4 7819.8 13675.4 11756.4 9830.2 26495.4 29394.3	#100 12608.2 28032.8 24776.8 7770.2 12152.6 13012.5 10090.4 26289.3 21921.1	2100 12166.2 28985.4 25055.7 8352.3 12168.2 12189.5 9208.3 23345.3 21288.8	12409 1 28752 7 25036 6 8347 5 13332 1 12319 5 9743 0 25376 7 22201 4
8	3.085 0.042 3.048 877.734 0.683 0.045 0.638 510.008 0.37 0.32 0.32 0.32 0.32 0.32 0.32 0.32	1.28 .2 048 .234 1051.728 .2 682 .0 044 .3 638 .510.619 .2 38 .3 045 .9 335 .252.035	0.000 0.000	0.042 0.173 124.53 0.415 0.043 0.372 282.4 0.236 0.236 252.774 0.162 0.116 79.199	0.177 126.082 0.413 0.042 0.266 280.328 0.372 0.043 0.93 247.768 0.156 0.042 0.114 77.702	0.172 121.662 0.435 0.035 0.035 299.854 0.043 0.043 0.043 250.557 0.172 0.042 0.135 93.523	0.143 99.302 0.384 0.043 0.255 264.954 0.358 0.043 0.313 233.943 0.112 76.431	0.145 100.904 0.383 0.944 262.893 0.238 0.043 0.295 219.211 0.15 0.344 0.106 71.588	0.133 92.083 0.356 0.044 0.312 233.453 0.32 0.043 0.287 212.888 0.149 0.649 0.106 71.737	Det in the state of the state o	ta necentratio ta ta necentratio ta ta necentratio ta necentratio ta necentratio ta necentratio	Gen 3 Rep initiation 1st run Gen 3 Scale up 1st run Gen 2 Rep initiation 1st run Gen 2 Rep initiation 1st run Gen 3 Scale up 1st run Gen 3 Rep initiation 2nd run Gen 3 Scale up 2nd run Gen 1 Rep initiation 2nd run Gen 2 Rep initiation 2nd run Gen 2 Rep initiation 2nd run	A 124,530 282,400 252,774 79,199 136,754 117,564 99,302 264,954 233,943	Reading B 126.082 280.328 247.768 77.702 131.526 130.125 100.904 262.893 219.211 71.588 132.695	121.662 299.854 250.557 93.523 131.682 121.895 92.083 233.453 212.888	A*100 12453.0 28240.0 25277.4 7619.6 13675.4 11756.4 9930.2 26495.4 23384.3 7643.1 14780.7	12608.2 28032.8 24776.8 7770.2 12152.8 13012.5 10090.4 26289.3 21921.1	2100 12166.2 2998.5.4 25055.7 9352.3 12168.2 12189.5 9208.3 21345.3 21288.8	12409 1 28752 7 25036 6 8347 5 13332 1 12319 5 9743 0 25376 7 22201 4
	3.085 3.048 877.734 4.6683 5.048 510.008 2.37 0.043 9.328 246.046 0.042	1281 9 048 1294 1051 728 9 682 0 044 9 638 510 619 9 38 9 38 9 38 2 52 035 6 219 9 042	0.047 027 0.888 0.044 0.637 508.261 0.382 0.043 0.338 254.91 0.22 0.045	0.042 0.173 124.53 0.415 0.043 0.372 282.4 0.376 0.042 0.396 252.774 0.162 0.116 79.199 0.205 0.044	0 177 126 082 0 442 0 269 280 328 0 372 0 43 247 768 0 156 0 042 0 114 77 702 0 227 0 043	0 173 121.662 5.435 9.042 0.393 299.854 9.378 0.043 5.337 250.557 0.177 0.042 0.135 93.523 93.523	0 143 99 302 5 384 9 043 6 355 264 954 9 339 6 343 9 313 9 313 0 155 9 043 0 112 76 431 9 253	0.145 100.904 9.383 9.044 0.346 262.893 0.328 0.043 0.295 219.211 0.15 9.344 0.106 71.588 0.235	0.133 92.083 9.356 9.944 0.312 233.453 0.287 212.888 0.149 0.049 0.106 71.73 0.222	Det in the state of the state o	ta Discontratio Discontratio Discontratio Discontratio Discontratio Discontratio Discontratio Discontratio Discontratio	Gen 3 Rep initiation 1st run Gen 3 Scale up 1st run Gen 2 Rep initiation 1st run Gen 2 Rep initiation 1st run Gen 3 Scale up 1st run Gen 3 Rep initiation 2nd run Gen 3 Scale up 2nd run Gen 1 Rep initiation 2nd run Gen 2 Rep initiation 2nd run Gen 2 Rep initiation 2nd run	A 124.530 282.400 252.774 79.199 136.754 117.564 99.302 264.954 233.943 76.431 147.807	Reading B 126.082 280.328 247.768 77.702 131.526 130.125 100.904 262.893 219.211 71.588 132.695	121.662 299.854 250.557 93.523 131.682 121.895 92.083 233.453 212.888	A*100 12453.0 28240.0 25277.4 7619.6 13675.4 11756.4 9930.2 26495.4 23384.3 7643.1 14780.7	12908 2 28032 8 24778 8 7770 2 12152 9 13012 5 10090 4 26289 3 21921 1 7158 8 19269 5	2100 12166.2 2998.5.4 25055.7 9352.3 12168.2 12189.5 9208.3 21345.3 21288.8	12409 1 28752 7 25036 6 8347 5 13332 1 12319 5 9743 0 25376 7 22201 4
	3 Q85 C Q47 3 Q48 3 Q48 6 77 73 C Q43 C Q4	1281 0.04e 1257-728 0.682 0.044 0.639 510.619 0.38 0.045 0.335 252.035 0.219 0.042 0.176 124.995 0.132	2.047 1047 0.27 6 88 0.044 9.637 508.261 0.382 0.043 0.338 254.91 0.22 0.045 0.175 123.909 0.133	2.042 2.175 124.53 9.415 5.043 6.572 282.4 0.396 252.774 0.166 0.116 79.199 0.295 3.044 0.191 136.754 0.21	0.177 126.082 0.413 0.042 0.289 280.328 0.33 0.47.768 0.156 0.042 0.114 77.702 0.227 0.043 0.33	0 173 121.662 0 435 0.042 0.298 0 043 0.378 0.043 0.433 0.250.557 0.177 0.042 0.135 93.523 0.043 0.288 0.043	0.143 99.302 0.384 9.043 0.264 9.64 9.64 9.64 9.64 9.64 9.64 9.64 9.	0.145 100.904 0.383 0.044 0.345 262.893 0.225 0.043 0.295 219.211 0.15 0.344 0.106 71.588 0.231 0.045 0.106	0.133 92.083 0.356 9.944 0.312 233.453 0.33 0.033 0.0287 212.888 0.146 0.106 71.737 0.222 0.945 0.945 0.945 0.945 0.945 0.945 0.945 0.945 0.945 0.945 0.945 0.945 0.944 0.9	Det de	ta micentratio ta ta noncentratio ta noncentratio ta noncentratio ta noncentratio noncentratio	Gen 3 Rep initiation 1st run Gen 3 Scale up 1st run Gen 2 Rep initiation 1st run Gen 2 Rep initiation 1st run Gen 3 Scale up 1st run Gen 3 Rep initiation 2nd run Gen 3 Scale up 2nd run Gen 1 Rep initiation 2nd run Gen 2 Rep initiation 2nd run Gen 2 Rep initiation 2nd run	A 124.530 282.400 252.774 79.199 136.754 117.564 99.302 264.954 233.943 76.431 147.807	Reading B 126.082 280.328 247.768 77.702 131.526 130.125 100.904 262.893 219.211 71.588 132.695	121.662 299.854 250.557 93.523 131.682 121.895 92.083 233.453 212.888	A*100 12453.0 28240.0 25277.4 7619.6 13675.4 11756.4 9930.2 26495.4 23384.3 7643.1 14780.7	12908 2 28032 8 24778 8 7770 2 12152 9 13012 5 10090 4 26289 3 21921 1 7158 8 19269 5	2100 12166.2 2998.5.4 25055.7 9352.3 12168.2 12189.5 9208.3 21345.3 21288.8	12409 1 28752 7 25036 6 8347 5 13332 1 12319 5 9743 0 25376 7 22201 4
	0,000 0,001 1,008 877.734 0,682 0,045 510,008 0,37 0,003 0,32 246,046 0,216 0,043 0,173 122,514 0,133 0,043	1281 2348 228 1051.728 2.682 0.044 0.639 510.619 2.38 0.339 252.035 0.219 0.042 0.176 124.992 0.193 0.	8.047 1047 027 5 88 5 044 5 637 508 261 0 382 6 043 9 398 254.91 0 22 9 045 6 175 123.909 0 5044	2.042 2.175 124.53 0.415 0.043 0.372 282.4 0.036 0.043 0.036 0.042 0.096 0.116 79.199 0.225 0.042 0.042 0.044 0.116 0.116 0.116 0.116 0.116 0.116 0.116 0.043 0.043 0.045 0.046	0.177 126.082 0.413 0.048 280.328 0.372 0.043 0.33 247.768 0.156 0.042 0.114 77.702 0.22 0.23 0.23 0.23 0.23 0.23 0.23 0.	0.173 121.662 0.435 0.043 0.043 299.854 0.043 250.557 0.177 0.043 93.523 0.135 93.523 0.228 0.043 0.185 131.682	0.143 99.302 0.384 9.042 0.045 0.255 264.954 0.043 0.339 0.313 233.943 0.112 76.431 0.253 0.255 147.807 0.253	0.145 100.904 0.389 0.944 0.346 262.893 0.043 0.285 219.211 0.15 0.944 0.106 71.588 0.231 0.186 0.186 0.232 0.233	0.133 92.083 0.356 0.024 0.312 233.453 0.39 0.043 0.287 212.888 0.149 0.106 71.737 0.222 0.045 0.177 125.539 0.265 0.177 125.539	Det in the control of	ta Oncentratio Italian ta Italian Gen 3 Rep initiation 1st run Gen 3 Scale up 1st run Gen 2 Rep initiation 1st run Gen 2 Rep initiation 1st run Gen 3 Scale up 1st run Gen 3 Rep initiation 2nd run Gen 3 Scale up 2nd run Gen 1 Rep initiation 2nd run Gen 2 Rep initiation 2nd run Gen 2 Rep initiation 2nd run	A 124.530 282.400 252.774 79.199 136.754 117.564 99.302 264.954 233.943 76.431 147.807	Reading B 126.082 280.328 247.768 77.702 131.526 130.125 100.904 262.893 219.211 71.588 132.695	121.662 299.854 250.557 93.523 131.682 121.895 92.083 233.453 212.888	A*100 12453.0 28240.0 25277.4 7619.6 13675.4 11756.4 9930.2 26495.4 23384.3 7643.1 14780.7	12908 2 28032 8 24778 8 7770 2 12152 9 13012 5 10090 4 26289 3 21921 1 7158 8 19269 5	2100 12166.2 2998.5.4 25055.7 9352.3 12168.2 12189.5 9208.3 21345.3 21288.8	12409 1 28752 7 25036 6 8347 5 13332 1 12319 5 9743 0 25376 7 22201 4	
3	\$ 085 6 047 8 048 8 77 734 6 683 0 045 5 10 008 5 10 008 2 46 046 0 043 0 173 122 514 0 137 0 049	0.044 0.044 0.051,728 0.0682 0.044 0.035 0.045 0.335 252,035 0.043 0.044 0.	8.047 1047.027 5.88 5.044 6.637 5.08.25 6.043 9.382 2.043 9.392 2.045 6.175 123.909 0.132 0.044 0.089	0.042 0.175 124.53 0.415 0.043 0.372 282.4 0.376 0.038 0.286 0.286 0.116 79.190 0.286 0.044 0.116 79.190 0.285 0.044 0.116 79.190 0.285 0.044 0.116 79.190 0.285 0.044 0.116 0.285 0.044 0.045 0	8,177 126,082 0,413 0,042 0,269 280,328 0,323 0,323 0,324 0,144 0,114 0,77,02 0,227 0,042 0,155 131,526 0,327 0,32	0.173 121.662 5.435 0.042 0.385 299.854 0.043 0.043 0.043 0.043 0.135 9.352 0.042 0.125 0.126 0.126 0.043 0.186 0.043	0.143 99.302 0.394 9.043 0.355 0.356 0.043 0.313 233.943 0.155 0.043 0.112 76.431 0.255 12.255 147.807 0.228 0.228	0 145 100 904 9 398 9 944 0 346 0 262 993 0 238 0 043 0 295 219 21 0 15 9 944 0 109 71 588 0 231 0 265 132 695 0 233 0 233 0 246	0.133 92.083 0.356 0.924 0.312 233.453 0.332 0.287 212.888 0.149 0.106 71.737 0.222 0.945 0.177 125.539 0.263 0.3645 0.263	Det in	ta Oncentratio Italian ta Italian Gen 3 Rep initiation 1st run Gen 3 Scale up 1st run Gen 2 Rep initiation 1st run Gen 2 Rep initiation 1st run Gen 3 Scale up 1st run Gen 3 Rep initiation 2nd run Gen 3 Scale up 2nd run Gen 1 Rep initiation 2nd run Gen 2 Rep initiation 2nd run Gen 2 Rep initiation 2nd run	A 124.530 282.400 252.774 79.199 136.754 117.564 99.302 264.954 233.943 76.431 147.807	Reading B 126.082 280.328 247.768 77.702 131.526 130.125 100.904 262.893 219.211 71.588 132.695	121.662 299.854 250.557 93.523 131.682 121.895 92.083 233.453 212.888	A*100 12453.0 28240.0 25277.4 7619.6 13675.4 11756.4 9930.2 26495.4 23384.3 7643.1 14780.7	12908 2 28032 8 24778 8 7770 2 12152 9 13012 5 10090 4 26289 3 21921 1 7158 8 19269 5	2100 12166.2 2998.5.4 25055.7 9352.3 12168.2 12189.5 9208.3 21345.3 21288.8	12409 1 28752 7 25036 6 8347 5 13332 1 12319 5 9743 0 25376 7 22201 4	
	088 9 042 3 048 877 734 9 682 9 048 9 10 08 9 37 9 043 9 326 24 046 0 042 0 173 122 514 0 137 0 048 9 173 1 0 137 0 048 9 173 1 0 137 0 048 9 173 1 0 08 9 173 1 0 08 9 173 1 0 137 1 0 08 9 173 1 0 08 9 175 9 175	0.044 0.044 0.044 0.032 0.044 0.033 0.045 0.335 252.035 0.042 0.042 0.042 0.042 0.043 0.044 0.043 0.044 0.043 0.044 0.044 0.045 0.04	\$ 047 \$ 247 \$ 247 \$ 268 \$ 0.044 \$ 637 \$ 508.261 \$ 238 \$ 254.91 \$ 0.22 \$ 0.045 \$ 175 \$ 123.909 \$ 0.133 \$ 0.044 \$ 0.089 \$ 59.116	2.042 2.172 124.53 2.412 3.043 3.372 282.4 3.372 3.372 3.043 3.277 4.042 3.277 4.042 5.046 79.199 6.044	0.177 126.082 0.413 0.048 280.328 0.372 0.043 0.33 247.768 0.156 0.042 0.114 77.702 0.22 0.23 0.23 0.23 0.23 0.23 0.23 0.	0.173 121.662 0.435 0.043 0.043 299.854 0.043 250.557 0.177 0.043 93.523 0.135 93.523 0.228 0.043 0.185 131.682	0.143 99.302 0.384 9.042 0.045 0.255 264.954 0.043 0.339 0.313 233.943 0.112 76.431 0.253 0.255 147.807 0.253	0.145 100.904 0.389 0.944 0.346 262.893 0.043 0.285 219.211 0.15 0.944 0.106 71.588 0.231 0.186 0.186 0.232 0.233	0.133 92.083 9.356 9.044 4.312 233.453 0.324 4.043 9.263 0.106 71.737 9.228 9.049 0.106 71.737 9.228 0.107 0.107 0.007 0	Det in the state of the state o	ta noncentratio	Gen 3 Rep initiation 1st run Gen 3 Scale up 1st run Gen 2 Rep initiation 1st run Gen 2 Rep initiation 1st run Gen 3 Scale up 1st run Gen 3 Rep initiation 2nd run Gen 3 Scale up 2nd run Gen 1 Rep initiation 2nd run Gen 2 Rep initiation 2nd run Gen 2 Rep initiation 2nd run	A 124.530 282.400 252.774 79.199 136.754 117.564 99.302 264.954 233.943 76.431 147.807	Reading B 126.082 280.328 247.768 77.702 131.526 130.125 100.904 262.893 219.211 71.588 132.695	121.662 299.854 250.557 93.523 131.682 121.895 92.083 233.453 212.888	A*100 12453.0 28240.0 28247.4 7619.6 13675.4 11756.4 9930.2 26495.4 23384.3 7643.1 14780.7	12908 2 28032 8 24778 8 7770 2 12152 9 13012 5 10090 4 26289 3 21921 1 7158 8 19269 5	2100 12166.2 2998.5.4 25055.7 9352.3 12168.2 12189.5 9208.3 21345.3 21288.8	12409 1 28752 7 25036 6 8347 5 13332 1 12319 5 9743 0 25376 7 22201 4
	G88 G G42 3 948 877 734 G 663 G 0 948 G 648 510 008 G 246 G	G 448 G 448 G 448 G 682 G 644 G 638 G 648 G 38 G 648 G 38 G 648 G 78 G 78 G 78 G 78 G 78 G 78 G 78 G 7	0.047 0.088 0.047 0.27 0.886 0.044 0.637 508 261 0.382 0.043 0.398 254 91 0.23 0.175 123 909 0.044 0.089 59 116 0.089	0.042 0.175 124.53 0.415 0.043 0.372 282.4 0.376 0.038 0.286 0.286 0.116 79.190 0.286 0.044 0.116 79.190 0.285 0.044 0.116 79.190 0.285 0.044 0.116 79.190 0.285 0.044 0.116 0.285 0.044 0.045 0	8,177 126,082 0,413 0,042 0,269 280,328 0,323 0,323 0,324 0,144 0,114 0,77,02 0,227 0,042 0,155 131,526 0,327 0,32	0.173 121.662 5.435 0.042 0.385 299.854 0.043 0.043 0.043 0.043 0.135 9.352 0.042 0.125 0.126 0.126 0.043 0.186 0.043	0.143 99.302 0.394 9.043 0.355 0.356 0.043 0.313 233.943 0.155 0.043 0.112 76.431 0.255 12.255 147.807 0.228 0.228	0 145 100 904 9 398 9 944 0 346 0 262 993 0 238 0 043 0 295 219 21 0 15 9 944 0 109 71 588 0 231 0 265 132 695 0 233 0 233 0 246	0.133 92.083 0.356 0.924 0.312 233.453 0.332 0.287 212.888 0.149 0.106 71.737 0.222 0.945 0.177 125.539 0.263 0.3645 0.263	Det in	ta noncentratio	Gen 3 Rep initiation 1st run Gen 3 Scale up 1st run Gen 2 Rep initiation 1st run Gen 2 Rep initiation 1st run Gen 3 Scale up 1st run Gen 3 Rep initiation 2nd run Gen 3 Scale up 2nd run Gen 1 Rep initiation 2nd run Gen 2 Rep initiation 2nd run Gen 2 Rep initiation 2nd run	A 124.530 282.400 252.774 79.199 136.754 117.564 99.302 264.954 233.943 76.431 147.807	Reading B 126.082 280.328 247.768 77.702 131.526 130.125 100.904 262.893 219.211 71.588 132.695	121.662 299.854 250.557 93.523 131.682 121.895 92.083 233.453 212.888	A*100 12453.0 28240.0 28247.4 7619.6 13675.4 11756.4 9930.2 26495.4 23384.3 7643.1 14780.7	12908 2 28032 8 24778 8 7770 2 12152 9 13012 5 10090 4 26289 3 21921 1 7158 8 19269 5	2100 12166.2 2998.5.4 25055.7 9352.3 12168.2 12189.5 9208.3 21345.3 21288.8	12409 1 28752 7 25036 6 8347 5 13332 1 12319 5 9743 0 25376 7 22201 4
	088 9 042 3 048 877 734 9 682 9 048 9 10 08 9 37 9 043 9 326 24 046 0 042 0 173 122 514 0 137 0 048 9 173 1 0 137 0 048 9 173 1 0 137 0 048 9 173 1 0 08 9 173 1 0 08 9 173 1 0 137 1 0 08 9 173 1 0 08 9 175 9 175	0.044 0.044 0.044 0.032 0.044 0.033 0.045 0.335 252.035 0.042 0.042 0.042 0.042 0.043 0.044 0.043 0.044 0.043 0.044 0.044 0.045 0.04	\$ 047 \$ 247 \$ 247 \$ 268 \$ 0.044 \$ 637 \$ 508.261 \$ 238 \$ 254.91 \$ 0.22 \$ 0.045 \$ 175 \$ 123.909 \$ 0.133 \$ 0.044 \$ 0.089 \$ 59.116	2.042 2.172 124.53 2.412 3.043 3.372 282.4 3.372 3.372 3.043 3.277 4.042 3.277 4.042 5.046 79.199 6.044	8,177 126,082 0,413 0,042 0,269 280,328 0,323 0,323 0,324 0,144 0,114 0,77,02 0,227 0,042 0,155 131,526 0,327 0,32	0.173 121.662 5.435 0.042 0.385 299.854 0.043 0.043 0.043 0.043 0.135 9.352 0.042 0.125 0.126 0.126 0.043 0.186 0.043	0.143 99.302 0.394 9.043 0.355 0.356 0.043 0.313 233.943 0.155 0.043 0.112 76.431 0.255 12.255 147.807 0.228 0.228	0 145 100 904 9 398 9 944 0 346 0 262 993 0 238 0 043 0 295 1 0 15 9 944 0 109 71 588 0 231 0 265 1 32 695 0 233 0 233 0 233 0 246	0.133 92.083 9.356 9.044 4.312 233.453 0.324 4.043 9.263 0.106 71.737 9.228 9.049 0.106 71.737 9.228 0.107 0.107 0.007 0	Det de	ta oncentratio D Italia Italia Italia Occupantatio D La Italia Occupantatio D La La La La La La La La La	Gen 3 Rep initiation 1st run Gen 3 Scale up 1st run Gen 2 Rep initiation 1st run Gen 2 Rep initiation 1st run Gen 3 Scale up 1st run Gen 3 Rep initiation 2nd run Gen 3 Scale up 2nd run Gen 1 Rep initiation 2nd run Gen 2 Rep initiation 2nd run Gen 2 Rep initiation 2nd run	A 124.530 282.400 252.774 79.199 136.754 117.564 99.302 264.954 233.943 76.431 147.807	Reading B 126.082 280.328 247.768 77.702 131.526 130.125 100.904 262.893 219.211 71.588 132.695	121.662 299.854 250.557 93.523 131.682 121.895 92.083 233.453 212.888	A*100 12453.0 28240.0 28247.4 7619.6 13675.4 11756.4 9930.2 26495.4 23384.3 7643.1 14780.7	12908 2 28032 8 24778 8 7770 2 12152 9 13012 5 10090 4 26289 3 21921 1 7158 8 19269 5	2100 12166.2 2998.5.4 25055.7 9352.3 12168.2 12189.5 9208.3 21345.3 21288.8	12409 1 28752 7 25036 6 8347 5 13332 1 12319 5 9743 0 25376 7 22201 4
	008 0 047 1 3948 877 734 0 663 0 048 0 638 1 1008 0 37 0 43 0 326 0 43 0 326 0 43 0 326 0 43 0 173 122 514 0 173 0 326 0 42 0 042 0 173 0 048 0	0.048 0.048 0.048 0.044 0.639 510.619 0.335 252.035 0.219 0.042 0.176 124.995 0.132 0.042 0.043 0.048	0.047 0.088 0.044 0.082 0.0382 0.0382 0.0382 0.0382 0.0382 0.045 0.175 123.909 0.175 123.909 0.044 0.089 59.116	2.042 2.172 124.53 2.412 3.043 3.372 282.4 3.372 3.372 3.043 3.277 4.042 3.277 4.042 5.046 79.199 6.044	0.177 126.082 0.413 0.042 0.289 280.328 0.372 0.043 0.39 247.768 0.156 0.042 0.114 77.702 0.227 0.943 0.185 131.52 0.322 0.944 0.185 131.52 0.322 0.322 0.323 0.323 0.33	0.173 121.662 5.435 0.042 0.385 299.854 0.043 0.043 0.043 0.043 0.135 9.352 0.042 0.125 0.126 0.126 0.043 0.186 0.043	0.143 99.302 0.384 0.043 0.285 264.954 0.339 0.313 233.943 0.115 76.431 0.255 0.048 0.112 76.431 0.255 0.048 0.205 147.807 0.205 147.807 0.208	0.145 100.904 0.389 0.944 0.346 262.893 0.228 0.043 0.295 219.211 0.15 0.944 0.106 71.588 0.231 0.295 0.186	0.133 92.083 9.356 9.044 4.312 233.453 0.324 4.043 9.263 0.106 71.737 9.228 9.049 0.106 71.737 9.228 0.107 0.107 0.007 0	Det de	ta necentratio ta ta necentratio ta ta ta ta necentratio ta ta necentratio ta necentratio ta necentratio ta necentratio ta necentratio ta necentratio	Gen 3 Rep initiation 1st run Gen 3 Scale up 1st run Gen 2 Rep initiation 1st run Gen 2 Rep initiation 1st run Gen 3 Scale up 1st run Gen 3 Rep initiation 2nd run Gen 3 Scale up 2nd run Gen 1 Rep initiation 2nd run Gen 2 Rep initiation 2nd run Gen 2 Rep initiation 2nd run	A 124.530 282.400 252.774 79.199 136.754 117.564 99.302 264.954 233.943 76.431 147.807	Reading B 126.082 280.328 247.768 77.702 131.526 130.125 100.904 262.893 219.211 71.588 132.695	121.662 299.854 250.557 93.523 131.682 121.895 92.083 233.453 212.888	A*100 12453.0 28240.0 28247.4 7619.6 13675.4 11756.4 9930.2 26495.4 23384.3 7643.1 14780.7	12908 2 28032 8 24778 8 7770 2 12152 9 13012 5 10090 4 26289 3 21921 1 7158 8 19269 5	2100 12166.2 2998.5.4 25055.7 9352.3 12168.2 12189.5 9208.3 21345.3 21288.8	12409 1 28752 7 25036 6 8347 5 13332 1 12319 5 9743 0 25376 7 22201 4
	988 6 997 3 948 877 734 6 683 0 948 5 10 008 2 37 6 043 0 328 246 046 0 216 0 943 0 173 122 514 0 137 0 088 0 046 2 0 088 0 046 2 0 088 0 046 0 088	0.044 0.044 0.051 728 0.682 0.044 0.034 0.038 0.045 0.335 0.219 0.043 0.176 124 995 0.132 0.043 0.089 58.969 0.089 58.969 0.043 0.046 0	2 047 2 047 2 088 5 024 5 637 5 082 5 043 5 382 5 043 5 382 5 043 6 37 6 175 123 909 0 193 0 044 0 089 5 9 116 0 089 5 9 116 0 044 0 084 0 089 0 094 0 0 094 0 0 094 0 0 094 0 0 094 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	9.042 9.172 124.53 9.472 104.53 9.372 282.4 9.276 9.396 252.772 9.046 9.116 79.199 0.255 9.462 9.116 79.199 0.255 9.462 0.116 79.199 0.255 9.462 0.116 79.199 0.255 1.064 0.116 0.255 1.064 0.116 0.255 1.064 0.116 0.255 1.064 0.116 0.255 1.064 0.116 0.255 1.064 0.116 0.255 1.064 0.116 0.255 1.064 0.16	0.177 126.082 0.413 0.042 0.289 280.328 0.372 0.043 0.39 247.768 0.156 0.042 0.114 77.702 0.227 0.043 0.185 131.52 0.322 0.044 0.185 131.52 0.322 0.322 0.323 0.323 0.323 0.33	0.173 121.662 0.435 0.042 0.383 299.854 0.043 0.379 0.042 0.177 0.042 0.135 93.523 0.228 0.042 0.185 131.685 131.685 0.244 0.172 121.895	0.143 99.302 0.384 0.043 0.285 264.954 0.339 0.313 233.943 0.115 76.431 0.255 0.048 0.112 76.431 0.255 0.048 0.205 147.807 0.205 147.807 0.208	0.145 100.904 0.389 0.944 0.346 262.893 0.228 0.043 0.295 219.211 0.15 0.944 0.106 71.588 0.231 0.295 0.186	0.133 62.083 0.356 0.024 0.324 0.312 0.33 0.043 0.287 212.888 0.146 0.948 0.106 71.737 0.225 0.945 0.177 125.539 0.285 0.29	Details of the control of the contro	ta necessistic 1 1 1 1 1 1 1 1 1 1 1 1 1	Gen 3 Rep initiation 1st run Gen 3 Scale up 1st run Gen 2 Rep initiation 1st run Gen 2 Rep initiation 1st run Gen 3 Scale up 1st run Gen 3 Rep initiation 2nd run Gen 3 Scale up 2nd run Gen 1 Rep initiation 2nd run Gen 2 Rep initiation 2nd run Gen 2 Rep initiation 2nd run	A 124.530 282.400 252.774 79.199 136.754 117.564 99.302 264.954 233.943 76.431 147.807	Reading B 126.082 280.328 247.768 77.702 131.526 130.125 100.904 262.893 219.211 71.588 132.695	121.662 299.854 250.557 93.523 131.682 121.895 92.083 233.453 212.888	A*100 12453.0 28240.0 28247.4 7619.6 13675.4 11756.4 9930.2 26495.4 23384.3 7643.1 14780.7	12908 2 28032 8 24778 8 7770 2 12152 9 13012 5 10090 4 26289 3 21921 1 7158 8 19269 5	2100 12166.2 2998.5.4 25055.7 9352.3 12168.2 12189.5 9208.3 21345.3 21288.8	12409 1 28752 7 25036 6 8347 5 13332 1 12319 5 9743 0 25376 7 22201 4
	088 0 000 3 048 877.734 0 693 0 048 0 37 0 043 0 328 240.046 0 042 0 137 122.514 0 089 59.482 0 088 0 042 0 088 0 042 0 088 0 042 0 068	0.049 0.049 0.051728 0.662 0.043 0.045 0.045 0.045 0.042 0.132 0.043 0.089 0.089 0.088 0.046 0.046 28.237 0.042	2.047 2.047 3.88 0.044 5.637 5.08 261 0.382 0.432 2.54 91 0.22 2.045 123 909 0.175 123 909 0.044 0.089 5.911 0.089 6.043 0.046 2.54 14 0.089 6.043 0.046 2.54 14 0.046 2.54 14 0.046 14 0.046 2.54 14 0.046 0.046 0.046 0.046 0.04	9.042 9.172 124.53 9.472 104.53 9.372 282.4 9.276 9.396 252.772 9.046 9.116 79.199 0.255 9.462 9.116 79.199 0.255 9.462 0.116 79.199 0.255 9.462 0.116 79.199 0.255 1.064 0.116 0.255 1.064 0.116 0.255 1.064 0.116 0.255 1.064 0.116 0.255 1.064 0.116 0.255 1.064 0.116 0.255 1.064 0.116 0.255 1.064 0.16	0.177 126.082 0.413 0.042 0.289 280.328 0.372 0.043 0.39 247.768 0.156 0.042 0.114 77.702 0.227 0.043 0.185 131.52 0.322 0.044 0.185 131.52 0.322 0.322 0.323 0.323 0.323 0.33	0.173 121.662 0.435 0.042 0.383 299.854 0.043 0.379 0.042 0.177 0.042 0.135 93.523 0.228 0.042 0.185 131.685 131.685 0.244 0.172 121.895	0.143 99.302 0.384 0.043 0.285 264.954 0.339 0.313 233.943 0.115 76.431 0.255 0.048 0.112 76.431 0.255 0.048 0.205 147.807 0.205 147.807 0.208	0.145 100.904 0.389 0.944 0.346 262.893 0.228 0.043 0.295 219.211 0.15 0.944 0.106 71.588 0.231 0.295 0.186	0.133 62.083 0.356 0.024 0.324 0.312 0.33 0.043 0.287 212.888 0.146 0.948 0.106 71.737 0.225 0.945 0.177 125.539 0.285 0.29	Details of the control of the contro	ta nocentratio 1 1 1 1 1 1 1 1 1 1 1 1 1	Gen 3 Rep initiation 1st run Gen 3 Scale up 1st run Gen 2 Rep initiation 1st run Gen 2 Rep initiation 1st run Gen 3 Scale up 1st run Gen 3 Rep initiation 2nd run Gen 3 Scale up 2nd run Gen 1 Rep initiation 2nd run Gen 2 Rep initiation 2nd run Gen 2 Rep initiation 2nd run	A 124.530 282.400 252.774 79.199 136.754 117.564 99.302 264.954 233.943 76.431 147.807	Reading B 126.082 280.328 247.768 77.702 131.526 130.125 100.904 262.893 219.211 71.588 132.695	121.662 299.854 250.557 93.523 131.682 121.895 92.083 233.453 212.888	A*100 12453.0 28240.0 25277.4 7619.6 13675.4 11756.4 9930.2 26495.4 23384.3 7643.1 14780.7	12908 2 28032 8 24778 8 7770 2 12152 9 13012 5 10090 4 26289 3 21921 1 7158 8 19269 5	2100 12166.2 2998.5.4 25055.7 9352.3 12168.2 12189.5 9208.3 21345.3 21288.8	12409 1 28752 7 25036 6 8347 5 13332 1 12319 5 9743 0 25376 7 22201 4
\$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$	988 6 997 3 948 877 734 6 683 0 948 5 10 008 2 37 6 043 0 328 246 046 0 216 0 943 0 173 122 514 0 137 0 088 0 046 2 0 088 0 046 2 0 088 0 046 0 088	0.044 0.044 0.051 728 0.682 0.044 0.034 0.038 0.045 0.335 0.219 0.043 0.176 124 995 0.132 0.043 0.089 58.969 0.089 58.969 0.043 0.046 0	2 047 2 047 2 088 5 024 5 637 5 082 5 043 5 382 5 043 5 382 5 043 6 37 6 175 123 909 0 193 0 044 0 089 5 9 116 0 089 5 9 116 0 044 0 084 0 089 0 094 0 0 094 0 0 094 0 0 094 0 0 094 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	9.042 9.172 124.53 9.472 104.53 9.372 282.4 9.276 9.396 252.772 9.046 9.116 79.199 0.255 9.462 9.116 79.199 0.255 9.462 0.116 79.199 0.255 9.462 0.116 79.199 0.255 1.064 0.116 0.255 1.064 0.116 0.255 1.064 0.116 0.255 1.064 0.116 0.255 1.064 0.116 0.255 1.064 0.116 0.255 1.064 0.116 0.255 1.064 0.16	6.177 126.082 9.413 0.094 0.269 280.328 0.372 0.043 0.39 247.768 0.144 0.114 77.702 0.227 0.043 0.38 0.38 0.114 0.142 0.114 0.227 0.044 0.143 0.227 0.044 0.143 0.227 0.044 0.143 0.227 0.044 0.143 0.227 0.044 0.143 0.	0.173 121.662 0.435 0.042 0.383 299.854 0.043 0.379 0.042 0.177 0.042 0.135 93.523 0.228 0.042 0.185 131.685 131.685 0.244 0.172 121.895	0.143 99.302 0.384 0.043 0.285 0.043 0.386 0.043 0.313 23.3943 0.112 76.431 0.285 0.043 0.112 76.431 0.285 0.043 0.205 147.807 0.285 0.205 147.807 0.285 0.205 147.807 0.285 0.205 147.807 0.285 0.295 1973.799	0.145 100.804 0.386 0.264 0.396 0.228 0.22	0.133 62.083 0.356 0.024 0.324 0.312 0.33 0.043 0.287 212.888 0.146 0.948 0.106 71.737 0.225 0.945 0.177 125.539 0.285 0.29	Det of the control of	ta nocentratio 1 1 1 1 1 1 1 1 1 1 1 1 1	Gen 3 Rep initiation 1st run Gen 3 Scale up 1st run Gen 2 Rep initiation 1st run Gen 2 Rep initiation 1st run Gen 3 Scale up 1st run Gen 3 Rep initiation 2nd run Gen 3 Scale up 2nd run Gen 1 Rep initiation 2nd run Gen 2 Rep initiation 2nd run Gen 2 Rep initiation 2nd run	A 124.530 282.400 252.774 79.199 136.754 117.564 99.302 264.954 233.943 76.431 147.807	Reading B 126.082 280.328 247.768 77.702 131.526 130.125 100.904 262.893 219.211 71.588 132.695	121.662 299.854 250.557 93.523 131.682 121.895 92.083 233.453 212.888	A*100 12453.0 28240.0 25277.4 7619.6 13675.4 11756.4 9930.2 26495.4 23384.3 7643.1 14780.7	12908 2 28032 8 24778 8 7770 2 12152 9 13012 5 10090 4 26289 3 21921 1 7158 8 19269 5	2100 12166.2 2998.5.4 25055.7 9352.3 12168.2 12189.5 9208.3 21345.3 21288.8	12409 1 28752 7 25036 6 8347 5 13332 1 12319 5 9743 0 25376 7 22201 4

Figure 34

Sample number #	Description	Glucose (g/L)	Lactate (g/L)	Ammonia (mmol/L)	Glutamine (mmol/L)	Glutamax (mmol/L)	Glutamax- Glutamine (mmol/L)
1 Gen 2	2-Rep initiation First Round #L4054	1.78	0.14	2.16	1.56	1.71	0.16
2 Gen 2	2-Scale Up First Round #L4054	1.36	0.89	1.40	1.76	1.90	0.15
3 Gen 2	2-Harvest First Round #L4054	0.83	1.68	2.46	1.69	1.85	0.17
4 Gen 3	3-REP initiation First Round #L4054	1.68	0.29	1.76	2.11	2.29	0.18
5 Gen 3	3-Scale Up First Round #L4054	1.28	0.94	1.64	1.70	1.87	0.16
6 Gen 3	3-Harvest First Round #L4054	1.07	1.53	2.23	1.39	1.54	0.14
7 Gen 2	2-Rep initiation Second Round #L4055	1.91	0.08	2.29	1.60	1.74	0.14
8 Gen 2	2-Scale up Second Round #L4055	1.61	0.77	1.40	1.78	1 .93	0.15
9 Gen 2	2-Harvest Second Round #L4055	0.85	1.86	2.46	1.39	1.55	0.16
10 Gen 3	3-REP initiation Second Round #L4055	1.77	0.18	1.74	2.06	2.23	0.17
	3-Scale up Second Round #L4055 3-Harvest Second Round #L4055	1.60 1.44	0.72 1.32	1.54 2.07	1.68 1.79	1.84 1.95	0.15 0.16

Figure 35

	\$FIL	S/L/1301 Geometr	S/L/Pt Geometric Mean (FL03-A)
A1 gen2L4054 neg	A1 gen2L4054 neg.fcs	34.5	3.24
A2 gen2L4054 neg	A2 gen2L4054 neg.fcs	34	3.19
A3 gen2L4054 po	A3 gen2L4054 pos.fcs	1834	70.6
A4 gen2L4054 po	A4 gen2L4054 pos.fcs	1872	70.3
A5 gen2L4055 neg	A5 gen2L4055 neg.fcs	31.9	4.23
A6 gen2L4055 neg	A6 gen2L4055 neg.fcs	32.4	4.87
A7 gen2L4055 po:	A7 gen2L4055 pos.fcs	1941	88.7
A8 gen2L4055 po:	A8 gen2L4055 pos.fcs	1933	91.1
B1 gen3L4054 neg	B1 gen3L4054 neg.fcs	31.2	3.45
B2 gen3L4054 neg	B2 gen3L4054 neg.fcs	31.9	3.39
B3 gen3L4054 pos	B3 gen3L4054 pos.fcs	2016	61.3
B4 gen3L4054 pos	B4 gen3L4054 pos.fcs	2014	76.2
B5 gen3L4055 neg	B5 gen3L4055 neg.fcs	33.7	6.76
B6 gen3L4055 neg	B6 gen3L4055 neg.fcs	35.4	6.7
B7 gen3L4055 pos	B7 gen3L4055 pos.fcs	2158	99.4
B8 gen3L4055 pos	B8 gen3L4055 pos.fcs	1938	99.5
Mean	-	998	43.3
SD	-	999	41.3

Figure 36

Study	Sample	Sample id	Species	Chain	Reads	CDR3	Unique CDR3	D50
20180511_Study1_FCA	Gen2-L4054	59990	TRB	h	1181732	1181732	8915	0
20180511_Study1_FCA	Gen3-L4054	59991	TRB	h	1145697	1145697	18130	0
20180511_Study1_FCA	Gen2-L4055	59987	TRB	h	1166465	1166465	12996	0.1
20180511_Study1_FCA	Gen3-L4055	59982	TRB	h	1059985	1059985	27246	0.9

Figure 37

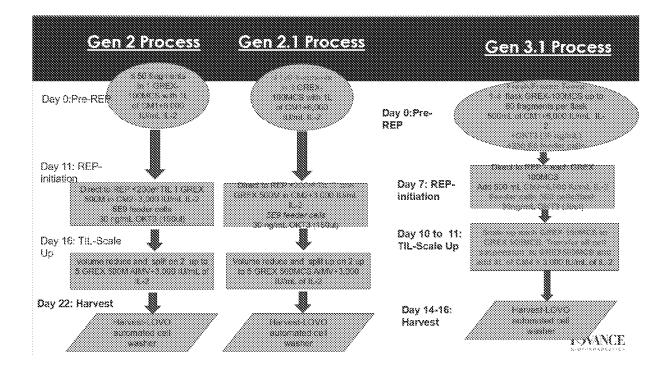


Figure 38

545 Freder Say 0	To the second se		President Properties of the Control
REP Initiation	Direct to REP-Day 11- <200 E6 TIL 1 G-Rev SOMICS	Direct to RGP- Day 11- <208 E8 Tit. Pre-formulated CM2 warmed media in one G-Rex 500MCS	Direct to REP. Day 7-all cells TIL- same G-Rex 100MCS (100MCS up to 4 GRSX), Standard media o Defined Media (Serum free). Addition Feeders 9 E8 cells +OXT-3 (30ng/mL)
Til. propagation or Scale up	1 to 5 (3-76 X 5005)CS Split day 16	2 to 5 G PCV 500MCS See Completed (MA we ned media Spila day 16	From CSEEX 1004CS transfer TIL execution in C RES SCOMES - up to 4 GREX NRS MCS. Standard mode or Cellined Media (Serum Free Scale up on day 10 or 11
Hervesi	Harvest day 22 LOVO-automated cell wester	Narvost day 22, LOVO outomated cell washer (5 wash cycle)	Harvest day 14 or 16 LOVO- automated cell washer (5 wash cycle)
Final formulation	Compressive Product Structure Control of the Guidge Statute	Cyclyneeried Product SCHOOL COCK IN N. SUCCES ARQUIS	Chapteserved probad 300k/ns k. 2-CS10 in EN ₂ hulfide eliquate
Process time	22 days	22 days	16 days

Figure 39

	Media CM1	500 mL
	IL-2 (6000 (U/mL)	*
Cay 0-	OKT-3 (30ng/mL)	,
pre REP initiation	Feeders (250 E+06)	
racess Day	Concilion: C.	
	Media CM2	500 mL
	IL-2 (6000 IU/mL)	*
Day 7-	OKT-3 (30ng/mL) added on Day 7	*
REP Initiation	Feeders Added on Day 7	500 E06
	Total Feeders at Day	750 E+06
tocess Day	Condition	Gen 1.1
Day 9-11 -Scale Up	From G-REX 100MCS transfer Tit.	Yes
	suspension to 1 GREX 900NCS (up to 3 GREX 500NCS)	

LOVO- automated cell washer

Day 16- Harvest

Yes

Figure 40

Projects Companison	Key Process Changes	Senefit
Gen 2 : Gen 2.1	 Initiate process with two flasks instead of one flask Divide REP initiation feeder layer between 2 G-Rex500MCS Flasks Pre-formulate media and warm prior to use 	 Potential doubling of final cell count (dose) with increased TIL repertoire. Process redundancy throughout process
	 Fresh or Frozen tumor 14-16 day process (from 22 day) Reduce total feeder layer on process Feeder layer and OKT3 	 Increased potency Improved phenotype Decreased process time Reduced reagent testing
Gen 2.1 : Gen 3.1	present at Day 0 REP initiated with fragments 100MCS scales to 500MCS Scales to multiple pre-REP flasks Standard Media and Defined Media (Serum Free)	 Decreased process variability Defined reagents Increased repertoire Reduce impurities (feeder) Comparable or Higher Dose.

Figure 41

Process Compenie	•	Desiret Improvemen	Criteria for Success	Outcome
Gen 2 : Gen 3.0	14-16 days Initiate REP with fragments up to 4 flask 100MCS scales to 500MCS	 Increased potency Improved phenotype Decreased process time 	Increase potency as measured by INF-g / Comparable phenotype / Comparable Dose / Comparable purity / (feeder cell) Maintain clonal diversity /	Potency increased over Gen2 Improved expression of CD28 on CD8 cells Maximum capacity of flask reached by day 16 on Gen 3.1 Reduced feeder cell usage Increased diversity

Figure 42

Process	Gen 2	Gen 3
L4054	Standard Media	Standard Media
L4055	Standard Media	Standard Media
MIUSSI	Standard Media	Standard Media

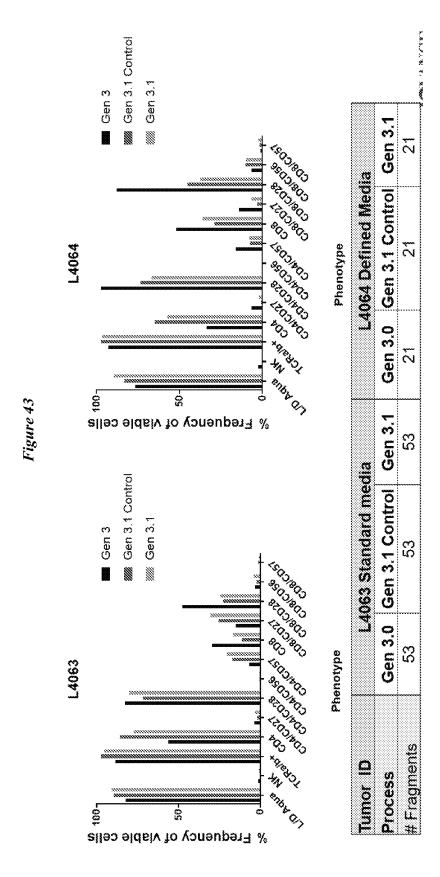
Process	Gens	Clear Sill Continue	Cont
1,4063	Standard	Standard	Standard
	Media	Media	Viette
L4064	Defined	Defined	Defined
	Media	Media	Media

Standard Media:

Pre REP: CM1 REP initiation : CM2 Split or Scale up : CM4

Defined Media:

CTS Optimizer (Serum Free Media) in each day of the process



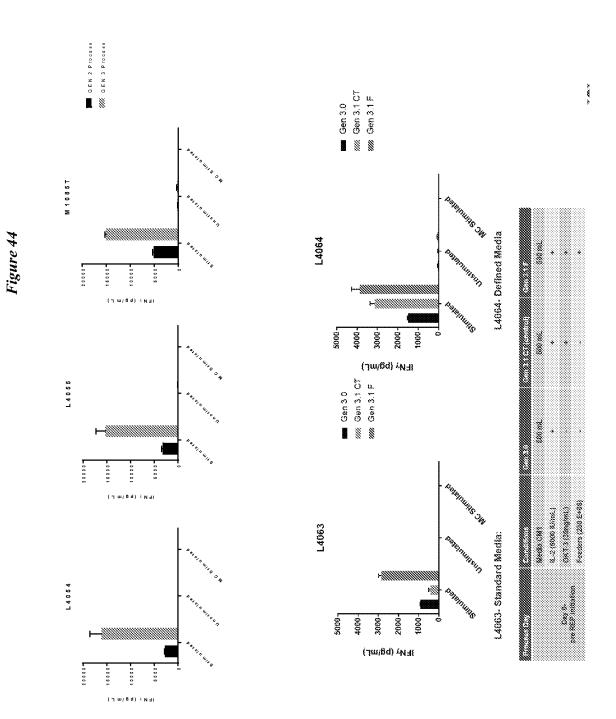
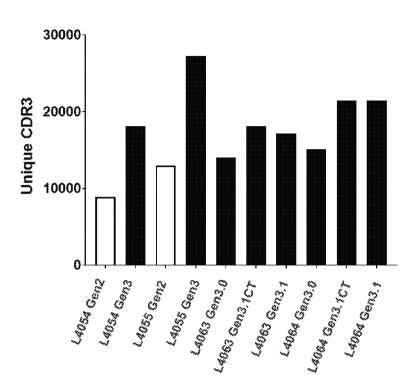


Figure 45



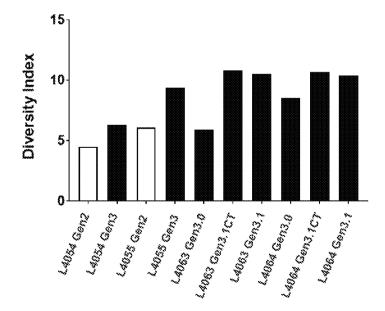


Figure 46

Media		500 mL		500 mL	50	OmL		L876A
IL-2 (6E+06)		+		+		*		
OKT-3 (30ng/mL)				*		*	Gen 3.0	
Feeders (250 E+0	8)	*		٠		٠		
		iicomal.						68868
1	A	ll uCDR3's	5 §	Top	80% uCD	R3's		dillino
Number of uCDR3		Gen 3.1	5	Тор	80% uCD Gen 3.1	R3's	Gen 3.1	
Number of uCDR3 (% Overlap)		·t		Top Gen 3.1	Gen 3.1	R3's Gen 3.1	Gen 3.1 Control	
		Gen 3.1			Gen 3.1			
		Gen 3.1 Control	Gen 3.1		Gen 3.1 control 1000			
(% Overlap)	Gen 3.0	Gen 3.1 Control 3240	Gen 3.1 2959	Gen 3.1	Gen 3.1 control 1000	Gen 3.1		1036C

Figure 47

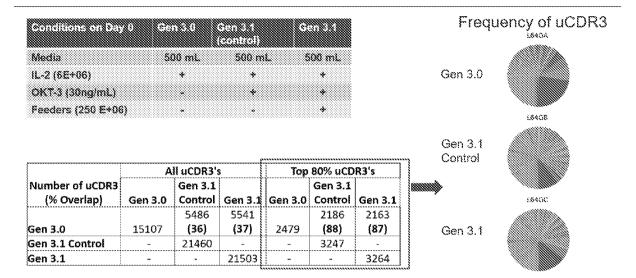


Figure 48

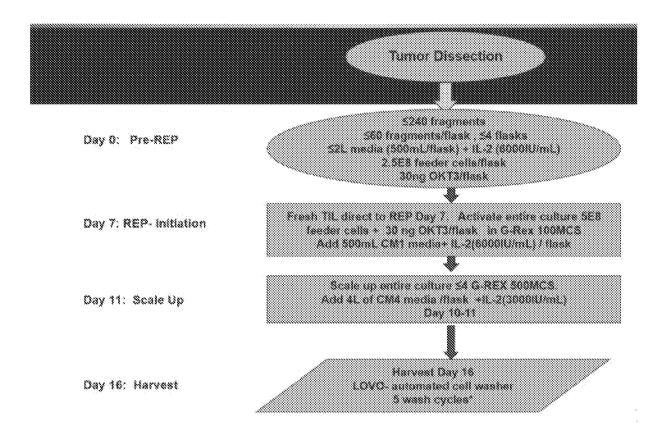


Figure 49

0370

- •Isolate T cell fraction (CD3+,CD45+) from an apheresis product enriched for lymphocytes, whole blood, or tumor digest (fresh or thawed) using positve or negative selection methods,i.e removing the T-cells using a T-cell marker (CD2,CD3,etc, or removing other cells leaving T-cells), or gradient centrifugation.
- •Enter Gen 3.1 process by seeding ~1x10 7 cells/ flask according to Gen3 process

•Reactivate per Gen3

•Scale up per Gen 3

•Harvest per Gen 3

Figure 50

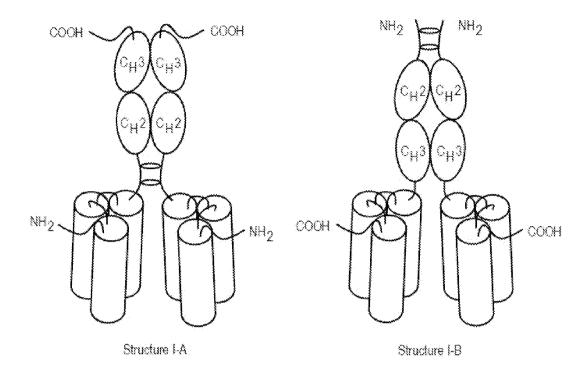


Figure 51

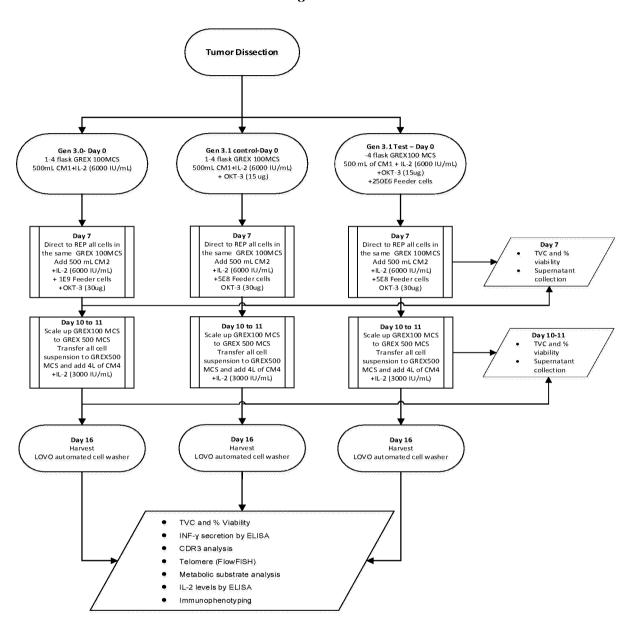


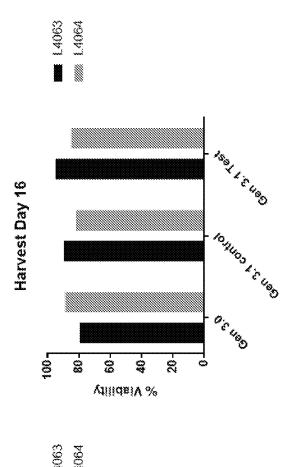
Figure 52

	Conditions	
	Medis CMT	S00 mL
	IL-2 (6000 IU/mL)	*
0 800	OKT3 (15 ug)	•
pre REP initiation	Feeders (250 E+08)	*
1871	Conditions	Court As Treat
	Media CM2	\$00 m.
	1L-2 (6000 IU/mL)	٠
	OKT-3 (30 ug) added on Day 7	•
AEP initiation	Feeders Added on Day 7	500 E06
	Total Feeders at Day	750 E+06
Day 9-11 - Scale Up	From G.REX 100MCS transfer TIL suspension to 1 G-REX 500MCS (up to 3 GREX 500MCS)	8.00
Day 16- Harvest	LOVO- automated cell washer	Yes

igure 53

Tumor ID	3	L4063 in Standard Media	ledia	14064	L4064 in CTS Optimizer Media	Media
Process	Gen 3.0	Gen 3.1 Control Gen 3.1 Test	Gen 3.1 Test	Gen 3.0	Gen 3.1 Control Gen 3.1 Test	Gen 3.1 Test
Number of fragments	53	ဇ	53	21	77	21
Average TVC per fragment	1,37E+08	3.19£+08	3.53E+08	5.90E+08	7.57E+08	9.29E+08
% viability at Harvest	79.53%	89,43%	94.80%	88.80%	81.90%	84.90%
TVC Harvest	7.26E+09	1.69€+10	1.87E+10 *	1.24E+10	7.26E+09 1.69E+10 1.87E+10* 1.24E+10 1.59E+10 1.95E+10*	1.95E+10 *





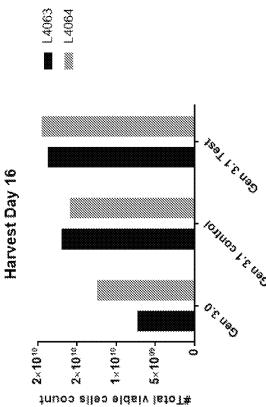
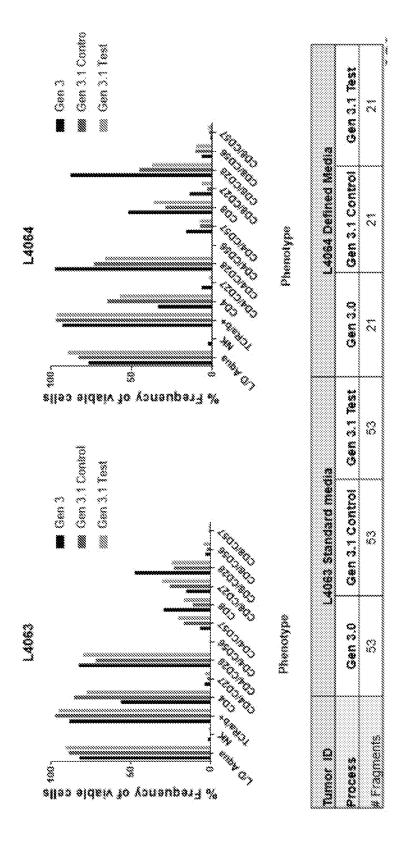


Figure 55



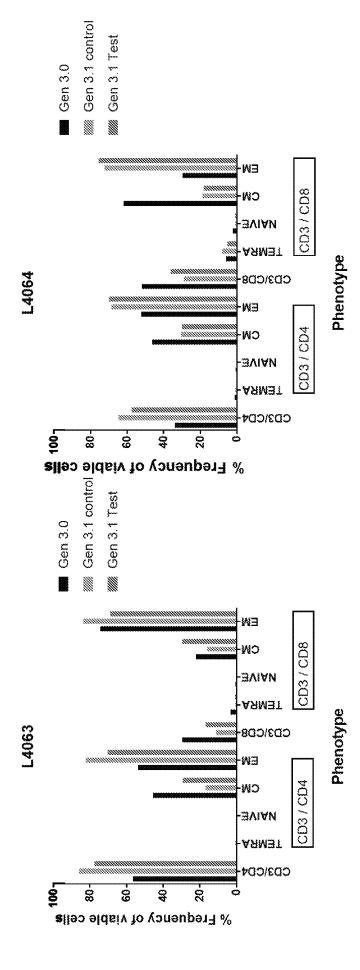
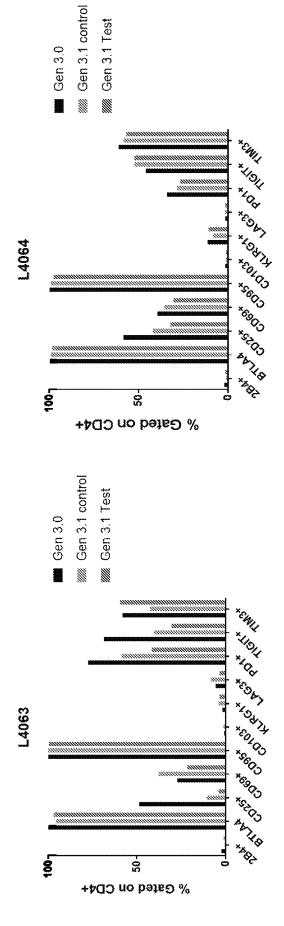
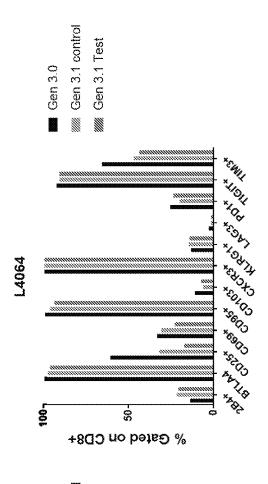


Figure 56









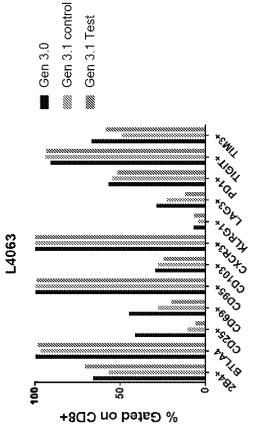
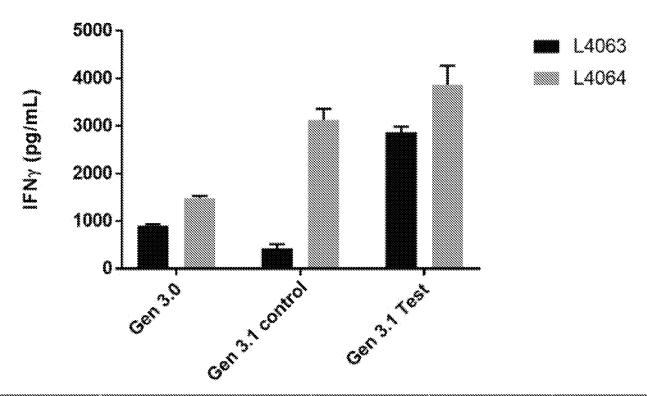
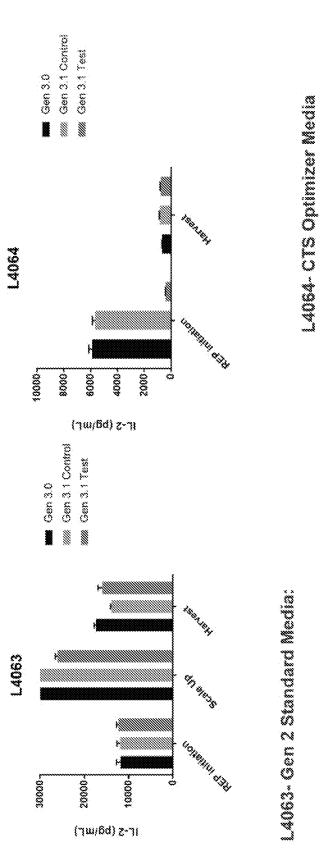


Figure 59



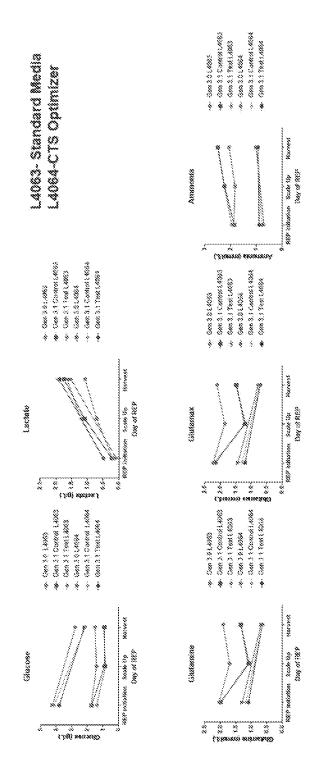
	G. C. C.			
	Media CM1	500 mL	500 mL	500 mL
	IL-2 (6000 IU/mL)	٠	*	*
Day 0-	OKT3 (30ng/mL)		+	+
	Feeders (250 E+06)		.oso, germogo como	# . Ke apvadad





*ELISA performed with AIM V diluent

Figure 61





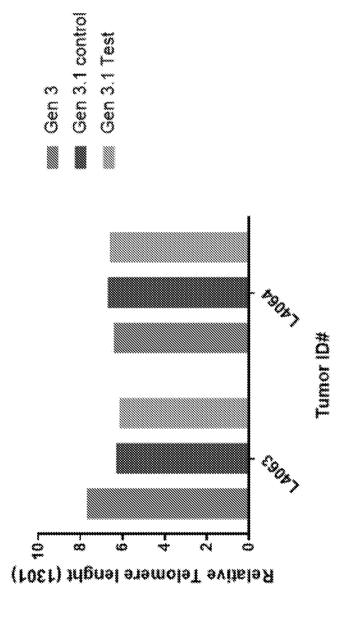


Figure 63

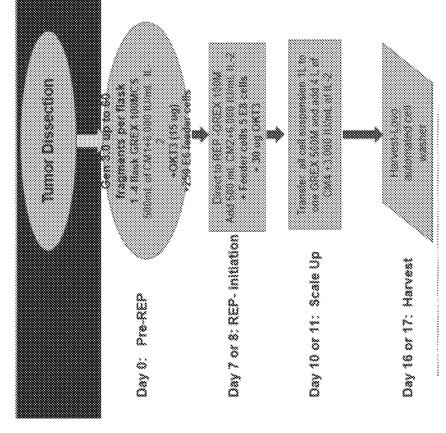


Figure 64

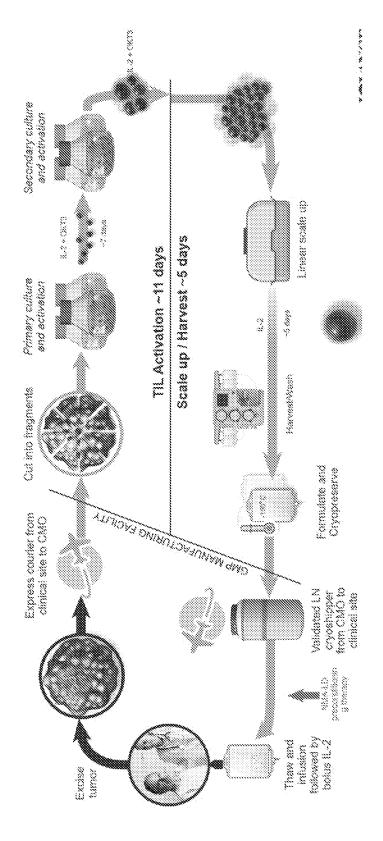


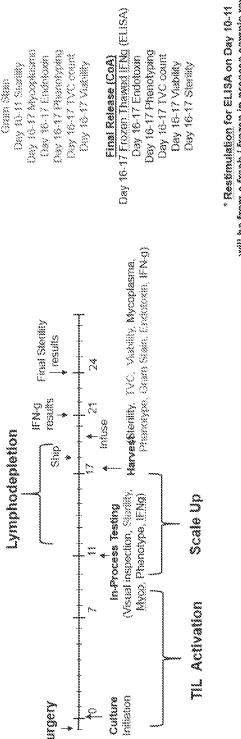
Figure 65A

	ALCO ALCO ALCO ALCO ALCO ALCO ALCO ALCO	2 (C)
10 (0 1) (1) (1) (1) (1) (1) (1)		E
	State agreements or These	Sita Tragmente Stack in up to 4 flasks
	11. Single addition	1L - 2 x 50 lent. accelluns
	22.000 111.	All cels camed findush continuous pracess
STATE OF THE STATE	No screen	No syraen
	Moselectron	Bac-Laterility, visual inspection for contaminants
Kenter		Reduced by 240%
and the second s	Contains HSAB	Defined
		Figsiks scaled linearly and heated as
	BrOS.	VI
	aco (C)	High days
	97	4.
	LOS Paraco	
150	1001000	FORT CADT
motorio	11 CS10 500 CBSC)	0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.0
Stiputent	Varor phase LN Thousan in granty	Vapor phase IN Trapecotive gravin

Figure 65B

***************************************	***************************************
	stati fragments flack at up to
1L - Single addition	112 x 500ml, additions
11.000	
Mo serven	Mich Scriedin
	Bac Tatenity, visual inspection for contaminants
	Reduced by 240%
Contains HSAB	paupag
Footest culture	Flames served transmy and treated as
	subcomponents
Sing.	Kilibug at max scale
8-1	**
Vapor phase IA	Vajor phass IN
tra and a	





Release for infusion on:

Day 10-11 Phenotype

Day 10-11 myco Day 10-11 fFNg*

LD on: Day 10-11 Viability

' Restimulation for ELISA on Day 14-11 will be from a fresh / frozen in-process sample reportable On Day 14

Figure 67

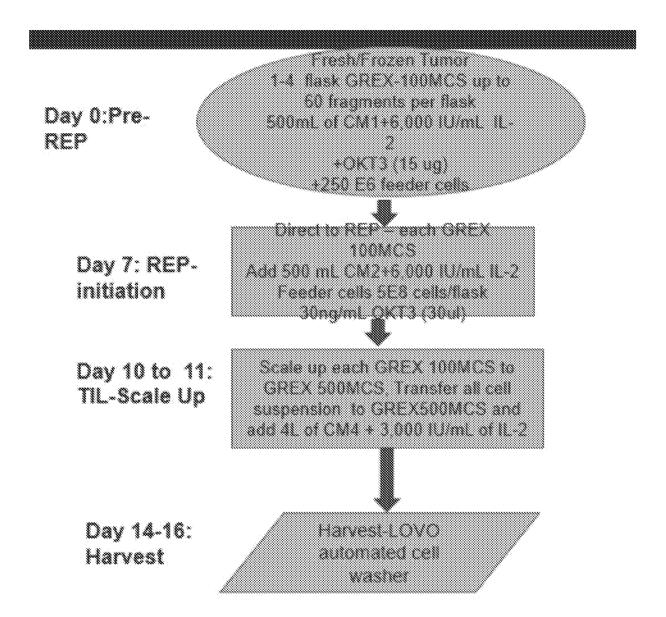


Figure 68

9,837 0000 0000 30,003 25 March 2010 48.2E+09 % 88 88 No organisms detected 91.02 Hotele 10 Pending (*) 46.18+09 198 9 6 1 38.4E+08 Negative ii B % % 9 128.9% 19,235 % 88 88 No organisms detected Eng. Pun Day 1 Pending (*) 17.3E+09 17.9E+09 00 Z 75% Negative 8 10 05 103.5% 11.63 8183 888 8 % 0.88 % Data Summary of testing Day 16/17 Endotoxin (total EQ units) Midery & OXOTHER TVC Post LOVO % Post-LOVO TVC Pre-LOVO TVC State State S IFNy (pg/mL) Mycoplasma Recovery Sterility

908 8

986

Figure 69

"Adds up to entire TiL sample (100% Live, CD14-, except for monocytes)

	1.5	0.2	000 000	96.3	1.6	988
Eng run #1	\$33	6.2	ôô	87.1	1.8	99.4
			A Company of the Comp	7,550 (5.0)	1,000,00 (3)	

		····					;			
	Eng rus #2	9.1	84.4	7.7	6.3	180.5		Engrun#2	71.8	27.8
	Eng run #1	0.0	92.2	££	9.1	100.0		Eng run #1	388	16.0
"Adds up to 100% TORab	20			PARTICIPATION OF THE PROPERTY	(86) PARESPORT (1807) STEW BATTERS		*Adds up to 100% Live, CD14-			

Figure 70

"Adds up to entire TiL sample (100% Live, CD14-, except for monocytes)

	PD an #1 L4963	PD ma #2 L4364
(ed feeting engle) specially	1.04	
Brooks (CDX A CD Line)	0,0076	0.013
Address pages (ATATAS) PA	0.032	0.043
16.500.000	\$5.5	£.388.7
Constitution (Constitution)	2	1.86
	988	99.14
*Adds up to 100%, TCRab		
	PD run #1 L4063	PD run #2 L4064
	8.35	0.07
	97.4	98.7
	1,39	2.78
	0.88	8,44
Serve Se	\$ O\$)	3833
	PD nn #1 L4663	PD ms #2 1.4864
100 May 100 May 1		57.4
	18.8	36.1
	9.4.3.	0.9 5

Figure 71

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FR ER, Frozen turnor, Early REP *, Condition not tested *, Sampling issue, low TVC count or non-viable cells on thawing

Figure 72

	Hierarchy	Eng nm #1	Eng run #1
	S1/S2/All/Live/CD14-/CD3-/NK Freq. of null (%)	(C)	S.
	\$1/52/All/tive/CD14-/CD19 { Freq. of null (%)	6.2	6.2
	\$1/\$2/All/tiwe/CD14+ Freq. of Parent (%)	9.6	3.5
Section 1	S1/52/All/Live/CD14-/TCRab { Freq. of null {%}	87.3	888
160,000,000	\$1/\$2/All/Live/CD14-/TCRgd Freg. of null (%)	3.2	3:
	\$1/52/All/Live/CD14-/TCRab/CD4 Freq. of Parent (%)	33.5	90,50
	\$1/52/All/Lwe/CD14-/TCRab/CD8 Freq. of Parent (%)	40.0	27.8
	S1/52/Ail/iwe/CD14-/TCRab/Q2: CCR7+ , CD45RA+ } Freq. of Parent (%)	an	0.1
	S1/52/All/Live/CD14-/TCRab/Q4: CCR7- , CD45RA- { Freq. of Parent {%}	92.2	84.4
	\$1/52/All/Live/CD14-/TCRab/Q3: CCR7+ , CD45RA- Freq. of Parent (%)	£ Ł	15.5
	\$1/\$2/All/[we]CD14-/TCRab/O1: CCR7-, CD45RA+ Freq. of Parent (%)	6.3	60.7
	S1/52/All/Live/CD14-/TCRsb/Q6: CD62L+, CD45RA+ Freq. of Parent (%)	6.2	6.1
	\$1/\$2/All/Live/CD14-/TCRab/Q8: CD62L-, CD45RA- Freg. of Parent (%)	7.18	49.5
	S1/S2/All/live/CD14-/TCRab/Q7: CD621+ , CD45RA- Freq. of Parent [%]	52.4	58.4
	\$1/\$2/Ail/Live/CD14-/TCRab/Q5: CD62L- , CD45RA+ { Freq. of Parent {%}	ب ش	30

*Adds up to CD3+CD45+ %

Eng run #2	87.1	æ. ∠	
Eng ran #1 Bag ran #2	27.3	1.2	ପ୍ରଥନ୍ତ
Change (Error)			

		CD4+	++	+8CD	+
Characteristic	Hierarchy	Eng run #1	Eng run #2	Eng run #1	Eng run #2
(4) + 24 to	\$1/\$2/All/Live/CD14-/TCRab/CD4 or CD8/CD4+/8+CD27+ } Freq. of Parent [%]	9.7	2.0	2.1	12.7
(9) - 27/08	\$1/52/A!!/Uve/CD14-/TCRab/CD4 or CD8/CD4+/8+CD28+ } Freq. of Parent (%)	41.2	50.1	3.6	13.9
(0.) ********	\$1/\$2/All/Live/CD14-/TCRab/CD4/CD4/8+CD57+ Freq of Parent (%)	1.0	6.9	0.1	3.7
284+ (%)	:D3/CD4 or CD8/btla 1	4.5	5.5	69.1	55.7
BILAGE [W]	5/5/Live/CD3/CD4 or CD8/2b4 Freq. of Parent {%}	67.5	86.1	79.6	89.1
(%) +6400	\$/5/tive/CD3/CD4 or CD8/CCR4+ { Freq. of Parent {%}	94.1	93.6	84.2	96.6
(M) +GZQ3	S/5/live/CD3/CD4 or CD8/CD25 Freq. of Parent (%)	63.1	61.0	47.5	51.8
CD49+ (%)	\$/5/tive/CD3/CD4 or CD8/CD69 Freq. of Parent (%)	47.0	22.8	45.4	25.8
(30) + (30)	S/S/live/CD3/CD4 or CD8/CD95 Freq. of Parent (%)	99.2	98.1	99.1	97.6
CD110:34 (%)	\$/\$/Live/CD3/CD4 or CD8/CD103 Freq. of Parent (%)	4.2	10.7	25.0	36.9
0801634	5/5/tive/CD3/CD4 or CD8/CXCR3 { Freq. of Parent (%)	58.1	76.7	89.3	88.3
KLEGI4 (%)	S/S/Live/CD3/CD4 or CD8/KLRG1 J Freq. of Parent (%)	0.3	6.8	3.1	35.8
(%) +85%)	S/S/Live/CD3/CD4 or CD8/Lag3 { Freq. of Parent {%}	5.0	3.3	19.4	21.2
(%) *TQE	S/S/Uve/CD3/CD4 or CD8/PD1 Freq. of Parent (%)	29,3	22.1	11.2	7.2
TGIT+ (%)	\$/\$/tive/CD3/CD4 or CD8/Tigit Freq. of Parent [%]	68.1	53.2	74.9	65.8
1188.54 (%)	S/S/Live/CD3/CD4 or CD8/TIM3 Freq. of Parent (%)	93.6	81.8	91.2	84.4

igure 74

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4:200 5	44	16033.00 14083.24 11006.88 15254.59 12534.24 5985.88 14237.22 11669.82 13089.81	2445 624 2108 37 1727 42 1932 96 1565 52 1119 657 1611 132 1158 179 1753 84	34766 20 31611 13 26385.05 30652 42 23752 34 26475 43 53462 43 29728 52 29579 46	16478 69 16506 51 16659 69 16385 60 17083 39 15419.07 15663 49 14960 40 16092 97
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	Sample	Eng 2 Sumulated 316	Eng 2 Unstimulated	Eng 2 Stimulated Ctri 21	Eng 2 Unstimulated Ctri
	Sample	Eng 2 Sumulated 316	Eng 2 Unstimulated	Eng 2 Stimulated Ctrl 21	Eng 2 Unstimulated Ctt!

Figure 75A

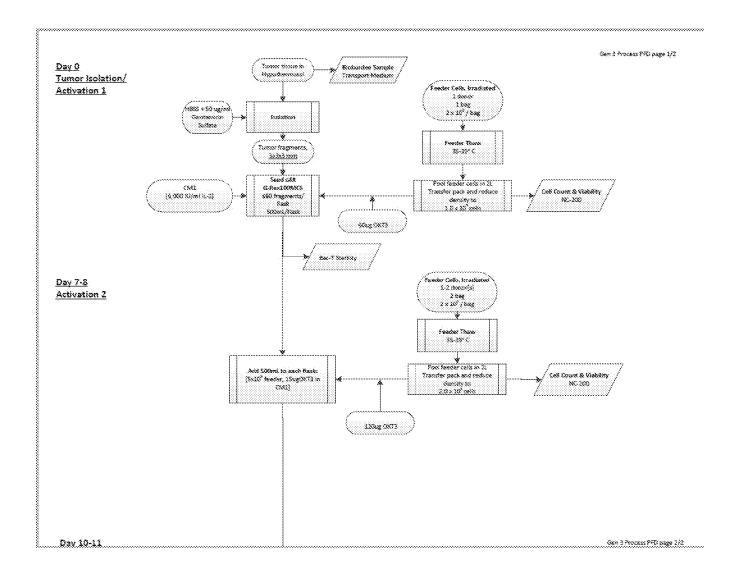
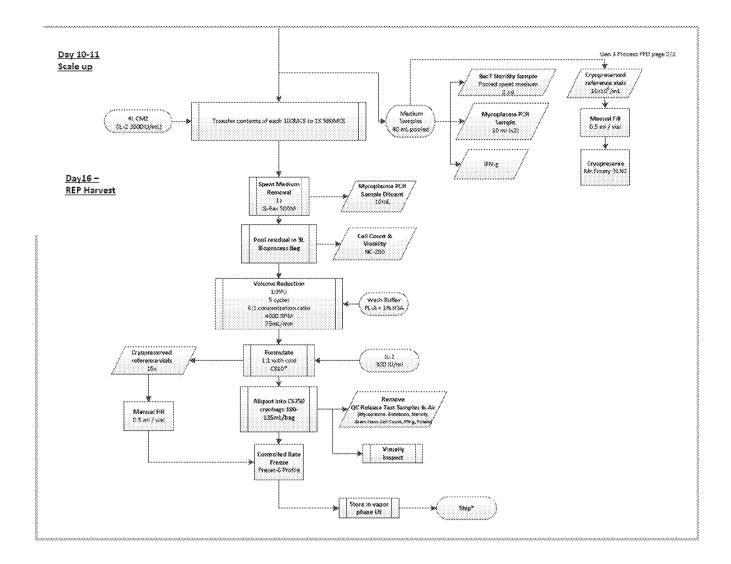


Figure 75B



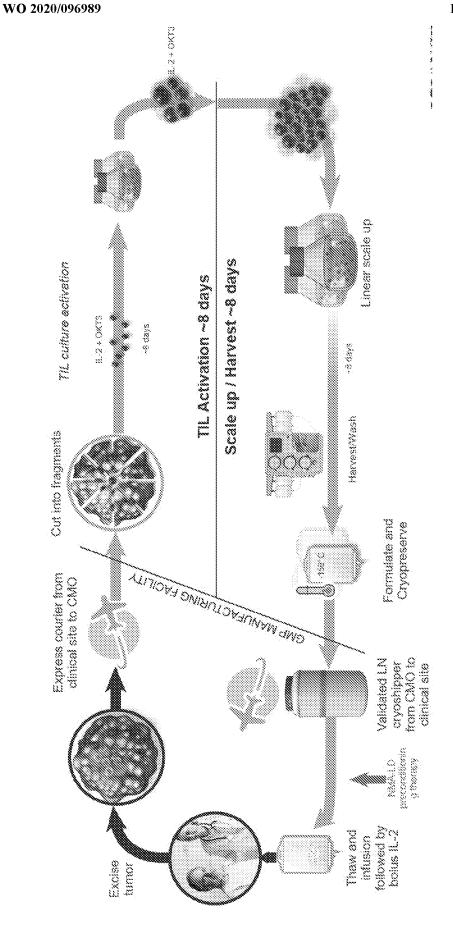


Figure 77

Cont.21	freshor fraces famor With a transfer with a stiff agreement up to followers For the famous famous famous famor For derivation and the famous famou	Direct to REP. Day 7-all cells TiL. same G-Rex 100MCS (100MCS up to 4 GREX), Standard media or Defined Media (Serum free). Addition Feeders 500e6 cells +OKT-3 (30ug)	From GATEX COMICS transfer Tit, suspension to GATEX COMICS Standard media of Total Micros Scientific Scientifi	Harvest day 14 or 16 LOVO- automated cell washer (5 wash cycle)	Compression very production CA.	16 days
Cap 2.1	s 18.0 fragments/ 3 (3-Rex Pro-terminates CMT warmed media 10.000 3 - 11 days	Direct to REP. Day 11. <200 ef Tit. Pre-formulated CM2 warmed media in one G-Rex 500MCS	Programme Child Agentical Spirit day 10	Harvest day 22, LOVC-automated cell washer (5 wash cycle)	Cryopreserved Product 300Limit(2) CS10 m LN, multiple allocation	22 days
SHEP	\$ 50 tragments 1 G-Per 1000CS 11 days	Direct to REP. Day 11. <200e* 7tt. 1 G-Rex 500MCS	Tro Score Associates Spirit day 18	Marvest day 22, LOVO-automated cell washer	Chropieserved Product 300H/mil R.2 - CS10 in LNs. multiple algunds	22 days
	Pre REP. day 0	REP Initiation	TL propagation of Scale up	Harveat	from that	Process time

igure 78

	Selfman (Orstendar)	Millerenness
	 Initiate process with two 	Potential doubling of
Gen 2:	flasks instead of one flask	
Gen 2.1	Divide REP initiation feeder	with increased Till.
	layer between 2.0-	repertore
	Rex500MCS Flasks	· Process redundancy
	Pre-formulate media and	throughout process
	warm prior to use	
	 Fresh or Frozen tumor 	 Increased potency
	 14-16 day process (from 22 	 Improved phenotype
	(day)	Decreased process
	 Reduce total feeder layer on 	time
	process	. Reduced reagent
	 Feeder layer and OKT3 	testing
 8 8 8	present at Day 0	Decreased process
Cen 33.1	 REP initiated with fragments 	Variability
	· 100MCS scales to 500MCS	· Defined reagents
	 Scales to multiple pre-REP 	Increased repertoire
	flasks	Reduce impurities
	 Standard Media and Defined 	(leader)
	Media (Serum Free)	 Comparable or Higher
		Dose

Figure 79

i ame e. L'excimitati di Sen o opinineanon comunicio	omo nonvenundo e :	Historia.		
Process Day	Conditions	Gen 3.0	Gen 3.1 control	Gen 3.1 Test
Day 0 :	Media (*)	500 mL	500 mi.	508 mL
Tumor Fragment Isolation and Activation	£-2	BOCO IU/m£	6000 IU/mL	6000 IU/mi.
	OKT-3	1	\$5 ug	15 ug
	Feeders	-	1	2.5E+06
Process Day	Conditions	Gen 3.0	Gen 3.1 control	Gen 3.1 Test
Day 7-8:	Media (*)	500 mL	500 mL	500 mL
TIL Culture Reactivation	1L-2	6000 IU/mL	6000 IU/mL	8000 IUmi
	OKT-3	රිග ලද	30 ng	30 ng
	Feeders	80+∃↓	500 E+06	500E+06
	Total Feeders added through Day 7	\$0+3 L	500 E+06	750E+06
Process Day	Conditions	ევ სმე	Gen 3.1 control	Gen 3.1 Test
Day 10-11: Culture Scale Up	From GREX 100 to	ransfer whole TIL sur media with IL-2	From GREX 100 transfer whole TIL suspension to 1 GREX 500 containing 4L media with IL-2 (3000 IU/mL)	500 containing 4L
Process Day	Conditions	Gen 3.0	Gen 3.1 control	Gen 3.1 Test
Day 16 –17: Harvest/Wash/Formulate	LOVO auto	mated cell washer a	LOVO automated cell washer and cryopreservation with CS10	with CS10.

(*) Media can be standard media or CTS serum free media.

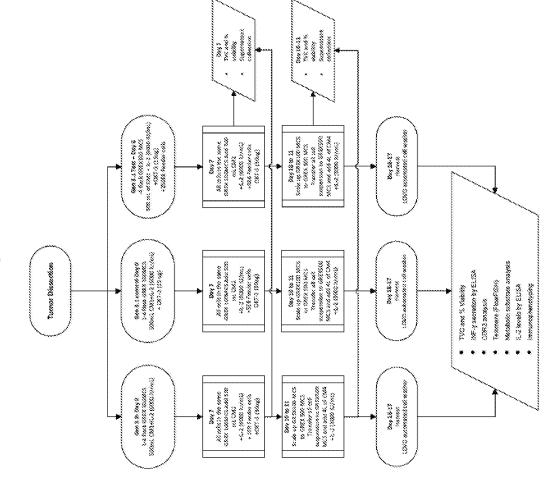


Figure 80

Figure 81

	14063	L4063 in Standard Media	edia	14064	14064 in Serum Free Media	Vedia
		Gen 3.1			Gen 3.1	
Process Day	Gen 3.0	Control	Gen 3.1 Test	Gen 3.0	Control	Gen 3.1 Test
Number of fragments	83	m in	533	21	21	21
Average TVC at harvest per fragment	1.37E+08	3.19E+08	3.53E+08	5.90E+08	7.57E+08	9.29E+08
TVC day 7 (*)	2.59E+07	6.43£+07	1.45E+08	7.35E+06	9.28£+07	1.39E+08
Tvc day 10/114*)	6.07E+08	1.66£+09	1.83E+09	7.48E+08	1.28E+09	1.72E+09
TVC harvest day 16/17	7.26E+09	1.69£+10	1.87E+10	1.24€+10	1.59E+10	1.95E+10
Fold Expansion (day 10 or 11 /day 7)	23,4	25.8	12.6	101.8	13.8	12.4
Fold Expansion (Harvest day 16 / day 7)	280.3	262.8	129.0	1687.1	171.3	140.3

Based on the design of the process, samples were pulled directly from each flask after swirling its contents without volume reduction. As such, analysis and conclusions of cell count data from these samples is limited by the nature of the sampling methodology. (*) Cell counts for Day 7 and Day 10/11 were taken FIO.

Figure 82

	14063	L4063 in Standard media	i a	14064	L4064 in CTS Serum Free media	Free media
Process Day	Gen 3.0	Gen 3.1 Control	Gen 3.1 Test	Gen 3.0	Gen 3.1 Control	Gen 3.1 Test
Reactivation	74.6%	92.1%	88.7%	88.0%	92.8%	95.0%
Stale up	92.1%	95.4%	94.0%	90.4%	94.3%	95.1%
Harvest	79.5%	89.4%	94.8%	88.8%	81.9%	84.9%

Figure 83

Tumor ID	14063	3 in Standard media	nedia	L4064 in	L4064 in CTS Serum Free media	e media
		Gen 3.1	Gen 3.1		Gen 3.1	Gen 3.1
Markers	Gen 3.0	Control	Test	Gen 3.0	Control	Test
L/D Aqua	82.2	89.4	91.0	76.6	83.1	89.5
N.	£.3	0.4	0.	2.5	0.2	0.5
TCRa/b+	38.6	97.5	95.5	93.0	97.3	96.7
CD4	56.4	85.8	77.5	33.8	64.8	57.4
CD4/CD27	80. 100	\ <u>\</u>	3,4	6.7	0.7	2.2
CD4/CD28	82.7	73.8	80.2	97.5	73.5	8.99
CD4/CD56	7.0	0.5	0.7	0.5	0.5	0.3
CD4/CD57	6.7	17.0	20.5	16.0	7.6	0.8
CD8	29.6	1.2	16.8	51.9	28.9	36.1
CD8/CD27	15.0	25.6	30.5	######################################	K, K	6,7
CD8/CD28	47.5	23.0	24.5	88.0	45.1	37.3
CD8/CD56	ಜ್	2.3	4.2	9,6	10.3	10.0
CD8/CD57	0.3	1.2	****	1.3	2.0	2.5

Figure 84

Tumor ID	14063	363 in Standard media	nedia	L4064 in	L4064 in CTS Serum Free media	e media
Markers	Gen 3.0	Gen 3.1 Control	Gen 3.1 Test	Gen 3.0	Gen 3.1 Control	Gen 3.1 Test
CD3/CD4	56.4	85.8	77.5	33.8	64.8	57.4
TEMRA of CD4	9.0	0.7	0,4	****	<i>L</i> '0	0.2
NAIVE of CD4	0.3	0.2	0.2	0.5	10	0.0
CM of CD4	45.6	16.8	29.3	46.3	9'08	29.9
EM of CD4	53.7	82.3	70.2	52.1	68.6	69.9
CD3/CD8	29.6	11.2	16.8	51.9	28.9	36.1
TEMRA of CD8	3.1	0.5	0.9	6.1	8.0	5.4
NAIVE of CD8	0.7	0.1	0.4	2.2	6.7	₩ ©.
CM of CD8	22.0	15.8	29.7	61.9	18.9	18.2
EM of CD8	74.3	83.5	69.0	29.8	72.4	75.5

Figure 85

Tumor ID	14063	4063 in Standard media	nedia	L4064 in	L4064 in CTS Serum Free media	ee media
		Gen 3.1	Gen 3.1		Gen 3.1	Gen 3.1
Markers	Gen 3.0	Control	Test	Gen 3.0	Control	Test
284+	2.1	0.6	1.0	2.0	1.2	43
BTLA4	99.7	95.4	6.96	99.5	98.8	98.1
CD25+	48.6	10.5	3.9	58.2	41.7	32.1
+69 Q)	27.1	37.7	21.5	39.4	35.6	30.5
CD95+	99.9	99.9	99.5	9.66	0.66	97.3
CD103+	0.7	****	0.4	* .	eri eri	i
KLRG1+	9.ï	3.7	w w	**** **** ****	₩.	10.7
LAG3+	5.6	8.7	en en	 	1.6	#! \$\frac{1}{2}
PD1+	77.4	58.4	41.6	34.1	28.4	26.7
TIGIT+	68.5	40.3	30.3	45.8	5 M	52.2
™3 +	58.0	42.4	59.4	0.10	58.4	56.8

Figure 8

Tumor ID	14063	L4063 in Standard media	media	L4064 in (L4064 in CTS Serum Free media	ee media
		Gen 3.1	Gen 3.1		Gen 3.1	Gen 3.1
Markers	Gen 3.0	Control	Test	Gen 3.0	Control	Test
284+	65.8	9.95	70.5	13.6	21.5	20.7
BTLA4	99.5	9'96	38.2	99.3	97.4	96.1
CD25+	41.4	10.5	5.9	60.6	32.0	17.1
+69G)	44.9	28.0	20.0	33.2	30.6	22.7
+56 Q)	9.66	9'66	686	98.9	96.1	93.5
CD103+	29.4	27.9	24.5	10.9	6.0	7.3
CXCR3+	6.06	99.9	99.8	99.3	99.2	99.2
KLRG1+	7.1	4.6	6.7	13.2	14.5	14.1
LAG3+	28.6	22.5	11.9	2.8	1.6	1.4
PD1+	56.9	54.5	51.7	25.4	20.0	23.6
TIGIT+	90.8	93.7	93.3	92.1	90.4	90.5
TIM3+	66.7	49.1	58.6	65.6	46.8	43.6

Figure 87

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Results are reported as mean of triplicate samples from one representative experiment

Figure 88

nedia	Gen 3.1 Test	389,4(1)	*	768.9
L4064 in CTS Serum Free media	Gen 3.1 Control	5671.8	**	826.2
L4064 in CT	Gen 3.0	5891.6	*	656.0
	Gen 3.1 Test	11786.7	26145.0	16019.2
in Standard media	Gen 3.1 Control	11928.7	30368.6	13828.4
L4063 in Sta	Gen 3.0	12319.6	32095.1	17309.3
	Process Day	Reactivation	Scale Up	Harvest

Results are reported as mean of triplicate samples from one representative experiment

(*) Spent media from day 10711 on L4064 was not collected during the execution of the runs.

values for Gen 3.1 control and Gen 3.0 conditions. Due to the low amount of sample taken, it was (1) The data for Gen 3.1 Test L4064 on reactivation day was significantly below the corresponding not possible to repeat the assay to verify the accuracy of this number.

Figure 89

	e media	Gen 3.1	Test	3.8	*	2.2
	L4064 in CTS Serum Free media	Gen 3.1	Control	4.1	*	2.1
	L4064 in CT;		Gen 3.0	4.3	*	2.8
	3	Gen 3.1	Test	1.4	0.8	1.0
	in Standard media	Gen 3.1	Control	£ 7	6.0	6'0
	L4063 in Sta		Gen 3.0	1.8	1.2	**** \$\displaystarker{\pi}
Glucose (g/L)			Process Day	Reactivation	Scale Up	Harvest

(*) Spent media from day 10 /11 on L4064 was not collected during the execution of the runs.

Figure 90

Lactate (g/L)						
	L4063 in Sta	in Standard media		14064 in CT	14064 in CTS Serum Free media	media
		Gen 3.1	Gen 3.1		Gen 3.1	Gen 3.1
Process Day	Gen 3.0	Control	Test	Gen 3.0	Control	Test
Reactivation	0.2	0.7	0.5	0.1	0.2	0.5
Scale Up	0.7	6004 6004	1.2	*	*	*
Harvest	****	£.;	1.6	£.5	2.0	1.9

(*) Spent media from day 10 /11 on L4064 was not collected during the execution of the runs.

Figure 91

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Glutamine (mmol/L)			Process Day	Reactivation	Scale Up	Harvest
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(*) Spent media from day 10/11 on L4064 was not collected during the execution of the runs.

Figure 92

	14063	in Standard media	a	L4064 in Cl	L4064 in CTS Serum Free media	e media
Process Day	Gen 3.0	Gen 3.1 Control	Gen 3.1 Test	Gen 3.0	Gen 3.1 Control	Gen 3.1 Test
Reactivation	2.2	2.2	2.2	# # # # # # # # # # # # # # # # # # #	н	<u>ښ</u>
Scale Up	<u>ښ</u>	1.2	1.2	*	*	**
Harvest	7.	พ	1.5	0.8	0.7	0.7

(*) Spent media from day 10 /11 on L4064 was not collected during the execution of the runs.

WO 2020/096989

Ammonia (mmol/L	4					
	L4063 in Sta	53 in Standard media	-	L4064 in CI	L4064 in CTS Serum Free media	media
Process Day	Gen 3.0	Gen 3.1 Control	Gen 3.1 Test	Gen 3.0	Gen 3.1 Control	Gen 3.1 Test
Reactivation	1.9	6.1	2.0	0.7	0.8	6.0
Scale Up	1.8	2.2	2.3	*	*	*
Harvest	2.4	2,5	2.5	м О	0	6.0

(*) Spent media from day 10 /11 on L4064 was not collected during the execution of the runs.

Figure 94

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Figure 95

	L4063 in Sta	in Standard media	_	L4064 in CT	L4064 in CTS Serum Free media	media
1		Gen 3.1	Gen 3.1		Gen 3.1	Gen 3.1
Characterization	Gen 3.0	Control	Test	Gen 3.0	Control	Test
uCD3	14005.0	18149.0	17181.0	15107.0	21460.0	21503.0
Shanon Entropy	C L	Ç	, (	r	100	*
Index	ņ	IU.&	10,0	&.J	10.7	40.4

Figure 96

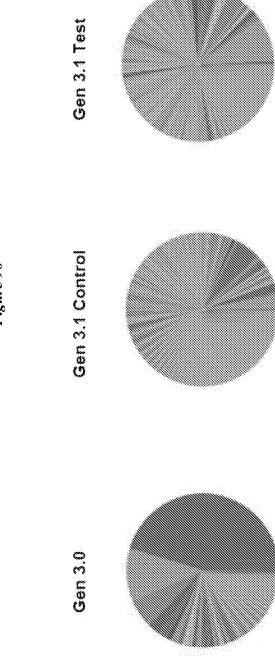


Figure 97

Number of u	All uCDR3's			Top 80% uCDR3's	3/8	
(%overlap) L4063	Gen 3.0	Gen 3.1 Control	Gen 3.1 Test	Gen 3.0	Gen 3.1 Control	Gen 3.1 Test
Gen 3.0	14005	3240 (23%)	2959 (21%)	1104	1000 (90 %)	975 (88%)
Gen 3.1 Control	,	18149		,	2437	
Gen 3.1 Test	1	,	17181	ı	,	2331

Figure 98

Number of u All uCDR3's	All uCDR3's			Top 80% uCDR3's	13/5	
(%overlap) 14064	Gen 3.0	Gen 3.1 Control	Gen 3.1 Test	Gen 3.0	Gen 3.1 Control	Gen 3.1 Test
Gen 3.0	15107	5486 (36%)	5541 (36%)	2478	2186 (88%)	2163 (87%)
Gen 3.1 Control	ı	21460	1	,	3246	1
Gen 3.1 Test	,	ı	21503	1	ì	3263



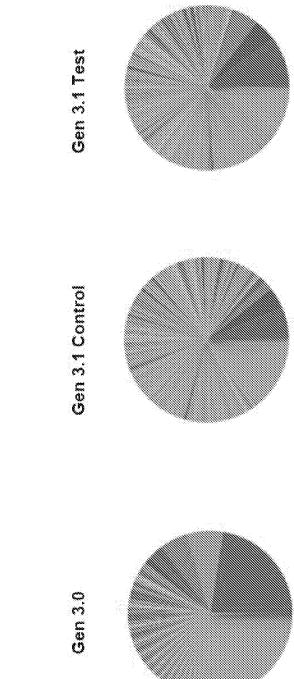


Figure 100

Process Gen 3-Optimized	<pre> &lt;240 fragments  &lt;60 fragments/flask  &lt;4 flasks  &lt;21 media (500mL/flask)  1L-2 (6000lU/mL)  2.5x10⁸ feeder cells/flask  15ug OKT3/flask </pre>	Fresh TIL direct to REP Activate entire culture 5x10 ³ feeder cells 30 ug OKT3/flask G-Rex 100MCS Add 500mL media+ IL-2(6000IU/mL)	\$4 G-REX 500MCS Scale up entire culture transferring 1L from GREX 100MCS into GREX 500MCS and add 4L of media +IL-2 (3000 IU/mL) /flask	Harvest LOVO- automated cell washer Cryopreservation on Plasmalyte 1% HSA: CS10
Step	Day 0 Tumor isolation and Activation	Day 7 - 8 Reactivation	Day 10 – 11 Scale up or TIL Sub-culture	Day 16 -17 Harvest

Figure 101

Test	Acceptance Criteria	Gen 3.1Test vs Gen 3.0 Process
Cell Count (TVC)	Gen 3.1 > 30% to Process Gen 3.0	Met
% Viability	≥70% Viability	Met
Immunophenotyping (%CD3+/ %CD45+)	≤5% difference between Gen 3.1 and Gen 3.0 process	Met
IFNy secretion	Gen 3.1≥ to Process Gen 3.0	Met

Figure 102

Cell counts reactivation Day

### Average*Volume **Total Cells** 8.88E+06 6.438+07 5.49E+06 1.64E+08 1,458+08 8.35£+06 7.35£+86 1.00E+06 1.00E+08 9.28E+07 7,23E+06 1.46E+08 1.39€+08 7.238+06 3.48E+07 2.59E+07 6.98E+07 1.85E+07 (cells/mt) 1.40E+05 1.298+05 1.10E+04 2.90E+05 2,00E+05 1.86E+05 2.78€+05 5.18E+04 1,785+04 3,27£+05 3,715+04 1.675+04 1.47E+04 2.00E+03 1.45E+04 2.93E+05 1.45E+04 Average 6.96E+04 74.55% 92.10% 88.65% 88,00% 92.80% 95,00% (cells/mt) Count 3 91.20% 1.98E+05 95.60% 5.09E+04 1.725+04 74.80% 1.388+05 1.26E+05 1.21E+04 3.288+05 2.96E+05 3.16E+04 1.55E+04 88.50% 1.83£+05 1.51E+04 92,40% 3.15E+05 3.01E+05 1.38E+04 6.81E+04 90.30% 1.75E+04 2.02E+03 cells/mt) Count 2 93.00% 87.00% 94.40% 1.835+04 1,31£+05 9.84E+03 2.835+05 4,25E+04 1.598+04 1.39£+04 1.98£+03 2.02E+05 1.888.405 1.385+04 2.55£+05 1.518+04 7.105+04 5,275+04 74.30% 1,415+05 3.265+05 87.50% 2,78£405 93,20% cells/mt} Count 1 % Viability % Viability % Viability % Viability % Viability % Viability Dead Dead Dead Dead Dead Dead Total Total Total Total Total Total 32.5 ٠ د 3 E. Ke 300 e E Volume (mL) 388 500 500 388 500 58 Gen 3.1 Test L4063 Gen 3.1 Test 14064 Gen 3.1 Control Gen 3.1 Control Gen 3.0 (A) Gen 3.0 (A) 14063 1,4064 14064 14063 Ω

Figure 103

## Cell counts Scale Up Day

g	Y change (and)		Count 1	Count 3	Count 2	Average	Total Cells
2	v undine (ma.)		(cells/mt)	(cells/mt)	(cells/m1)	(cells/mL)	Average*Volume
		Total	6.57£+05	6.61E+05		6.59£+05	6.59€+08
Gen 3.0 (A)	1000	Live	6.00€+05	6,14E+05		6,07£+05	6.07£+08
14063	1000	Dead	5.71£+04	4.68E+04		5,20£+04	5.20E+07
		% Viability	91.30%	92.90%		92.10%	
	-	Total	1.66£+06	1.82E+06		1.74€+06	1.74E+09
Gen 3.1 Control	000	Live	1.598+06	1,726+06		1.662+06	1.668+09
14063	TWAT	Dead	7.17E+04	9.07£+04		8.12£+04	8,12E+07
		% Viability	95.70%	95.00%		95.35%	
		Total	1,885+06	2.00E+06		1.945+06	1.94E+09
2000 C 4000 C 4000 C	\$	Five	1.76£+06	1.89£+06		1.83£+06	1.83£+09
Gen 3.1 rest 14085	TOOT.	Dead	1,20€+05	1.15E+05		1.18E+05	1.18£+08
		% Viability	93.60%	94,30%		93.95%	
		Total	7,95£+05	8.58E+05		8,27£+05	8.27E+08
Gen 3.0 (A)	1000	Live	7.17E+05	7.78E+05		7.48£+05	7,48E+08
14064	4000	Dead	7.85£+04	8.05E+04		7,95E+04	7.95£+07
		% Viability	90.10%	90.60%		90.35%	
		Total	1.38£+06	1.32E+06		1.35£+06	1.358+09
Gen 3,1 Control	0007	Live	1.315+06	1,24E+06		1.28£+06	1.28E+09
14064	7,000	Dead	7.20E+04	8,13£+04		7.67£+04	7.67E+07
		% Viability	94.80%	93.80%		94.30%	
		Total	1.85£+06	1.76E+06		1.81£+06	1.81E+09
Con 3 4 Tock 1 4054	2007	Live	1.76E+06	1.67£+06		1.726+06	1.72E+09
G61 2.1 1631 14024	O O	Dead	8.62E+04	8.95€+04		8.79£+04	8,79E+07
		% Viability	95.30%	94.90%		95.10%	

Figure 104

## Cell counts Harvest L4063

22	Mohima fmi i		Count 1	Count 2	Count 3	Average	Total Cells
à	x wranne group		(cells/mt)	(cells/mt)	(cells/mt)	{cells/ml.}	Average*Volume
		Totai	1.68E+07	1.705+07		1.695+07	1.025+10
Gen 3.0 (A)	× 600	Live	1.52£+07	1.54E+07		1.53£+07	9.22£+09
14063 pre 10VO	\$7.3CB	Dead	1.60£+06	1.65E+06		1,63€+06	80+364'6
		% Viability	%05.0%	90,30%		90.40%	
		Total	3.395+07	3,90€+07		3.65£407	1.81£+10
Gen 3.1 Control	* F00	an;	3.25E+07	3.73£+07		3,49£+07	1.73£+10
14063 pre 10VO	4.764	Dead	1.416+06	1.63£+06		1.528406	7.56£+08
		% Viability	95.80%	95.80%		95.80%	
		Totai	3,718+07	3.62£+07		3.67£+07	2.02£+10
Gen 3.1 Test 14063	e e ii	<i>वस्</i>	3.56E+07	3.51£+07		3.548+07	1.95£+10
ovol and	334.3	Dead	1.50€+06	1.095+06		1.30£+06	7.15£+08
		% Viability	36.00%	37.00%		96.50%	
		Total	5.378+07	S.73E+07	5.50E+07	5.53£+07	9,135+09
Gen 3.0 (A)	325	Live	4.32E+07	4.52E+07	4.36E+07	4,40£+07	7,26£+09
14063 post LOVO	527	Dead	1.04E+07	1,216+07	1.14E+07	1.13£407	1.86£+09
		% Viability	80,50%	78.80%	79,30%	79.53%	
		Totai	1.218+08	1,015+08	1.22E+08	1.15£+08	1.89£+10
Gen 3.1 Control	u u	Live	1.10£+08	8,85E+07	1.09£+08	1.03E+08	1.69£+10
L4063 post LOVO	pa7	Dead	1.116+07	1.23E+07	1.27£+07	1.205+07	1.998+09
		% Viability	90.90%	87.80%	89.60%	89,43%	
		Total	1.05E+08	1.20E+08		1.138+08	1.97£+10
Gen 3,1 Test 14063	175	Live	9.93E+07	1.146+08		1.078+08	1.87£+10
DVC Rod	7 57	Dead	5.51E+06	6.14E+06		5,83£+06	1.02£+09
		% Viability	94,70%	94,90%		94.80%	

Figure 105

## Cell counts Harvest L4064

ؿ	( ) and comments ( )		Count 1	Count 2	Count 3	Average	Total Cells
3	v chunc {min		(cells/mL)	(cells/mt)	(cells/mL)	(cells/mt)	Average*Volume
		Total	1.99£+07	1.946+07		1.97£+07	1.26E+10
Gen 3.0 (A)	0 80 80	Líve	1.83E+07	1.94E+07		1.89E+07	1.21E+10
L4064 pre LOVO	041. J	Dead	1.60£+06	1.68€+06		1.64E+06	1,05£+09
		% Viability	92.00%	92.00%		92.00%	
		Total	3.98£+07	3.87E+07		3.93£+07	1.94E+10
Gen 3.1 Control	402 8	Live	3,65£+07	3.55E+07		3,60€+07	1.78E+10
14064 pre LOVO	r S S S	Dead	3.316+06	3.22E+06		3.27£+06	1,61E+09
		% Viability	91.70%	91.70%		91.70%	
		Total	3.92E+07	3.79E+07		3.86E+07	2.29E+10
Gen 3,1 Test L4064	2 603	Live	3,675+07	3.54E+07		3.61E+07	2,146+10
DAG TOMO	732,4	Dead	2.55£+06	2.50E+06		2.53£+06	1,50E+09
		% Viability	93.50%	93.40%		93.45%	
		Total	8.58E+07	8.34E+07		8.46E+07	1.40E+10
Gen 3.0 (A)	2,50	Live	7.56E+07	7.46E+07		7.51E+07	1.246+10
L4064 post LOVO	103	Dead	1.02E+07	8.79E+06		9.50E+06	1.57E+09
		% Viability	88.10%	89.50%		88.80%	
		Total	1.13E+08	1.22E+08	1.15E+08	1.18E+08	1.94E+10
Gen 3.1 Control	n n	Live	9,216+07	1.01E+08	9.45E+07	9.668.407	1.59E+10
L4064 post LOVO	4004	Dead	2.14E+07	2.13E+07	2.07E+07	2.148+07	3.52E+09
		% Viability	81,20%	82.60%	82.10%	81.90%	
		Total	1.33£+08	1.45E+08		1.39£+08	2.29E+10
Gen 3.1 Test 14064	, to	Live	1.14E+08	1.22E+08		1.18£+08	1.95E+10
post 1,07/0	4004	Dead	1.94E+07	2.26E+07		2.10E+07	3.47E+09
		% Viability	85.40%	84.40%		84.90%	

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Figure 11.

							Skatamas-
Sample number #	Description Gen 3.1 Optimication	Glucose (g/L)	Lectate (g/l.)	Ammenia {mmol/L}	Gutzmine (mmol/1)	Glutamax (mmol/t)	Glutamine (mmol/L)
on wi	13 Gen 3.0-Day 16 First Round #LANE3	2.52	1.83	2.88	*** & ***	god god Prij	88
**	14 Gen 3.1 Control-Eny 16 First Round M. 4063	8	1.74	2.50	1.3%	3.49	23.52
	15 Gen 3.1 Test-Day 16 First Round #14/63	(S) (S) (S)	3	2.43		1.47	2,50
	16 Gest 3.0 Oay 11 Frest Roomd #24463	905 905 844	8.78	2.83	2.30	20 80 80	0.38
	🕻 🕇 Gen 3.1 Control Day II Frst Raund #LdG63	කි ත්	8	2.2%	1.07	क्षा स्टब्स स्टब्स	6.11
***	18 Gen 3.1 Test-Gay 11 First Round #1,4063	ф 86.	1.21	2.25	1.13	es P	9.12
eri eri	19 Seen 3.0 Day 7 First Round #1,4053	% %	8.28	88	707	2.23	8139
	20 Gen 3.1 Control-Cay 7 First Round #1,4063	87 67	0.22	2.886	2002	2.39	2,18
N	21 Gen 3.1 Test-Day ? First Round #4,4863	44 94 54	0.50	2.9% 2.9%	88 60 er	64 84 80	8.17
22	22 Gen 3.0-Day 16 Second Round #14064	2.76	3.5 52.5	188	88 Ci	8.77	20
23	23 Sen 3.1 Connol-Day 15 Second Round MASSA	2.34	30.5	880	200	0.73	85
22	24 Gen 3.1 Test. Day 15 Second Round #LADEs	2.20	&) &) **	76.0	980	8.73	0.07
13 13 13 13 13 13 13 13 13 13 13 13 13 1	25 Gen 3.0 Clay 7 Second Round # 4064	4.26	8800	202	1.23	£.8.3	2 13
***	26 Sen 3.1 Canack-Day 7 Second Round #UMSS	 	8.22	0.78	Pr. 1446 1446 1446	Øi Pil wi	2
in N	27 Gen 3.1 Test-Day 7 Second Round #L4064	3.82	0.43	88 10	1.09	3.20	2,11

Figure 114

_			Geometra	Geometri Geometri			
			c Mean	c Mean	Awerage	Antonio Company	Length relative to
			Probe-fitte-	Probe-fitc Probe-fitc	1381	್ಷ ವಿಜಿಪ್ಪಾಪ್ತಿಸ್ಟ	1301
Order	Name		~	≪.			
A3		A1 10,1.fcs	98	42.5			
4 2	C201 2 B 1 1 10 C2	42 10,2,fcs	85.4	47.3	85.7	4.54 4.04	
A3	C00%7-0*C U20	A3 10,3,fcs	4585	203			
44		A4 10.4.fcs	4389	216	4487	211.5	7.684093
AS		AS 11,1,fcs	82.7	33.3			
A6	Gen 3.1 Control-	48 11.2.fcs	88	32.5	84.35	33.3	
A7	1,4063	A7 11.3,fcs	3634	180			
AS		AS 11.4.fcs	4641	175	4668.5	177.5	6.299968
83		81 12,1,fcs	35.1	28.8			
82	Gen 3.1 Test-	82 12,2,fcs	84.7	26.7	89.9	27.75	
83	14063	83 12.3.fcs	4764	169			
84	-	84 12 4.fcs	4800	174	4782	171.5	6.12732
82	<u> </u>	85 13.1.fcs	101	40.3			
93	8008	8£ 13.2.fcs	9.68	34.3	95.3	33.2	
87	56H 3.0 ~ C#204	87 13.3.7cs	CO 54	174			
88		88 13.4.fcs	4367	172	4333.5	173	5,408381
CI		C1 14,1,fcs	92.1	504 504 505			
22	Gen 3.1 Control-	C2 14, 2, fcs	88.6	29.6	90,35	30.35	and the second
C3	14064	C3 14.3.fcs	4313	169			
3		C4 14.4.fcs	4443	372	4277	170.5	6.69509
ಐ		CS 15,1,fcs	83.7	25.3			
90	Gen 3.1 Test-	C6 15, 2, fcs	85.7	24.7	87.7	25.3	
23	14064	C7 15.3.fcs	4342	172			
2	-	C8 15.4.fcs	4560	166	4451	169	6.591341

Figure 115

Shared Frequencies

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	make acted count Compa			4,063 (2,653 3,27	1263 Een 3.2 cantoo)	4060 Gen 2 3 Test				1064 Gen 2.1 Yest
	ample LuCitità count Compa			2063 Cen 3.0	.4063 Een 3.2 cantos	.4065 Gen 2.3 3cs				4064 Gen 3.2 Test
	Samule uCINR3 count Compa			12063 Sen 3.2	L4063 Sen 3.2 (antos)	14065 Gen 3.2 3est				£4064 Gen 3.2 Test
	Sample UCING count Compa			< 12063 Sen 3.2	 14063 Sen 3.1 (antos) 	× 14065 Gen 3.33cg				× 64064 Gen 3.2 Test
	al Sample UCDR3 count Compa			4 14063 Sen 3.0	< 14063 Sen 3.1 (antos)	= £4663 Gen 3.33est				=14064 Gen 3.2 Test
	sal Sample UCBR3 count Compa			4 = 1,4263 5,653 3.2	8 = 14063 Sen 3.1 (antos)	C = 64063 Gen 3.2 Test				C = £4064 Gen 2 3 Test
	stal Sample: UCINES count, Compa			64 + 1,4145 (1em 3.1)	.8 + 14063 Cen 3.1 : antrol	S. + 64663 Gen 3 3 3 8 st				S. = 14064 Geo. 2 (Test
	ginal Sample uCBR3 count Compa			KA = 1 4 263 5 557 3 2	6.8 = 14063 Sen 3.1 central	101. × 141.83 Gen 3.2 Test				6.5. = 6.4064 Gen 3.3.1est
	spisal Sample uCDR3 count Compa			00.4 × 1.406.3 f.em 3.2	36.8 = 14063 Gen 3.1 : antos)	30£ + 1466 Gen 3 3 lest				40C × 14064 Gen 3 2 Tess
	Riginal Sample: UCINES count, Compa			\$604 + 14043 Sen 3.1	636.8 = 14063 Cen 3.1 (antos)	63UL = 14(63 Gen 3.3 Test				64.55 × 14.664 Gen 3.2.3 est
	Original Sample: UCBR3 count, Compa			18804 - 18183 Den 3.0	(5368 = 14063 Een 3.1 (anto)	163UL = 14661 Gen 3 2 Jest				1545.C = 14764 Gen 2 2 Test
	Original Sample: UCING count. Companed Sample: UCORS count count			15804 × 14063 tem 3.0	£5368 = 14063 Gen 3.1 (antos)	16355 × 14763 Gen 3 3 3 est		15404 - 14064 Cen 30	15458 - 14064 Gen 3.2 central	16451 = 14164 Gen 3.3 Test
	Original Sample: UCINI3 count, Compa			15804 - 12123 Len 3.2	1.537.8 - 1.429.3 Gen 3.1 centrol	1630C + 14663 Gen 3.3 Test				16401 = 14064 Gen 2 2 Test
	Original Sample: UCDR3 count, Compa			15804 - 19183 (1873.)	£536.8 ± £406.3 Gen 3.1 control	16301 = 14063 Gen 3.2 Text				6435 × 64064 600 3.3 788
	Original Sample UCINI3 count Compa			15804 - 14063 Den 3.0	£5308 = £4063 Gen 3.2 centos	16301 = 14063 Gen 3 3 3 est				16451. = 14764 (sen 2.2.185)
				15304 × 14003 000 3.2	£5368 = £4283 Gen 3.2 (antos)	18355 × 14683 Gen 3 2 3 est				16451. = 14064 Gen 3.3 Test
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					£5368 = £4283 Een 3.2 (antos)	16355 = 14763 Gen 3.3 Test				U401 = 14064 Gen 3.3 Test
					16308 + 14063 Cen 3.1 (entro)	16355 = 14063 Gen 3.3.3est				16401 = 14064 Gen 3 1 Test
					£5368 ÷ £4063 Gen 3.2 centro)	163UL = 14/63 Gen 2.3 Test				10401 × 14064 Gen 3 2 7ess
					15368 = 14083 Gen 3.1 (antos)	16355 = 14063 Gen 3.3.3est				16401 = 14064 Gen 2.17cm
	Subject Original Sample (UCIRES count, Compa			Code 15004 - 14003 5813.2	15308 + 14063 Cen 3.1 (anto)	16301 × 14661 Gen 3.3 3est				16401 × 14764 600 3 2 185

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