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(54) Bezeichnung: **HETEROLOGE EXPRESSION VON NEISSERIA-PROTEINEN**

Beschreibung

GEBIET DER ERFINDUNG

[0001] Diese Erfindung bezieht sich auf das Gebiet der Proteinexpression. Speziell betrifft sie die heterologe Expression von Proteinen aus Neisseria (z.B. N. gonorrhoeae oder bevorzugt N. meningitidis).

STAND DER TECHNIK

[0002] Die internationalen Patentanmeldungen WO 99/24578, WO 99/36544, WO 99/57280 und WO 00/22430 offenbaren Proteine von Neisseria meningitidis und Neisseria gonorrhoeae. Diese Proteine werden üblicherweise als in E. coli exprimiert beschrieben (d.h. heterologe Expression), entweder als N-terminale GST-Fusionen oder als C-terminale His-Tag-Fusionen, obgleich auch andere Expressionssysteme, einschließlich der Expression in nativen Neisseria offenbart sind. FR-A-2720408 offenbart die heterologe Produktion eines N. meningitidis-Proteins, in dem mindestens eine Domäne deletiert worden ist.

[0003] Es ist ein Ziel der vorliegenden Erfindung, alternative und verbesserte Methoden für die heterologe Expression dieser Proteine bereitzustellen. Diese Methoden wirken sich typischerweise auf den Expressionsspiegel, die Einfachheit der Aufreinigung, die zelluläre Lokalisierung der Expression und/oder die immunologischen Eigenschaften des exprimierten Proteins aus.

OFFENBARUNG DER ERFINDUNG

[0004] Die Erfindung betrifft das Protein ‚961', welches in WO 99/57280 offenbart ist. Die in WO 99/24578, WO 99/36544 und WO 99/57280 verwendeten Konventionen der Benennung werden hierin verwendet (z.B. ‚ORF4', ‚ORF40', ‚ORF40-1' etc. wie in WO 99/24578 und in WO 99/36544 verwendet; ‚m919', ‚g919' und ‚a919' etc. wie in WO 99/527280 verwendet.

[0005] Das bevorzugte Protein der Erfindung '961' wird in N. meningitidis der Serogruppe B gefunden.

[0006] Das zur Verwendung gemäß der Erfindung bevorzugte Protein '961' stammt von dem N. meningitidis-Stamm 2996 der Serogruppe B oder vom Stamm 394/98 (einem Stamm aus Neuseeland). Sofern nicht anderweitig angegeben, sind die hierin erwähnten Proteine aus dem N. meningitidis-Stamm 2996. Es versteht sich jedoch, dass die Erfindung nicht allgemein auf den Stamm beschränkt ist. Bezugnahmen auf ein bestimmtes Protein (z.B. ‚287', ‚919' etc.) können so aufgefasst werden, dass sie jenes Protein von einem beliebigen Stamm einschließen.

Auf Domänen basierende Expression

[0007] Bei dieser Methode einer heterologen Expression wird das Protein ‚961' in Form von Domänen exprimiert. Dies kann in Verbindung mit Fusionssystemen (z.B. GST- oder His-Tag-Fusionen) verwendet werden.

[0008] Somit stellt die Erfindung ein Verfahren zur heterologen Expression des Proteins ‚961' von N. meningitidis bereit, wobei

(a) das Protein 961 die Aminosäuresequenz '961' in Stamm MC58 hat:

MSMKHFPAKVLTTAILATFCSGALAATSDDDVKKAATVAIVAAYNNGQEINGFKAGETIYDIGE
DGTITQKDATAADVEADDFKGLGLKKVVTNLTKTVNENKQNVDAKVKAAESEIEKLTTKLADTD
AALADTDAALDETTNALNKLGENITTFAEETKTNIVKIDEKLEAVADTVDKHAEAFNDIADSLD
ETNTKADEAVKTANEAKQTAEETKQNVDAKVKAAETAAGKAEAAAGTANTAADKAEAVAAKVTD
IKADIATNKADIAKNSARIDSLDKNVANLRKETRQGLAEQAALSGLFQPYNVGRFNVTAAVGGY
KSESAVAIGTGFRFTENFAAKAGVAVGTSSGSSAAYHVGVNYEW

und wobei

(b) zumindest eine Domäne des Proteins deletiert wurde, wobei die Domänen von ‚961' in Stamm MC58 folgendermaßen sind: (1) Aminosäuren 1 bis 23; (2) Aminosäuren 24 bis 268; (3) Aminosäuren 269 bis 307; und (4) Aminosäuren 308 bis 364,

und wobei das '961'-Protein in einer Wirtszelle exprimiert wird.

[0009] Das Verfahren wird normalerweise die Schritte umfassen: Erlangen einer Nucleinsäure, die ein Protein codiert; Bearbeiten dieser Nucleinsäure, um mindestens eine Domäne aus dem Protein zu entfernen. Die so erhaltene Nucleinsäure kann in einen Expressionsvektor eingesetzt werden oder kann bereits Teil eines Expressionsvektors sein. In Fällen, in denen keine Fusionspartner verwendet werden, ist die erste Aminosäure des exprimierten Proteins diejenige einer Domäne des Proteins.

[0010] Ein Protein wird normalerweise in vermutete Domänen unterteilt, indem man es mit bekannten Sequenzen in Datenbanken abgleicht und dann Regionen des Proteins bestimmt, die voneinander unterschiedliche Anordnungsmuster zeigen.

[0011] Wenn man ein Protein in Domänen unterteilt hat, können diese (a) einzeln exprimiert werden, (b) aus dem Protein deletiert werden, z.B. Protein ABCD → ABD, ACD, BCD etc. oder (c) neu angeordnet werden, z.B. Protein ABC → ACB, CAB etc. Diese drei Strategien können, sofern gewünscht, mit Fusionspartnern kombiniert werden.

[0012] Die Domänen des Proteins ‚961' sind in Fig. 12 dargestellt.

Hybridproteine

[0013] Das Protein ‚961' kann Teil eines Hybrids von zwei oder mehreren (z.B. 3, 4, 5, 6 oder mehr) Neisseria-Proteinen sein, die als ein einziges Hybridprotein exprimiert werden. Es ist bevorzugt, dass kein Nicht-Neisseria-Fusionspartner (z.B. GST oder His-Tag) verwendet wird.

[0014] Dies bietet zwei Vorteile. Erstens, kann ein Protein, das alleine unstabil ist oder gering exprimiert wird, durch das Hinzufügen eines geeigneten Hybridpartners unterstützt werden, der dieses Problem überwindet. Zweitens wird die kommerzielle Herstellung vereinfacht – es muss nur eine Expression und Aufreinigung durchgeführt werden, um zwei für sich gesehen nützliche Proteine zu produzieren.

[0015] Somit stellt die Erfindung ein Verfahren für die gleichzeitige heterologe Expression von Protein 961 mit einem oder mehreren Neisseria-Proteinen bereit, in dem die Proteine fusioniert sind (d.h. sie werden als einzelne Polypeptidkette translatiert). Das Verfahren wird typischerweise die Schritte umfassen: Erlangen einer ersten Nucleinsäure, welche ein erstes erfindungsgemäßes Protein codiert; Erlangen einer zweiten Nucleinsäure, welche ein zweites erfindungsgemäßes Protein codiert; Ligieren der ersten und der zweiten Nucleinsäure. Die so erhaltene Nucleinsäure kann in einen Expressionsvektor eingesetzt werden oder kann bereits Teil eines Expressionsvektors sein.

[0016] Bevorzugt werden die ProteinBestandteile in einem Hybridprotein gemäß der Erfindung vom selben Stamm kommen.

[0017] Die fusionierten Proteine in dem Hybrid können direkt miteinander verbunden sein oder können über ein Linkerpeptid verknüpft sein, z.B. über einen Poly-Glycin-Linker (z.B. G_n, wobei n = 3, 4, 5, 6, 7, 8, 9, 10 oder mehr ist) oder über eine kurze Peptidsequenz, was die Clonierung erleichtert. Es ist offensichtlich bevorzugt, nicht ein ΔG-Protein mit dem C-Terminus eines Poly-Glycin-Linkers zu verknüpfen.

[0018] Den fusionierten Proteinen können native Leader-Peptide fehlen oder diese können die Leader-Peptidsequenz des N-terminalen Fusionspartners beinhalten.

[0019] Die mit „X" bezeichneten Hybride der Form NH_2-A-B-COOH in der folgenden Tabelle sind bevorzugt:

↓A B→	ORF46.1	287	741	919	953	961	983
ORF46.1						X	
287						X	
741						X	
919						X	
953						X	
961	X	X	X	X	X		X
983						X	

[0020] Bevorzugte Proteine, die als Hybride mit dem Protein ‚961' exprimiert werden sollen, sind somit ORF46.1, 287, 741, 919, 953 und 983. Diese können in ihrer im Wesentlichen Volllänge-Form verwendet werden oder man kann Poly-Glycin-Deletionsformen (ΔG) verwenden (z.B. ΔG-287, ΔGTgbp2, ΔG741, ΔG983 etc.) oder man kann verkürzte Formen verwenden (z.B. Δ1-287, Δ2-287 etc.) oder man kann Versionen verwenden, in denen Domänen deletiert wurden (z.B. 287B, 287C, 287BC, $ORF46_{1-433}$, $ORF46_{433-608}$, 961c etc.).

[0021] In Fällen, in denen 287 verwendet wird, geschieht dies bevorzugt am C-terminalen Ende eines Hybrids; wenn es am N-Terminus verwendet werden soll, ist es bevorzugt, eine ΔG-Form von 287 zu verwenden (z.B. als den N-Terminus eines Hybrids mit 961).

[0022] In Fällen, in denen 287 verwendet wird, stammt dies bevorzugt vom Stamm 2996 oder vom Stamm 394/98.

[0023] ‚961' ist bevorzugt am N-Terminus. In solchen Hybriden werden bevorzugt Domänen-Formen von 961 verwendet. Anordnungen von polymorphen Formen von ORF46, 287, 919 und 953 sind in WO 00/66741 offenbart. Jede beliebige dieser polymorphen Formen kann gemäß der vorliegenden Erfindung verwendet werden.

Heterologer Wirt

[0024] Während eine Expression des Proteins 961 oder eines Hybrids davon in dem nativen Wirt stattfinden kann (d.h. dem Organismus, in dem das Protein in der Natur exprimiert wird), verwendet die vorliegende Erfindung einen heterologen Wirt. Der heterologe Wirt kann eukaryontisch oder prokaryontisch sein. Bevorzugt handelt es sich dabei um E. coli, aber andere geeignete Wirte umfassen Bacillus subtilis, Vibrio cholerae, Salmonella typhi, Salmonella typhimurium, Neisseria meningitidis, Neisseria gonorrhoeae, Neisseria lactamica, Neisseria cinerea, Mycobacteria (z.B. M. tuberculosis), Hefe etc.

Vektoren etc.

[0025] Ebenso wie die vorstehend beschriebenen Verfahren stellt die Erfindung (a) Nucleinsäuren und Vektoren bereit, die für diese Verfahren nützlich sind, (b) Wirtszellen, welche diese Vektoren enthalten, (c) Proteine, welche durch die Verfahren exprimiert werden oder mit deren Hilfe exprimierbar sind, (d) Zusammensetzungen, welche diese Proteine umfassen, die zum Beispiel als Impfstoffe oder als diagnostische Reagenzien oder als immunogene Zusammensetzungen geeignet sein können, (e) diese Zusammensetzungen zur Verwendung als Medikamente (z.B. als Impfstoffe) oder als diagnostische Reagenzien, (f) die Verwendung dieser Zusammensetzungen bei der Herstellung (1) eines Medikaments zur Behandlung oder zur Vorbeugung einer auf Neisseria zurückzuführenden Infektion, (2) eines diagnostischen Reagenz zum Nachweis des Vorhandenseins von Neisseria-Bakterien oder von Antikörpern, welche gegen Neisseria-Bakterien induziert worden sind und/oder (3) eines Reagenz, welches Antikörper gegen Neisseria-Bakterien induzieren kann und (g) ein Verfahren zur Behandlung eines Patienten, umfassend das Verabreichen einer therapeutisch wirksamen Menge dieser Zusammensetzungen an den Patienten.

Sequenzen

[0026] Die Erfindung stellt auch ein Protein oder eine Nucleinsäure bereit, welche eine beliebige der in den folgenden Beispielen dargelegten Sequenzen aufweisen. Sie stellt auch Proteine und Nucleinsäuren bereit, die mit diesen Sequenz-identisch sind. Wie vorstehend beschrieben, ist der Grad der Sequenzidentität bevorzugt größer als 50% (z.B. 60%, 70%, 80%, 90%, 95%, 99% oder mehr).

[0027] Darüber hinaus stellt die Erfindung Nucleinsäuren bereit, welche an die in den Beispielen offenbarten Nucleinsäuren hybridisieren können, bevorzugt unter Bedingungen hoher Stringenz (z.B. 65°C in einer 0,1 × SSC, 0,5% SDS-Lösung).

[0028] Die Erfindung verwendet auch Nucleinsäuren, die Proteine codieren, welche in der Erfindung verwendet werden.

[0029] Man sollte sich auch im Klaren darüber sein, dass die Erfindung Nucleinsäuren bereitstellt, die Sequenzen umfassen, welche komplementär zu denjenigen sind, die vorstehend beschrieben sind (z.B. für Antisense- oder Sonden-Zwecke).

[0030] Eine erfindungsgemäße Nucleinsäure kann natürlich auf viele Arten hergestellt werden (z.B. durch chemische Synthese, aus genomischen oder cDNA-Banken, aus dem Organismus selbst etc.) und kann verschiedene Formen annehmen (z.B. einzelsträngig, doppelsträngig, Vektoren, Sonden etc.).

[0031] Darüber hinaus schließt der Begriff „Nucleinsäure" DNA und RNA ein, und auch deren Analoga wie z.B. jene, die modifizierte Gerüste enthalten, und auch Peptidnucleinsäuren (PNA) etc.

Kurze Beschreibung der Zeichnungen

[0032] Fig. 4 zeigt Expressionsdaten für das Protein 961.

[0033] Fig. 12 zeigt Domänen des Proteins 961.

[0034] Fig. 14 zeigt 26 erfindungsgemäße Hybridproteine.

ARTEN, DIE ERFINDUNG AUSZUFÜHREN

Beispiel 5 – pSM214 und pET-24b-Vektoren

[0035] Das Protein 953 wurde mit seiner nativen Leader-Sequenz und ohne Fusionspartner von dem pET-Vektor und auch von pSM214 [Velati Bellini et al., J. Biotechnol. 18: 177-192 (1991)] exprimiert.

[0036] Die Sequenz 953 wurde als ein Volllänge-Gen in pSM214 cloniert, wobei der E. coli-Stamm MM294-1 als Wirt verwendet wurde. Um dies zu tun, wurde die gesamte Sequenz des 953-Gens (vom ATG bis zum Stopcodon) mittels PCR amplifiziert, wobei die folgenden Primer verwendet wurden:

953L for/2	CCGGAATTCTTATGAAAAAAATCATCTTCGCCGC	EcoRI
953L rev/2	GCCCAAGCTTTTATTGTTTGGCTGCCTCGATT	HindIII

welche EcoRI- bzw. HindIII-Restriktionsstellen enthalten. Das amplifizierte Fragment wurde mit EcoRI und HindIII verdaut und mit dem Vektor pSM214 ligiert, der mit denselben zwei Enzymen verdaut worden war. Das ligierte Plasmid wurde in E. coli MM294-1-Zellen transformiert (durch eine Inkubation in Eis für 65 Minuten bei 37°C) und die Bakterienzellen auf LB-Agar ausplattiert, welcher 20 µg/ml Chloramphenicol enthielt.

[0037] Man ließ rekombinante Kolonien über Nacht bei 37°C in 4 ml LB-Nährmedium wachsen, das 20 µg/ml Chloramphenicol enthielt; die Bakterienzellen wurden abzentrifugiert und Plasmid-DNA extrahiert und durch Restriktion mit EcoRI und HindIII analysiert. Um die Fähigkeit der rekombinanten Kolonien zu untersuchen, das Protein zu exprimieren, impfte man diese in LB-Nährmedium an, welches 20 µg/ml Chloramphenicol enthielt und ließ sie für 16 Stunden bei 37°C wachsen. Die Bakterienzellen wurden abzentrifugiert und in PBS resuspendiert. Die Expression des Proteins wurde mittels SDS-PAGE und Färbung mit Coomassie-Blau untersucht.

[0038] Die Expressionsspiegel von dem Plasmid pSM214 waren unerwartet hoch.

[0039] Die Oligos, die dazu verwendet wurden, ‚961'-Sequenzen in die pSM214-Vektoren zu clonieren, waren wie folgt:

961L (pSM-214)	Fwd	CCGGAATTCATATG-AAACACTTTCCATCC	EcoRI
	Rev	GCCCAAGCTT-TTACCACTCGTAATTGAC	HindIII
961 (pSM-214)	Fwd	CCGGAATTCATATG-GCCACAAGCGACGAC	EcoRI
	Rev	GCCCAAGCTT-TTACCACTCGTAATTGAC	HindIII
961c L pSM-214	Fwd	CCGGAATTCTTATG-AAACACTTTCCATCC	EcoRI
	Rev	GCCCAAGCTT-TCAACCCACGTTGTAAGGTTG	HindIII
961c pSM-214	Fwd	CCGGAATTCTTATG-GCCACAAACGACGACG	EcoRI
	Rev	GCCCAAGCTT-TCAACCCACGTTGTAAGGTTG	HindIII

[0040] Diese Sequenzen wurden wie für 953L beschrieben bearbeitet, cloniert und exprimiert.

[0041] Für den Vektor pET-24 wurden die Sequenzen cloniert und die Proteine in pET-24 exprimiert, wie nachstehend für pET21 beschrieben. pET2 weist dieselbe Sequenz auf wie pET-21, jedoch mit der Kanamycin-Resistenz-Kassette an Stelle der Ampicillin-Kassette.

[0042] Die Oligonucleotide, die dazu verwendet wurden, Sequenzen in den Vektor pET-2b4 zu clonieren, waren wie folgt:

961 K (MC58)	Fwd	CGCGGATCCCATATG-GCCACAAGCGACGACGA	NdeI
	Rev	CCCGCTCGAG-TTACCACTCGTAATTGAC	XhoI
961a K	Fwd	CGCGGATCCCATATG-GCCACAAACGACG	NdeI
	Rev	CCCGCTCGAG-TCATTTAGCAATATTATCTTTGTTC	XhoI
961b K	Fwd	CGCGGATCCCATATG-AAAGCAAACAGTGCCGAC	NdeI
	Rev	CCCGCTCGAG-TTACCACTCGTAATTGAC	XhoI
961c K	Fwd	CGCGGATCCCATATG-GCCACAAACGACG	NdeI
	Rev	CCCGCTCGAG-TTAACCCACGTTGTAAGGT	XhoI
961cL K	Fwd	CGCGGATCCCATATG-ATGAAACACTTTCCATCC	NdeI
	Rev	CCCGCTCGAG-TTAACCCACGTTGTAAGGT	XhoI
961d K	Fwd	CGCGGATCCCATATG-GCCACAAACGACG	NdeI
	Rev	CCCGCTCGAG-TCAGTCTGACACTGTTTTATCC	XhoI

ΔG 287-961 K	Fwd	CGCGGATCCGCTAGC-CCCGATGTTAAATCGGC	NheI
	Rev	CCCGCTCGAG-TTACCACTCGTAATTGAC	XhoI

*Dieser Primer wurde als Rückwärts-Primer für alle 287-Formen eingesetzt.
§Vorwärts-Primer, welche in Kombination mit dem Rückwärts-Primer ΔG278K verwendet werden.

Beispiel 9 – Protein 961

[0043] Das vollständige Protein 961 aus N. meningitidis (Serogruppe B, Stamm MC58) weist die folgende Sequenz auf:

```
  1 MSMKHFPAKV LTTAILATFC SGALAATSDD DVKKAATVAI VAAYNNGQEI
 51 NGFKAGETIY DIGEDGTITQ KDATAADVEA DDFKGLGLKK VVTNLTKTVN
101 ENKQNVDAKV KAAESEIEKL TTKLADTDAA LADTDAALDE TTNALNKLGE
151 NITTFAEETK TNIVKIDEKL EAVADTVDKH AEAFNDIADS LDETNTKADE
201 AVKTANEAKQ TAEETKQNVD AKVKAAETAA GKAEAAAGTA NTAADKAEAV
251 AAKVTDIKAD IATNKADIAK NSARIDSLDK NVANLRKETR QGLAEQAALS
301 GLFQPYNVGR FNVTAAVGGY KSESAVAIGT GFRFTENFAA KAGVAVGTSS
351 GSSAAYHVGV NYEW*
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[0044] Das Leader-Peptid ist unterstrichen.

[0045] Es wurden drei Methoden zur Expression von 961 verwendet:
1) 961 unter Verwendung einer GST-Fusion, gemäß WO 99/57280 (‚GST961');
2) 961 mit seinem eigenen Leader-Peptid aber ohne irgendeinen Fusionspartner (‚961L'); und
3) 961 ohne sein Leader-Peptid und ohne irgendeinen Fusionspartner (‚961^{untagged}'), wobei das Leader-Peptid weggelassen wurde, indem der PCR-Primer am 5'-Ende so konstruiert wurde, dass er stromabwärts von der vorhergesagten Leader-Sequenz lag.

[0046] Alle drei Formen des Proteins wurden exprimiert. Das GST-Fusionsprotein konnte aufgereinigt werden und Antikörper gegen dieses bestätigten, dass 961 exponiert an der Oberfläche vorliegt (Fig. 4). Das Protein wurde dazu verwendet, Mäuse zu immunisieren und die so erhaltenen Seren lieferten hervorragende Ergebnisse in dem Bakterizidie-Assay. 961L konnte ebenfalls aufgereinigt werden und ergab sehr hohe ELISA-Titer.

[0047] Das Protein 961 scheint in verschiedenen Phasen unterschiedlich zu sein. Des Weiteren findet man es nicht in allen Stämmen von N. meningitidis.

Beispiel 22 – Domänen in 961

[0048] Wie in Beispiel 9 vorstehend beschrieben war die GST-Fusion von 961 diejenige, die in E. coli am besten exprimiert wurde. Um die Expression zu verbessern, wurde das Protein in Domänen unterteilt (Fig. 12).

[0049] Die Domänen von 961 wurden auf der Grundlage von YadA konstruiert (einem von Yersinia produzierten Adhäsin, von dem gezeigt worden ist, dass es ein auf der Bakterienoberfläche befindliches Adhäsin ist, welches Oligomere bildet, die eine Ausbuchtung der Oberfläche erzeugt [Hoiczyk et al., EMBO J. 19: 5989-99 (2000)], und bei diesen handelt es sich um: Leader-Peptid, Kopfdomäne, „Coiled coil"-Region (Stiel) und Membranverankerungsdomäne.

[0050] Diese Domänen wurden mit oder ohne das Leader-Peptid exprimiert und gegebenenfalls entweder an das C-terminale His-Tag oder an das N-terminale GST fusioniert. Clone von E. coli, die verschiedene Domänen von 961 exprimierten, wurden mittels SDS-PAGE und Western Blot auf die Produktion und die Lokalisierung des exprimierten Proteins aus einer Übernachtkultur (O/N) oder nach 3 Stunden Induktion mit IPTG untersucht. Die Ergebnisse waren:

	Gesamtlysat (Western Blot)	Periplasma (Western Blot)	Überstand (Western Blot)	OMV SDS-PAGE
961 (o/n) 961 (IPTG)	– +/–	– –	– –	
961-L (o/n) 961-L (IPTG)	+ +	– –	– –	+ +
961c-L (o/n) 961c-L (IPTG)	– +	– +	– +	
961Δ_1-L (o/n) 961Δ_1-L (IPTG)	– +	– –	– –	+

[0051] Die Ergebnisse zeigen, dass in E. coli:
- 961-L hoch exprimiert und in der äußeren Membran lokalisiert ist. Durch Western Blot-Analyse sind zwei spezifische Banden nachgewiesen worden: eine bei ~ 45 kDa (das vorhergesagte Molekulargewicht) und eine bei 180 kDa, was darauf hinweist, dass 961-L Oligomere bilden kann. Außerdem sind diese Aggregate mehr in der Übernachtkultur (ohne IPTG-Induktion) exprimiert. OMV (Vesikel der äußeren Membran)-Präparate dieses Clons wurden dazu verwendet, um Mäuse zu immunisieren, und es wurde Serum gewonnen. Bei Verwendung einer Übernachtkultur (vorherrschend durch die oligomere Form) war das Serum bakterizid; die mit IPTG induzierte Kultur (vorherrschend monomer) war nicht bakterizid.
- 961Δ_1-L (mit einer partiellen Deletion in der Ankerregion) wird hoch exprimiert und ist auf der äußeren Membran lokalisiert, bildet jedoch keine Oligomere;
- 961c-L (ohne die Ankerregion) wird in löslicher Form hergestellt und in den Überstand exportiert.

[0052] Die Titer im ELISA und in dem Serum-Bakterizidie-Assay bei Verwendung der His-Fusionen waren wie folgt:

	ELISA	Bakterizidie
961a (aa 24-268)	24397	4096
961b (aa 269-405)	7763	64
961c-L	29770	8192
961c (2996)	30774	> 65536
961c (MC58)	33437	16384
961d	26069	> 65536

[0053] E. coli-Clone, die verschiedene Formen von 961 exprimierten (961, 961-L, 961D1-L und 961c-L), wurden eingesetzt um zu erforschen, ob es sich bei dem 961 um ein Adhäsin handelt (vgl. YadA). Es wurde ein Adhäsions-Assay durchgeführt, wobei (a) die menschlichen Epithelzellen und (b) E. coli-Clone entweder nach einer Übernachtkultur oder nach drei Stunden Induktion mit IPTG verwendet wurden. 961-L, welches man über Nacht hatte wachsen lassen (961Δ_1-L), und mit IPTG induziertes 961c-L (die Clone, welche Protein auf der

Oberfläche exprimieren) adhärieren an menschliche Epithelzellen.

[0054] 961c wurde ebenfalls in Hybridproteinen verwendet (siehe vorstehend). Da 961 und seine Domänenvarianten eine effiziente Expression steuern, sind sie ideal als der N-terminale Teil eines Hybridproteins geeignet.

Beispiel 23 – Weitere Hybride des Proteins 961

[0055] Weitere Hybridproteine der Erfindung sind nachstehend gezeigt (siehe auch Fig. 14). Diese sind im Vergleich zu den einzelnen Proteinen vorteilhaft:

961-ORF46.1

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   1   ATGGCCACAA ACGACGACGA TGTTAAAAAA GCTGCCACTG TGGCCATTGC
  51   TGCTGCCTAC AACAATGGCC AAGAAATCAA CGGTTTCAAA GCTGGAGAGA
 101   CCATCTACGA CATTGATGAA GACGGCACAA TTACCAAAAA AGACGCAACT
 151   GCAGCCGATG TTGAAGCCGA CGACTTTAAA GGTCTGGGTC TGAAAAAAGT
 201   CGTGACTAAC CTGACCAAAA CCGTCAATGA AAACAAACAA AACGTCGATG
 251   CCAAAGTAAA AGCTGCAGAA TCTGAAATAG AAAAGTTAAC AACCAAGTTA
 301   GCAGACACTG ATGCCGCTTT AGCAGATACT GATGCCGCTC TGGATGCAAC
 351   CACCAACGCC TTGAATAAAT TGGGAGAAAA TATAACGACA TTTGCTGAAG
 401   AGACTAAGAC AAATATCGTA AAAATTGATG AAAAATTAGA AGCCGTGGCT
 451   GATACCGTCG ACAAGCATGC CGAAGCATTC AACGATATCG CCGATTCATT
 501   GGATGAAACC AACACTAAGG CAGACGAAGC CGTCAAAACC GCCAATGAAG
 551   CCAAACAGAC GGCCGAAGAA ACCAAACAAA ACGTCGATGC CAAAGTAAAA
 601   GCTGCAGAAA CTGCAGCAGG CAAAGCCGAA GCTGCCGCTG GCACAGCTAA
 651   TACTGCAGCC GACAAGGCCG AAGCTGTCGC TGCAAAAGTT ACCGACATCA
 701   AAGCTGATAT CGCTACGAAC AAAGATAATA TTGCTAAAAA AGCAAACAGT
 751   GCCGACGTGT ACACCAGAGA AGAGTCTGAC AGCAAATTTG TCAGAATTGA
 801   TGGTCTGAAC GCTACTACCG AAAAATTGGA CACACGCTTG GCTTCTGCTG
 851   AAAAATCCAT TGCCGATCAC GATACTCGCC TGAACGGTTT GGATAAAACA
 901   GTGTCAGACC TGCGCAAAGA AACCCGCCAA GGCCTTGCAG AACAAGCCGC
 951   GCTCTCCGGT CTGTTCCAAC CTTACAACGT GGGTCGGTTC AATGTAACGG
1001   CTGCAGTCGG CGGCTACAAA TCCGAATCGG CAGTCGCCAT CGGTACCGGC
1051   TTCCGCTTTA CCGAAAACTT TGCCGCCAAA GCAGGCGTGG CAGTCGGCAC
1101   TTCGTCCGGT TCTTCCGCAG CCTACCATGT CGGCGTCAAT TACGAGTGGG
1151   GATCCGGAGG AGGAGGATCA GATTTGGCAA ACGATTCTTT TATCCGGCAG
1201   GTTCTCGACC GTCAGCATTT CGAACCCGAC GGGAAATACC ACCTATTCGG
1251   CAGCAGGGGG GAACTTGCCG AGCGCAGCGG CCATATCGGA TTGGGAAAAA
1301   TACAAAGCCA TCAGTTGGGC AACCTGATGA TTCAACAGGC GGCCATTAAA
1351   GGAAATATCG GCTACATTGT CCGCTTTTCC GATCACGGGC ACGAAGTCCA
1401   TTCCCCCTTC GACAACCATG CCTCACATTC CGATTCTGAT GAAGCCGGTA
1451   GTCCCGTTGA CGGATTTAGC CTTTACCGCA TCCATTGGGA CGGATACGAA
1501   CACCATCCCG CCGACGGCTA TGACGGGCCA CAGGGCGGCG GCTATCCCGC
1551   TCCCAAAGGC GCGAGGGATA TATACAGCTA CGACATAAAA GGCGTTGCCC
1601   AAAATATCCG CCTCAACCTG ACCGACAACC GCAGCACCGG ACAACGGCTT
1651   GCCGACCGTT TCCACAATGC CGGTAGTATG CTGACGCAAG GAGTAGGCGA
1701   CGGATTCAAA CGCGCCACCC GATACAGCCC CGAGCTGGAC AGATCGGGCA
1751   ATGCCGCCGA AGCCTTCAAC GGCACTGCAG ATATCGTTAA AAACATCATC
1801   GGCGCGGCAG GAGAAATTGT CGGCGCAGGC GATGCCGTGC AGGGCATAAG
1851   CGAAGGCTCA AACATTGCTG TCATGCACGG CTTGGGTCTG CTTTCCACCG
1901   AAAACAAGAT GGCGCGCATC AACGATTTGG CAGATATGGC GCAACTCAAA
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2001   CGCACAAGGC ATAGAAGCCG TCAGCAATAT CTTTATGGCA GCCATCCCCA
2051   TCAAAGGGAT TGGAGCTGTT CGGGGAAAAT ACGGCTTGGG CGGCATCACG
2101   GCACATCCTA TCAAGCGGTC GCAGATGGGC GCGATCGCAT TGCCGAAAGG
2151   GAAATCCGCC GTCAGCGACA ATTTTGCCGA TGCGGCATAC GCCAAATACC
2201   CGTCCCCTTA CCATTCCCGA AATATCCGTT CAAACTTGGA GCAGCGTTAC
2251   GGCAAAGAAA ACATCACCTC CTCAACCGTG CCGCCGTCAA ACGGCAAAAA
2301   TGTCAAACTG GCAGACCAAC GCCACCCGAA GACAGGCGTA CCGTTTGACG
2351   GTAAAGGGTT TCCGAATTTT GAGAAGCACG TGAAATATGA TACGCTCGAG
2401   CACCACCACC ACCACCACTG A
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  51   AADVEADDFK GLGLKKVVTN LTKTVNENKQ NVDAKVKAAE SEIEKLTTKL
 101   ADTDAALADT DAALDATTNA LNKLGENITT FAEETKTNIV KIDEKLEAVA
 151   DTVDKHAEAF NDIADSLDET NTKADEAVKT ANEAKQTAEE TKQNVDAKVK
 201   AAETAAGKAE AAAGTANTAA DKAEAVAAKV TDIKADIATN KDNIAKKANS
 251   ADVYTREESD SKFVRIDGLN ATTEKLDTRL ASAEKSIADH DTRLNGLDKT
 301   VSDLRKETRQ GLAEQAALSG LFQPYNVGRF NVTAAVGGYK SESAVAIGTG
 351   FRFTENFAAK AGVAVGTSSG SSAAYHVGVN YEWGSGGGGS DLANDSFIRQ
 401   VLDRQHFEPD GKYHLFGSRG ELAERSGHIG LGKIQSHQLG NLMIQQAAIK
 451   GNIGYIVRFS DHGHEVHSPF DNHASHSDSD EAGSPVDGFS LYRIHWDGYE
 501   HHPADGYDGP QGGGYPAPKG ARDIYSYDIK GVAQNIRLNL TDNRSTGQRL
 551   ADRFHNAGSM LTQGVGDGFK RATRYSPELD RSGNAAEAFN GTADIVKNII
 601   GAAGEIVGAG DAVQGISEGS NIAVMHGLGL LSTENKMARI NDLADMAQLK
 651   DYAAAAIRDW AVQNPNAAQG IEAVSNIFMA AIPIKGIGAV RGKYGLGGIT
 701   AHPIKRSQMG AIALPKGKSA VSDNFADAAY AKYPSPYHSR NIRSNLEQRY
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 801   HHHHHH*
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961-741

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 151   GCAGCCGATG TTGAAGCCGA CGACTTTAAA GGTCTGGGTC TGAAAAAAGT
 201   CGTGACTAAC CTGACCAAAA CCGTCAATGA AAACAAACAA AACGTCGATG
 251   CCAAAGTAAA AGCTGCAGAA TCTGAAATAG AAAAGTTAAC AACCAAGTTA
 301   GCAGACACTG ATGCCGCTTT AGCAGATACT GATGCCGCTC TGGATGCAAC
 351   CACCAACGCC TTGAATAAAT TGGGAGAAAA TATAACGACA TTTGCTGAAG
 401   AGACTAAGAC AAATATCGTA AAAATTGATG AAAAATTAGA AGCCGTGGCT
 451   GATACCGTCG ACAAGCATGC CGAAGCATTC AACGATATCG CCGATTCATT
 501   GGATGAAACC AACACTAAGG CAGACGAAGC CGTCAAAACC GCCAATGAAG
 551   CCAAACAGAC GGCCGAAGAA ACCAAACAAA ACGTCGATGC CAAAGTAAAA
 601   GCTGCAGAAA CTGCAGCAGG CAAAGCCGAA GCTGCCGCTG GCACAGCTAA
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 701   AAGCTGATAT CGCTACGAAC AAAGATAATA TTGCTAAAAA AGCAAACAGT
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 801   TGGTCTGAAC GCTACTACCG AAAAATTGGA CACACGCTTG GCTTCTGCTG
 851   AAAAATCCAT TGCCGATCAC GATACTCGCC TGAACGGTTT GGATAAAACA
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 951   GCTCTCCGGT CTGTTCCAAC CTTACAACGT GGGTCGGTTC AATGTAACGG
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1051   TTCCGCTTTA CCGAAAACTT TGCCGCCAAA GCAGGCGTGG CAGTCGGCAC
1101   TTCGTCCGGT TCTTCCGCAG CCTACCATGT CGGCGTCAAT TACGAGTGGG
1151   GATCCGGAGG GGGTGGTGTC GCCGCCGACA TCGGTGCGGG GCTTGCCGAT
1201   GCACTAACCG CACCGCTCGA CCATAAAGAC AAAGGTTTGC AGTCTTTGAC
1251   GCTGGATCAG TCCGTCAGGA AAAACGAGAA ACTGAAGCTG GCGGCACAAG
1301   GTGCGGAAAA AACTTATGGA AACGGTGACA GCCTCAATAC GGGCAAATTG
1351   AAGAACGACA AGGTCAGCCG TTTCGACTTT ATCCGCCAAA TCGAAGTGGA
1401   CGGGCAGCTC ATTACCTTGG AGAGTGGAGA GTTCCAAGTA TACAAACAAA
1451   GCCATTCCGC CTTAACCGCC TTTCAGACCG AGCAAATACA AGATTCGGAG
1501   CATTCCGGGA AGATGGTTGC GAAACGCCAG TTCAGAATCG GCGACATAGC
1551   GGGCGAACAT ACATCTTTTG ACAAGCTTCC CGAAGGCGGC AGGGCGACAT
1601   ATCGCGGGAC GGCGTTCGGT TCAGACGATG CCGGCGGAAA ACTGACCTAC
1651   ACCATAGATT TCGCCGCCAA GCAGGGAAAC GGCAAAATCG AACATTTGAA
1701   ATCGCCAGAA CTCAATGTCG ACCTGGCCGC CGCCGATATC AAGCCGGATG
1751   GAAAACGCCA TGCCGTCATC AGCGGTTCCG TCCTTTACAA CCAAGCCGAG
1801   AAAGGCAGTT ACTCCCTCGG TATCTTTGGC GGAAAAGCCC AGGAAGTTGC
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1901   CCGCCAAGCA ACTCGAGCAC CACCACCACC ACCACTGA

   1   MATNDDDVKK AATVAIAAAY NNGQEINGFK AGETIYDIDE DGTITKKDAT
  51   AADVEADDFK GLGLKKVVTN LTKTVNENKQ NVDAKVKAAE SEIEKLTTKL
 101   ADTDAALADT DAALDATTNA LNKLGENITT FAEETKTNIV KIDEKLEAVA
 151   DTVDKHAEAF NDIADSLDET NTKADEAVKT ANEAKQTAEE TKQNVDAKVK
 201   AAETAAGKAE AAAGTANTAA DKAEAVAAKV TDIKADIATN KDNIAKKANS
 251   ADVYTREESD SKFVRIDGLN ATTEKLDTRL ASAEKSIADH DTRLNGLDKT
 301   VSDLRKETRQ GLAEQAALSG LFQPYNVGRF NVTAAVGGYK SESAVAIGTG
 351   FRFTENFAAK AGVAVGTSSG SSAAYHVGVN YEWGSGGGGV AADIGAGLAD
 401   ALTAPLDHKD KGLQSLTLDQ SVRKNEKLKL AAQGAEKTYG NGDSLNTGKL
 451   KNDKVSRFDF IRQIEVDGQL ITLESGEFQV YKQSHSALTA FQTEQIQDSE
 501   HSGKMVAKRQ FRIGDIAGEH TSFDKLPEGG RATYRGTAFG SDDAGGKLTY
 551   TIDFAAKQGN GKIEHLKSPE LNVDLAAADI KPDGKRHAVI SGSVLYNQAE
 601   KGSYSLGIFG GKAQEVAGSA EVKTVNGIRH IGLAAKQLEH HHHHH*
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961-983

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 151   GCAGCCGATG TTGAAGCCGA CGACTTTAAA GGTCTGGGTC TGAAAAAAGT
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 251   CCAAAGTAAA AGCTGCAGAA TCTGAAATAG AAAAGTTAAC AACCAAGTTA
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 351   CACCAACGCC TTGAATAAAT TGGGAGAAAA TATAACGACA TTTGCTGAAG
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 451   GATACCGTCG ACAAGCATGC CGAAGCATTC AACGATATCG CCGATTCATT
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 701   AAGCTGATAT CGCTACGAAC AAAGATAATA TTGCTAAAAA AGCAAACAGT
 751   GCCGACGTGT ACACCAGAGA AGAGTCTGAC AGCAAATTTG TCAGAATTGA
 801   TGGTCTGAAC GCTACTACCG AAAAATTGGA CACACGCTTG GCTTCTGCTG
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1101   TTCGTCCGGT TCTTCCGCAG CCTACCATGT CGGCGTCAAT TACGAGTGGG
1151   GATCCGGCGG AGGCGGCACT TCTGCGCCCG ACTTCAATGC AGGCGGTACC
1201   GGTATCGGCA GCAACAGCAG AGCAACAACA GCGAAATCAG CAGCAGTATC
1251   TTACGCCGGT ATCAAGAACG AAATGTGCAA AGACAGAAGC ATGCTCTGTG
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1401   CAAGAATTTG ATCAACCTCA AACCTGCAAT TGAAGCAGGC TATACAGGAC
1451   GCGGGGTAGA GGTAGGTATC GTCGACACAG GCGAATCCGT CGGCAGCATA
1501   TCCTTTCCCG AACTGTATGG CAGAAAAGAA CACGGCTATA ACGAAAATTA
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1801   AAGAACGAAA TGATGGTTGC AGCCATCCGC AATGCATGGG TCAAGCTGGG
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2001   CCTGATGCAA CAGAGCGATT ACGGCAACCT GTCCTACCAC ATCCGTAATA
2051   AAAACATGCT TTTCATCTTT TCGACAGGCA ATGACGCACA AGCTCAGCCC
2101   AACACATATG CCCTATTGCC ATTTTATGAA AAAGACGCTC AAAAAGGCAT
2151   TATCACAGTC GCAGGCGTAG ACCGCAGTGG AGAAAAGTTC AAACGGGAAA
2201   TGTATGGAGA ACCGGGTACA GAACCGCTTG AGTATGGCTC CAACCATTGC
2251   GGAATTACTG CCATGTGGTG CCTGTCGGCA CCCTATGAAG CAAGCGTCCG
2301   TTTCACCCGT ACAAACCCGA TTCAAATTGC CGGAACATCC TTTTCCGCAC
2351   CCATCGTAAC CGGCACGGCG GCTCTGCTGC TGCAGAAATA CCCGTGGATG
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2451   TGCAGTCGGC GTGGACAGCA AGTTCGGCTG GGGACTGCTG GATGCGGGTA
2501   AGGCCATGAA CGGACCCGCG TCCTTTCCGT TCGGCGACTT TACCGCCGAT
2551   ACGAAAGGTA CATCCGATAT TGCCTACTCC TTCCGTAACG ACATTTCAGG
2601   CACGGGCGGC CTGATCAAAA AAGGCGGCAG CCAACTGCAA CTGCACGGCA
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2701   TACGGCAACA ACAAATCGGA TATGCGCGTC GAAACCAAAG GTGCGCTGAT
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3201   ACACGCCGTA GAACAGGGCG GCAGCAATCT GGAAAACCTG ATGGTCGAAC
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3601   GGCATTGCCG CGAAAACCGG CGAAAATACG ACAGCAGCCG CCACACTGGG
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3701   GCATTAGTCT GTTTGCAGGC ATACGGCACG ATGCGGGCGA TATCGGCTAT
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3801   CACCGGTGCG GACGAACATG CGGAAGGCAG CGTCAACGGC ACGCTGATGC
3851   AGCTGGGCGC ACTGGGCGGT GTCAACGTTC CGTTTGCCGC AACGGGAGAT
3901   TTGACGGTCG AAGGCGGTCT GCGCTACGAC CTGCTCAAAC AGGATGCATT
3951   CGCCGAAAAA GGCAGTGCTT TGGGCTGGAG CGGCAACAGC CTCACTGAAG
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4101   CGACTACACG GTAACGGGCG GCTTTACCGG CGCGACTGCA GCAACCGGCA
4151   AGACGGGGGC ACGCAATATG CCGCACACCC GTCTGGTTGC CGGCCTGGGC
4201   GCGGATGTCG AATTCGGCAA CGGCTGGAAC GGCTTGGCAC GTTACAGCTA
4251   CGCCGGTTCC AAACAGTACG GCAACCACAG CGGACGAGTC GGCGTAGGCT
4301   ACCGGTTCCT CGAGCACCAC CACCACCACC ACTGA
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   1   MATNDDDVKK AATVAIAAAY NNGQEINGFK AGETIYDIDE DGTITKKDAT
  51   AADVEADDFK GLGLKKVVTN LTKTVNENKQ NVDAKVKAAE SEIEKLTTKL
 101   ADTDAALADT DAALDATTNA LNKLGENITT FAEETKTNIV KIDEKLEAVA
 151   DTVDKHAEAF NDIADSLDET NTKADEAVKT ANEAKQTAEE TKQNVDAKVK
 201   AAETAAGKAE AAAGTANTAA DKAEAVAAKV TDIKADIATN KDNIAKKANS
 251   ADVYTREESD SKFVRIDGLN ATTEKLDTRL ASAEKSIADH DTRLNGLDKT
 301   VSDLRKETRQ GLAEQAALSG LFQPYNVGRF NVTAAVGGYK SESAVAIGTG
 351   FRFTENFAAK AGVAVGTSSG SSAAYHVGVN YEWGSGGGGT SAPDFNAGGT
 401   GIGSNSRATT AKSAAVSYAG IKNEMCKDRS MLCAGRDDVA VTDRDAKINA
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 501   SFPELYGRKE HGYNENYKNY TAYMRKEAPE DGGGKDIEAS FDDEAVIETE
 551   AKPTDIRHVK EIGHIDLVSH IIGGRSVDGR PAGGIAPDAT LHIMNTNDET
 601   KNEMMVAAIR NAWVKLGERG VRIVNNSFGT TSRAGTADLF QIANSEEQYR
 651   QALLDYSGGD KTDEGIRLMQ QSDYGNLSYH IRNKNMLFIF STGNDAQAQP
 701   NTYALLPFYE KDAQKGIITV AGVDRSGEKF KREMYGEPGT EPLEYGSNHC
 751   GITAMWCLSA PYEASVRFTR TNPIQIAGTS FSAPIVTGTA ALLLQKYPWM
 801   SNDNLRTTLL TTAQDIGAVG VDSKFGWGLL DAGKAMNGPA SFPFGDFTAD
 851   TKGTSDIAYS FRNDISGTGG LIKKGGSQLQ LHGNNTYTGK TIIEGGSLVL
 901   YGNNKSDMRV ETKGALIYNG AASGGSLNSD GIVYLADTDQ SGANETVHIK
 951   GSLQLDGKGT LYTRLGKLLK VDGTAIIGGK LYMSARGKGA GYLNSTGRRV
1001   PFLSAAKIGQ DYSFFTNIET DGGLLASLDS VEKTAGSEGD TLSYYVRRGN
1051   AARTASAAAH SAPAGLKHAV EQGGSNLENL MVELDASESS ATPETVETAA
1101   ADRTDMPGIR PYGATFRAAA AVQHANAADG VRIFNSLAAT VYADSTAAHA
1151   DMQGRRLKAV SDGLDHNGTG LRVIAQTQQD GGTWEQGGVE GKMRGSTQTV
1201   GIAAKTGENT TAAATLGMGR STWSENSANA KTDSISLFAG IRHDAGDIGY
1251   LKGLFSYGRY KNSISRSTGA DEHAEGSVNG TLMQLGALGG VNVPFAATGD
1301   LTVEGGLRYD LLKQDAFAEK GSALGWSGNS LTEGTLVGLA GLKLSQPLSD
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961c-ORF46.1

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 151   GCAGCCGATG TTGAAGCCGA CGACTTTAAA GGTCTGGGTC TGAAAAAAGT
 201   CGTGACTAAC CTGACCAAAA CCGTCAATGA AAACAAACAA AACGTCGATG
 251   CCAAAGTAAA AGCTGCAGAA TCTGAAATAG AAAAGTTAAC AACCAAGTTA
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 351   CACCAACGCC TTGAATAAAT TGGGAGAAAA TATAACGACA TTTGCTGAAG
 401   AGACTAAGAC AAATATCGTA AAAATTGATG AAAAATTAGA AGCCGTGGCT
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 501   GGATGAAACC AACACTAAGG CAGACGAAGC CGTCAAAACC GCCAATGAAG
 551   CCAAACAGAC GGCCGAAGAA ACCAAACAAA ACGTCGATGC CAAAGTAAAA
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 701   AAGCTGATAT CGCTACGAAC AAAGATAATA TTGCTAAAAA AGCAAACAGT
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1051   CATTTCGAAC CCGACGGGAA ATACCACCTA TTCGGCAGCA GGGGGGAACT
1101   TGCCGAGCGC AGCGGCCATA TCGGATTGGG AAAAATACAA AGCCATCAGT
1151   TGGGCAACCT GATGATTCAA CAGGCGGCCA TTAAAGGAAA TATCGGCTAC
1201   ATTGTCCGCT TTTCCGATCA CGGGCACGAA GTCCATTCCC CCTTCGACAA
1251   CCATGCCTCA CATTCCGATT CTGATGAAGC CGGTAGTCCC GTTGACGGAT
1301   TTAGCCTTTA CCGCATCCAT TGGGACGGAT ACGAACACCA TCCCGCCGAC
1351   GGCTATGACG GGCCACAGGG CGGCGGCTAT CCCGCTCCCA AAGGCGCGAG
1401   GGATATATAC AGCTACGACA TAAAAGGCGT TGCCCAAAAT ATCCGCCTCA
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1501   AATGCCGGTA GTATGCTGAC GCAAGGAGTA GGCGACGGAT TCAAACGCGC
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2151   CCAACGCCAC CCGAAGACAG GCGTACCGTT TGACGGTAAA GGGTTTCCGA
2201   ATTTTGAGAA GCACGTGAAA TATGATACGC TCGAGCACCA CCACCACCAC
2251   CACTGA

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 351   HFEPDGKYHL FGSRGELAER SGHIGLGKIQ SHQLGNLMIQ QAAIKGNIGY
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751   H*
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961c-741

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 251   ADVYTREESD SKFVRIDGLN ATTEKLDTRL ASAEKSIADH DTRLNGLDKT
 301   VSDLRKETRQ GLAEQAALSG LFQPYNVGGS GGGGVAADIG AGLADALTAP
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961c-983

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3851 TCGCGGGTCT GAAGCTGTCG CAACCCTTGA GCGATAAAGC CGTCCTGTTT

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3951   GGGCGGCTTT ACCGGCGCGA CTGCAGCAAC CGGCAAGACG GGGGCACGCA
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961cL-ORF46.1

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1401   ACACCATCCC GCCGACGGCT ATGACGGGCC ACAGGGCGGC GGCTATCCCG
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2301   CGAG
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961cL-741

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 801   TAAAAAAGCA AACAGTGCCG ACGTGTACAC CAGAGAAGAG TCTGACAGCA
 851   AATTTGTCAG AATTGATGGT CTGAACGCTA CTACCGAAAA ATTGGACACA
 901   CGCTTGGCTT CTGCTGAAAA ATCCATTGCC GATCACGATA CTCGCCTGAA
 951   CGGTTTGGAT AAAACAGTGT CAGACCTGCG CAAAGAAACC CGCCAAGGCC
1001   TTGCAGAACA AGCCGCGCTC TCCGGTCTGT TCCAACCTTA CAACGTGGGT
1051   GGATCCGGAG GGGGTGGTGT CGCCGCCGAC ATCGGTGCGG GGCTTGCCGA
1101   TGCACTAACC GCACCGCTCG ACCATAAAGA CAAAGGTTTG CAGTCTTTGA
1151   CGCTGGATCA GTCCGTCAGG AAAAACGAGA AACTGAAGCT GGCGGCACAA
1201   GGTGCGGAAA AAACTTATGG AAACGGTGAC AGCCTCAATA CGGGCAAATT
1251   GAAGAACGAC AAGGTCAGCC GTTTCGACTT TATCCGCCAA ATCGAAGTGG
1301   ACGGGCAGCT CATTACCTTG GAGAGTGGAG AGTTCCAAGT ATACAAACAA
1351   AGCCATTCCG CCTTAACCGC CTTTCAGACC GAGCAAATAC AAGATTCGGA
1401   GCATTCCGGG AAGATGGTTG CGAAACGCCA GTTCAGAATC GGCGACATAG
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1451  CGGGCGAACA TACATCTTTT GACAAGCTTC CCGAAGGCGG CAGGGCGACA
1501  TATCGCGGGA CGGCGTTCGG TTCAGACGAT GCCGGCGGAA AACTGACCTA
1551  CACCATAGAT TTCGCCGCCA AGCAGGGAAA CGGCAAAATC GAACATTTGA
1601  AATCGCCAGA ACTCAATGTC GACCTGGCCG CCGCCGATAT CAAGCCGGAT
1651  GGAAAACGCC ATGCCGTCAT CAGCGGTTCC GTCCTTTACA ACCAAGCCGA
1701  GAAAGGCAGT TACTCCCTCG GTATCTTTGG CGGAAAAGCC CAGGAAGTTG
1751  CCGGCAGCGC GGAAGTGAAA ACCGTAAACG GCATACGCCA TATCGGCCTT
1801  GCCGCCAAGC AACTCGAGCA CCACCACCAC CACCACTGA
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  1  MKHFPSKVLT TAILATFCSG ALAATNDDDV KKAATVAIAA AYNNGQEING
 51  FKAGETIYDI DEDGTITKKD ATAADVEADD FKGLGLKKVV TNLTKTVNEN
101  KQNVDAKVKA AESEIEKLTT KLADTDAALA DTDAALDATT NALNKLGENI
151  TTFAEETKTN IVKIDEKLEA VADTVDKHAE AFNDIADSLD ETNTKADEAV
201  KTANEAKQTA EETKQNVDAK VKAAETAAGK AEAAAGTANT AADKAEAVAA
251  KVTDIKADIA TNKDNIAKKA NSADVYTREE SDSKFVRIDG LNATTEKLDT
301  RLASAEKSIA DHDTRLNGLD KTVSDLRKET RQGLAEQAAL SGLFQPYNVG
351  GSGGGGVAAD IGAGLADALT APLDHKDKGL QSLTLDQSVR KNEKLKLAAQ
401  GAEKTYGNGD SLNTGKLKND KVSRFDFIRQ IEVDGQLITL ESGEFQVYKQ
451  SHSALTAFQT EQIQDSEHSG KMVAKRQFRI GDIAGEHTSF DKLPEGGRAT
501  YRGTAFGSDD AGGKLTYTID FAAKQGNGKI EHLKSPELNV DLAAADIKPD
551  GKRHAVISGS VLYNQAEKGS YSLGIFGGKA QEVAGSAEVK TVNGIRHIGL
601  AAKQLEHHHH HH*
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961cL-983

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   1  ATGAAACACT TTCCATCCAA AGTACTGACC ACAGCCATCC TTGCCACTTT
  51  CTGTAGCGGC GCACTGGCAG CCACAAACGA CGACGATGTT AAAAAAGCTG
 101  CCACTGTGGC CATTGCTGCT GCCTACAACA ATGGCCAAGA AATCAACGGT
 151  TTCAAAGCTG GAGAGACCAT CTACGACATT GATGAAGACG GCACAATTAC
 201  CAAAAAAGAC GCAACTGCAG CCGATGTTGA AGCCGACGAC TTTAAAGGTC
 251  TGGGTCTGAA AAAAGTCGTG ACTAACCTGA CCAAAACCGT CAATGAAAAC
 301  AAACAAAACG TCGATGCCAA AGTAAAAGCT GCAGAATCTG AAATAGAAAA
 351  GTTAACAACC AAGTTAGCAG ACACTGATGC CGCTTTAGCA GATACTGATG
 401  CCGCTCTGGA TGCAACCACC AACGCCTTGA ATAAATTGGG AGAAAATATA
 451  ACGACATTTG CTGAAGAGAC TAAGACAAAT ATCGTAAAAA TTGATGAAAA
 501  ATTAGAAGCC GTGGCTGATA CCGTCGACAA GCATGCCGAA GCATTCAACG
 551  ATATCGCCGA TTCATTGGAT GAAACCAACA CTAAGGCAGA CGAAGCCGTC
 601  AAAACCGCCA ATGAAGCCAA ACAGACGGCC GAAGAAACCA AACAAAACGT
 651  CGATGCCAAA GTAAAAGCTG CAGAAACTGC AGCAGGCAAA GCCGAAGCTG
 701  CCGCTGGCAC AGCTAATACT GCAGCCGACA AGGCCGAAGC TGTCGCTGCA
 751  AAAGTTACCG ACATCAAAGC TGATATCGCT ACGAACAAAG ATAATATTGC
 801  TAAAAAAGCA AACAGTGCCG ACGTGTACAC CAGAGAAGAG TCTGACAGCA
 851  AATTTGTCAG AATTGATGGT CTGAACGCTA CTACCGAAAA ATTGGACACA
 901  CGCTTGGCTT CTGCTGAAAA ATCCATTGCC GATCACGATA CTCGCCTGAA
 951  CGGTTTGGAT AAAACAGTGT CAGACCTGCG CAAAGAAACC CGCCAAGGCC
1001  TTGCAGAACA AGCCGCGCTC TCCGGTCTGT TCCAACCTTA CAACGTGGGT
1051  GGATCCGGCG GAGGCGGCAC TTCTGCGCCC GACTTCAATG CAGGCGGTAC
1101  CGGTATCGGC AGCAACAGCA GAGCAACAAC AGCGAAATCA GCAGCAGTAT
1151  CTTACGCCGG TATCAAGAAC GAAATGTGCA AAGACAGAAG CATGCTCTGT
1201  GCCGGTCGGG ATGACGTTGC GGTTACAGAC AGGGATGCCA AAATCAATGC
1251  CCCCCCCCCG AATCTGCATA CCGGAGACTT TCCAAACCCA AATGACGCAT
1301  ACAAGAATTT GATCAACCTC AAACCTGCAA TTGAAGCAGG CTATACAGGA
1351  CGCGGGGTAG AGGTAGGTAT CGTCGACACA GGCGAATCCG TCGGCAGCAT
1401  ATCCTTTCCC GAACTGTATG GCAGAAAAGA ACACGGCTAT AACGAAAATT
1451  ACAAAAACTA TACGGCGTAT ATGCGGAAGG AAGCGCCTGA AGACGGAGGC
1501  GGTAAAGACA TTGAAGCTTC TTTCGACGAT GAGGCCGTTA TAGAGACTGA
1551  AGCAAAGCCG ACGGATATCC GCCACGTAAA AGAAATCGGA CACATCGATT
1601  TGGTCTCCCA TATTATTGGC GGGCGTTCCG TGGACGGCAG ACCTGCAGGC
1651  GGTATTGCGC CCGATGCGAC GCTACACATA ATGAATACGA ATGATGAAAC
1701  CAAGAACGAA ATGATGGTTG CAGCCATCCG CAATGCATGG GTCAAGCTGG
1751  GCGAACGTGG CGTGCGCATC GTCAATAACA GTTTTGGAAC AACATCGAGG
1801  GCAGGCACTG CCGACCTTTT CCAAATAGCC AATTCGGAGG AGCAGTACCG
1851  CCAAGCGTTG CTCGACTATT CCGGCGGTGA TAAAACAGAC GAGGGTATCC
1901  GCCTGATGCA ACAGAGCGAT TACGGCAACC TGTCCTACCA CATCCGTAAT
1951  AAAAACATGC TTTTCATCTT TTCGACAGGC AATGACGCAC AAGCTCAGCC
2001  CAACACATAT GCCCTATTGC CATTTTATGA AAAAGACGCT CAAAAAGGCA
2051  TTATCACAGT CGCAGGCGTA GACCGCAGTG GAGAAAAGTT CAAACGGGAA
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2101   ATGTATGGAG AACCGGGTAC AGAACCGCTT GAGTATGGCT CCAACCATTG
2151   CGGAATTACT GCCATGTGGT GCCTGTCGGC ACCCTATGAA GCAAGCGTCC
2201   GTTTCACCCG TACAAACCCG ATTCAAATTG CCGGAACATC CTTTTCCGCA
2251   CCCATCGTAA CCGGCACGGC GGCTCTGCTG CTGCAGAAAT ACCCGTGGAT
2301   GAGCAACGAC AACCTGCGTA CCACGTTGCT GACGACGGCT CAGGACATCG
2351   GTGCAGTCGG CGTGGACAGC AAGTTCGGCT GGGGACTGCT GGATGCGGGT
2401   AAGGCCATGA ACGGACCCGC GTCCTTTCCG TTCGGCGACT TTACCGCCGA
2451   TACGAAAGGT ACATCCGATA TTGCCTACTC CTTCCGTAAC GACATTTCAG
2501   GCACGGGCGG CCTGATCAAA AAAGGCGGCA GCCAACTGCA ACTGCACGGC
2551   AACAACACCT ATACGGGCAA AACCATTATC GAAGGCGGTT CGCTGGTGTT
2601   GTACGGCAAC AACAAATCGG ATATGCGCGT CGAAACCAAA GGTGCGCTGA
2651   TTTATAACGG GGCGGCATCC GGCGGCAGCC TGAACAGCGA CGGCATTGTC
2701   TATCTGGCAG ATACCGACCA ATCCGGCGCA AACGAAACCG TACACATCAA
2751   AGGCAGTCTG CAGCTGGACG GCAAAGGTAC GCTGTACACA CGTTTGGGCA
2801   AACTGCTGAA AGTGGACGGT ACGGCGATTA TCGGCGGCAA GCTGTACATG
2851   TCGGCACGCG GCAAGGGGGC AGGCTATCTC AACAGTACCG GACGACGTGT
2901   TCCCTTCCTG AGTGCCGCCA AAATCGGGCA GGATTATTCT TTCTTCACAA
2951   ACATCGAAAC CGACGGCGGC CTGCTGGCTT CCCTCGACAG CGTCGAAAAA
3001   ACAGCGGGCA GTGAAGGCGA CACGCTGTCC TATTATGTCC GTCGCGGCAA
3051   TGCGGCACGG ACTGCTTCGG CAGCGGCACA TTCCGCGCCC GCCGGTCTGA
3101   AACACGCCGT AGAACAGGGC GGCAGCAATC TGGAAAACCT GATGGTCGAA
3151   CTGGATGCCT CCGAATCATC CGCAACACCC GAGACGGTTG AAACTGCGGC
3201   AGCCGACCGC ACAGATATGC CGGGCATCCG CCCCTACGGC GCAACTTTCC
3251   GCGCAGCGGC AGCCGTACAG CATGCGAATG CCGCCGACGG TGTACGCATC
3301   TTCAACAGTC TCGCCGCTAC CGTCTATGCC GACAGTACCG CCGCCCATGC
3351   CGATATGCAG GGACGCCGCC TGAAAGCCGT ATCGGACGGG TTGGACCACA
3401   ACGGCACGGG TCTGCGCGTC ATCGCGCAAA CCCAACAGGA CGGTGGAACG
3451   TGGGAACAGG GCGGTGTTGA AGGCAAAATG CGCGGCAGTA CCCAAACCGT
3501   CGGCATTGCC GCGAAAACCG GCGAAAATAC GACAGCAGCC GCCACACTGG
3551   GCATGGGACG CAGCACATGG AGCGAAAACA GTGCAAATGC AAAAACCGAC
3601   AGCATTAGTC TGTTTGCAGG CATACGGCAC GATGCGGGCG ATATCGGCTA
3651   TCTCAAAGGC CTGTTCTCCT ACGGACGCTA CAAAAACAGC ATCAGCCGCA
3701   GCACCGGTGC GGACGAACAT GCGGAAGGCA GCGTCAACGG CACGCTGATG
3751   CAGCTGGGCG CACTGGGCGG TGTCAACGTT CCGTTTGCCG CAACGGGAGA
3801   TTTGACGGTC GAAGGCGGTC TGCGCTACGA CCTGCTCAAA CAGGATGCAT
3851   TCGCCGAAAA AGGCAGTGCT TTGGGCTGGA GCGGCAACAG CCTCACTGAA
3901   GGCACGCTGG TCGGACTCGC GGGTCTGAAG CTGTCGCAAC CCTTGAGCGA
3951   TAAAGCCGTC CTGTTTGCAA CGGCGGGCGT GGAACGCGAC CTGAACGGAC
4001   GCGACTACAC GGTAACGGGC GGCTTTACCG GCGCGACTGC AGCAACCGGC
4051   AAGACGGGGG CACGCAATAT GCCGCACACC CGTCTGGTTG CCGGCCTGGG
4101   CGCGGATGTC GAATTCGGCA ACGGCTGGAA CGGCTTGGCA CGTTACAGCT
4151   ACGCCGGTTC CAAACAGTAC GGCAACCACA GCGGACGAGT CGGCGTAGGC
4201   TACCGGTTCT GACTCGAG

   1   MKHFPSKVLT TAILATFCSG ALAATNDDDV KKAATVAIAA AYNNGQEING
  51   FKAGETIYDI DEDGTITKKD ATAADVEADD FKGLGLKKVV TNLTKTVNEN
 101   KQNVDAKVKA AESEIEKLTT KLADTDAALA DTDAALDATT NALNKLGENI
 151   TTFAEETKTN IVKIDEKLEA VADTVDKHAE AFNDIADSLD ETNTKADEAV
 201   KTANEAKQTA EETKQNVDAK VKAAETAAGK AEAAAGTANT AADKAEAVAA
 251   KVTDIKADIA TNKDNIAKKA NSADVYTREE SDSKFVRIDG LNATTEKLDT
 301   RLASAEKSIA DHDTRLNGLD KTVSDLRKET RQGLAEQAAL SGLFQPYNVG
 351   GSGGGGTSAP DFNAGGTGIG SNSRATTAKS AAVSYAGIKN EMCKDRSMLC
 401   AGRDDVAVTD RDAKINAPPP NLHTGDFPNP NDAYKNLINL KPAIEAGYTG
 451   RGVEVGIVDT GESVGSISFP ELYGRKEHGY NENYKNYTAY MRKEAPEDGG
 501   GKDIEASFDD EAVIETEAKP TDIRHVKEIG HIDLVSHIIG GRSVDGRPAG
 551   GIAPDATLHI MNTNDETKNE MMVAAIRNAW VKLGERGVRI VNNSFGTTSR
 601   AGTADLFQIA NSEEQYRQAL LDYSGGDKTD EGIRLMQQSD YGNLSYHIRN
 651   KNMLFIFSTG NDAQAQPNTY ALLPFYEKDA QKGIITVAGV DRSGEKFKRE
 701   MYGEPGTEPL EYGSNHCGIT AMWCLSAPYE ASVRFTRTNP IQIAGTSFSA
 751   PIVTGTAALL LQKYPWMSND NLRTTLLTTA QDIGAVGVDS KFGWGLLDAG
 801   KAMNGPASFP FGDFTADTKG TSDIAYSFRN DISGTGGLIK KGGSQLQLHG
 851   NNTYTGKTII EGGSLVLYGN NKSDMRVETK GALIYNGAAS GGSLNSDGIV
 901   YLADTDQSGA NETVHIKGSL QLDGKGTLYT RLGKLLKVDG TAIIGGKLYM
 951   SARGKGAGYL NSTGRRVPFL SAAKIGQDYS FFTNIETDGG LLASLDSVEK
1001   TAGSEGDTLS YYVRRGNAAR TASAAAHSAP AGLKHAVEQG GSNLENLMVE
1051   LDASESSATP ETVETAAADR TDMPGIRPYG ATFRAAAAVQ HANAADGVRI
1101   FNSLAATVYA DSTAAHADMQ GRRLKAVSDG LDHNGTGLRV IAQTQQDGGT
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1151    WEQGGVEGKM RGSTQTVGIA AKTGENTTAA ATLGMGRSTW SENSANAKTD
1201    SISLFAGIRH DAGDIGYLKG LFSYGRYKNS ISRSTGADEH AEGSVNGTLM
1251    QLGALGGVNV PFAATGDLTV EGGLRYDLLK QDAFAEKGSA LGWSGNSLTE
1301    GTLVGLAGLK LSQPLSDKAV LFATAGVERD LNGRDYTVTG GFTGATAATG
1351    KTGARNMPHT RLVAGLGADV EFGNGWNGLA RYSYAGSKQY GNHSGRVGVG
1401    YRF*
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[0056] Es versteht sich von selbst, dass die Erfindung nur als Beispiel beschrieben worden ist und dass daran Änderungen vorgenommen werden können, während man innerhalb des Schutzbereichs der Erfindung bleibt. Zum Beispiel ist die Verwendung von Proteinen aus anderen Stämmen vorgesehen [siehe z.B. WO 00/66741 für polymorphe Sequenzen für ORF4, ORF40, ORF46, 225, 235, 287, 519, 726, 919 und 953].

EXPERIMENTELLE DETAILS

Clonierungsstrategie und Konstruktion der Oligonucleotide

[0057] Gene, welche für das Antigen von Interesse codierten, wurden mittels PCR amplifiziert, wobei Oligonucleotide verwendet wurden, die auf der Grundlage der genomischen Sequenz von N. meningitidis B MC58 konstruiert worden waren. Es wurde immer genomische DNA vom Stamm 2966 als Matrize für die PCR-Reaktionen verwendet, soweit nichts anderes angegeben ist, und die amplifizierten Fragmente wurden in den Expressionsvektor pET21b+ (Novagen) cloniert, um das Protein als C-terminal mit einem His-Tag versehenes Produkt zu exprimieren, oder in pET24b+ (Novagen), um das Protein in einer Form ohne Tag zu exprimieren (z.B. ΔG287K).

[0058] In den Fällen, in denen ein Protein ohne Fusionspartner und mit seinem eigenen Leader-Peptid (sofern vorhanden) exprimiert wurde, wurde eine Amplifikation des offene Leserahmens (ATG bis zu den Stopcodons) durchgeführt.

[0059] In den Fällen, in denen ein Protein in der Form ohne Tag exprimiert wurde, wurde das Leader-Peptid weggelassen, indem man die Amplifikations-Primer am 5'-Ende so konstruierte, dass sie stromabwärts von der vorhergesagten Leader-Sequenz lagen.

[0060] Die Schmelztemperatur der in der PCR verwendeten Primer war von der Anzahl und der Art der hybridisierenden Nucleotide in dem gesamten Primer abhängig und wurde mit Hilfe der folgenden Formeln bestimmt:

$T_{m1} = 4\,(G + C) + 2\,(A + T)$ (ohne Schwanz)

$T_{m2} = 64{,}9 + 0{,}41\,(\%\ GC) - 600/N$ (gesamter Primer)

[0061] Die Schmelztemperaturen der ausgewählten Oligonucleotide lagen üblicherweise bei 65-70°C für das gesamte Oligo und bei 50-60°C für die hybridisierende Region allein.

[0062] Die Oligonucleotide wurden unter Verwendung eines Perkin Elmer 394 DNA/RNA-Synthesegeräts synthetisiert, in 2,0 ml NH_4OH von den Säulen eluiert und durch 5 Stunden Inkubation bei 56°C von den Schutzgruppen befreit. Die Oligos wurden durch Zugabe von 0,3 M Na-Acetat und 2 Volumina Ethanol präzipitiert. Die Proben wurden abzentrifugiert und die Pellets in Wasser resuspendiert.

[0063] Zu den Oligonucleotiden, welche dazu verwendet wurden, die 961-Proteine und Hybride der Erfindung herzustellen, gehören:

Orf46.1L	Fwd	GGGAATTCCATATG-GGCATTTCCCGCAAAATATC	NdeI
	Rev	CCCGCTCGAG-TTACGTATCATATTTCACGTGC	XhoI
orf46. (His-GST)	Fwd	GGGAATTCCATATGCACGTGAAATATGATACGAAG	BamHI-NdeI
	Rev	CCCGCTCGAGTTTACTCCTATAACGAGGTCTCTTAAC	XhoI
orf46.1-His	Fwd	GGGAATTCCATATGTCAGATTTGGCAAACGATTCTT	NdeI
	Rev	CCCGCTCGAGCGTATCATATTTCACGTGC	XhoI
287L	Fwd	CTAGCTAGC-TTTAAACGCAGCGTAATCGCAATGG	NheI
	Rev	CCCGCTCGAG-TCAATCCTGCTCTTTTTTGCC	XhoI
287	Fwd	CTAGCTAGC-GGGGGCGGCGGTGGCG	NheI
	Rev	CCCGCTCGAG-TCAATCCTGCTCTTTTTTGCC	XhoI
287LOrf4	Fwd	CTAGCTAGCGCTCATCCTCGCCGCC-TGCGGGGGCGGCGGT	NheI
	Rev	CCCGCTCGAG-TCAATCCTGCTCTTTTTTGCC	XhoI
287-fu	Fwd	CGGGGATCC-GGGGGCGGCGGTGGCG	BamHI
	Rev	CCCGCTCGAG-TCAATCCTGCTCTTTTTTGCC	XhoI
287-His	Fwd	CTAGCTAGC-GGGGGCGGCGGTGGCG	NheI
	Rev	CCCGCTCGAG-ATCCTGCTCTTTTTTGCC *	XhoI
287-His(2996)	Fwd	CTAGCTAGC-TGCGGGGGCGGCGGTGGCG	NheI
	Rev	CCCGCTCGAG-ATCCTGCTCTTTTTTGCC	XhoI
Δ1 287-His	Fwd	CGCGGATCCGCTAGC-CCCGATGTTAAATCGGC §	NheI
Δ2 287-His	Fwd	CGCGGATCCGCTAGC-CAAGATATGGCGGCAGT §	NheI
Δ3 287-His	Fwd	CGCGGATCCGCTAGC-GCCGAATCCGCAAATCA §	NheI
Δ4 287-His	Fwd	CGCGCTAGC-GGAAGGGTTGATTTGGCTAATGG §	NheI
Δ4 287MC58-His	Fwd	CGCGCTAGC-GGAAGGGTTGATTTGGCTAATGG §	NheI
287a-His	Fwd	CGCCATATG-TTTAAACGCAGCGTAATCGC	NdeI
	Rev	CCCGCTCGAG-AAAATTGCTACCGCCATTCGCAGG	XhoI
287b-His	Fwd	CGCCATATG-GGAAGGGTTGATTTGGCTAATGG	NdeI
287b-2996-His	Rev	CCCGCTCGAG-CTTGTCTTTATAAATGATGACATATTTG	XhoI
287b-MC58-His	Rev	CCCGCTCGAG-TTTATAAAAGATAATATATTGATTGATTCC	XhoI
287c-2996-His	Fwd	CGCGCTAGC-ATGCCGCTGATTCCCGTCAATC §	NheI
‘287$^{\text{untagged}}$’(2996)	Fwd	CTAGCTAGC-GGGGGCGGCGGTGGCG	NheI
	Rev	CCCGCTCGAG-TCAATCCTGCTCTTTTTTGCC	XhoI
ΔG287-His *	Fwd	CGCGGATCCGCTAGC-CCCGATGTTAAATCGGC	NheI
	Rev	CCCGCTCGAG-ATCCTGCTCTTTTTTGCC	XhoI
ΔG287K(2996)	Fwd	CGCGGATCCGCTAGC-CCCGATGTTAAATCGGC	NheI
	Rev	CCCGCTCGAG-TCAATCCTGCTCTTTTTTGCC	XhoI
ΔG 287-Orf4L	Fwd	CGCGGATCCGCTAGC-AAAACCTTCTTCAAAACCCTTTCCGCCGCCGCACTCGCGCTCATCCTCGCCGCCTGC TCGCCCGATGTTAAATCG	NheI
	Rev	CCCGCTCGAG-TCAATCCTGCTCTTTTTTGCC	XhoI

741-His (MC58)	Fwd	CGCGGATCCCATATG-AGCAGCGGAGGGGGTG	NdeI
	Rev	CCCGCTCGAG-TTGCTTGGCGGCAAGGC	XhoI
ΔG741-His (MC58)	Fwd	CGCGGATCCCATATG-GTCGCCGCCGACATCG	NdeI
	Rev	CCCGCTCGAG-TTGCTTGGCGGCAAGGC	XhoI
919L	Fwd	CGCGGATCCCATATG-AAAAAATACCTATTCCGC	NdeI
	Rev	CCCGCTCGAG-TTACGGGCGGTATTCGG	XhoI
919	Fwd	CGCGGATCCCATATG-CAAAGCAAGAGCATCCAAA	NdeI
	Rev	CCCGCTCGAG-TTACGGGCGGTATTCGG	XhoI
919L Orf4	Fwd	GGGAATTCCATATGAAAACCTTCTTCAAAACCCTTTCCG CCGCCGCGCTAGCGCTCATCCTCGCCGCC-TGCCAAAGCAAGAGCATC	NdeI-(NheI)
	Rev	CCCGCTCGAG-TTACGGGCGGTATTCGGGCTTCATACCG	XhoI
953L	Fwd	GGGAATTCCATATG-AAAAAAATCATCTTCGCCG	NdeI
	Rev	CCCGCTCGAG-TTATTGTTTGGCTGCCTCGAT	XhoI
953-fu	Fwd	GGGAATTCCATATG-GCCACCTACAAAGTGGACG	NdeI
	Rev	CGGGGATCC-TTGTTTGGCTGCCTCGATTTG	BamHI

961L	Fwd	CGCGGATCCCATATG-AAACACTTTCCATCC	NdeI
	Rev	CCCGCTCGAG-TTACCACTCGTAATTGAC	XhoI
961	Fwd	CGCGGATCCCATATG-GCCACAAGCGACGAC	NdeI
	Rev	CCCGCTCGAG-TTACCACTCGTAATTGAC	XhoI
961 c (His/GST)	Fwd	CGCGGATCCCATATG-GCCACAAACGACG	BamHI-NdeI
	Rev	CCCGCTCGAG-ACCCACGTTGTAAGGTTG	XhoI
961 c-(His/GST) (MC58)	Fwd	CGCGGATCCCATATG-GCCACAAGCGACGACGA	BamHI-NdeI
	Rev	CCCGCTCGAG-ACCCACGTTGTAAGGTTG	XhoI
961 c-L	Fwd	CGCGGATCCCATATG-ATGAAACACTTTCCATCC	NdeI
	Rev	CCCGCTCGAG-TTAACCCACGTTGTAAGGT	XhoI
961 c-L (MC58)	Fwd	CGCGGATCCCATATG-ATGAAACACTTTCCATCC	NdeI
	Rev	CCCGCTCGAG-TTAACCCACGTTGTAAGGT	XhoI
961 d (His/GST)	Fwd	CGCGGATCCCATATG-GCCACAAACGACG	BamHI-NdeI
	Rev	CCCGCTCGAG-GTCTGACACTGTTTTATCC	XhoI
961 ΔI-L	Fwd	CGCGGATCCCATATG-ATGAAACACTTTCCATCC	NdeI
	Rev	CCCGCTCGAG-TTATGCTTTGGCGGCAAAG	XhoI
fu 961-...	Fwd	CGCGGATCCCATATG- GCCACAAACGACGAC	NdeI
	Rev	CGCGGATCC-CCACTCGTAATTGACGCC	BamHI
fu 961-... (MC58)	Fwd	CGCGGATCCCATATG-GCCACAAGCGACGAC	NdeI
	Rev	CGCGGATCC-CCACTCGTAATTGACGCC	BamHI
fu 961 c -...	Fwd	CGCGGATCCCATATG-GCCACAAACGACGAC	NdeI
	Rev	CGCGGATCC -ACCCACGTTGTAAGGTTG	BamHI
fu 961 c-L-...	Fwd	CGCGGATCCCATATG- ATGAAACACTTTCCATCC	NdeI
	Rev	CGCGGATCC -ACCCACGTTGTAAGGTTG	BamHI
fu (961)-741(MC58)-His	Fwd	CGCGGATCC -GGAGGGGGTGGTGTCG	BamHI
	Rev	CCCGCTCGAG-TTGCTTGGCGGCAAGGC	XhoI
fu (961)-983-His	Fwd	CGCGGATCC - GGCGGAGGCGGCACTT	BamHI
	Rev	CCCGCTCGAG-GAACCGGTAGCCTACG	XhoI
fu (961)- Orf46.1-His	Fwd	CGCGGATCCGGTGGTGGTGGT-TCAGATTTGGCAAACGATTC	BamHI
	Rev	CCCGCTCGAG-CGTATCATATTTCACGTGC	XhoI
fu (961 c-L)-741(MC58)	Fwd	CGCGGATCC -GGAGGGGGTGGTGTCG	BamHI
	Rev	CCCGCTCGAG-TTATTGCTTGGCGGCAAG	XhoI
fu (961c-L)-983	Fwd	CGCGGATCC - GGCGGAGGCGGCACTT	BamHI
	Rev	CCCGCTCGAG-TCAGAACCGGTAGCCTAC	XhoI
fu (961c-L)-Orf46.1	Fwd	CGCGGATCCGGTGGTGGTGGT-TCAGATTTGGCAAACGATTC	BamHI
	Rev	CCCGCTCGAG-TTACGTATCATATTTCACGTGC	XhoI
961-(His/GST)	Fwd	CGCGGATCCCATATG-GCCACAAGCGACGACG	BamHI-NdeI

(MC58)	Rev	CCCGCTCGAG-CCACTCGTAATTGACGCC	XhoI
961 Δ1-His	Fwd	CGCGGATCCCATATG-GCCACAAACGACGAC	NdeI
	Rev	CCCGCTCGAG-TGCTTTGGCGGCAAAGTT	XhoI
961a-(His/GST)	Fwd	CGCGGATCCCATATG-GCCACAAACGACGAC	BamHI-NdeI
	Rev	CCCGCTCGAG-TTTAGCAATATTATCTTTGTTCGTAGC	XhoI
961b-(His/GST)	Fwd	CGCGGATCCCATATG-AAAGCAAACCGTGCCGA	BamHI-NdeI
	Rev	CCCGCTCGAG-CCACTCGTAATTGACGCC	XhoI
961-His/GST ^{GATE}	Fwd	ggggacaagtttgtacaaaaaagcaggctGCAGCCACAAACGACGACG ATGTTAAAAAAGC	*attB1*
	Rev	ggggaccactttgtacaagaaagctgggtTTACCACTCGTAATTGACGC CGACATGGTAGG	*attB2*
983-His (2996)	Fwd	CGCGGATCCGCTAGC-TTAGGCGGCGGCGGAG	NheI
	Rev	CCCGCTCGAG-GAACCGGTAGCCTACG	XhoI
ΔG983-His (2996)	Fwd	CCCCTAGCTAGC-ACTTCTGCGCCCGACTT	NheI
	Rev	CCCGCTCGAG-GAACCGGTAGCCTACG	XhoI
983-His	Fwd	CGCGGATCCGCTAGC-TTAGGCGGCGGCGGAG	NheI
	Rev	CCCGCTCGAG-GAACCGGTAGCCTACG	XhoI
ΔG983-His	Fwd	CGCGGATCCGCTAGC-ACTTCTGCGCCCGACTT	NheI
	Rev	CCCGCTCGAG-GAACCGGTAGCCTACG	XhoI
983L	Fwd	CGCGGATCCGCTAGC-CGAACGACCCCAACCTTCCCTACAAAAACTTTCAA	NheI
	Rev	CCCGCTCGAG-TCAGAACCGACGTGCCAAGCCGTTC	XhoI

*Dieser Primer wurde als Rückwärts-Primer für alle C-terminalen Fusionen von 287 mit dem His-Tag eingesetzt.

§Vorwärts-Primer, welche in Kombination mit dem Rückwärts-Primer 287-His verwendet werden. Anm. – Alle PCR-Reaktionen verwenden Stamm 2996 sofern nicht anderweitig angegeben (z.B. Stamm MC58)

[0064] In allen Konstrukten, die mit einem ATG beginnen, welches nicht von einer einmal vorkommenden NheI-Stelle gefolgt wird, ist das ATG-Codon ein Teil der für die Clonierung verwendeten NheI-Stelle. Die Konstrukte, die unter Verwendung der NheI-Stelle als Clonierungsstelle am 5'-Ende hergestellt worden sind (z.B. alle diejenigen, welche 287 am N-Terminus enthalten), weisen zwei zusätzliche Codons (GCT AGC) auf, die an die codierende Sequenz des Antigens fusioniert sind.

Herstellung von chromosomalen DNA-Matrizen

[0065] Man ließ die N. meningitidis-Stämme 2996, MC58, 394.98, 1000 und BZ232 (und andere) in 100 ml GC-Medium bis zur exponentiellen Phase wachsen, erntete sie durch Zentrifugation und resuspendierte sie in 5 ml Puffer (20% w/v Saccharose, 50 mM Tris-HCl, 50 mM EDTA, pH 8). Nach 10 Minuten Inkubation auf Eis wurden die Bakterien durch Zugabe von 10 ml Lyse-Lösung (50 mM NaCl, 1% Na-Sarkosyl, 50 µg/ml Proteinase K) lysiert und die Suspension wurde für 2 Stunden bei 37°C inkubiert. Es wurden zwei Phenolextraktionen (äquilibriert auf pH 8) und eine $CHCl_3$/Isoamylalkohol (24:1)-Extraktion durchgeführt. Die DNA wurde durch Zugabe von 0,3 M Natriumacetat und 2 Volumina Ethanol präzipitiert und mittels Zentrifugation aufgefangen. Das Pellet wurde einmal mit 70% (v/v) Ethanol gewaschen und in 4,0 ml TE-Puffer (10 mM Tris-HCl, 1 mM EDTA, pH 8,0) wieder gelöst. Die Konzentration der DNA wurde gemessen, indem die OD_{260} abgelesen wurde.

PCR-Amplifikation

[0066] Das Standard-PCR-Protokoll war wie folgt: 200 ng genomische DNA aus dem Stamm 2996, MC58, 1000 oder BZ232 oder 10 ng einer Plasmid-DNA-Präparation von rekombinanten Clonen wurden als Matrize in Gegenwart von jeweils 40 µM von jedem Oligonucleotid-Primer, 400-800 µM dNTP-Lösung, 1 × PCR-Puffer (einschließlich 1,5 mM $MgCl_2$), 2,5 Einheiten TaqI-DNA-Polymerase (wobei Perkin-Elmer AmpliTaq, Boehringer Mannheim Expand^{TM} Long Template verwendet wurde) eingesetzt.

[0067] Nach einer einleitenden 3-minütigen Inkubation des gesamten Gemisches bei 95°C durchlief jede Probe eine zweistufige Amplifikation: die ersten 5 Zyklen wurden bei der Hybridisierungstemperatur durchgeführt, die den Restriktionsenzym-Schwanz des Primers ausschloss (T_{m1}). Daran schlossen sich 30 Zyklen an, die der Hybridisierungstemperatur entsprachen, welche für die Volllänge-Oligos berechnet worden waren (T_{m2}). Die Zeiten für die Elongation, welche bei 68°C oder 72°C durchgeführt wurde, variierten je nach Länge des zu amplifizierenden ORF. Im Fall von ORF1 wurde die Elongationszeit, ausgehend von 3 Minuten, in jedem Zyklus um 15 Sekunden verlängert. Die Zyklen wurden mit einem 10-minütigen Extensionsschritt bei 72°C abgeschlossen.

[0068] Die amplifizierte DNA wurde direkt auf ein 1% Agarosegel geladen. Das DNA-Fragment, das der Bande mit der korrekten Größe entsprach, wurde aus dem Gel aufgereinigt, wobei das Qiagen Gel Extraktion Kit gemäß den Vorschriften des Herstellers verwendet wurde.

Verdauung der PCR-Fragmente und der Clonierungsvektoren

[0069] Die aufgereinigte DNA, die dem amplifizierten Fragment entsprach, wurde mit den geeigneten Restriktionsenzymen für die Clonierung in pET-21b+, pET22b+ oder pET-24b+ verdaut. Die verdauten Fragmente wurden mit Hilfe des QIAquick PCR Purification Kits (gemäß den Vorschriften des Herstellers) aufgereinigt und entweder mit H_2O oder mit 10 mM Tris, pH 8,5 eluiert. Die Plasmidvektoren wurden mit den geeigneten Restriktionsenzymen verdaut, auf ein 1,0% Agarosegel geladen, und die dem verdauten Vektor entsprechende Bande wurde aufgereinigt, wobei das Qiagen QIAquick Gel Extraction Kit verwendet wurde.

Clonierung

[0070] Die jedem Gen entsprechenden Gene, die zuvor verdaut und aufgereinigt worden waren, wurden in pET-21b+, pET22b+ oder pET-24b+ ligiert. Es wurde ein molares Verhältnis Fragment/Vektor von 3:1 eingesetzt, mit T4-DNA-Ligase in dem vom Hersteller gelieferten Ligierungspuffer.

[0071] Rekombinantes Plasmid wurde in kompetente E. coli DH5 oder HB101 transformiert, indem die Ligasereaktionslösung und die Bakterien für 40 Minuten auf Eis inkubiert wurden, dann für 3 Minuten bei 37°C.

[0072] Dies war gefolgt von der Zugabe von 800 µl LB-Nährlösung und Inkubation für 20 Minuten bei 37°C. Die Zellen wurden bei maximaler Geschwindigkeit in einer Eppendorf-Microfuge abzentrifugiert, in ungefähr 200 µl des Überstands resuspendiert und auf LB-Ampicillin (100 mg/ml) – Agar ausplattiert.

[0073] Eine Durchmusterung auf rekombinante Clone wurde durchgeführt, indem man nach dem Zufallsprinzip ausgewählte Kolonien über Nacht bei 37°C in 4,0 ml LB-Nährlösung + 100 µg/ml Ampicillin wachsen ließ. Man pelletierte die Zellen und extrahierte Plasmid-DNA unter Verwendung des Qiagen QIAprep Spin Miniprep Kits gemäß den Vorschriften des Herstellers. Ungefähr 1 µg von jedem einzelnen Miniprep wurde mit den geeigneten Restriktionsenzymen verdaut und der Verdau parallel zu einem Molekulargewichtsmarker (1 kb DNA Ladder, GIBCO) auf ein 1-1,5% Agarosegel geladen (je nach der erwarteten Größe der Insertion). Positive Clone wurden auf der Grundlage der Größe der Insertion ausgewählt.

Expression

[0074] Nachdem jedes Gen in den Expressionsvektor cloniert worden war, wurden rekombinante Plasmide in E. coli-Stämme transformiert, die für eine Expression des rekombinanten Proteins geeignet sind. Es wurde 1 µl von jedem Konstrukt eingesetzt, um E. coli BL21-DE3 wie vorstehend beschrieben zu transformieren. Einzelne rekombinante Kolonien wurden in 2 ml LB+Amp (100 µg/ml) angeimpft, bei 37°C über Nacht inkubiert, danach 1:30 in 20 ml LB+Amp (100 µg/ml) in 100 ml-Kolben verdünnt, um eine OD_{600} zwischen 0,1 und 0,2 zu ergeben. Die Kolben wurden bei 30°C oder 37°C in einem Schüttelwasserbad inkubiert, bis die OD_{600} ein exponentielles Wachstum anzeigte, welches für die Induktion der Expression geeignet ist (0,4-0,8 OD). Die Proteinexpression wurde durch Zugabe von 1,0 mM IPTG induziert. Nach 3 Stunden Inkubation bei 30°C oder 37°C wurde die OD_{600} gemessen und die Expression untersucht. 1,0 ml von jeder Probe wurden in einer Mikrozentrifuge abzentrifugiert, das Pellet in PBS resuspendiert und durch SDS-PAGE und Färbung mit Coomassie-Blau analysiert.

Gateway – Clonierung und Expression

[0075] Mit GATE markierte Sequenzen wurden cloniert und exprimiert, wobei die GATEWAY Clonierungs-Technologie (Gibco-BRL) verwendet wurde. Clonierung via Rekombination (RC) basiert auf den Rekombinationsreaktionen, welche die Integration und die Excision von Phagen in das bzw. aus dem E. coli-Genom heraus vermitteln. Die Integration beinhaltet eine Rekombination der attP-Stelle der Phagen-DNA innerhalb der attB-Stelle, die in dem bakteriellen Genom liegt (BP-Reaktion). Die Excision rekombiniert die attL- und attR-Stellen zurück in die attP- und attB-Stellen (LR-Reaktion). Die Integrationsreaktion benötigt zwei Enzyme [das Phagenprotein Integrase (Int) und das bakterielle Protein Integrations-Wirtsfaktor (IHF)] (BP Clonase). Die Excisionsreaktion benötigt Int, IHF und ein weiteres Phagenenzym, Excisionase (Xis)(LR Clonase). Künstliche Derivate der 25 bp großen bakteriellen attB-Rekombinationsstelle, welche als B1 und B2 bezeichnet werden, wurden an das 5'-Ende der Primer hinzugefügt, die in den PCR-Reaktionen verwendet wurden, um Neisseria-ORFs zu amplifizieren. Die so erhaltenen Produkte wurden in einen „Donor-Vektor" BP cloniert, welcher komplementäre Derivate der Phagen-Rekombinationsstelle attP (P1 und P2) enthielt, wobei BP Clonase verwendet wurde. Die so erhaltenen „Eingangsclone" enthalten ORFs, die von Derivaten der attL-Stelle (L1 und L2) flankiert sind, und wurden in die Expressions-„Bestimmungsvektoren" subcloniert, welche Derivate der attL-kompatiblen attR-Stellen (R1 und R2) enthalten, wobei LR Clonase verwendet wird. Dies führte zu „Expressionsclonen", in denen die ORFs von B1 und B2 flankiert und im gleichen Leseraster mit den N-terminalen GST- oder His-Tags fusioniert sind.

[0076] Bei dem für die GATEWAY-Expression verwendeten E. coli-Stamm handelt es sich um BL21-SI. Zellen von diesem Stamm werden zur Expression der T7-RNA-Polymerase durch Wachstum in Medium induziert, das Salz enthält (0,3 M NaCl).

[0077] Beachten Sie, dass dieses System zu N-terminalen His-Tags führt.

Präparation von Membran-Proteinen

[0078] Fraktionen, die hauptsächlich entweder aus innerer, äußerer oder Gesamtmembran zusammengesetzt waren, wurden isoliert, um rekombinante Proteine zu gewinnen, die mit Leader-Sequenzen für die Membran-Lokalisierung exprimiert worden waren. Das Verfahren zur Präparation von Membran-Fraktionen, welche für rekombinante Proteine angereichert sind, wurde von Filip et al. [J. Bact. 115: 717-722 (1973)] und Davies et al. [J. Immunol. Meth. 143: 215-225 (1990)] angepasst. Man ließ einzelne Kolonien, die das Plasmid von Interesse beherbergten, über Nacht bei 37°C in 20 ml einer LB/Amp (100 µg/ml) – Flüssigkultur wachsen. Man verdünnte die Bakterien 1:30 in 1,0 l frisches Medium und ließ sie über Nacht entweder bei 30°C oder bei 37°C wachsen, bis die OD_{550} 0,6-0,8 erreichte. Expression von rekombinantem Protein wurde mit IPTG in einer Endkonzentration von 1,0 mM induziert. Nach 3 Stunden Inkubation wurden die Bakterien durch Zentrifugation bei 8000 × g für 15 Minuten bei 4°C geerntet und in 20 ml 20 mM Tris-HCl, (pH 7,5) und den „Complete" Protease-Hemmern (Boehringer Mannheim) resuspendiert. Alle nachfolgenden Arbeitsschritte wurden bei 4°C oder auf Eis durchgeführt.

[0079] Die Zellen wurden durch Ultraschallbehandlung mit einem Branson Sonifier 450 aufgeschlossen und bei 5.000 × g für 20 Minuten abzentrifugiert, um nicht aufgebrochene Zellen und Einschlusskörper zu sedimentieren. Der Membranen und Zelltrümmer enthaltende Überstand wurde bei 50.000 × g abzentrifugiert (Beckman Ti50, 29.000 UpM), mit 20 mM Bis-Tris-propan (pH 6,5), 1,0 M NaCl, 10% (v/v) Glycerin gewaschen und nochmals für 75 Minuten bei 50.000 × g sedimentiert. Das Pellet wurde in 20 mM Tris-HCl, (pH 7,5), 2,0% (v/v) Sarkosyl, „Complete" Protease-Hemmer (Endkonzentration 1,0 mM EDTA) resuspendiert und für 20 Minuten inkubiert um die innere Membran aufzulösen. Zelltrümmer wurden durch eine 10-minütige Zentrifugation bei 5.000 × g pelletiert und der Überstand für 75 Minuten bei 75.000 × g zentrifugiert (Beckman Ti50, 33.000 UpM). Man fand, dass die Proteine 008L und 519L im Überstand vorlagen, was auf eine Lokalisierung in der inneren Membran hindeutet. Für diese Proteine wurden sowohl Fraktionen der inneren Membran als auch der Gesamtmembran (wie vorstehend mit NaCl gewaschen) verwendet, um Mäuse zu immunisieren. Äußere Membranvesikel, die aus dem 75.000 × g-Pellet gewonnen worden waren, wurden mit 20 mM Tris-HCl, (pH 7,5), gewaschen und bei 75.000 × g für 75 Min oder über Nacht abzentrifugiert. Die OMV wurden schließlich in 500 µl 20 mM Tris-HCl, (pH 7,5), 10% v/v Glycerin resuspendiert. Orf1L und Orf40L waren beide in der Fraktion der äußeren Membran lokalisiert und angereichert, welche dazu verwendet wurde, Mäuse zu immunisieren. Die Protein-Konzentration wurde mit Hilfe des Standard Bradford-Assays (Bio-Rad) bestimmt, während die Protein-Konzentration der Fraktion der inneren Membran mit dem DC-Protein-Assay (Bio-Rad) bestimmt wurde. Verschiedene Fraktionen aus dem Aufreinigungsverfahren wurden mit SDS-PAGE getestet.

Aufreinigung von mit einem His-Tag markierten Proteinen

[0080] Aus den Stämmen 2996 und MC58 wurden verschiedene Formen von 287 cloniert. Diese wurden mit einer Fusion eines His-Tag am C-Terminus konstruiert und umfassten eine reife Form (aa 18-427), Konstrukte mit Deletionen (Δ1, Δ2, Δ3 und Δ4) sowie Clone, die entweder aus B- oder C-Domänen zusammengesetzt waren. Für jeden Clon, der als eine His-Fusion aufgereinigt wurde, wurde eine einzelne Kolonie ausgestrichen und über Nacht bei 37°C auf einer LB/Amp (100 µg/ml) – Agarplatte wachsen gelassen. Eine vereinzelte Kolonie von dieser Platte wurde in 20 ml LB/Amp (100 µg/ml) – Flüssigmedium angeimpft und über Nacht unter Schütteln bei 37°C wachsen gelassen. Die Übernachtkultur wurde 1:30 in 1,0 l LB/Amp (100 µg/ml)-Flüssigmedium verdünnt und bei der optimalen Temperatur (30°C oder 37°C) wachsen gelassen, bis die OD_{550} 0,6-0,8 erreichte. Die Expression von rekombinantem Protein wurde durch Zugabe von IPTG (Endkonzentration 1,0 mM) induziert und die Kultur für weitere 3 Stunden inkubiert. Die Bakterien wurden durch eine 15-minütige Zentrifugation bei 8.000 × g und 4°C geerntet. Das bakterielle Pellet wurde in 7,5 ml von entweder (i) kaltem Puffer A (300 mM NaCl, 50 ml Phosphatpuffer, 10 mM Imidazol, pH 8,0) für lösliche Proteine oder (ii) Puffer B (10 mM Tris-HCl, 100 mM Phosphatpuffer, pH 8,8 und gegebenenfalls 8 M Harnstoff) für unlösliche Proteine. Zu den Proteinen, die in einer löslichen Form aufgereinigt wurden, gehörten 287-His, Δ1, Δ2, Δ3 und Δ4287-His, Δ4287MC58-His, 287c-His und 287cMC58-His. Das Protein 287bMC58-His war unlöslich und wurde entsprechend aufgereinigt. Zellen wurden durch Ultraschallbehandlung auf Eis, vier Mal 30 Sek. bei 40 W unter Verwendung eines Branson Sonifier 450 aufgeschlossen und bei 13.000 × g für 30 Minuten bei 4°C abzentrifugiert. Für unlösliche Proteine wurden die Pellets in 2,0 ml Puffer C (6 M Guanidinhydrochlorid, 100 mM Phosphatpuffer, 10 mM Tris-HCl, (pH 7,5) resuspendiert und mit 10 Durchgängen in einem Dounce-Homogenisator behandelt. Das Homogenat wurde bei 13.000 × g für 30 Minuten abzentrifugiert und der Überstand zurückbehalten. Die Überstände für sowohl lösliche als auch unlösliche Präparationen wurden mit 150 µl Ni^{2+}-Harz (welches zuvor mit entweder Puffer A oder Puffer B, wie jeweils anwendbar, äquilibriert worden war) gemischt und für 30 Minuten bei Raumtemperatur unter sanftem Schütteln inkubiert. Bei dem Harz handelte es sich um Chelating Sepharose Fast Flow (Pharmacia), welche gemäß den Vorschriften des Herstellers vorbereitet worden war. Die im Batchverfahren bearbeitete Präparation wurde bei 700 × g für 5 Min. bei 4°C zentrifugiert und der Überstand verworfen. Das Harz wurde zwei Mal (in Batches) mit 10 ml Puffer A oder B für 10 Min. gewaschen, in 1,0 ml Puffer A oder B resuspendiert und auf eine Wegwerf-Säule geladen. Das Harz wurde weiter mit entweder (i) Puffer A bei 4°C oder (ii) Puffer B bei Raumtemperatur gewaschen, bis die OD_{280} des Durchflusses 0,02-0,01 erreichte. Das Harz wurde weiter mit entweder (i) kaltem Puffer C (300 mM NaCl, 50 mM Phosphatpuffer, 20 mM Imidazol, pH 8,0) oder (ii) Puffer D (10 mM Tris-HCl, 100 mM Phosphatpuffer, pH 6,3 und gegebenenfalls 8 M Harnstoff) gewaschen, bis die OD_{280} des Durchflusses 0,02-0,01 erreichte. Das His-Fusionsprotein wurde durch Zugabe von 700 µl von entweder (i) kaltem Elutionspuffer A (300 mM NaCl, 50 mM Phosphatpuffer, 250 mM Imidazol, pH 8,0) oder (ii) Elutionspuffer B (10 mM Tris-HCl, 100 mM Phosphatpuffer, pH 4,5 und gegebenenfalls 8 M Harnstoff) eluiert und Fraktionen gesammelt, bis die OD_{280} anzeigte, dass das gesamte rekombinante Protein aufgefangen worden war. 20 µl-Aliquots von jeder Elutionsfraktion wurden mittel SDS-PAGE analysiert. Protein-Konzentrationen wurden mit Hilfe des Bradford-Assays bestimmt.

Denaturierung denaturierter His-Fusionsproteine

[0081] Eine Denaturierung war erforderlich, um 287bMC58 zu solubilisieren, daher wurde ein Renaturierungsschritt vor der Immunisierung eingesetzt. Zu den vorstehend gewonnenen Fraktionen wurde Glycerin hinzugefügt, um eine Endkonzentration von 10% v/v zu erreichen. Die Proteine wurden auf 200 µg/ml verdünnt, wobei Dialysepuffer I (10% v/v Glycerin, 0,5 M Arginin, 50 mM Phosphatpuffer, 5,0 mM reduziertes Glutathion, 0,5 mM oxidiertes Glutathion, 2,0 M Harnstoff, pH 8,8) verwendet wurde, und für 12-14 Stunden bei 4°C gegen den gleichen Puffer dialysiert. Eine weitere Dialyse wurde mit Puffer II (10% v/v Glycerin, 0,5 M Arginin, 50 mM Phosphatpuffer, 5,0 mM reduziertes Glutathion, 0,5 mM oxidiertes Glutathion, pH 8,8) für 12-14 Stunden bei 4°C durchgeführt. Die Protein-Konzentration wurde mit Hilfe der folgenden Formel bestimmt:

$$\text{Protein (mg/ml)} = (1{,}55 \times OD_{280}) - (0{,}76 \times OD_{260})$$

Aminosäuresequenz-Analyse

[0082] Eine automatisierte Sequenzanalyse des N-Terminus von Proteinen wurde nach den Empfehlungen des Herstellers auf einem Beckman Sequenziergerät (LF 3000) durchgeführt, das mit einer Online-Phenylthiohydantoin-Aminosäuren-Analyseeinheit (System Gold) ausgestattet war.

Immunisierung

[0083] BALG/c-Mäuse wurden an den Tagen 0, 21 und 35 mit Antigenen immunisiert und die Seren am Tag 49 untersucht.

Serumanalyse – ELISA

[0084] Der nicht verkapselte MenB M7 und die verkapselten Stämme wurden auf Schokolade-Agarplatten ausplattiert und über Nacht bei 37°C mit 5% CO_2 inkubiert. Bakterielle Kolonien wurden von den Agarplatten mit einem sterilen „Dracon"-Tupfer abgenommen und in Mueller-Hinton-Nährlösung (Difco) angeimpft, welche 0,25% Glucose enthielt. Das Wachstum der Bakterien wurde alle 30 Minuten überwacht, indem die OD_{620} verfolgt wurde. Man ließ die Bakterien wachsen, bis die OD den Wert 0,4-0,5 erreichte. Die Kultur wurde für 10 Minuten bei 4.000 UpM abzentrifugiert. Der Überstand wurde verworfen und die Bakterien wurden zwei Mal mit PBS gewaschen, in PBS resuspendiert, welches 0,025% Formaldehyd enthielt und für 1 Stunde bei 37°C und dann über Nacht bei 4°C ohne Schütteln inkubiert. 100 µl Bakterienzellen wurden zu jeder Vertiefung einer Greiner-Platte mit 96 Vertiefungen hinzugegeben und über Nacht bei 4°C inkubiert. Die Vertiefungen wurden drei Mal mit PBT-Waschpuffer (0,1% Tween-20 in PBS) gewaschen. 200 µl Sättigungspuffer (2,7% Polyvinylpyrrolidon 10 in Wasser) wurden zu jeder Vertiefung hinzugegeben und die Platten für 2 Stunden bei 37°C inkubiert. Die Vertiefungen wurden drei Mal mit PBT gewaschen. 200 µl der verdünnten Seren (Verdünnungspuffer: 1% BSA, 0,1% Tween-20, 0,1% NaN_3 in PBS) wurden zu jeder Vertiefung hinzugegeben und die Platten für 2 Stunden bei 37°C inkubiert. Die Vertiefungen wurden drei Mal mit PBT gewaschen. 100 µl von HRP-konjugiertem Kaninchen-Anti-Maus-Serum (Dako), welches 1:2000 in Verdünnungspuffer verdünnt war, wurden zu jeder Vertiefung hinzugegeben und die Platten wurden 90 Minuten bei 37°C inkubiert. Die Vertiefungen wurden drei Mal mit PBT gewaschen. 100 µl Substratpuffer für HRP (25 ml Citratpuffer, pH 5, 10 mg O-Phenyldiamin und 10 µl H_2O_2) wurden zu jeder Vertiefung hinzugegeben und die Platten wurden für 20 Minuten bei Raumtemperatur stehen gelassen. Zu jeder Vertiefung wurden 100 µl 12,5% H_2SO_4 hinzugegeben und die OD_{490} wurde verfolgt. Die ELISA-Titer wurden willkürlich als die Serumverdünnung berechnet, die einen OD_{490}-Wert von 0,4 über dem Spiegel der Präimmunseren ergab. Der ELISA wurde als positiv gewertet, wenn die Verdünnung von Seren mit einer OD_{490} von 0,4 höher als 1:400 war.

Serumanalyse – FACS Scan Bakterien-Bindungsassay

[0085] Der nicht verkapselte MenB M7-Stamm wurde auf Schokolade-Agarplatten ausplattiert und über Nacht bei 37°C mit 5% CO_2 inkubiert. Bakterielle Kolonien wurden mit einem sterilen Dracon-Tupfer von den Agarplatten abgenommen und in 4 Röhrchen angeimpft, die 8 ml Mueller-Hinton-Nährlösung (Difco) enthielten, welche 0,25% Glucose enthielt. Das Wachstum der Bakterien wurde alle 30 Minuten überwacht, indem die OD_{620} verfolgt wurde. Man ließ die Bakterien wachsen, bis die OD den Wert 0,35-0,5 erreichte. Die Kultur wurde für 10 Minuten bei 4.000 UpM abzentrifugiert. Der Überstand wurde verworfen und das Pellet in Blockierungspuffer (1% BSA in PBS, 0,4% NaN_3) resuspendiert und 5 Minuten bei 4.000 UpM zentrifugiert. Die Zellen wurden in Blockierungspuffer resuspendiert, so dass sie eine OD_{620} von 0,05 erreichten. 100 µl Bakterienzellen wurden zu jeder Vertiefung einer Costar-Platte mit 96 Vertiefungen hinzugegeben. 100 µl von verdünnten (1:100, 1:200, 1:400) Seren (in Blockierungspuffer) wurden zu jeder Vertiefung hinzugegeben und die Platten für 2 Stunden bei 4°C inkubiert. Die Zellen wurden für 5 Minuten bei 4.000 UpM abzentrifugiert, der Überstand abgesaugt und die Zellen durch Zugabe von 200 µl Blockierungspuffer in jede Vertiefung gewaschen. Zu jeder Vertiefung wurden 100 µl von 1:100 verdünntem, mit R-Phycoerythrin konjugiertem Ziege-Anti-Maus-$F(ab)_2$ hinzugegeben und die Platten für 1 Stunde bei 4°C inkubiert. Die Zellen wurden durch eine 5-minütige Zentrifugation bei 4.000 UpM abzentrifugiert und durch Zugabe von 200 µl Blockierungspuffer/Vertiefung gewaschen. Der Überstand wurde abgesaugt und die Zellen in 200 µl/Vertiefung von PBS, 0,25% Formaldehyd resuspendiert. Die Proben wurden in FACS-Röhrchen überführt und gemessen. Die Einstellungen für den FACScan (Laserleistung 15 mW) waren: FL2 an; FSC-H-Schwelle: 92; FSC PMT-Spannung: E 01; SSC PMT: 474; Amp. Verstärkung 6.1; FL-2 PMT: 586; Kompensationswert: 0.

Serumanalyse – Bakterizidie-Assay

[0086] Man ließ den N. meningitidis-Stamm 2996 über Nacht bei 37°C auf Schokolade-Agarplatten (ausgehend von einem eingefrorenen Vorrat) mit 5% CO_2 wachsen. Kolonien wurden abgenommen und dazu verwendet, 7 ml Mueller-Hinton-Nährlösung anzuimpfen, welche 0,25% Glucose enthielt, um eine OD_{620} von 0,05-0,08 zu erreichen. Die Kultur wurde für ungefähr 1,5 Stunden bei 37°C unter Schütteln inkubiert, bis die OD_{620} einen Wert von 0,23-0,24 erreichte. Die Bakterien verdünnte man zu einer Arbeitskonzentration von 10^5 CFU/ml in 50 mM Phosphatpuffer, pH 7,2, der 10 mM $MgCl_2$, 10 mM $CaCl_2$ und 0,5% (w/v) BSA enthielt (Assaypuffer). Das Gesamtvolumen des endgültigen Reaktionsgemisches war 50 µl mit 25 µl einer Verdünnungsreihe fortlaufender zweifacher Verdünnungen von Testserum, 12,5 µl Bakterien in der Arbeitsverdünnung, 12,5 µl Komplement von Kaninchen-Jungen (Endkonzentration 25%).

[0087] Die Kontrollen enthielten Bakterien, welche mit Komplement-Serum inkubiert worden waren, Immunseren, die mit Bakterien und mit Komplement inkubiert worden waren, das durch Erhitzen bei 56°C für 30 Minuten inaktiviert worden war. Unmittelbar nach der Zugabe des Kaninchen-Jungen-Komplements wurden 10 µl der Kontrollen auf Mueller-Hinton-Agarplatten ausplattiert, wobei die Kippmethode angewandt wurde (Zeit 0). Die Platte mit 96 Vertiefungen wurde für 1 Stunde bei 37°C unter kreisförmiger Bewegung inkubiert. 7 µl von jeder Probe wurden punktförmig auf Mueller-Hinton Agarplatten ausplattiert, wohingegen 10 µl der Kontrollen mit der Kippmethode auf Mueller-Hinton Agarplatten plattiert wurden (Zeit 1). Die Agarplatten wurden für 18 Stunden bei 37°C inkubiert und die der Zeit 0 und der Zeit 1 entsprechenden Kolonien wurden ausgezählt.

Serumanalyse – Western Blot

[0088] Aufgereinigte Proteine (500 ng/Spur), äußere Membranvesikel (5 µg) und Gesamt-Zellextrakte (25 µg), welche von dem MenB-Stamm 2996 abgeleitet waren, wurden auf ein 12,5% SDS-Polyacrylamidgel aufgetragen und auf eine Nitrocellulose-Membran transferiert. Der Transfer wurde für 2 Stunden bei 150 mA bei 4°C mit Transfer-Puffer (0,3% Tris-Base, 1,44% Glycin, 20% (v/v) Methanol) durchgeführt. Die Membran wurde durch eine Inkubation über Nacht bei 4°C in Sättigungspuffer (10% Magermilch, 0,1% Triton X-100 in PBS) abgesättigt. Die Membran wurde zwei Mal mit Waschpuffer (3% Magermilch, 0,1% Triton X-100) gewaschen und für 2 Stunden bei 37°C mit 1:200 in Waschpuffer verdünntem Maus-Serum inkubiert. Die Membran wurde zwei Mal gewaschen und für 90 Minuten mit einer 1:2000 Verdünnung von mit Meerrettichperoxidase markiertem Anti-Maus-Ig inkubiert. Die Membran wurde zwei Mal mit 0,1% Triton X-100 in PBS gewaschen und mit dem Opti-4CN Substratkit (Bio-Rad) entwickelt. Die Reaktion wurde durch Zugabe von Wasser gestoppt.

[0089] Die OMVs wurden wie folgt präpariert: man ließ den N. meningitidis-Stamm 2996 über Nacht bei 37°C mit 5% CO_2 auf 5 GC-Platten wachsen, erntete ihn mit einer Impföse und resuspendierte ihn in 10 ml 20 mM Tris-HCl, pH 7,5, 2 mM EDTA. Eine Hitzeinaktivierung wurde für 45 Minuten bei 56°C durchgeführt und die Bakterien durch eine 5-minütige Ultraschallbehandlung auf Eis (50% Arbeitszyklus, 50% Leistung, Branson Sonifier 3 mm Mikrospitze) aufgebrochen. Nicht aufgebrochene Zellen wurden durch eine 10-minütige Zentrifugation bei 5.000 × g entfernt, der die gesamte Zellhüll-Fraktion enthaltende Überstand zurückgewonnen und weiter über Nacht bei 50.000 × g bei einer Temperatur von 4°C zentrifugiert. Das die Membranen enthaltende Pellet wurde in 2% Sarkosyl, 20 mM Tris-HCl, pH 7,5, 2 mM EDTA resuspendiert und für 20 Minuten bei Raumtemperatur inkubiert, um die inneren Membranen zu solubilisieren. Die Suspension wurde für 10 Minuten bei 10.000 × g zentrifugiert, um Aggregate zu entfernen, der Überstand wurde weiter für 3 Stunden bei 50.000 × g zentrifugiert. Das Pellet, welches die äußeren Membranen enthielt, wurde in PBS gewaschen und in dem gleichen Puffer resuspendiert. Die Proteinkonzentration wurde mit dem D.C. Bio-Rad Protein Assay (modifizierte Lowry-Methode) gemessen, wobei BSA als Standard verwendet wurde.

[0090] Gesamt-Zellextrakte wurden wie folgt präpariert: man ließ den N. meningitidis-Stamm 2996 über Nacht auf einer GC-Platte wachsen, erntete ihn mit einer Impföse und resuspendierte ihn in 1 ml 20 mM Tris-Hcl. Eine Hitzeinaktivierung wurde für 30 Minuten bei 56°C durchgeführt.

Untersuchungen der Domänen von 961

[0091] Präparation zellulärer Fraktionen: man stellte Gesamtlysat, Periplasma, Überstand und OMV von E. coli-Clonen her, die verschiedene Domänen von 961 exprimierten, indem man Bakterien von Übernachtkulturen oder nach 3 Stunden Induktion mit IPTG verwendete. In Kürze, das Periplasma wurde gewonnen, indem man Bakterien in 25% Saccharose und 50 mM Tris (pH 8) mit 100 µg/ml Polymyxin aufnahm. Nach 1 Stunde bei Raumtemperatur wurden die Bakterien für 15 Minuten bei 13.000 UpM abzentrifugiert und der Überstand wurde gesammelt. Der Kulturüberstand wurde mit 0,2 µm gefiltert und mit 50% TCA für 2 Stunden im Eis präzipitiert. Nach einer Zentrifugation (30 Min. bei 13.000 UpM) wurden die Pellets zwei Mal mit 70% Ethanol gespült und in PBS aufgenommen. Die OMV-Präparation wurde wie zuvor beschrieben durchgeführt. Jede zelluläre Fraktion wurde in einer SDS-PAGE oder in einem Western Blot untersucht, wobei das gegen GST-961 hergestellte polyclonale Antiserum verwendet wurde.

[0092] Adhäsions-Assay: Chang Epithelzellen (Wong-Kilbourne-Derivat, Clon 1-5c-4, menschliche Bindehaut) wurden in DMEM (Gibco) gehalten, welches mit 10% hitzeinaktiviertem FCS, 15 mM L-Glutamin und Antibiotika ergänzt war.

[0093] Für den Adhärenz-Assay wurde eine subkonfluente Kultur von Chang-Epithelzellen mit PBS gespült und mit Trypsin-EDTA (Gibco) behandelt, um sie von dem Plastikträgermaterial freizusetzen. Die Zellen wurden dann in PBS aufgenommen, gezählt und in PBS auf 5 × 10^5 Zellen/ml verdünnt.

[0094] Bakterien von Übernachtkulturen oder nach Induktion mit IPTG wurden pelletiert und zwei Mal mit PBS gewaschen, indem man sie für 5 Min. bei 13.000 abzentrifugierte. Ungefähr 2-3 × 10^8 (cfu) wurden mit 0,5 mg/ml FITC (Sigma) für 30 Min. bei Raumtemperatur im Dunkeln in 1 ml Puffer inkubiert, der 50 mM $NaHCO_3$ und 100 mM NaCl, pH 8 enthielt. Mit FITC markierte Bakterien wurden 2-3 Mal gewaschen und in einer Konzentration von 1-1,5 × 10^9/ml in PBS aufgenommen. 200 µl dieser Suspension (2-3 × 10^8) wurden mit 200 µl (1 × 10^5) Epithelzellen für 30 Min. bei 37°C inkubiert. Die Zellen wurden dann bei 2.000 UpM für 5 Min. abzentrifugiert, um die nicht adhärenten Bakterien zu entfernen, in 200 µl PBS aufgenommen, in FACScan-Röhrchen überführt und gemessen.

Sequenzprotokoll

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Lys Tyr Ile Arg Ile Gly Tyr Ala Asp Lys Asn Glu His Pro Tyr Val
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Thr Ser Met Gln Gly Ile Lys Ala Tyr Met Arg Gln Asn Pro Gln Arg
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Leu Gly Cys Ala Asn Leu Lys Asn Arg Gln Gly Trp Gln Asp Val Cys
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Phe Glu Arg Tyr Phe Thr Pro Trp Gln Val Ala Gly Asn Gly Ser Leu
            100                 105                 110

Ala Gly Thr Val Thr Gly Tyr Tyr Glu Pro Val Leu Lys Gly Asp Asp
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Arg Arg Thr Ala Gln Ala Arg Phe Pro Ile Tyr Gly Ile Pro Asp Asp
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Phe Ile Ser Val Pro Leu Pro Ala Gly Leu Arg Ser Gly Lys Ala Leu
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Val Arg Ile Arg Gln Thr Gly Lys Asn Ser Gly Thr Ile Asp Asn Thr
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Gly Gly Thr His Thr Ala Asp Leu Ser Arg Phe Pro Ile Thr Ala Arg
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Thr Thr Ala Ile Lys Gly Arg Phe Glu Gly Ser Arg Phe Leu Pro Tyr
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Lys Gly Asp Asp Arg Arg Thr Ala Gln Ala Arg Phe Pro Ile Tyr Gly
145                 150                 155                 160

Ile Pro Asp Asp Phe Ile Ser Val Pro Leu Pro Ala Gly Leu Arg Ser
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Gly Lys Ala Leu Val Arg Ile Arg Gln Thr Gly Lys Asn Ser Gly Thr
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Phe Leu Pro Tyr His Thr Arg Asn Gln Ile Asn Gly Gly Ala Leu Asp
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Gly Lys Ala Pro Ile Leu Gly Tyr Ala Glu Asp Pro Val Glu Leu Phe
                245                 250                 255

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            260                 265                 270

Tyr Ile Arg Ile Gly Tyr Ala Asp Lys Asn Glu His Pro Tyr Val Ser
        275                 280                 285

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Asp Ala Leu Ala Thr Leu Gly Phe Asp Tyr Pro Arg Arg Ala Gly Phe
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Phe Gln Lys Glu Leu Val Glu Leu Leu Lys Leu Ala Lys Glu Glu Gly
    50                  55                  60

Gly Asp Val Phe Ala Phe Lys Gly Ser Tyr Ala Gly Ala Met Gly Met
65                  70                  75                  80

Pro Gln Phe Met Pro Ser Ser Tyr Arg Lys Trp Ala Val Asp Tyr Asp
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Asp Ala Leu Ala Thr Leu Ser Phe Asn Tyr Pro Arg Arg Ala Glu Tyr
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Phe Ser Gly Glu Leu Glu Thr Phe Leu Leu Met Ala Arg Asp Glu Gln
    50                  55                  60

Asp Asp Pro Leu Asn Leu Lys Gly Ser Phe Ala Gly Ala Met Gly Tyr
65                  70                  75                  80

Gly Gln Phe Met Pro Ser Ser Tyr Lys Gln Tyr Ala Val Asp Phe Ser
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        35                  40                  45

Tyr Val Ser Ile Gly Arg Tyr Met Ala Asp Lys Gly Tyr Leu Lys Leu
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Gly Gln Thr Ser Met Gln Gly Ile Lys Ser Tyr Met Arg Gln Asn Pro
65                  70                  75                  80

Gln Arg Leu Ala Glu Val Leu Gly Gln Asn Pro Ser Tyr Ile Phe Phe
                85                  90                  95

Arg Glu Leu Ala Gly Ser Ser Asn Asp Gly Pro Val Gly Ala Leu Gly
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Thr Pro Leu Met Gly Glu Tyr Ala Gly Ala Val Asp Arg His Tyr Ile
        115                 120                 125

Thr Leu Gly Ala Pro Leu Phe Val Ala Thr Ala His Pro Val Thr Arg
    130                 135                 140

Lys Ala Leu Asn Arg Leu Ile Met Ala Gln Asp Thr Gly Ser Ala Ile
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Lys Gly Ala Val Arg Val Asp Tyr Phe Trp Gly Tyr Gly Asp Glu Ala
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Glu Asp Met Ser Met Gln Ala Ile Arg His Trp Gly Glu Thr His Ser
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Glu Ala Glu Val Arg Glu Leu Leu Glu Gln Asn Pro Ser Phe Val Phe
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Phe Lys Pro Gln Ser Phe Ala Pro Val Lys Gly Ala Ser Ala Val Pro
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ccggaattct tatgtcgccc gatgttaaat cggcgga 37

<210> 21
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 21
gcccaagctt tcaatcctgc tctttttgc cg 32

<210> 22
<211> 34
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<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 22
ccggaattct tatgagccaa gatatggcgg cagt 34

<210> 23
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 23
gcccaagctt tcaatcctgc tctttttgc cg 32

<210> 24
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 24
ccggaattct tatgtccgcc gaatccgcaa atca 34

<210> 25
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 25
gcccaagctt tcaatcctgc tctttttgc cg 32

<210> 26
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 26
ccggaattct tatgggaagg gttgatttgg ctaatg 36

<210> 27
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 27
gcccaagctt tcaatcctgc tcttttttgc cg 32

<210> 28
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 28
ccggaattct tatgtcagat ttggcaaacg attctt 36

<210> 29
<211> 35
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 29
gcccaagctt ttacgtatca tatttcacgt gcttc 35

<210> 30
<211> 37
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 30
ccggaattct tatgtcgccc gatgttaaat cggcgga 37

<210> 31
<211> 35
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 31
gcccaagctt ttacgtatca tatttcacgt gcttc 35

<210> 32
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

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<400>   32
ccggaattct tatgcaaagc aagagcatcc aaacct                                36

<210>   33
<211>   30
<212>   DNA
<213>   Artificial Sequence

<220>
<223>   Oligonucleotide

<400>   33
gcccaagctt ttacgggcgg tattcgggct                                       30

<210>   34
<211>   29
<212>   DNA
<213>   Artificial Sequence

<220>
<223>   Oligonucleotide

<400>   34
ccggaattca tatgaaacac tttccatcc                                        29

<210>   35
<211>   28
<212>   DNA
<213>   Artificial Sequence

<220>
<223>   Oligonucleotide

<400>   35
gcccaagctt ttaccactcg taattgac                                         28

<210>   36
<211>   29
<212>   DNA
<213>   Artificial Sequence

<220>
<223>   Oligonucleotide

<400>   36
ccggaattca tatggccaca agcgacgac                                        29

<210>   37
<211>   28
<212>   DNA
<213>   Artificial Sequence

<220>
<223>   Oligonucleotide

<400>   37
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gcccaagctt ttaccactcg taattgac 28

<210> 38
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 38
ccggaattct tatgaaacac tttccatcc 29

<210> 39
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 39
gcccaagctt tcaacccacg ttgtaaggtt g 31

<210> 40
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
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<400> 40
ccggaattct tatggccaca aacgacgacg 30

<210> 41
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
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<400> 41
gcccaagctt tcaacccacg ttgtaaggtt g 31

<210> 42
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 42
ccggaattct tatggccacc tacaaagtgg acga 34

<210> 43
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 43
gcccaagctt ttattgtttg gctgcctcga tt 32

<210> 44
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 44
cgcggatccg ctagccccga tgttaaatcg gc 32

<210> 45
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 45
cccgctcgag tcaatcctgc tcttttttgc c 31

<210> 46
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 46
cgcggatccg ctagccaaga tatggcggca gt 32

<210> 47
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 47
cgcggatccg ctagcgccga atccgcaaat ca 32

<210> 48
<211> 32

<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 48
cgcgctagcg gaagggttga tttggctaat gg 32

<210> 49
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 49
gggaattcca tatgggcatt tcccgcaaaa tatc 34

<210> 50
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 50
cccgctcgag ttacgtatca tatttcacgt gc 32

<210> 51
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 51
gggaattcca tatgggcatt tcccgcaaaa tatc 34

<210> 52
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 52
cccgctcgag ttattctatg ccttgtgcgg cat 33

<210> 53
<211> 32
<212> DNA
<213> Artificial Sequence

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<220>
<223>   Oligonucleotide

<400>   53
cgcggatccc atatggccac aagcgacgac ga                          32

<210>   54
<211>   28
<212>   DNA
<213>   Artificial Sequence

<220>
<223>   Oligonucleotide

<400>   54
cccgctcgag ttaccactcg taattgac                               28

<210>   55
<211>   28
<212>   DNA
<213>   Artificial Sequence

<220>
<223>   Oligonucleotide

<400>   55
cgcggatccc atatggccac aaacgacg                               28

<210>   56
<211>   35
<212>   DNA
<213>   Artificial Sequence

<220>
<223>   Oligonucleotide

<400>   56
cccgctcgag tcatttagca atattatctt tgttc                       35

<210>   57
<211>   33
<212>   DNA
<213>   Artificial Sequence

<220>
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<400>   57
cgcggatccc atatgaaagc aaacagtgcc gac                         33

<210>   58
<211>   28
<212>   DNA
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<220>
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<223> Oligonucleotide

<400> 58
cccgctcgag ttaccactcg taattgac 28

<210> 59
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 59
cgcggatccc atatggccac aaacgacg 28

<210> 60
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 60
cccgctcgag ttaacccacg ttgtaaggt 29

<210> 61
<211> 33
<212> DNA
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<220>
<223> Oligonucleotide

<400> 61
cgcggatccc atatgatgaa acactttcca tcc 33

<210> 62
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 62
cccgctcgag ttaacccacg ttgtaaggt 29

<210> 63
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 63
cgcggatccc atatggccac aaacgacg 28

<210> 64
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 64
cccgctcgag tcagtctgac actgttttat cc 32

<210> 65
<211> 32
<212> DNA
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<220>
<223> Oligonucleotide

<400> 65
cgcggatccg ctagccccga tgttaaatcg gc 32

<210> 66
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 66
cccgctcgag ttacgggcgg tattcgg 27

<210> 67
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 67
cgcggatccg ctagccccga tgttaaatcg gc 32

<210> 68
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 68
cccgctcgag ttacgtatca tatttcacgt gc 32

<210> 69
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 69
cgcggatccg ctagccccga tgttaaatcg gc 32

<210> 70
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 70
cccgctcgag ttaccactcg taattgac 28

<210> 71
<211> 1457
<212> PRT
<213> Neisseria meningitidis

<400> 71
Met Lys Thr Thr Asp Lys Arg Thr Thr Glu Thr His Arg Lys Ala Pro
1 5 10 15

Lys Thr Gly Arg Ile Arg Phe Ser Pro Ala Tyr Leu Ala Ile Cys Leu
20 25 30

Ser Phe Gly Ile Leu Pro Gln Ala Trp Ala Gly His Thr Tyr Phe Gly
35 40 45

Ile Asn Tyr Gln Tyr Tyr Arg Asp Phe Ala Glu Asn Lys Gly Lys Phe
50 55 60

Ala Val Gly Ala Lys Asp Ile Glu Val Tyr Asn Lys Lys Gly Glu Leu
65 70 75 80

Val Gly Lys Ser Met Thr Lys Ala Pro Met Ile Asp Phe Ser Val Val
85 90 95

Ser Arg Asn Gly Val Ala Ala Leu Val Gly Asp Gln Tyr Ile Val Ser
100 105 110

Val Ala His Asn Gly Gly Tyr Asn Asn Val Asp Phe Gly Ala Glu Gly
115 120 125

Arg Asn Pro Asp Gln His Arg Phe Thr Tyr Lys Ile Val Lys Arg Asn
130 135 140

Asn Tyr Lys Ala Gly Thr Lys Gly His Pro Tyr Gly Gly Asp Tyr His

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145                 150                 155                 160

Met Pro Arg Leu His Lys Phe Val Thr Asp Ala Glu Pro Val Glu Met
                165                 170                 175

Thr Ser Tyr Met Asp Gly Arg Lys Tyr Ile Asp Gln Asn Asn Tyr Pro
            180                 185                 190

Asp Arg Val Arg Ile Gly Ala Gly Arg Gln Tyr Trp Arg Ser Asp Glu
        195                 200                 205

Asp Glu Pro Asn Asn Arg Glu Ser Ser Tyr His Ile Ala Ser Ala Tyr
    210                 215                 220

Ser Trp Leu Val Gly Gly Asn Thr Phe Ala Gln Asn Gly Ser Gly Gly
225                 230                 235                 240

Gly Thr Val Asn Leu Gly Ser Glu Lys Ile Lys His Ser Pro Tyr Gly
                245                 250                 255

Phe Leu Pro Thr Gly Gly Ser Phe Gly Asp Ser Gly Ser Pro Met Phe
            260                 265                 270

Ile Tyr Asp Ala Gln Lys Gln Lys Trp Leu Ile Asn Gly Val Leu Gln
        275                 280                 285

Thr Gly Asn Pro Tyr Ile Gly Lys Ser Asn Gly Phe Gln Leu Val Arg
    290                 295                 300

Lys Asp Trp Phe Tyr Asp Glu Ile Phe Ala Gly Asp Thr His Ser Val
305                 310                 315                 320

Phe Tyr Glu Pro Arg Gln Asn Gly Lys Tyr Ser Phe Asn Asp Asp Asn
                325                 330                 335

Asn Gly Thr Gly Lys Ile Asn Ala Lys His Glu His Asn Ser Leu Pro
            340                 345                 350

Asn Arg Leu Lys Thr Arg Thr Val Gln Leu Phe Asn Val Ser Leu Ser
        355                 360                 365

Glu Thr Ala Arg Glu Pro Val Tyr His Ala Ala Gly Gly Val Asn Ser
    370                 375                 380

Tyr Arg Pro Arg Leu Asn Asn Gly Glu Asn Ile Ser Phe Ile Asp Glu
385                 390                 395                 400

Gly Lys Gly Glu Leu Ile Leu Thr Ser Asn Ile Asn Gln Gly Ala Gly
                405                 410                 415

Gly Leu Tyr Phe Gln Gly Asp Phe Thr Val Ser Pro Glu Asn Asn Glu
            420                 425                 430

Thr Trp Gln Gly Ala Gly Val His Ile Ser Glu Asp Ser Thr Val Thr
        435                 440                 445

Trp Lys Val Asn Gly Val Ala Asn Asp Arg Leu Ser Lys Ile Gly Lys
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    450                 455                 460

Gly Thr Leu His Val Gln Ala Lys Gly Glu Asn Gln Gly Ser Ile Ser
465                 470                 475                 480

Val Gly Asp Gly Thr Val Ile Leu Asp Gln Gln Ala Asp Asp Lys Gly
                485                 490                 495

Lys Lys Gln Ala Phe Ser Glu Ile Gly Leu Val Ser Gly Arg Gly Thr
            500                 505                 510

Val Gln Leu Asn Ala Asp Asn Gln Phe Asn Pro Asp Lys Leu Tyr Phe
        515                 520                 525

Gly Phe Arg Gly Gly Arg Leu Asp Leu Asn Gly His Ser Leu Ser Phe
    530                 535                 540

His Arg Ile Gln Asn Thr Asp Glu Gly Ala Met Ile Val Asn His Asn
545                 550                 555                 560

Gln Asp Lys Glu Ser Thr Val Thr Ile Thr Gly Asn Lys Asp Ile Ala
                565                 570                 575

Thr Thr Gly Asn Asn Asn Ser Leu Asp Ser Lys Lys Glu Ile Ala Tyr
            580                 585                 590

Asn Gly Trp Phe Gly Glu Lys Asp Thr Thr Lys Thr Asn Gly Arg Leu
        595                 600                 605

Asn Leu Val Tyr Gln Pro Ala Ala Glu Asp Arg Thr Leu Leu Leu Ser
    610                 615                 620

Gly Gly Thr Asn Leu Asn Gly Asn Ile Thr Gln Thr Asn Gly Lys Leu
625                 630                 635                 640

Phe Phe Ser Gly Arg Pro Thr Pro His Ala Tyr Asn His Leu Asn Asp
                645                 650                 655

His Trp Ser Gln Lys Glu Gly Ile Pro Arg Gly Glu Ile Val Trp Asp
            660                 665                 670

Asn Asp Trp Ile Asn Arg Thr Phe Lys Ala Glu Asn Phe Gln Ile Lys
        675                 680                 685

Gly Gly Gln Ala Val Val Ser Arg Asn Val Ala Lys Val Lys Gly Asp
    690                 695                 700

Trp His Leu Ser Asn His Ala Gln Ala Val Phe Gly Val Ala Pro His
705                 710                 715                 720

Gln Ser His Thr Ile Cys Thr Arg Ser Asp Trp Thr Gly Leu Thr Asn
                725                 730                 735

Cys Val Glu Lys Thr Ile Thr Asp Asp Lys Val Ile Ala Ser Leu Thr
            740                 745                 750

Lys Thr Asp Ile Ser Gly Asn Val Asp Leu Ala Asp His Ala His Leu
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755 760 765

Asn Leu Thr Gly Leu Ala Thr Leu Asn Gly Asn Leu Ser Ala Asn Gly
770 775 780

Asp Thr Arg Tyr Thr Val Ser His Asn Ala Thr Gln Asn Gly Asn Leu
785 790 795 800

Ser Leu Val Gly Asn Ala Gln Ala Thr Phe Asn Gln Ala Thr Leu Asn
805 810 815

Gly Asn Thr Ser Ala Ser Gly Asn Ala Ser Phe Asn Leu Ser Asp His
820 825 830

Ala Val Gln Asn Gly Ser Leu Thr Leu Ser Gly Asn Ala Lys Ala Asn
835 840 845

Val Ser His Ser Ala Leu Asn Gly Asn Val Ser Leu Ala Asp Lys Ala
850 855 860

Val Phe His Phe Glu Ser Ser Arg Phe Thr Gly Gln Ile Ser Gly Gly
865 870 875 880

Lys Asp Thr Ala Leu His Leu Lys Asp Ser Glu Trp Thr Leu Pro Ser
885 890 895

Gly Thr Glu Leu Gly Asn Leu Asn Leu Asp Asn Ala Thr Ile Thr Leu
900 905 910

Asn Ser Ala Tyr Arg His Asp Ala Ala Gly Ala Gln Thr Gly Ser Ala
915 920 925

Thr Asp Ala Pro Arg Arg Arg Ser Arg Arg Ser Arg Arg Ser Leu Leu
930 935 940

Ser Val Thr Pro Pro Thr Ser Val Glu Ser Arg Phe Asn Thr Leu Thr
945 950 955 960

Val Asn Gly Lys Leu Asn Gly Gln Gly Thr Phe Arg Phe Met Ser Glu
965 970 975

Leu Phe Gly Tyr Arg Ser Asp Lys Leu Lys Leu Ala Glu Ser Ser Glu
980 985 990

Gly Thr Tyr Thr Leu Ala Val Asn Asn Thr Gly Asn Glu Pro Ala Ser
995 1000 1005

Leu Glu Gln Leu Thr Val Val Glu Gly Lys Asp Asn Lys Pro Leu Ser
1010 1015 1020

Glu Asn Leu Asn Phe Thr Leu Gln Asn Glu His Val Asp Ala Gly Ala
1025 1030 1035 1040

Trp Arg Tyr Gln Leu Ile Arg Lys Asp Gly Glu Phe Arg Leu His Asn
1045 1050 1055

Pro Val Lys Glu Gln Glu Leu Ser Asp Lys Leu Gly Lys Ala Glu Ala

1060 1065 1070

Lys Lys Gln Ala Glu Lys Asp Asn Ala Gln Ser Leu Asp Ala Leu Ile
1075 1080 1085

Ala Ala Gly Arg Asp Ala Val Glu Lys Thr Glu Ser Val Ala Glu Pro
1090 1095 1100

Ala Arg Gln Ala Gly Gly Glu Asn Val Gly Ile Met Gln Ala Glu Glu
1105 1110 1115 1120

Glu Lys Lys Arg Val Gln Ala Asp Lys Asp Thr Ala Leu Ala Lys Gln
1125 1130 1135

Arg Glu Ala Glu Thr Arg Pro Ala Thr Thr Ala Phe Pro Arg Ala Arg
1140 1145 1150

Arg Ala Arg Arg Asp Leu Pro Gln Leu Gln Pro Gln Pro Gln Pro Gln
1155 1160 1165

Pro Gln Arg Asp Leu Ile Ser Arg Tyr Ala Asn Ser Gly Leu Ser Glu
1170 1175 1180

Phe Ser Ala Thr Leu Asn Ser Val Phe Ala Val Gln Asp Glu Leu Asp
1185 1190 1195 1200

Arg Val Phe Ala Glu Asp Arg Arg Asn Ala Val Trp Thr Ser Gly Ile
1205 1210 1215

Arg Asp Thr Lys His Tyr Arg Ser Gln Asp Phe Arg Ala Tyr Arg Gln
1220 1225 1230

Gln Thr Asp Leu Arg Gln Ile Gly Met Gln Lys Asn Leu Gly Ser Gly
1235 1240 1245

Arg Val Gly Ile Leu Phe Ser His Asn Arg Thr Glu Asn Thr Phe Asp
1250 1255 1260

Asp Gly Ile Gly Asn Ser Ala Arg Leu Ala His Gly Ala Val Phe Gly
1265 1270 1275 1280

Gln Tyr Gly Ile Asp Arg Phe Tyr Ile Gly Ile Ser Ala Gly Ala Gly
1285 1290 1295

Phe Ser Ser Gly Ser Leu Ser Asp Gly Ile Gly Gly Lys Ile Arg Arg
1300 1305 1310

Arg Val Leu His Tyr Gly Ile Gln Ala Arg Tyr Arg Ala Gly Phe Gly
1315 1320 1325

Gly Phe Gly Ile Glu Pro His Ile Gly Ala Thr Arg Tyr Phe Val Gln
1330 1335 1340

Lys Ala Asp Tyr Arg Tyr Glu Asn Val Asn Ile Ala Thr Pro Gly Leu
1345 1350 1355 1360

Ala Phe Asn Arg Tyr Arg Ala Gly Ile Lys Ala Asp Tyr Ser Phe Lys

1365 1370 1375

Pro Ala Gln His Ile Ser Ile Thr Pro Tyr Leu Ser Leu Ser Tyr Thr
1380 1385 1390

Asp Ala Ala Ser Gly Lys Val Arg Thr Arg Val Asn Thr Ala Val Leu
1395 1400 1405

Ala Gln Asp Phe Gly Lys Thr Arg Ser Ala Glu Trp Gly Val Asn Ala
1410 1415 1420

Glu Ile Lys Gly Phe Thr Leu Ser Leu His Ala Ala Ala Ala Lys Gly
1425 1430 1435 1440

Pro Gln Leu Glu Ala Gln His Ser Ala Gly Ile Lys Leu Gly Tyr Arg
1445 1450 1455

Trp

<210> 72
<211> 21
<212> PRT
<213> Escherichia coli

<400> 72
Met Lys Lys Thr Ala Ile Ala Ile Ala Val Ala Leu Ala Gly Phe Ala
1 5 10 15

Thr Val Ala Gln Ala
20

<210> 73
<211> 1439
<212> PRT
<213> Neisseria meningitidis

<400> 73
Met Lys Lys Thr Ala Ile Ala Ile Ala Val Ala Leu Ala Gly Phe Ala
1 5 10 15

Thr Val Ala Gln Ala Ala Ser Ala Gly His Thr Tyr Phe Gly Ile Asn
20 25 30

Tyr Gln Tyr Tyr Arg Asp Phe Ala Glu Asn Lys Gly Lys Phe Ala Val
35 40 45

Gly Ala Lys Asp Ile Glu Val Tyr Asn Lys Lys Gly Glu Leu Val Gly
50 55 60

Lys Ser Met Thr Lys Ala Pro Met Ile Asp Phe Ser Val Val Ser Arg
65 70 75 80

Asn Gly Val Ala Ala Leu Val Gly Asp Gln Tyr Ile Val Ser Val Ala
85 90 95

His Asn Gly Gly Tyr Asn Asn Val Asp Phe Gly Ala Glu Gly Arg Asn

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            100                 105                 110

Pro Asp Gln His Arg Phe Thr Tyr Lys Ile Val Lys Arg Asn Asn Tyr
        115                 120                 125

Lys Ala Gly Thr Lys Gly His Pro Tyr Gly Gly Asp Tyr His Met Pro
    130                 135                 140

Arg Leu His Lys Phe Val Thr Asp Ala Glu Pro Val Glu Met Thr Ser
145                 150                 155                 160

Tyr Met Asp Gly Arg Lys Tyr Ile Asp Gln Asn Asn Tyr Pro Asp Arg
                165                 170                 175

Val Arg Ile Gly Ala Gly Arg Gln Tyr Trp Arg Ser Asp Glu Asp Glu
            180                 185                 190

Pro Asn Asn Arg Glu Ser Ser Tyr His Ile Ala Ser Ala Tyr Ser Trp
        195                 200                 205

Leu Val Gly Gly Asn Thr Phe Ala Gln Asn Gly Ser Gly Gly Gly Thr
    210                 215                 220

Val Asn Leu Gly Ser Glu Lys Ile Lys His Ser Pro Tyr Gly Phe Leu
225                 230                 235                 240

Pro Thr Gly Gly Ser Phe Gly Asp Ser Gly Ser Pro Met Phe Ile Tyr
                245                 250                 255

Asp Ala Gln Lys Gln Lys Trp Leu Ile Asn Gly Val Leu Gln Thr Gly
            260                 265                 270

Asn Pro Tyr Ile Gly Lys Ser Asn Gly Phe Gln Leu Val Arg Lys Asp
        275                 280                 285

Trp Phe Tyr Asp Glu Ile Phe Ala Gly Asp Thr His Ser Val Phe Tyr
    290                 295                 300

Glu Pro Arg Gln Asn Gly Lys Tyr Ser Phe Asn Asp Asp Asn Asn Gly
305                 310                 315                 320

Thr Gly Lys Ile Asn Ala Lys His Glu His Asn Ser Leu Pro Asn Arg
                325                 330                 335

Leu Lys Thr Arg Thr Val Gln Leu Phe Asn Val Ser Leu Ser Glu Thr
            340                 345                 350

Ala Arg Glu Pro Val Tyr His Ala Ala Gly Gly Val Asn Ser Tyr Arg
        355                 360                 365

Pro Arg Leu Asn Asn Gly Glu Asn Ile Ser Phe Ile Asp Glu Gly Lys
    370                 375                 380

Gly Glu Leu Ile Leu Thr Ser Asn Ile Asn Gln Gly Ala Gly Gly Leu
385                 390                 395                 400

Tyr Phe Gln Gly Asp Phe Thr Val Ser Pro Glu Asn Asn Glu Thr Trp
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405 410 415

Gln Gly Ala Gly Val His Ile Ser Glu Asp Ser Thr Val Thr Trp Lys
420 425 430

Val Asn Gly Val Ala Asn Asp Arg Leu Ser Lys Ile Gly Lys Gly Thr
435 440 445

Leu His Val Gln Ala Lys Gly Glu Asn Gln Gly Ser Ile Ser Val Gly
450 455 460

Asp Gly Thr Val Ile Leu Asp Gln Gln Ala Asp Asp Lys Gly Lys Lys
465 470 475 480

Gln Ala Phe Ser Glu Ile Gly Leu Val Ser Gly Arg Gly Thr Val Gln
485 490 495

Leu Asn Ala Asp Asn Gln Phe Asn Pro Asp Lys Leu Tyr Phe Gly Phe
500 505 510

Arg Gly Gly Arg Leu Asp Leu Asn Gly His Ser Leu Ser Phe His Arg
515 520 525

Ile Gln Asn Thr Asp Glu Gly Ala Met Ile Val Asn His Asn Gln Asp
530 535 540

Lys Glu Ser Thr Val Thr Ile Thr Gly Asn Lys Asp Ile Ala Thr Thr
545 550 555 560

Gly Asn Asn Asn Ser Leu Asp Ser Lys Lys Glu Ile Ala Tyr Asn Gly
565 570 575

Trp Phe Gly Glu Lys Asp Thr Thr Lys Thr Asn Gly Arg Leu Asn Leu
580 585 590

Val Tyr Gln Pro Ala Ala Glu Asp Arg Thr Leu Leu Leu Ser Gly Gly
595 600 605

Thr Asn Leu Asn Gly Asn Ile Thr Gln Thr Asn Gly Lys Leu Phe Phe
610 615 620

Ser Gly Arg Pro Thr Pro His Ala Tyr Asn His Leu Asn Asp His Trp
625 630 635 640

Ser Gln Lys Glu Gly Ile Pro Arg Gly Glu Ile Val Trp Asp Asn Asp
645 650 655

Trp Ile Asn Arg Thr Phe Lys Ala Glu Asn Phe Gln Ile Lys Gly Gly
660 665 670

Gln Ala Val Val Ser Arg Asn Val Ala Lys Val Lys Gly Asp Trp His
675 680 685

Leu Ser Asn His Ala Gln Ala Val Phe Gly Val Ala Pro His Gln Ser
690 695 700

His Thr Ile Cys Thr Arg Ser Asp Trp Thr Gly Leu Thr Asn Cys Val

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705                 710                 715                 720

Glu Lys Thr Ile Thr Asp Asp Lys Val Ile Ala Ser Leu Thr Lys Thr
                725                 730                 735

Asp Ile Ser Gly Asn Val Asp Leu Ala Asp His Ala His Leu Asn Leu
            740                 745                 750

Thr Gly Leu Ala Thr Leu Asn Gly Asn Leu Ser Ala Asn Gly Asp Thr
        755                 760                 765

Arg Tyr Thr Val Ser His Asn Ala Thr Gln Asn Gly Asn Leu Ser Leu
    770                 775                 780

Val Gly Asn Ala Gln Ala Thr Phe Asn Gln Ala Thr Leu Asn Gly Asn
785                 790                 795                 800

Thr Ser Ala Ser Gly Asn Ala Ser Phe Asn Leu Ser Asp His Ala Val
                805                 810                 815

Gln Asn Gly Ser Leu Thr Leu Ser Gly Asn Ala Lys Ala Asn Val Ser
            820                 825                 830

His Ser Ala Leu Asn Gly Asn Val Ser Leu Ala Asp Lys Ala Val Phe
        835                 840                 845

His Phe Glu Ser Ser Arg Phe Thr Gly Gln Ile Ser Gly Gly Lys Asp
    850                 855                 860

Thr Ala Leu His Leu Lys Asp Ser Glu Trp Thr Leu Pro Ser Gly Thr
865                 870                 875                 880

Glu Leu Gly Asn Leu Asn Leu Asp Asn Ala Thr Ile Thr Leu Asn Ser
                885                 890                 895

Ala Tyr Arg His Asp Ala Ala Gly Ala Gln Thr Gly Ser Ala Thr Asp
            900                 905                 910

Ala Pro Arg Arg Arg Ser Arg Arg Ser Arg Arg Ser Leu Leu Ser Val
        915                 920                 925

Thr Pro Pro Thr Ser Val Glu Ser Arg Phe Asn Thr Leu Thr Val Asn
    930                 935                 940

Gly Lys Leu Asn Gly Gln Gly Thr Phe Arg Phe Met Ser Glu Leu Phe
945                 950                 955                 960

Gly Tyr Arg Ser Asp Lys Leu Lys Leu Ala Glu Ser Ser Glu Gly Thr
                965                 970                 975

Tyr Thr Leu Ala Val Asn Asn Thr Gly Asn Glu Pro Ala Ser Leu Glu
            980                 985                 990

Gln Leu Thr Val Val Glu Gly Lys Asp Asn Lys Pro Leu Ser Glu Asn
        995                 1000                1005

Leu Asn Phe Thr Leu Gln Asn Glu His Val Asp Ala Gly Ala Trp Arg
```

1010 1015 1020

Tyr Gln Leu Ile Arg Lys Asp Gly Glu Phe Arg Leu His Asn Pro Val
1025 1030 1035 1040

Lys Glu Gln Glu Leu Ser Asp Lys Leu Gly Lys Ala Glu Ala Lys Lys
1045 1050 1055

Gln Ala Glu Lys Asp Asn Ala Gln Ser Leu Asp Ala Leu Ile Ala Ala
1060 1065 1070

Gly Arg Asp Ala Val Glu Lys Thr Glu Ser Val Ala Glu Pro Ala Arg
1075 1080 1085

Gln Ala Gly Gly Glu Asn Val Gly Ile Met Gln Ala Glu Glu Glu Lys
1090 1095 1100

Lys Arg Val Gln Ala Asp Lys Asp Thr Ala Leu Ala Lys Gln Arg Glu
1105 1110 1115 1120

Ala Glu Thr Arg Pro Ala Thr Thr Ala Phe Pro Arg Ala Arg Arg Ala
1125 1130 1135

Arg Arg Asp Leu Pro Gln Leu Gln Pro Gln Pro Gln Pro Gln Pro Gln
1140 1145 1150

Arg Asp Leu Ile Ser Arg Tyr Ala Asn Ser Gly Leu Ser Glu Phe Ser
1155 1160 1165

Ala Thr Leu Asn Ser Val Phe Ala Val Gln Asp Glu Leu Asp Arg Val
1170 1175 1180

Phe Ala Glu Asp Arg Arg Asn Ala Val Trp Thr Ser Gly Ile Arg Asp
1185 1190 1195 1200

Thr Lys His Tyr Arg Ser Gln Asp Phe Arg Ala Tyr Arg Gln Gln Thr
1205 1210 1215

Asp Leu Arg Gln Ile Gly Met Gln Lys Asn Leu Gly Ser Gly Arg Val
1220 1225 1230

Gly Ile Leu Phe Ser His Asn Arg Thr Glu Asn Thr Phe Asp Asp Gly
1235 1240 1245

Ile Gly Asn Ser Ala Arg Leu Ala His Gly Ala Val Phe Gly Gln Tyr
1250 1255 1260

Gly Ile Asp Arg Phe Tyr Ile Gly Ile Ser Ala Gly Ala Gly Phe Ser
1265 1270 1275 1280

Ser Gly Ser Leu Ser Asp Gly Ile Gly Gly Lys Ile Arg Arg Arg Val
1285 1290 1295

Leu His Tyr Gly Ile Gln Ala Arg Tyr Arg Ala Gly Phe Gly Gly Phe
1300 1305 1310

Gly Ile Glu Pro His Ile Gly Ala Thr Arg Tyr Phe Val Gln Lys Ala

1315 1320 1325

Asp Tyr Arg Tyr Glu Asn Val Asn Ile Ala Thr Pro Gly Leu Ala Phe
1330 1335 1340

Asn Arg Tyr Arg Ala Gly Ile Lys Ala Asp Tyr Ser Phe Lys Pro Ala
1345 1350 1355 1360

Gln His Ile Ser Ile Thr Pro Tyr Leu Ser Leu Ser Tyr Thr Asp Ala
1365 1370 1375

Ala Ser Gly Lys Val Arg Thr Arg Val Asn Thr Ala Val Leu Ala Gln
1380 1385 1390

Asp Phe Gly Lys Thr Arg Ser Ala Glu Trp Gly Val Asn Ala Glu Ile
1395 1400 1405

Lys Gly Phe Thr Leu Ser Leu His Ala Ala Ala Ala Lys Gly Pro Gln
1410 1415 1420

Leu Glu Ala Gln His Ser Ala Gly Ile Lys Leu Gly Tyr Arg Trp
1425 1430 1435

<210> 74
<211> 164
<212> PRT
<213> Neisseria meningitidis

<400> 74
Met Lys Lys Asn Ile Leu Glu Phe Trp Val Gly Leu Phe Val Leu Ile
1 5 10 15

Gly Ala Ala Ala Val Ala Phe Leu Ala Phe Arg Val Ala Gly Gly Ala
20 25 30

Ala Phe Gly Gly Ser Asp Lys Thr Tyr Ala Val Tyr Ala Asp Phe Gly
35 40 45

Asp Ile Gly Gly Leu Lys Val Asn Ala Pro Val Lys Ser Ala Gly Val
50 55 60

Leu Val Gly Arg Val Gly Ala Ile Gly Leu Asp Pro Lys Ser Tyr Gln
65 70 75 80

Ala Arg Val Arg Leu Asp Leu Asp Gly Lys Tyr Gln Phe Ser Ser Asp
85 90 95

Val Ser Ala Gln Ile Leu Thr Ser Gly Leu Leu Gly Glu Gln Tyr Ile
100 105 110

Gly Leu Gln Gln Gly Gly Asp Thr Glu Asn Leu Ala Ala Gly Asp Thr
115 120 125

Ile Ser Val Thr Ser Ser Ala Met Val Leu Glu Asn Leu Ile Gly Lys
130 135 140

Phe Met Thr Ser Phe Ala Glu Lys Asn Ala Asp Gly Gly Asn Ala Glu

145 150 155 160

Lys Ala Ala Glu

<210> 75
<211> 21
<212> PRT
<213> Erwinia carotovora

<400> 75
Met Lys Tyr Leu Leu Pro Thr Ala Ala Ala Gly Leu Leu Leu Ala Ala
1 5 10 15

Gln Pro Ala Met Ala
20

<210> 76
<211> 608
<212> PRT
<213> Neisseria meningitidis ORF46

<400> 76
Leu Gly Ile Ser Arg Lys Ile Ser Leu Ile Leu Ser Ile Leu Ala Val
1 5 10 15

Cys Leu Pro Met His Ala His Ala Ser Asp Leu Ala Asn Asp Ser Phe
20 25 30

Ile Arg Gln Val Leu Asp Arg Gln His Phe Glu Pro Asp Gly Lys Tyr
35 40 45

His Leu Phe Gly Ser Arg Gly Glu Leu Ala Glu Arg Ser Gly His Ile
50 55 60

Gly Leu Gly Lys Ile Gln Ser His Gln Leu Gly Asn Leu Met Ile Gln
65 70 75 80

Gln Ala Ala Ile Lys Gly Asn Ile Gly Tyr Ile Val Arg Phe Ser Asp
85 90 95

His Gly His Glu Val His Ser Pro Phe Asp Asn His Ala Ser His Ser
100 105 110

Asp Ser Asp Glu Ala Gly Ser Pro Val Asp Gly Phe Ser Leu Tyr Arg
115 120 125

Ile His Trp Asp Gly Tyr Glu His His Pro Ala Asp Gly Tyr Asp Gly
130 135 140

Pro Gln Gly Gly Gly Tyr Pro Ala Pro Lys Gly Ala Arg Asp Ile Tyr
145 150 155 160

Ser Tyr Asp Ile Lys Gly Val Ala Gln Asn Ile Arg Leu Asn Leu Thr
165 170 175

Asp Asn Arg Ser Thr Gly Gln Arg Leu Ala Asp Arg Phe His Asn Ala

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            180                 185                 190

Gly Ser Met Leu Thr Gln Gly Val Gly Asp Gly Phe Lys Arg Ala Thr
        195                 200                 205

Arg Tyr Ser Pro Glu Leu Asp Arg Ser Gly Asn Ala Ala Glu Ala Phe
    210                 215                 220

Asn Gly Thr Ala Asp Ile Val Lys Asn Ile Ile Gly Ala Ala Gly Glu
225                 230                 235                 240

Ile Val Gly Ala Gly Asp Ala Val Gln Gly Ile Ser Glu Gly Ser Asn
                245                 250                 255

Ile Ala Val Met His Gly Leu Gly Leu Leu Ser Thr Glu Asn Lys Met
            260                 265                 270

Ala Arg Ile Asn Asp Leu Ala Asp Met Ala Gln Leu Lys Asp Tyr Ala
        275                 280                 285

Ala Ala Ala Ile Arg Asp Trp Ala Val Gln Asn Pro Asn Ala Ala Gln
    290                 295                 300

Gly Ile Glu Ala Val Ser Asn Ile Phe Met Ala Ala Ile Pro Ile Lys
305                 310                 315                 320

Gly Ile Gly Ala Val Arg Gly Lys Tyr Gly Leu Gly Gly Ile Thr Ala
                325                 330                 335

His Pro Ile Lys Arg Ser Gln Met Gly Ala Ile Ala Leu Pro Lys Gly
            340                 345                 350

Lys Ser Ala Val Ser Asp Asn Phe Ala Asp Ala Ala Tyr Ala Lys Tyr
        355                 360                 365

Pro Ser Pro Tyr His Ser Arg Asn Ile Arg Ser Asn Leu Glu Gln Arg
    370                 375                 380

Tyr Gly Lys Glu Asn Ile Thr Ser Ser Thr Val Pro Pro Ser Asn Gly
385                 390                 395                 400

Lys Asn Val Lys Leu Ala Asp Gln Arg His Pro Lys Thr Gly Val Pro
                405                 410                 415

Phe Asp Gly Lys Gly Phe Pro Asn Phe Glu Lys His Val Lys Tyr Asp
            420                 425                 430

Thr Lys Leu Asp Ile Gln Glu Leu Ser Gly Gly Gly Ile Pro Lys Ala
        435                 440                 445

Lys Pro Val Ser Asp Ala Lys Pro Arg Trp Glu Val Asp Arg Lys Leu
    450                 455                 460

Asn Lys Leu Thr Thr Arg Glu Gln Val Glu Lys Asn Val Gln Glu Ile
465                 470                 475                 480

Arg Asn Gly Asn Lys Asn Ser Asn Phe Ser Gln His Ala Gln Leu Glu
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                485                 490                 495

Arg Glu Ile Asn Lys Leu Lys Ser Ala Asp Glu Ile Asn Phe Ala Asp
            500                 505                 510

Gly Met Gly Lys Phe Thr Asp Ser Met Asn Asp Lys Ala Phe Ser Arg
        515                 520                 525

Leu Val Lys Ser Val Lys Glu Asn Gly Phe Thr Asn Pro Val Val Glu
    530                 535                 540

Tyr Val Glu Ile Asn Gly Lys Ala Tyr Ile Val Arg Gly Asn Asn Arg
545                 550                 555                 560

Val Phe Ala Ala Glu Tyr Leu Gly Arg Ile His Glu Leu Lys Phe Lys
                565                 570                 575

Lys Val Asp Phe Pro Val Pro Asn Thr Ser Trp Lys Asn Pro Thr Asp
            580                 585                 590

Val Leu Asn Glu Ser Gly Asn Val Lys Arg Pro Arg Tyr Arg Ser Lys
        595                 600                 605


<210>   77
<211>   584
<212>   PRT
<213>   Artificial Sequence

<220>
<223>   ORF46-2

<400>   77
Ser Asp Leu Ala Asn Asp Ser Phe Ile Arg Gln Val Leu Asp Arg Gln
1               5                   10                  15

His Phe Glu Pro Asp Gly Lys Tyr His Leu Phe Gly Ser Arg Gly Glu
            20                  25                  30

Leu Ala Glu Arg Ser Gly His Ile Gly Leu Gly Lys Ile Gln Ser His
        35                  40                  45

Gln Leu Gly Asn Leu Met Ile Gln Gln Ala Ala Ile Lys Gly Asn Ile
    50                  55                  60

Gly Tyr Ile Val Arg Phe Ser Asp His Gly His Glu Val His Ser Pro
65                  70                  75                  80

Phe Asp Asn His Ala Ser His Ser Asp Ser Asp Glu Ala Gly Ser Pro
                85                  90                  95

Val Asp Gly Phe Ser Leu Tyr Arg Ile His Trp Asp Gly Tyr Glu His
            100                 105                 110

His Pro Ala Asp Gly Tyr Asp Gly Pro Gln Gly Gly Gly Tyr Pro Ala
        115                 120                 125
```

Pro Lys Gly Ala Arg Asp Ile Tyr Ser Tyr Asp Ile Lys Gly Val Ala
130 135 140

Gln Asn Ile Arg Leu Asn Leu Thr Asp Asn Arg Ser Thr Gly Gln Arg
145 150 155 160

Leu Ala Asp Arg Phe His Asn Ala Gly Ser Met Leu Thr Gln Gly Val
165 170 175

Gly Asp Gly Phe Lys Arg Ala Thr Arg Tyr Ser Pro Glu Leu Asp Arg
180 185 190

Ser Gly Asn Ala Ala Glu Ala Phe Asn Gly Thr Ala Asp Ile Val Lys
195 200 205

Asn Ile Ile Gly Ala Ala Gly Glu Ile Val Gly Ala Gly Asp Ala Val
210 215 220

Gln Gly Ile Ser Glu Gly Ser Asn Ile Ala Val Met His Gly Leu Gly
225 230 235 240

Leu Leu Ser Thr Glu Asn Lys Met Ala Arg Ile Asn Asp Leu Ala Asp
245 250 255

Met Ala Gln Leu Lys Asp Tyr Ala Ala Ala Ala Ile Arg Asp Trp Ala
260 265 270

Val Gln Asn Pro Asn Ala Ala Gln Gly Ile Glu Ala Val Ser Asn Ile
275 280 285

Phe Met Ala Ala Ile Pro Ile Lys Gly Ile Gly Ala Val Arg Gly Lys
290 295 300

Tyr Gly Leu Gly Gly Ile Thr Ala His Pro Ile Lys Arg Ser Gln Met
305 310 315 320

Gly Ala Ile Ala Leu Pro Lys Gly Lys Ser Ala Val Ser Asp Asn Phe
325 330 335

Ala Asp Ala Ala Tyr Ala Lys Tyr Pro Ser Pro Tyr His Ser Arg Asn
340 345 350

Ile Arg Ser Asn Leu Glu Gln Arg Tyr Gly Lys Glu Asn Ile Thr Ser
355 360 365

Ser Thr Val Pro Pro Ser Asn Gly Lys Asn Val Lys Leu Ala Asp Gln
370 375 380

Arg His Pro Lys Thr Gly Val Pro Phe Asp Gly Lys Gly Phe Pro Asn
385 390 395 400

Phe Glu Lys His Val Lys Tyr Asp Thr Lys Leu Asp Ile Gln Glu Leu
405 410 415

Ser Gly Gly Gly Ile Pro Lys Ala Lys Pro Val Ser Asp Ala Lys Pro
420 425 430

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Arg Trp Glu Val Asp Arg Lys Leu Asn Lys Leu Thr Thr Arg Glu Gln
        435                 440                 445

Val Glu Lys Asn Val Gln Glu Ile Arg Asn Gly Asn Lys Asn Ser Asn
    450                 455                 460

Phe Ser Gln His Ala Gln Leu Glu Arg Glu Ile Asn Lys Leu Lys Ser
465                 470                 475                 480

Ala Asp Glu Ile Asn Phe Ala Asp Gly Met Gly Lys Phe Thr Asp Ser
                485                 490                 495

Met Asn Asp Lys Ala Phe Ser Arg Leu Val Lys Ser Val Lys Glu Asn
            500                 505                 510

Gly Phe Thr Asn Pro Val Val Glu Tyr Val Glu Ile Asn Gly Lys Ala
        515                 520                 525

Tyr Ile Val Arg Gly Asn Asn Arg Val Phe Ala Ala Glu Tyr Leu Gly
    530                 535                 540

Arg Ile His Glu Leu Lys Phe Lys Lys Val Asp Phe Pro Val Pro Asn
545                 550                 555                 560

Thr Ser Trp Lys Asn Pro Thr Asp Val Leu Asn Glu Ser Gly Asn Val
                565                 570                 575

Lys Arg Pro Arg Tyr Arg Ser Lys
            580

<210>   78
<211>   364
<212>   PRT
<213>   Neisseria meningitidis

<400>   78
Met Ser Met Lys His Phe Pro Ala Lys Val Leu Thr Thr Ala Ile Leu
1               5                   10                  15

Ala Thr Phe Cys Ser Gly Ala Leu Ala Ala Thr Ser Asp Asp Asp Val
            20                  25                  30

Lys Lys Ala Ala Thr Val Ala Ile Val Ala Ala Tyr Asn Asn Gly Gln
        35                  40                  45

Glu Ile Asn Gly Phe Lys Ala Gly Glu Thr Ile Tyr Asp Ile Gly Glu
    50                  55                  60

Asp Gly Thr Ile Thr Gln Lys Asp Ala Thr Ala Ala Asp Val Glu Ala
65                  70                  75                  80

Asp Asp Phe Lys Gly Leu Gly Leu Lys Lys Val Val Thr Asn Leu Thr
                85                  90                  95

Lys Thr Val Asn Glu Asn Lys Gln Asn Val Asp Ala Lys Val Lys Ala
            100                 105                 110
```

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Ala Glu Ser Glu Ile Glu Lys Leu Thr Thr Lys Leu Ala Asp Thr Asp
        115                 120                 125

Ala Ala Leu Ala Asp Thr Asp Ala Ala Leu Asp Glu Thr Thr Asn Ala
    130                 135                 140

Leu Asn Lys Leu Gly Glu Asn Ile Thr Thr Phe Ala Glu Glu Thr Lys
145                 150                 155                 160

Thr Asn Ile Val Lys Ile Asp Glu Lys Leu Glu Ala Val Ala Asp Thr
                165                 170                 175

Val Asp Lys His Ala Glu Ala Phe Asn Asp Ile Ala Asp Ser Leu Asp
            180                 185                 190

Glu Thr Asn Thr Lys Ala Asp Glu Ala Val Lys Thr Ala Asn Glu Ala
        195                 200                 205

Lys Gln Thr Ala Glu Glu Thr Lys Gln Asn Val Asp Ala Lys Val Lys
    210                 215                 220

Ala Ala Glu Thr Ala Ala Gly Lys Ala Glu Ala Ala Ala Gly Thr Ala
225                 230                 235                 240

Asn Thr Ala Ala Asp Lys Ala Glu Ala Val Ala Ala Lys Val Thr Asp
                245                 250                 255

Ile Lys Ala Asp Ile Ala Thr Asn Lys Ala Asp Ile Ala Lys Asn Ser
            260                 265                 270

Ala Arg Ile Asp Ser Leu Asp Lys Asn Val Ala Asn Leu Arg Lys Glu
        275                 280                 285

Thr Arg Gln Gly Leu Ala Glu Gln Ala Ala Leu Ser Gly Leu Phe Gln
    290                 295                 300

Pro Tyr Asn Val Gly Arg Phe Asn Val Thr Ala Ala Val Gly Gly Tyr
305                 310                 315                 320

Lys Ser Glu Ser Ala Val Ala Ile Gly Thr Gly Phe Arg Phe Thr Glu
                325                 330                 335

Asn Phe Ala Ala Lys Ala Gly Val Ala Val Gly Thr Ser Ser Gly Ser
            340                 345                 350

Ser Ala Ala Tyr His Val Gly Val Asn Tyr Glu Trp
        355                 360

<210>   79
<211>   427
<212>   PRT
<213>   Neisseria meningitidis

<400>   79
Met Phe Glu Arg Ser Val Ile Ala Met Ala Cys Ile Phe Ala Leu Ser
1               5                   10                  15
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Ala Cys Gly Gly Gly Gly Gly Gly Ser Pro Asp Val Lys Ser Ala Asp
20 25 30

Thr Leu Ser Lys Pro Ala Ala Pro Val Val Ala Glu Lys Glu Thr Glu
35 40 45

Val Lys Glu Asp Ala Pro Gln Ala Gly Ser Gln Gly Gln Gly Ala Pro
50 55 60

Ser Thr Gln Gly Ser Gln Asp Met Ala Ala Val Ser Ala Glu Asn Thr
65 70 75 80

Gly Asn Gly Gly Ala Ala Thr Thr Asp Lys Pro Lys Asn Glu Asp Glu
85 90 95

Gly Pro Gln Asn Asp Met Pro Gln Asn Ser Ala Glu Ser Ala Asn Gln
100 105 110

Thr Gly Asn Asn Gln Pro Ala Asp Ser Ser Asp Ser Ala Pro Ala Ser
115 120 125

Asn Pro Ala Pro Ala Asn Gly Gly Ser Asn Phe Gly Arg Val Asp Leu
130 135 140

Ala Asn Gly Val Leu Ile Asp Gly Pro Ser Gln Asn Ile Thr Leu Thr
145 150 155 160

His Cys Lys Gly Asp Ser Cys Asn Gly Asp Asn Leu Leu Asp Glu Glu
165 170 175

Ala Pro Ser Lys Ser Glu Phe Glu Asn Leu Asn Glu Ser Glu Arg Ile
180 185 190

Glu Lys Tyr Lys Lys Asp Gly Lys Ser Asp Lys Phe Thr Asn Leu Val
195 200 205

Ala Thr Ala Val Gln Ala Asn Gly Thr Asn Lys Tyr Val Ile Ile Tyr
210 215 220

Lys Asp Lys Ser Ala Ser Ser Ser Ser Ala Arg Phe Arg Arg Ser Ala
225 230 235 240

Arg Ser Arg Arg Ser Leu Pro Ala Glu Met Pro Leu Ile Pro Val Asn
245 250 255

Gln Ala Asp Thr Leu Ile Val Asp Gly Glu Ala Val Ser Leu Thr Gly
260 265 270

His Ser Gly Asn Ile Phe Ala Pro Glu Gly Asn Tyr Arg Tyr Leu Thr
275 280 285

Tyr Gly Ala Glu Lys Leu Pro Gly Gly Ser Tyr Ala Leu Arg Val Gln
290 295 300

Gly Glu Pro Ala Lys Gly Glu Met Leu Ala Gly Thr Ala Val Tyr Asn
305 310 315 320

Gly Glu Val Leu His Phe His Thr Glu Asn Gly Arg Pro Tyr Pro Thr
325 330 335

Arg Gly Arg Phe Ala Ala Lys Val Asp Phe Gly Ser Lys Ser Val Asp
340 345 350

Gly Ile Ile Asp Ser Gly Asp Asp Leu His Met Gly Thr Gln Lys Phe
355 360 365

Lys Ala Ala Ile Asp Gly Asn Gly Phe Lys Gly Thr Trp Thr Glu Asn
370 375 380

Gly Gly Gly Asp Val Ser Gly Arg Phe Tyr Gly Pro Ala Gly Glu Glu
385 390 395 400

Val Ala Gly Lys Tyr Ser Tyr Arg Pro Thr Asp Ala Glu Lys Gly Gly
405 410 415

Phe Gly Val Phe Ala Gly Lys Lys Glu Gln Asp
420 425

<210> 80
<211> 410
<212> PRT
<213> Artificial Sequence

<220>
<223> 287untagged

<400> 80
Cys Gly Gly Gly Gly Gly Gly Ser Pro Asp Val Lys Ser Ala Asp Thr
1 5 10 15

Leu Ser Lys Pro Ala Ala Pro Val Val Ala Glu Lys Glu Thr Glu Val
20 25 30

Lys Glu Asp Ala Pro Gln Ala Gly Ser Gln Gly Gln Gly Ala Pro Ser
35 40 45

Thr Gln Gly Ser Gln Asp Met Ala Ala Val Ser Ala Glu Asn Thr Gly
50 55 60

Asn Gly Gly Ala Ala Thr Thr Asp Lys Pro Lys Asn Glu Asp Glu Gly
65 70 75 80

Pro Gln Asn Asp Met Pro Gln Asn Ser Ala Glu Ser Ala Asn Gln Thr
85 90 95

Gly Asn Asn Gln Pro Ala Asp Ser Ser Asp Ser Ala Pro Ala Ser Asn
100 105 110

Pro Ala Pro Ala Asn Gly Gly Ser Asn Phe Gly Arg Val Asp Leu Ala
115 120 125

Asn Gly Val Leu Ile Asp Gly Pro Ser Gln Asn Ile Thr Leu Thr His
130 135 140

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Cys Lys Gly Asp Ser Cys Asn Gly Asp Asn Leu Leu Asp Glu Glu Ala
145                 150                 155                 160

Pro Ser Lys Ser Glu Phe Glu Asn Leu Asn Glu Ser Glu Arg Ile Glu
                165                 170                 175

Lys Tyr Lys Lys Asp Gly Lys Ser Asp Lys Phe Thr Asn Leu Val Ala
            180                 185                 190

Thr Ala Val Gln Ala Asn Gly Thr Asn Lys Tyr Val Ile Ile Tyr Lys
        195                 200                 205

Asp Lys Ser Ala Ser Ser Ser Ser Ala Arg Phe Arg Arg Ser Ala Arg
    210                 215                 220

Ser Arg Arg Ser Leu Pro Ala Glu Met Pro Leu Ile Pro Val Asn Gln
225                 230                 235                 240

Ala Asp Thr Leu Ile Val Asp Gly Glu Ala Val Ser Leu Thr Gly His
                245                 250                 255

Ser Gly Asn Ile Phe Ala Pro Glu Gly Asn Tyr Arg Tyr Leu Thr Tyr
            260                 265                 270

Gly Ala Glu Lys Leu Pro Gly Gly Ser Tyr Ala Leu Arg Val Gln Gly
        275                 280                 285

Glu Pro Ala Lys Gly Glu Met Leu Ala Gly Thr Ala Val Tyr Asn Gly
    290                 295                 300

Glu Val Leu His Phe His Thr Glu Asn Gly Arg Pro Tyr Pro Thr Arg
305                 310                 315                 320

Gly Arg Phe Ala Ala Lys Val Asp Phe Gly Ser Lys Ser Val Asp Gly
                325                 330                 335

Ile Ile Asp Ser Gly Asp Asp Leu His Met Gly Thr Gln Lys Phe Lys
            340                 345                 350

Ala Ala Ile Asp Gly Asn Gly Phe Lys Gly Thr Trp Thr Glu Asn Gly
        355                 360                 365

Gly Gly Asp Val Ser Gly Arg Phe Tyr Gly Pro Ala Gly Glu Glu Val
    370                 375                 380

Ala Gly Lys Tyr Ser Tyr Arg Pro Thr Asp Ala Glu Lys Gly Gly Phe
385                 390                 395                 400

Gly Val Phe Ala Gly Lys Lys Glu Gln Asp
                405                 410
```

<210> 81
<211> 9
<212> PRT
<213> Artificial Sequence

<220>

<223> 920L N-terminal

<400> 81
His Arg Val Trp Val Glu Thr Ala His
1 5

<210> 82
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> 953L N-terminal

<400> 82
Ala Thr Tyr Lys Val Asp Glu Tyr His Ala Asn Ala Arg Phe Ala Phe
1 5 10 15

<210> 83
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 519.1L N-terminal

<400> 83
Met Glu Phe Phe Ile Ile Leu Leu Ala
1 5

<210> 84
<211> 488
<212> PRT
<213> Artificial Sequence

<220>
<223> deltaG287

<400> 84
Met Phe Lys Arg Ser Val Ile Ala Met Ala Cys Ile Phe Ala Leu Ser
1 5 10 15

Ala Cys Gly Gly Gly Gly Gly Gly Ser Pro Asp Val Lys Ser Ala Asp
20 25 30

Thr Leu Ser Lys Pro Ala Ala Pro Val Val Ser Glu Lys Glu Thr Glu
35 40 45

Ala Lys Glu Asp Ala Pro Gln Ala Gly Ser Gln Gly Gln Gly Ala Pro
50 55 60

Ser Ala Gln Gly Ser Gln Asp Met Ala Ala Val Ser Glu Glu Asn Thr
65 70 75 80

Gly Asn Gly Gly Ala Val Thr Ala Asp Asn Pro Lys Asn Glu Asp Glu
85 90 95

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Val Ala Gln Asn Asp Met Pro Gln Asn Ala Ala Gly Thr Asp Ser Ser
            100                 105                 110

Thr Pro Asn His Thr Pro Asp Pro Asn Met Leu Ala Gly Asn Met Glu
        115                 120                 125

Asn Gln Ala Thr Asp Ala Gly Glu Ser Ser Gln Pro Ala Asn Gln Pro
    130                 135                 140

Asp Met Ala Asn Ala Ala Asp Gly Met Gln Gly Asp Asp Pro Ser Ala
145                 150                 155                 160

Gly Gly Gln Asn Ala Gly Asn Thr Ala Ala Gln Gly Ala Asn Gln Ala
                165                 170                 175

Gly Asn Asn Gln Ala Ala Gly Ser Ser Asp Pro Ile Pro Ala Ser Asn
            180                 185                 190

Pro Ala Pro Ala Asn Gly Gly Ser Asn Phe Gly Arg Val Asp Leu Ala
        195                 200                 205

Asn Gly Val Leu Ile Asp Gly Pro Ser Gln Asn Ile Thr Leu Thr His
    210                 215                 220

Cys Lys Gly Asp Ser Cys Ser Gly Asn Asn Phe Leu Asp Glu Glu Val
225                 230                 235                 240

Gln Leu Lys Ser Glu Phe Glu Lys Leu Ser Asp Ala Asp Lys Ile Ser
                245                 250                 255

Asn Tyr Lys Lys Asp Gly Lys Asn Asp Lys Phe Val Gly Leu Val Ala
            260                 265                 270

Asp Ser Val Gln Met Lys Gly Ile Asn Gln Tyr Ile Ile Phe Tyr Lys
        275                 280                 285

Pro Lys Pro Thr Ser Phe Ala Arg Phe Arg Arg Ser Ala Arg Ser Arg
    290                 295                 300

Arg Ser Leu Pro Ala Glu Met Pro Leu Ile Pro Val Asn Gln Ala Asp
305                 310                 315                 320

Thr Leu Ile Val Asp Gly Glu Ala Val Ser Leu Thr Gly His Ser Gly
                325                 330                 335

Asn Ile Phe Ala Pro Glu Gly Asn Tyr Arg Tyr Leu Thr Tyr Gly Ala
            340                 345                 350

Glu Lys Leu Pro Gly Gly Ser Tyr Ala Leu Arg Val Gln Gly Glu Pro
        355                 360                 365

Ala Lys Gly Glu Met Leu Ala Gly Ala Ala Val Tyr Asn Gly Glu Val
    370                 375                 380

Leu His Phe His Thr Glu Asn Gly Arg Pro Tyr Pro Thr Arg Gly Arg
385                 390                 395                 400
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Phe Ala Ala Lys Val Asp Phe Gly Ser Lys Ser Val Asp Gly Ile Ile
                405                 410                 415

Asp Ser Gly Asp Asp Leu His Met Gly Thr Gln Lys Phe Lys Ala Ala
                420                 425                 430

Ile Asp Gly Asn Gly Phe Lys Gly Thr Trp Thr Glu Asn Gly Ser Gly
            435                 440                 445

Asp Val Ser Gly Lys Phe Tyr Gly Pro Ala Gly Glu Glu Val Ala Gly
        450                 455                 460

Lys Tyr Ser Tyr Arg Pro Thr Asp Ala Glu Lys Gly Gly Phe Gly Val
465                 470                 475                 480

Phe Ala Gly Lys Lys Glu Gln Asp
                485

<210>  85
<211>  712
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  TBP2

<400>  85
Met Asn Asn Pro Leu Val Asn Gln Ala Ala Met Val Leu Pro Val Phe
1               5                   10                  15

Leu Leu Ser Ala Cys Leu Gly Gly Gly Gly Ser Phe Asp Leu Asp Ser
            20                  25                  30

Val Asp Thr Glu Ala Pro Arg Pro Ala Pro Lys Tyr Gln Asp Val Phe
        35                  40                  45

Ser Glu Lys Pro Gln Ala Gln Lys Asp Gln Gly Gly Tyr Gly Phe Ala
    50                  55                  60

Met Arg Leu Lys Arg Arg Asn Trp Tyr Pro Gln Ala Lys Glu Asp Glu
65                  70                  75                  80

Val Lys Leu Asp Glu Ser Asp Trp Glu Ala Thr Gly Leu Pro Asp Glu
                85                  90                  95

Pro Lys Glu Leu Pro Lys Arg Gln Lys Ser Val Ile Glu Lys Val Glu
            100                 105                 110

Thr Asp Ser Asp Asn Asn Ile Tyr Ser Ser Pro Tyr Leu Lys Pro Ser
        115                 120                 125

Asn His Gln Asn Gly Asn Thr Gly Asn Gly Ile Asn Gln Pro Lys Asn
    130                 135                 140

Gln Ala Lys Asp Tyr Glu Asn Phe Lys Tyr Val Tyr Ser Gly Trp Phe
145                 150                 155                 160
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```
Tyr Lys His Ala Lys Arg Glu Phe Asn Leu Lys Val Glu Pro Lys Ser
                165                 170                 175

Ala Lys Asn Gly Asp Asp Gly Tyr Ile Phe Tyr His Gly Lys Glu Pro
            180                 185                 190

Ser Arg Gln Leu Pro Ala Ser Gly Lys Ile Thr Tyr Lys Gly Val Trp
        195                 200                 205

His Phe Ala Thr Asp Thr Lys Lys Gly Gln Lys Phe Arg Glu Ile Ile
    210                 215                 220

Gln Pro Ser Lys Ser Gln Gly Asp Arg Tyr Ser Gly Phe Ser Gly Asp
225                 230                 235                 240

Asp Gly Glu Glu Tyr Ser Asn Lys Asn Lys Ser Thr Leu Thr Asp Gly
                245                 250                 255

Gln Glu Gly Tyr Gly Phe Thr Ser Asn Leu Glu Val Asp Phe His Asn
            260                 265                 270

Lys Lys Leu Thr Gly Lys Leu Ile Arg Asn Asn Ala Asn Thr Asp Asn
        275                 280                 285

Asn Gln Ala Thr Thr Thr Gln Tyr Tyr Ser Leu Glu Ala Gln Val Thr
    290                 295                 300

Gly Asn Arg Phe Asn Gly Lys Ala Thr Ala Thr Asp Lys Pro Gln Gln
305                 310                 315                 320

Asn Ser Glu Thr Lys Glu His Pro Phe Val Ser Asp Ser Ser Ser Leu
                325                 330                 335

Ser Gly Gly Phe Phe Gly Pro Gln Gly Glu Glu Leu Gly Phe Arg Phe
            340                 345                 350

Leu Ser Asp Asp Gln Lys Val Ala Val Val Gly Ser Ala Lys Thr Lys
        355                 360                 365

Asp Lys Pro Ala Asn Gly Asn Thr Ala Ala Ala Ser Gly Gly Thr Asp
    370                 375                 380

Ala Ala Ala Ser Asn Gly Ala Ala Gly Thr Ser Ser Glu Asn Gly Lys
385                 390                 395                 400

Leu Thr Thr Val Leu Asp Ala Val Glu Leu Lys Leu Gly Asp Lys Glu
                405                 410                 415

Val Gln Lys Leu Asp Asn Phe Ser Asn Ala Ala Gln Leu Val Val Asp
            420                 425                 430

Gly Ile Met Ile Pro Leu Leu Pro Glu Ala Ser Glu Ser Gly Asn Asn
        435                 440                 445

Gln Ala Asn Gln Gly Thr Asn Gly Gly Thr Ala Phe Thr Arg Lys Phe
    450                 455                 460
```

Asp His Thr Pro Glu Ser Asp Lys Lys Asp Ala Gln Ala Gly Thr Gln
465 470 475 480

Thr Asn Gly Ala Gln Thr Ala Ser Asn Thr Ala Gly Asp Thr Asn Gly
485 490 495

Lys Thr Lys Thr Tyr Glu Val Glu Val Cys Cys Ser Asn Leu Asn Tyr
500 505 510

Leu Lys Tyr Gly Met Leu Thr Arg Lys Asn Ser Lys Ser Ala Met Gln
515 520 525

Ala Gly Glu Ser Ser Ser Gln Ala Asp Ala Lys Thr Glu Gln Val Glu
530 535 540

Gln Ser Met Phe Leu Gln Gly Glu Arg Thr Asp Glu Lys Glu Ile Pro
545 550 555 560

Ser Glu Gln Asn Ile Val Tyr Arg Gly Ser Trp Tyr Gly Tyr Ile Ala
565 570 575

Asn Asp Lys Ser Thr Ser Trp Ser Gly Asn Ala Ser Asn Ala Thr Ser
580 585 590

Gly Asn Arg Ala Glu Phe Thr Val Asn Phe Ala Asp Lys Lys Ile Thr
595 600 605

Gly Thr Leu Thr Ala Asp Asn Arg Gln Glu Ala Thr Phe Thr Ile Asp
610 615 620

Gly Asn Ile Lys Asp Asn Gly Phe Glu Gly Thr Ala Lys Thr Ala Glu
625 630 635 640

Ser Gly Phe Asp Leu Asp Gln Ser Asn Thr Thr Arg Thr Pro Lys Ala
645 650 655

Tyr Ile Thr Asp Ala Lys Val Gln Gly Gly Phe Tyr Gly Pro Lys Ala
660 665 670

Glu Glu Leu Gly Gly Trp Phe Ala Tyr Pro Gly Asp Lys Gln Thr Lys
675 680 685

Asn Ala Thr Asn Ala Ser Gly Asn Ser Ser Ala Thr Val Val Phe Gly
690 695 700

Ala Lys Arg Gln Gln Pro Val Arg
705 710

<210> 86
<211> 274
<212> PRT
<213> Artificial Sequence

<220>
<223> 741

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<400>  86
Val Asn Arg Thr Ala Phe Cys Cys Leu Ser Leu Thr Thr Ala Leu Ile
1               5                   10                  15

Leu Thr Ala Cys Ser Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly
            20                  25                  30

Ala Gly Leu Ala Asp Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys
        35                  40                  45

Gly Leu Gln Ser Leu Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys
    50                  55                  60

Leu Lys Leu Ala Ala Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp
65                  70                  75                  80

Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp
                85                  90                  95

Phe Ile Arg Gln Ile Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser
            100                 105                 110

Gly Glu Phe Gln Val Tyr Lys Gln Ser His Ser Ala Leu Thr Ala Phe
        115                 120                 125

Gln Thr Glu Gln Ile Gln Asp Ser Glu His Ser Gly Lys Met Val Ala
    130                 135                 140

Lys Arg Gln Phe Arg Ile Gly Asp Ile Ala Gly Glu His Thr Ser Phe
145                 150                 155                 160

Asp Lys Leu Pro Glu Gly Gly Arg Ala Thr Tyr Arg Gly Thr Ala Phe
                165                 170                 175

Gly Ser Asp Asp Ala Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala
            180                 185                 190

Ala Lys Gln Gly Asn Gly Lys Ile Glu His Leu Lys Ser Pro Glu Leu
        195                 200                 205

Asn Val Asp Leu Ala Ala Ala Asp Ile Lys Pro Asp Gly Lys Arg His
    210                 215                 220

Ala Val Ile Ser Gly Ser Val Leu Tyr Asn Gln Ala Glu Lys Gly Ser
225                 230                 235                 240

Tyr Ser Leu Gly Ile Phe Gly Gly Lys Ala Gln Glu Val Ala Gly Ser
                245                 250                 255

Ala Glu Val Lys Thr Val Asn Gly Ile Arg His Ile Gly Leu Ala Ala
            260                 265                 270

Lys Gln


<210>  87
<211>  1082
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<212>  PRT
<213>  Artificial Sequence

<220>
<223>  983

<400>  87
Met Arg Thr Thr Pro Thr Phe Pro Thr Lys Thr Phe Lys Pro Thr Ala
1               5                   10                  15

Met Ala Leu Ala Val Ala Thr Thr Leu Ser Ala Cys Leu Gly Gly Gly
            20                  25                  30

Gly Gly Gly Thr Ser Ala Pro Asp Phe Asn Ala Gly Gly Thr Gly Ile
        35                  40                  45

Gly Ser Asn Ser Arg Ala Thr Thr Ala Lys Ser Ala Ala Val Ser Tyr
    50                  55                  60

Ala Gly Ile Lys Asn Glu Met Cys Lys Asp Arg Ser Met Leu Cys Ala
65                  70                  75                  80

Gly Arg Asp Asp Val Ala Val Thr Asp Arg Asp Ala Lys Ile Asn Ala
                85                  90                  95

Pro Pro Pro Asn Leu His Thr Gly Asp Phe Pro Asn Pro Asn Asp Ala
            100                 105                 110

Tyr Lys Asn Leu Ile Asn Leu Lys Pro Ala Ile Glu Ala Gly Tyr Thr
        115                 120                 125

Gly Arg Gly Val Glu Val Gly Ile Val Asp Thr Gly Glu Ser Val Gly
    130                 135                 140

Ser Ile Ser Phe Pro Glu Leu Tyr Gly Arg Lys Glu His Gly Tyr Asn
145                 150                 155                 160

Glu Asn Tyr Lys Asn Tyr Thr Ala Tyr Met Arg Lys Glu Ala Pro Glu
                165                 170                 175

Asp Gly Gly Gly Lys Asp Ile Glu Ala Ser Phe Asp Asp Glu Ala Val
            180                 185                 190

Ile Glu Thr Glu Ala Lys Pro Thr Asp Ile Arg His Val Lys Glu Ile
        195                 200                 205

Gly His Ile Asp Leu Val Ser His Ile Ile Gly Gly Arg Ser Val Asp
    210                 215                 220

Gly Arg Pro Ala Gly Gly Ile Ala Pro Asp Ala Thr Leu His Ile Met
225                 230                 235                 240

Asn Thr Asn Asp Glu Thr Lys Asn Glu Met Met Val Ala Ala Ile Arg
                245                 250                 255

Asn Ala Trp Val Lys Leu Gly Glu Arg Gly Val Arg Ile Val Asn Asn
            260                 265                 270
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Ser Phe Gly Thr Thr Ser Arg Ala Gly Thr Ala Asp Leu Phe Gln Ile
275 280 285

Ala Asn Ser Glu Glu Gln Tyr Arg Gln Ala Leu Leu Asp Tyr Ser Gly
290 295 300

Gly Asp Lys Thr Asp Glu Gly Ile Arg Leu Met Gln Gln Ser Asp Tyr
305 310 315 320

Gly Asn Leu Ser Tyr His Ile Arg Asn Lys Asn Met Leu Phe Ile Phe
325 330 335

Ser Thr Gly Asn Asp Ala Gln Ala Gln Pro Asn Thr Tyr Ala Leu Leu
340 345 350

Pro Phe Tyr Glu Lys Asp Ala Gln Lys Gly Ile Ile Thr Val Ala Gly
355 360 365

Val Asp Arg Ser Gly Glu Lys Phe Lys Arg Glu Met Tyr Gly Glu Pro
370 375 380

Gly Thr Glu Pro Leu Glu Tyr Gly Ser Asn His Cys Gly Ile Thr Ala
385 390 395 400

Met Trp Cys Leu Ser Ala Pro Tyr Glu Ala Ser Val Arg Phe Thr Arg
405 410 415

Thr Asn Pro Ile Gln Ile Ala Gly Thr Ser Phe Ser Ala Pro Ile Val
420 425 430

Thr Gly Thr Ala Ala Leu Leu Leu Gln Lys Tyr Pro Trp Met Ser Asn
435 440 445

Asp Asn Leu Arg Thr Thr Leu Leu Thr Thr Ala Gln Asp Ile Gly Ala
450 455 460

Val Gly Val Asp Ser Lys Phe Gly Trp Gly Leu Leu Asp Ala Gly Lys
465 470 475 480

Ala Met Asn Gly Pro Ala Ser Phe Pro Phe Gly Asp Phe Thr Ala Asp
485 490 495

Thr Lys Gly Thr Ser Asp Ile Ala Tyr Ser Phe Arg Asn Asp Ile Ser
500 505 510

Gly Thr Gly Gly Leu Ile Lys Lys Gly Gly Ser Gln Leu Gln Leu His
515 520 525

Gly Asn Asn Thr Tyr Thr Gly Lys Thr Ile Ile Glu Gly Gly Ser Leu
530 535 540

Val Leu Tyr Gly Asn Asn Lys Ser Asp Met Arg Val Glu Thr Lys Gly
545 550 555 560

Ala Leu Ile Tyr Asn Gly Ala Ala Ser Gly Gly Ser Leu Asn Ser Asp
565 570 575

Gly Ile Val Tyr Leu Ala Asp Thr Asp Gln Ser Gly Ala Asn Glu Thr
580 585 590

Val His Ile Lys Gly Ser Leu Gln Leu Asp Gly Lys Gly Thr Leu Tyr
595 600 605

Thr Arg Leu Gly Lys Leu Leu Lys Val Asp Gly Thr Ala Ile Ile Gly
610 615 620

Gly Lys Leu Tyr Met Ser Ala Arg Gly Lys Gly Ala Gly Tyr Leu Asn
625 630 635 640

Ser Thr Gly Arg Arg Val Pro Phe Leu Ser Ala Ala Lys Ile Gly Gln
645 650 655

Asp Tyr Ser Phe Phe Thr Asn Ile Glu Thr Asp Gly Gly Leu Leu Ala
660 665 670

Ser Leu Asp Ser Val Glu Lys Thr Ala Gly Ser Glu Gly Asp Thr Leu
675 680 685

Ser Tyr Tyr Val Arg Arg Gly Asn Ala Ala Arg Thr Ala Ser Ala Ala
690 695 700

Ala His Ser Ala Pro Ala Gly Leu Lys His Ala Val Glu Gln Gly Gly
705 710 715 720

Ser Asn Leu Glu Asn Leu Met Val Glu Leu Asp Ala Ser Glu Ser Ser
725 730 735

Ala Thr Pro Glu Thr Val Glu Thr Ala Ala Ala Asp Arg Thr Asp Met
740 745 750

Pro Gly Ile Arg Pro Tyr Gly Ala Thr Phe Arg Ala Ala Ala Ala Val
755 760 765

Gln His Ala Asn Ala Ala Asp Gly Val Arg Ile Phe Asn Ser Leu Ala
770 775 780

Ala Thr Val Tyr Ala Asp Ser Thr Ala Ala His Ala Asp Met Gln Gly
785 790 795 800

Arg Arg Leu Lys Ala Val Ser Asp Gly Leu Asp His Asn Gly Thr Gly
805 810 815

Leu Arg Val Ile Ala Gln Thr Gln Gln Asp Gly Gly Thr Trp Glu Gln
820 825 830

Gly Gly Val Glu Gly Lys Met Arg Gly Ser Thr Gln Thr Val Gly Ile
835 840 845

Ala Ala Lys Thr Gly Glu Asn Thr Thr Ala Ala Ala Thr Leu Gly Met
850 855 860

Gly Arg Ser Thr Trp Ser Glu Asn Ser Ala Asn Ala Lys Thr Asp Ser
865 870 875 880

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Ile Ser Leu Phe Ala Gly Ile Arg His Asp Ala Gly Asp Ile Gly Tyr
                885                 890                 895

Leu Lys Gly Leu Phe Ser Tyr Gly Arg Tyr Lys Asn Ser Ile Ser Arg
            900                 905                 910

Ser Thr Gly Ala Asp Glu His Ala Glu Gly Ser Val Asn Gly Thr Leu
        915                 920                 925

Met Gln Leu Gly Ala Leu Gly Gly Val Asn Val Pro Phe Ala Ala Thr
    930                 935                 940

Gly Asp Leu Thr Val Glu Gly Gly Leu Arg Tyr Asp Leu Leu Lys Gln
945                 950                 955                 960

Asp Ala Phe Ala Glu Lys Gly Ser Ala Leu Gly Trp Ser Gly Asn Ser
                965                 970                 975

Leu Thr Glu Gly Thr Leu Val Gly Leu Ala Gly Leu Lys Leu Ser Gln
            980                 985                 990

Pro Leu Ser Asp Lys Ala Val Leu Phe Ala Thr Ala Gly Val Glu Arg
        995                 1000                1005

Asp Leu Asn Gly Arg Asp Tyr Thr Val Thr Gly Gly Phe Thr Gly Ala
    1010                1015                1020

Thr Ala Ala Thr Gly Lys Thr Gly Ala Arg Asn Met Pro His Thr Arg
1025                1030                1035                1040

Leu Val Ala Gly Leu Gly Ala Asp Val Glu Phe Gly Asn Gly Trp Asn
                1045                1050                1055

Gly Leu Ala Arg Tyr Ser Tyr Ala Gly Ser Lys Gln Tyr Gly Asn His
            1060                1065                1070

Ser Gly Arg Val Gly Val Gly Tyr Arg Phe
        1075                1080

<210>  88
<211>  2505
<212>  DNA
<213>  Artificial Sequence

<220>
<223>  deltaG287-919

<400>  88
atggctagcc ccgatgttaa atcggcggac acgctgtcaa aaccggccgc tcctgttgtt    60
gctgaaaaag agacagaggt aaaagaagat gcgccacagg caggttctca aggacagggc   120
gcgccatcca cacaaggcag ccaagatatg gcggcagttt cggcagaaaa tacaggcaat   180
ggcggtgcgg caacaacgga caaacccaaa aatgaagacg agggaccgca aaatgatatg   240
ccgcaaaatt ccgccgaatc cgcaaatcaa acagggaaca accaacccgc cgattcttca   300
gattccgccc ccgcgtcaaa ccctgcacct gcgaatggcg gtagcaattt tggaagggtt   360
gatttggcta atggcgtttt gattgatggg ccgtcgcaaa atataacgtt gacccactgt   420
aaaggcgatt cttgtaatgg tgataattta ttggatgaag aagcaccgtc aaaatcagaa   480
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tttgaaaatt taaatgagtc tgaacgaatt gagaaatata agaaagatgg gaaaagcgat   540
aaatttacta atttggttgc gacagcagtt caagctaatg gaactaacaa atatgtcatc   600
atttataaag acaagtccgc ttcatcttca tctgcgcgat tcaggcgttc tgcacggtcg   660
aggaggtcgc ttcctgccga gatgccgcta atccccgtca atcaggcgga tacgctgatt   720
gtcgatgggg aagcggtcag cctgacgggg cattccggca atatcttcgc gcccgaaggg   780
aattaccggt atctgactta cggggcggaa aaattgcccg gcggatcgta tgccctccgt   840
gtgcaaggcg aaccggcaaa aggcgaaatg cttgctggca cggccgtgta caacggcgaa   900
gtgctgcatt ttcatacgga aaacggccgt ccgtacccga ctagaggcag gtttgccgca   960
aaagtcgatt tcggcagcaa atctgtggac ggcattatcg acagcggcga tgatttgcat  1020
atgggtacgc aaaaattcaa agccgccatc gatggaaacg gctttaaggg gacttggacg  1080
gaaaatggcg gcggggatgt ttccggaagg ttttacggcc cggccggcga ggaagtggcg  1140
ggaaaataca gctatcgccc gacagatgcg gaaaagggcg gattcggcgt gtttgccggc  1200
aaaaaagagc aggatggatc cggaggagga ggatgccaaa gcaagagcat ccaaaccttt  1260
ccgcaacccg acacatccgt catcaacggc ccggaccggc cggtcggcat ccccgacccc  1320
gccggaacga cggtcggcgg cggcggggcc gtctataccg ttgtaccgca cctgtccctg  1380
ccccactggg cggcgcagga tttcgccaaa agcctgcaat ccttccgcct cggctgcgcc  1440
aatttgaaaa accgccaagg ctggcaggat gtgtgcgccc aagcctttca aacccccgtc  1500
cattcctttc aggcaaaaca gtttttgaa cgctatttca cgccgtggca ggttgcaggc  1560
aacggaagcc ttgccggtac ggttaccggc tattacgagc cggtgctgaa gggcgacgac  1620
aggcggacgg cacaagcccg cttcccgatt tacggtattc ccgacgattt tatctccgtc  1680
cccctgcctg ccggtttgcg gagcggaaaa gcccttgtcc gcatcaggca gacgggaaaa  1740
aacagcggca caatcgacaa taccggcggc acacataccg ccgacctctc ccgattcccc  1800
atcaccgcgc gcacaacggc aatcaaaggc aggtttgaag gaagccgctt cctcccctac  1860
cacacgcgca accaaatcaa cggcggcgcg cttgacggca aagccccgat actcggttac  1920
gccgaagacc ccgtcgaact ttttttatg cacatccaag gctcgggccg tctgaaaacc  1980
ccgtccggca aatacatccg catcggctat gccgacaaaa acgaacatcc ctacgtttcc  2040
atcggacgct atatggcgga caaaggctac ctcaagctcg ggcagacctc gatgcagggc  2100
atcaaagcct atatgcggca aaatccgcaa cgcctcgccg aagttttggg tcaaaacccc  2160
agctatatct tttccgcga gcttgccgga agcagcaatg acggtcccgt cggcgcactg  2220
ggcacgccgt tgatgggga atatgccggc gcagtcgacc ggcactacat taccttgggc  2280
gcgcccttat ttgtcgccac cgcccatccg gttacccgca aagccctcaa ccgcctgatt  2340
atggcgcagg ataccggcag cgcgattaaa ggcgcggtgc gcgtggatta tttttgggga  2400
tacggcgacg aagccggcga acttgccggc aaacagaaaa ccacgggtta cgtctggcag  2460
ctcctaccca acggtatgaa gcccgaatac cgcccgtaac tcgag                   2505
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<210>  89
<211>  832
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  deltaG287-919

<400>  89
Met Ala Ser Pro Asp Val Lys Ser Ala Asp Thr Leu Ser Lys Pro Ala
1               5                   10                  15

Ala Pro Val Val Ala Glu Lys Glu Thr Glu Val Lys Glu Asp Ala Pro
            20                  25                  30

Gln Ala Gly Ser Gln Gly Gln Gly Ala Pro Ser Thr Gln Gly Ser Gln
        35                  40                  45

Asp Met Ala Ala Val Ser Ala Glu Asn Thr Gly Asn Gly Gly Ala Ala
    50                  55                  60

Thr Thr Asp Lys Pro Lys Asn Glu Asp Glu Gly Pro Gln Asn Asp Met
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65                  70                  75                  80

Pro Gln Asn Ser Ala Glu Ser Ala Asn Gln Thr Gly Asn Asn Gln Pro
                85                  90                  95

Ala Asp Ser Ser Asp Ser Ala Pro Ala Ser Asn Pro Ala Pro Ala Asn
            100                 105                 110

Gly Gly Ser Asn Phe Gly Arg Val Asp Leu Ala Asn Gly Val Leu Ile
        115                 120                 125

Asp Gly Pro Ser Gln Asn Ile Thr Leu Thr His Cys Lys Gly Asp Ser
    130                 135                 140

Cys Asn Gly Asp Asn Leu Leu Asp Glu Glu Ala Pro Ser Lys Ser Glu
145                 150                 155                 160

Phe Glu Asn Leu Asn Glu Ser Glu Arg Ile Glu Lys Tyr Lys Lys Asp
                165                 170                 175

Gly Lys Ser Asp Lys Phe Thr Asn Leu Val Ala Thr Ala Val Gln Ala
            180                 185                 190

Asn Gly Thr Asn Lys Tyr Val Ile Ile Tyr Lys Asp Lys Ser Ala Ser
        195                 200                 205

Ser Ser Ser Ala Arg Phe Arg Arg Ser Ala Arg Ser Arg Arg Ser Leu
    210                 215                 220

Pro Ala Glu Met Pro Leu Ile Pro Val Asn Gln Ala Asp Thr Leu Ile
225                 230                 235                 240

Val Asp Gly Glu Ala Val Ser Leu Thr Gly His Ser Gly Asn Ile Phe
                245                 250                 255

Ala Pro Glu Gly Asn Tyr Arg Tyr Leu Thr Tyr Gly Ala Glu Lys Leu
            260                 265                 270

Pro Gly Gly Ser Tyr Ala Leu Arg Val Gln Gly Glu Pro Ala Lys Gly
        275                 280                 285

Glu Met Leu Ala Gly Thr Ala Val Tyr Asn Gly Glu Val Leu His Phe
    290                 295                 300

His Thr Glu Asn Gly Arg Pro Tyr Pro Thr Arg Gly Arg Phe Ala Ala
305                 310                 315                 320

Lys Val Asp Phe Gly Ser Lys Ser Val Asp Gly Ile Ile Asp Ser Gly
                325                 330                 335

Asp Asp Leu His Met Gly Thr Gln Lys Phe Lys Ala Ala Ile Asp Gly
            340                 345                 350

Asn Gly Phe Lys Gly Thr Trp Thr Glu Asn Gly Gly Gly Asp Val Ser
        355                 360                 365

Gly Arg Phe Tyr Gly Pro Ala Gly Glu Glu Val Ala Gly Lys Tyr Ser
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370 375 380

Tyr Arg Pro Thr Asp Ala Glu Lys Gly Gly Phe Gly Val Phe Ala Gly
385 390 395 400

Lys Lys Glu Gln Asp Gly Ser Gly Gly Gly Gly Cys Gln Ser Lys Ser
405 410 415

Ile Gln Thr Phe Pro Gln Pro Asp Thr Ser Val Ile Asn Gly Pro Asp
420 425 430

Arg Pro Val Gly Ile Pro Asp Pro Ala Gly Thr Thr Val Gly Gly Gly
435 440 445

Gly Ala Val Tyr Thr Val Val Pro His Leu Ser Leu Pro His Trp Ala
450 455 460

Ala Gln Asp Phe Ala Lys Ser Leu Gln Ser Phe Arg Leu Gly Cys Ala
465 470 475 480

Asn Leu Lys Asn Arg Gln Gly Trp Gln Asp Val Cys Ala Gln Ala Phe
485 490 495

Gln Thr Pro Val His Ser Phe Gln Ala Lys Gln Phe Phe Glu Arg Tyr
500 505 510

Phe Thr Pro Trp Gln Val Ala Gly Asn Gly Ser Leu Ala Gly Thr Val
515 520 525

Thr Gly Tyr Tyr Glu Pro Val Leu Lys Gly Asp Asp Arg Arg Thr Ala
530 535 540

Gln Ala Arg Phe Pro Ile Tyr Gly Ile Pro Asp Asp Phe Ile Ser Val
545 550 555 560

Pro Leu Pro Ala Gly Leu Arg Ser Gly Lys Ala Leu Val Arg Ile Arg
565 570 575

Gln Thr Gly Lys Asn Ser Gly Thr Ile Asp Asn Thr Gly Gly Thr His
580 585 590

Thr Ala Asp Leu Ser Arg Phe Pro Ile Thr Ala Arg Thr Thr Ala Ile
595 600 605

Lys Gly Arg Phe Glu Gly Ser Arg Phe Leu Pro Tyr His Thr Arg Asn
610 615 620

Gln Ile Asn Gly Gly Ala Leu Asp Gly Lys Ala Pro Ile Leu Gly Tyr
625 630 635 640

Ala Glu Asp Pro Val Glu Leu Phe Phe Met His Ile Gln Gly Ser Gly
645 650 655

Arg Leu Lys Thr Pro Ser Gly Lys Tyr Ile Arg Ile Gly Tyr Ala Asp
660 665 670

Lys Asn Glu His Pro Tyr Val Ser Ile Gly Arg Tyr Met Ala Asp Lys

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        675                 680                 685

Gly Tyr Leu Lys Leu Gly Gln Thr Ser Met Gln Gly Ile Lys Ala Tyr
    690                 695                 700

Met Arg Gln Asn Pro Gln Arg Leu Ala Glu Val Leu Gly Gln Asn Pro
705                 710                 715                 720

Ser Tyr Ile Phe Phe Arg Glu Leu Ala Gly Ser Ser Asn Asp Gly Pro
                725                 730                 735

Val Gly Ala Leu Gly Thr Pro Leu Met Gly Glu Tyr Ala Gly Ala Val
            740                 745                 750

Asp Arg His Tyr Ile Thr Leu Gly Ala Pro Leu Phe Val Ala Thr Ala
        755                 760                 765

His Pro Val Thr Arg Lys Ala Leu Asn Arg Leu Ile Met Ala Gln Asp
    770                 775                 780

Thr Gly Ser Ala Ile Lys Gly Ala Val Arg Val Asp Tyr Phe Trp Gly
785                 790                 795                 800

Tyr Gly Asp Glu Ala Gly Glu Leu Ala Gly Lys Gln Lys Thr Thr Gly
                805                 810                 815

Tyr Val Trp Gln Leu Leu Pro Asn Gly Met Lys Pro Glu Tyr Arg Pro
            820                 825                 830


<210>   90
<211>   1746
<212>   DNA
<213>   Artificial Sequence

<220>
<223>   deltaG287-953

<400>   90
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gctgaaaaag agacagaggt aaaagaagat gcgccacagg caggttctca aggacagggc    120
gcgccatcca cacaaggcag ccaagatatg gcggcagttt cggcagaaaa tacaggcaat    180
ggcggtgcgg caacaacgga caaacccaaa aatgaagacg agggaccgca aaatgatatg    240
ccgcaaaatt ccgccgaatc cgcaaatcaa acagggaaca accaacccgc cgattcttca    300
gattccgccc ccgcgtcaaa ccctgcacct gcgaatggcg gtagcaattt tggaagggtt    360
gatttggcta atggcgtttt gattgatggg ccgtcgcaaa atataacgtt gacccactgt    420
aaaggcgatt cttgtaatgg tgataattta ttggatgaag aagcaccgtc aaaatcagaa    480
tttgaaaatt taaatgagtc tgaacgaatt gagaaatata agaaagatgg gaaaagcgat    540
aaatttacta atttggttgc gacagcagtt caagctaatg gaactaacaa atatgtcatc    600
atttataaag acaagtccgc ttcatcttca tctgcgcgat tcaggcgttc tgcacggtcg    660
aggaggtcgc ttcctgccga gatgccgcta atccccgtca atcaggcgga tacgctgatt    720
gtcgatgggg aagcggtcag cctgacgggg cattccggca atatcttcgc gcccgaaggg    780
aattaccggt atctgactta cggggcggaa aaattgcccg gcggatcgta tgccctccgt    840
gtgcaaggcg aaccggcaaa aggcgaaatg cttgctggca cggccgtgta caacggcgaa    900
gtgctgcatt ttcatacgga aaacggccgt ccgtacccga ctagaggcag gtttgccgca    960
aaagtcgatt tcggcagcaa atctgtggac ggcattatcg acagcggcga tgatttgcat   1020
atgggtacgc aaaaattcaa agccgccatc gatggaaacg gctttaaggg gacttggacg   1080
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gaaaatggcg gcggggatgt ttccggaagg ttttacggcc cggccggcga ggaagtggcg   1140
ggaaaataca gctatcgccc gacagatgcg gaaaagggcg gattcggcgt gtttgccggc   1200
aaaaaagagc aggatggatc cggaggagga ggagccacct acaaagtgga cgaatatcac   1260
gccaacgccc gtttcgccat cgaccatttc aacaccagca ccaacgtcgg cggtttttac   1320
ggtctgaccg gttccgtcga gttcgaccaa gcaaaacgcg acggtaaaat cgacatcacc   1380
atccccgttg ccaacctgca aagcggttcg caacacttta ccgaccacct gaaatcagcc   1440
gacatcttcg atgccgccca atatccggac atccgctttg tttccaccaa attcaacttc   1500
aacggcaaaa aactggtttc cgttgacggc aacctgacca tgcacggcaa aaccgccccc   1560
gtcaaactca aagccgaaaa attcaactgc taccaaagcc cgatggcgaa aaccgaagtt   1620
tgcggcggcg acttcagcac caccatcgac cgcaccaaat ggggcgtgga ctacctcgtt   1680
aacgttggta tgaccaaaag cgtccgcatc gacatccaaa tcgaggcagc caaacaataa   1740
ctcgag                                                              1746

<210>  91
<211>  579
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  deltaG287-953

<400>  91
Met Ala Ser Pro Asp Val Lys Ser Ala Asp Thr Leu Ser Lys Pro Ala
1               5                   10                  15

Ala Pro Val Val Ala Glu Lys Glu Thr Glu Val Lys Glu Asp Ala Pro
            20                  25                  30

Gln Ala Gly Ser Gln Gly Gln Gly Ala Pro Ser Thr Gln Gly Ser Gln
        35                  40                  45

Asp Met Ala Ala Val Ser Ala Glu Asn Thr Gly Asn Gly Gly Ala Ala
    50                  55                  60

Thr Thr Asp Lys Pro Lys Asn Glu Asp Glu Gly Pro Gln Asn Asp Met
65                  70                  75                  80

Pro Gln Asn Ser Ala Glu Ser Ala Asn Gln Thr Gly Asn Asn Gln Pro
                85                  90                  95

Ala Asp Ser Ser Asp Ser Ala Pro Ala Ser Asn Pro Ala Pro Ala Asn
            100                 105                 110

Gly Gly Ser Asn Phe Gly Arg Val Asp Leu Ala Asn Gly Val Leu Ile
        115                 120                 125

Asp Gly Pro Ser Gln Asn Ile Thr Leu Thr His Cys Lys Gly Asp Ser
    130                 135                 140

Cys Asn Gly Asp Asn Leu Leu Asp Glu Glu Ala Pro Ser Lys Ser Glu
145                 150                 155                 160

Phe Glu Asn Leu Asn Glu Ser Glu Arg Ile Glu Lys Tyr Lys Lys Asp
                165                 170                 175

Gly Lys Ser Asp Lys Phe Thr Asn Leu Val Ala Thr Ala Val Gln Ala
            180                 185                 190
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Asn Gly Thr Asn Lys Tyr Val Ile Ile Tyr Lys Asp Lys Ser Ala Ser
        195                 200                 205

Ser Ser Ser Ala Arg Phe Arg Arg Ser Ala Arg Ser Arg Arg Ser Leu
    210                 215                 220

Pro Ala Glu Met Pro Leu Ile Pro Val Asn Gln Ala Asp Thr Leu Ile
225                 230                 235                 240

Val Asp Gly Glu Ala Val Ser Leu Thr Gly His Ser Gly Asn Ile Phe
                245                 250                 255

Ala Pro Glu Gly Asn Tyr Arg Tyr Leu Thr Tyr Gly Ala Glu Lys Leu
            260                 265                 270

Pro Gly Gly Ser Tyr Ala Leu Arg Val Gln Gly Glu Pro Ala Lys Gly
        275                 280                 285

Glu Met Leu Ala Gly Thr Ala Val Tyr Asn Gly Glu Val Leu His Phe
    290                 295                 300

His Thr Glu Asn Gly Arg Pro Tyr Pro Thr Arg Gly Arg Phe Ala Ala
305                 310                 315                 320

Lys Val Asp Phe Gly Ser Lys Ser Val Asp Gly Ile Ile Asp Ser Gly
                325                 330                 335

Asp Asp Leu His Met Gly Thr Gln Lys Phe Lys Ala Ala Ile Asp Gly
            340                 345                 350

Asn Gly Phe Lys Gly Thr Trp Thr Glu Asn Gly Gly Gly Asp Val Ser
        355                 360                 365

Gly Arg Phe Tyr Gly Pro Ala Gly Glu Glu Val Ala Gly Lys Tyr Ser
    370                 375                 380

Tyr Arg Pro Thr Asp Ala Glu Lys Gly Gly Phe Gly Val Phe Ala Gly
385                 390                 395                 400

Lys Lys Glu Gln Asp Gly Ser Gly Gly Gly Gly Ala Thr Tyr Lys Val
                405                 410                 415

Asp Glu Tyr His Ala Asn Ala Arg Phe Ala Ile Asp His Phe Asn Thr
            420                 425                 430

Ser Thr Asn Val Gly Gly Phe Tyr Gly Leu Thr Gly Ser Val Glu Phe
        435                 440                 445

Asp Gln Ala Lys Arg Asp Gly Lys Ile Asp Ile Thr Ile Pro Val Ala
    450                 455                 460

Asn Leu Gln Ser Gly Ser Gln His Phe Thr Asp His Leu Lys Ser Ala
465                 470                 475                 480

Asp Ile Phe Asp Ala Ala Gln Tyr Pro Asp Ile Arg Phe Val Ser Thr
                485                 490                 495
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Lys Phe Asn Phe Asn Gly Lys Lys Leu Val Ser Val Asp Gly Asn Leu
            500                 505                 510

Thr Met His Gly Lys Thr Ala Pro Val Lys Leu Lys Ala Glu Lys Phe
        515                 520                 525

Asn Cys Tyr Gln Ser Pro Met Ala Lys Thr Glu Val Cys Gly Gly Asp
    530                 535                 540

Phe Ser Thr Thr Ile Asp Arg Thr Lys Trp Gly Val Asp Tyr Leu Val
545                 550                 555                 560

Asn Val Gly Met Thr Lys Ser Val Arg Ile Asp Ile Gln Ile Glu Ala
                565                 570                 575

Ala Lys Gln


<210>   92
<211>   2388
<212>   DNA
<213>   Artificial Sequence

<220>
<223>   deltaG287-961

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gcgccatcca cacaaggcag ccaagatatg gcggcagttt cggcagaaaa tacaggcaat  180
ggcggtgcgg caacaacgga caaacccaaa aatgaagacg agggaccgca aaatgatatg  240
ccgcaaaatt ccgccgaatc cgcaaatcaa acagggaaca accaacccgc cgattcttca  300
gattccgccc ccgcgtcaaa ccctgcacct gcgaatggcg gtagcaattt tggaagggtt  360
gatttggcta atggcgtttt gattgatggg ccgtcgcaaa atataacgtt gacccactgt  420
aaaggcgatt cttgtaatgg tgataattta ttggatgaag aagcaccgtc aaaatcagaa  480
tttgaaaatt taaatgagtc tgaacgaatt gagaaatata agaaagatgg gaaaagcgat  540
aaatttacta atttggttgc gacagcagtt caagctaatg gaactaacaa atatgtcatc  600
atttataaag acaagtccgc ttcatcttca tctgcgcgat tcaggcgttc tgcacggtcg  660
aggaggtcgc ttcctgccga gatgccgcta atccccgtca atcaggcgga tacgctgatt  720
gtcgatgggg aagcggtcag cctgacgggg cattccggca atatcttcgc gcccgaaggg  780
aattaccggt atctgactta cggggcggaa aaattgcccg gcggatcgta tgccctccgt  840
gtgcaaggcg aaccggcaaa aggcgaaatg cttgctggca cggccgtgta caacggcgaa  900
gtgctgcatt ttcatacgga aaacggccgt ccgtacccga ctagaggcag gtttgccgca  960
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gaaaatggcg gcggggatgt ttccggaagg ttttacggcc cggccggcga ggaagtggcg 1140
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ctgaccaaaa ccgtcaatga aaacaaacaa aacgtcgatg ccaaagtaaa agctgcagaa 1500
tctgaaatag aaaagttaac aaccaagtta gcagacactg atgccgcttt agcagatact 1560
gatgccgctc tggatgcaac caccaacgcc ttgaataaat tgggagaaaa tataacgaca 1620
tttgctgaag agactaagac aaatatcgta aaaattgatg aaaaattaga agccgtggct 1680
gataccgtcg acaagcatgc cgaagcattc aacgatatcg ccgattcatt ggatgaaacc 1740
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gctgccgctg gcacagctaa tactgcagcc gacaaggccg aagctgtcgc tgcaaaagtt   1920
accgacatca aagctgatat cgctacgaac aaagataata ttgctaaaaa agcaaacagt   1980
gccgacgtgt acaccagaga agagtctgac agcaaatttg tcagaattga tggtctgaac   2040
gctactaccg aaaaattgga cacacgcttg gcttctgctg aaaaatccat tgccgatcac   2100
gatactcgcc tgaacggttt ggataaaaca gtgtcagacc tgcgcaaaga aacccgccaa   2160
ggccttgcag aacaagccgc gctctccggt ctgttccaac cttacaacgt gggtcggttc   2220
aatgtaacgg ctgcagtcgg cggctacaaa tccgaatcgg cagtcgccat cggtaccggc   2280
ttccgcttta ccgaaaactt tgccgccaaa gcaggcgtgg cagtcggcac ttcgtccggt   2340
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<210>  93
<211>  793
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  deltaG287-961

<400>  93
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Ala Pro Val Val Ala Glu Lys Glu Thr Glu Val Lys Glu Asp Ala Pro
            20                  25                  30

Gln Ala Gly Ser Gln Gly Gln Gly Ala Pro Ser Thr Gln Gly Ser Gln
        35                  40                  45

Asp Met Ala Ala Val Ser Ala Glu Asn Thr Gly Asn Gly Gly Ala Ala
    50                  55                  60

Thr Thr Asp Lys Pro Lys Asn Glu Asp Glu Gly Pro Gln Asn Asp Met
65                  70                  75                  80

Pro Gln Asn Ser Ala Glu Ser Ala Asn Gln Thr Gly Asn Asn Gln Pro
                85                  90                  95

Ala Asp Ser Ser Asp Ser Ala Pro Ala Ser Asn Pro Ala Pro Ala Asn
            100                 105                 110

Gly Gly Ser Asn Phe Gly Arg Val Asp Leu Ala Asn Gly Val Leu Ile
        115                 120                 125

Asp Gly Pro Ser Gln Asn Ile Thr Leu Thr His Cys Lys Gly Asp Ser
    130                 135                 140

Cys Asn Gly Asp Asn Leu Leu Asp Glu Glu Ala Pro Ser Lys Ser Glu
145                 150                 155                 160

Phe Glu Asn Leu Asn Glu Ser Glu Arg Ile Glu Lys Tyr Lys Lys Asp
                165                 170                 175

Gly Lys Ser Asp Lys Phe Thr Asn Leu Val Ala Thr Ala Val Gln Ala
            180                 185                 190
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Asn Gly Thr Asn Lys Tyr Val Ile Ile Tyr Lys Asp Lys Ser Ala Ser
195 200 205

Ser Ser Ser Ala Arg Phe Arg Arg Ser Ala Arg Ser Arg Arg Ser Leu
210 215 220

Pro Ala Glu Met Pro Leu Ile Pro Val Asn Gln Ala Asp Thr Leu Ile
225 230 235 240

Val Asp Gly Glu Ala Val Ser Leu Thr Gly His Ser Gly Asn Ile Phe
245 250 255

Ala Pro Glu Gly Asn Tyr Arg Tyr Leu Thr Tyr Gly Ala Glu Lys Leu
260 265 270

Pro Gly Gly Ser Tyr Ala Leu Arg Val Gln Gly Glu Pro Ala Lys Gly
275 280 285

Glu Met Leu Ala Gly Thr Ala Val Tyr Asn Gly Glu Val Leu His Phe
290 295 300

His Thr Glu Asn Gly Arg Pro Tyr Pro Thr Arg Gly Arg Phe Ala Ala
305 310 315 320

Lys Val Asp Phe Gly Ser Lys Ser Val Asp Gly Ile Ile Asp Ser Gly
325 330 335

Asp Asp Leu His Met Gly Thr Gln Lys Phe Lys Ala Ala Ile Asp Gly
340 345 350

Asn Gly Phe Lys Gly Thr Trp Thr Glu Asn Gly Gly Gly Asp Val Ser
355 360 365

Gly Arg Phe Tyr Gly Pro Ala Gly Glu Glu Val Ala Gly Lys Tyr Ser
370 375 380

Tyr Arg Pro Thr Asp Ala Glu Lys Gly Gly Phe Gly Val Phe Ala Gly
385 390 395 400

Lys Lys Glu Gln Asp Gly Ser Gly Gly Gly Gly Ala Thr Asn Asp Asp
405 410 415

Asp Val Lys Lys Ala Ala Thr Val Ala Ile Ala Ala Ala Tyr Asn Asn
420 425 430

Gly Gln Glu Ile Asn Gly Phe Lys Ala Gly Glu Thr Ile Tyr Asp Ile
435 440 445

Asp Glu Asp Gly Thr Ile Thr Lys Lys Asp Ala Thr Ala Ala Asp Val
450 455 460

Glu Ala Asp Asp Phe Lys Gly Leu Gly Leu Lys Lys Val Val Thr Asn
465 470 475 480

Leu Thr Lys Thr Val Asn Glu Asn Lys Gln Asn Val Asp Ala Lys Val
485 490 495

```
Lys Ala Ala Glu Ser Glu Ile Glu Lys Leu Thr Thr Lys Leu Ala Asp
            500                 505                 510

Thr Asp Ala Ala Leu Ala Asp Thr Asp Ala Ala Leu Asp Ala Thr Thr
        515                 520                 525

Asn Ala Leu Asn Lys Leu Gly Glu Asn Ile Thr Thr Phe Ala Glu Glu
    530                 535                 540

Thr Lys Thr Asn Ile Val Lys Ile Asp Glu Lys Leu Glu Ala Val Ala
545                 550                 555                 560

Asp Thr Val Asp Lys His Ala Glu Ala Phe Asn Asp Ile Ala Asp Ser
                565                 570                 575

Leu Asp Glu Thr Asn Thr Lys Ala Asp Glu Ala Val Lys Thr Ala Asn
            580                 585                 590

Glu Ala Lys Gln Thr Ala Glu Glu Thr Lys Gln Asn Val Asp Ala Lys
        595                 600                 605

Val Lys Ala Ala Glu Thr Ala Ala Gly Lys Ala Glu Ala Ala Ala Gly
    610                 615                 620

Thr Ala Asn Thr Ala Ala Asp Lys Ala Glu Ala Val Ala Ala Lys Val
625                 630                 635                 640

Thr Asp Ile Lys Ala Asp Ile Ala Thr Asn Lys Asp Asn Ile Ala Lys
                645                 650                 655

Lys Ala Asn Ser Ala Asp Val Tyr Thr Arg Glu Glu Ser Asp Ser Lys
            660                 665                 670

Phe Val Arg Ile Asp Gly Leu Asn Ala Thr Thr Glu Lys Leu Asp Thr
        675                 680                 685

Arg Leu Ala Ser Ala Glu Lys Ser Ile Ala Asp His Asp Thr Arg Leu
    690                 695                 700

Asn Gly Leu Asp Lys Thr Val Ser Asp Leu Arg Lys Glu Thr Arg Gln
705                 710                 715                 720

Gly Leu Ala Glu Gln Ala Ala Leu Ser Gly Leu Phe Gln Pro Tyr Asn
                725                 730                 735

Val Gly Arg Phe Asn Val Thr Ala Ala Val Gly Gly Tyr Lys Ser Glu
            740                 745                 750

Ser Ala Val Ala Ile Gly Thr Gly Phe Arg Phe Thr Glu Asn Phe Ala
        755                 760                 765

Ala Lys Ala Gly Val Ala Val Gly Thr Ser Ser Gly Ser Ser Ala Ala
    770                 775                 780

Tyr His Val Gly Val Asn Tyr Glu Trp
785                 790
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<210>  94
<211>  2700
<212>  DNA
<213>  Artificial Sequence

<220>
<223>  deltaG287NZ-919

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gcgccatccg cacaaggcgg tcaagatatg gcggcggttt cggaagaaaa tacaggcaat   180
ggcggtgcgg cagcaacgga caaacccaaa aatgaagacg agggggcgca aaatgatatg   240
ccgcaaaatg ccgccgatac agatagtttg acaccgaatc acaccccggc ttcgaatatg   300
ccggccggaa atatggaaaa ccaagcaccg gatgccgggg aatcggagca gccggcaaac   360
caaccggata tggcaaatac ggcggacgga atgcagggtg acgatccgtc ggcaggcggg   420
gaaaatgccg gcaatacggc tgcccaaggt acaaatcaag ccgaaaacaa tcaaaccgcc   480
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ggaaggacga acgtgggcaa ttctgttgtg attgacgggc cgtcgcaaaa tataacgttg   600
acccactgta aaggcgattc ttgtagtggc aataatttct tggatgaaga agtacagcta   660
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aagaatgacg ggaagaatga taaatttgtc ggtttggttg ccgatagtgt gcagatgaag   780
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gcggatacgc tgattgtcga tggggaagcg gtcagcctga cggggcattc cggcaatatc   960
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gtgtacaacg gcgaagtgct gcattttcat acggaaaacg gccgtccgtc cccgtccaga  1140
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ctctcccgat tccccatcac cgcgcgcaca acggcaatca aaggcaggtt tgaaggaagc  2040
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ccgatactcg gttacgccga agaccccgtc gaactttttt ttatgcacat ccaaggctcg  2160
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ctcaaccgcc tgattatggc gcaggatacc ggcagcgcga ttaaaggcgc ggtgcgcgtg  2580
gattattttt ggggatacgg cgacgaagcc ggcgaacttg ccggcaaaca gaaaaccacg  2640
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<210>  95
<211>  897
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<212>   PRT
<213>   Artificial Sequence

<220>
<223>   deltaG287NZ-919

<400>   95
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Ala Pro Val Val Ser Glu Lys Glu Thr Glu Ala Lys Glu Asp Ala Pro
                20                  25                  30

Gln Ala Gly Ser Gln Gly Gln Gly Ala Pro Ser Ala Gln Gly Gly Gln
            35                  40                  45

Asp Met Ala Ala Val Ser Glu Glu Asn Thr Gly Asn Gly Gly Ala Ala
        50                  55                  60

Ala Thr Asp Lys Pro Lys Asn Glu Asp Glu Gly Ala Gln Asn Asp Met
65                  70                  75                  80

Pro Gln Asn Ala Ala Asp Thr Asp Ser Leu Thr Pro Asn His Thr Pro
                85                  90                  95

Ala Ser Asn Met Pro Ala Gly Asn Met Glu Asn Gln Ala Pro Asp Ala
            100                 105                 110

Gly Glu Ser Glu Gln Pro Ala Asn Gln Pro Asp Met Ala Asn Thr Ala
        115                 120                 125

Asp Gly Met Gln Gly Asp Asp Pro Ser Ala Gly Gly Glu Asn Ala Gly
    130                 135                 140

Asn Thr Ala Ala Gln Gly Thr Asn Gln Ala Glu Asn Asn Gln Thr Ala
145                 150                 155                 160

Gly Ser Gln Asn Pro Ala Ser Ser Thr Asn Pro Ser Ala Thr Asn Ser
                165                 170                 175

Gly Gly Asp Phe Gly Arg Thr Asn Val Gly Asn Ser Val Val Ile Asp
            180                 185                 190

Gly Pro Ser Gln Asn Ile Thr Leu Thr His Cys Lys Gly Asp Ser Cys
        195                 200                 205

Ser Gly Asn Asn Phe Leu Asp Glu Glu Val Gln Leu Lys Ser Glu Phe
    210                 215                 220

Glu Lys Leu Ser Asp Ala Asp Lys Ile Ser Asn Tyr Lys Lys Asp Gly
225                 230                 235                 240

Lys Asn Asp Gly Lys Asn Asp Lys Phe Val Gly Leu Val Ala Asp Ser
                245                 250                 255

Val Gln Met Lys Gly Ile Asn Gln Tyr Ile Ile Phe Tyr Lys Pro Lys
            260                 265                 270
```

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Pro Thr Ser Phe Ala Arg Phe Arg Arg Ser Ala Arg Ser Arg Arg Ser
        275                 280                 285

Leu Pro Ala Glu Met Pro Leu Ile Pro Val Asn Gln Ala Asp Thr Leu
    290                 295                 300

Ile Val Asp Gly Glu Ala Val Ser Leu Thr Gly His Ser Gly Asn Ile
305                 310                 315                 320

Phe Ala Pro Glu Gly Asn Tyr Arg Tyr Leu Thr Tyr Gly Ala Glu Lys
                325                 330                 335

Leu Pro Gly Gly Ser Tyr Ala Leu Arg Val Gln Gly Glu Pro Ser Lys
            340                 345                 350

Gly Glu Met Leu Ala Gly Thr Ala Val Tyr Asn Gly Glu Val Leu His
        355                 360                 365

Phe His Thr Glu Asn Gly Arg Pro Ser Pro Ser Arg Gly Arg Phe Ala
    370                 375                 380

Ala Lys Val Asp Phe Gly Ser Lys Ser Val Asp Gly Ile Ile Asp Ser
385                 390                 395                 400

Gly Asp Gly Leu His Met Gly Thr Gln Lys Phe Lys Ala Ala Ile Asp
                405                 410                 415

Gly Asn Gly Phe Lys Gly Thr Trp Thr Glu Asn Gly Gly Gly Asp Val
            420                 425                 430

Ser Gly Lys Phe Tyr Gly Pro Ala Gly Glu Glu Val Ala Gly Lys Tyr
        435                 440                 445

Ser Tyr Arg Pro Thr Asp Ala Glu Lys Gly Gly Phe Gly Val Phe Ala
    450                 455                 460

Gly Lys Lys Glu Gln Asp Gly Ser Gly Gly Gly Gly Cys Gln Ser Lys
465                 470                 475                 480

Ser Ile Gln Thr Phe Pro Gln Pro Asp Thr Ser Val Ile Asn Gly Pro
                485                 490                 495

Asp Arg Pro Val Gly Ile Pro Asp Pro Ala Gly Thr Thr Val Gly Gly
            500                 505                 510

Gly Gly Ala Val Tyr Thr Val Val Pro His Leu Ser Leu Pro His Trp
        515                 520                 525

Ala Ala Gln Asp Phe Ala Lys Ser Leu Gln Ser Phe Arg Leu Gly Cys
    530                 535                 540

Ala Asn Leu Lys Asn Arg Gln Gly Trp Gln Asp Val Cys Ala Gln Ala
545                 550                 555                 560

Phe Gln Thr Pro Val His Ser Phe Gln Ala Lys Gln Phe Phe Glu Arg
                565                 570                 575
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Tyr Phe Thr Pro Trp Gln Val Ala Gly Asn Gly Ser Leu Ala Gly Thr
            580                 585                 590

Val Thr Gly Tyr Tyr Glu Pro Val Leu Lys Gly Asp Asp Arg Arg Thr
        595                 600                 605

Ala Gln Ala Arg Phe Pro Ile Tyr Gly Ile Pro Asp Asp Phe Ile Ser
    610                 615                 620

Val Pro Leu Pro Ala Gly Leu Arg Ser Gly Lys Ala Leu Val Arg Ile
625                 630                 635                 640

Arg Gln Thr Gly Lys Asn Ser Gly Thr Ile Asp Asn Thr Gly Gly Thr
                645                 650                 655

His Thr Ala Asp Leu Ser Arg Phe Pro Ile Thr Ala Arg Thr Thr Ala
            660                 665                 670

Ile Lys Gly Arg Phe Glu Gly Ser Arg Phe Leu Pro Tyr His Thr Arg
        675                 680                 685

Asn Gln Ile Asn Gly Gly Ala Leu Asp Gly Lys Ala Pro Ile Leu Gly
    690                 695                 700

Tyr Ala Glu Asp Pro Val Glu Leu Phe Phe Met His Ile Gln Gly Ser
705                 710                 715                 720

Gly Arg Leu Lys Thr Pro Ser Gly Lys Tyr Ile Arg Ile Gly Tyr Ala
                725                 730                 735

Asp Lys Asn Glu His Pro Tyr Val Ser Ile Gly Arg Tyr Met Ala Asp
            740                 745                 750

Lys Gly Tyr Leu Lys Leu Gly Gln Thr Ser Met Gln Gly Ile Lys Ala
        755                 760                 765

Tyr Met Arg Gln Asn Pro Gln Arg Leu Ala Glu Val Leu Gly Gln Asn
    770                 775                 780

Pro Ser Tyr Ile Phe Phe Arg Glu Leu Ala Gly Ser Ser Asn Asp Gly
785                 790                 795                 800

Pro Val Gly Ala Leu Gly Thr Pro Leu Met Gly Glu Tyr Ala Gly Ala
                805                 810                 815

Val Asp Arg His Tyr Ile Thr Leu Gly Ala Pro Leu Phe Val Ala Thr
            820                 825                 830

Ala His Pro Val Thr Arg Lys Ala Leu Asn Arg Leu Ile Met Ala Gln
        835                 840                 845

Asp Thr Gly Ser Ala Ile Lys Gly Ala Val Arg Val Asp Tyr Phe Trp
    850                 855                 860

Gly Tyr Gly Asp Glu Ala Gly Glu Leu Ala Gly Lys Gln Lys Thr Thr
865                 870                 875                 880
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Gly Tyr Val Trp Gln Leu Leu Pro Asn Gly Met Lys Pro Glu Tyr Arg
885 890 895

Pro

<210> 96
<211> 1941
<212> DNA
<213> Artificial Sequence

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<223> deltaG287NZ-953

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gcgccatccg cacaaggcgg tcaagatatg gcggcggttt cggaagaaaa tacaggcaat 180
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ccgcaaaatg ccgccgatac agatagtttg acaccgaatc acaccccggc ttcgaatatg 300
ccggccggaa atatggaaaa ccaagcaccg gatgccgggg aatcggagca gccggcaaac 360
caaccggata tggcaaatac ggcggacgga atgcagggtg acgatccgtc ggcaggcggg 420
gaaaatgccg gcaatacggc tgcccaaggt acaaatcaag ccgaaaacaa tcaaaccgcc 480
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aaatcagaat ttgaaaaatt aagtgatgca gacaaaataa gtaattacaa gaaagatggg 720
aagaatgacg ggaagaatga taaatttgtc ggtttggttg ccgatagtgt gcagatgaag 780
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gcgaaaaccg aagtttgcgg cggcgacttc agcaccacca tcgaccgcac caaatggggc 1860
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gcagccaaac aataaaagct t 1941

<210> 97
<211> 644
<212> PRT
<213> Artificial Sequence

<220>
<223> deltaG287NZ-953

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Ala Pro Val Val Ser Glu Lys Glu Thr Glu Ala Lys Glu Asp Ala Pro
            20                  25                  30

Gln Ala Gly Ser Gln Gly Gln Gly Ala Pro Ser Ala Gln Gly Gly Gln
        35                  40                  45

Asp Met Ala Ala Val Ser Glu Glu Asn Thr Gly Asn Gly Gly Ala Ala
    50                  55                  60

Ala Thr Asp Lys Pro Lys Asn Glu Asp Glu Gly Ala Gln Asn Asp Met
65                  70                  75                  80

Pro Gln Asn Ala Ala Asp Thr Asp Ser Leu Thr Pro Asn His Thr Pro
                85                  90                  95

Ala Ser Asn Met Pro Ala Gly Asn Met Glu Asn Gln Ala Pro Asp Ala
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Gly Glu Ser Glu Gln Pro Ala Asn Gln Pro Asp Met Ala Asn Thr Ala
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Asp Gly Met Gln Gly Asp Asp Pro Ser Ala Gly Gly Glu Asn Ala Gly
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Asn Thr Ala Ala Gln Gly Thr Asn Gln Ala Glu Asn Asn Gln Thr Ala
145                 150                 155                 160

Gly Ser Gln Asn Pro Ala Ser Ser Thr Asn Pro Ser Ala Thr Asn Ser
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Gly Gly Asp Phe Gly Arg Thr Asn Val Gly Asn Ser Val Val Ile Asp
            180                 185                 190

Gly Pro Ser Gln Asn Ile Thr Leu Thr His Cys Lys Gly Asp Ser Cys
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Ser Gly Asn Asn Phe Leu Asp Glu Glu Val Gln Leu Lys Ser Glu Phe
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Glu Lys Leu Ser Asp Ala Asp Lys Ile Ser Asn Tyr Lys Lys Asp Gly
225                 230                 235                 240

Lys Asn Asp Gly Lys Asn Asp Lys Phe Val Gly Leu Val Ala Asp Ser
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Val Gln Met Lys Gly Ile Asn Gln Tyr Ile Ile Phe Tyr Lys Pro Lys
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Pro Thr Ser Phe Ala Arg Phe Arg Arg Ser Ala Arg Ser Arg Arg Ser
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Leu Pro Ala Glu Met Pro Leu Ile Pro Val Asn Gln Ala Asp Thr Leu
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Ile Val Asp Gly Glu Ala Val Ser Leu Thr Gly His Ser Gly Asn Ile
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Phe Ala Pro Glu Gly Asn Tyr Arg Tyr Leu Thr Tyr Gly Ala Glu Lys
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Leu Pro Gly Gly Ser Tyr Ala Leu Arg Val Gln Gly Glu Pro Ser Lys
            340                 345                 350

Gly Glu Met Leu Ala Gly Thr Ala Val Tyr Asn Gly Glu Val Leu His
        355                 360                 365

Phe His Thr Glu Asn Gly Arg Pro Ser Pro Ser Arg Gly Arg Phe Ala
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Ala Lys Val Asp Phe Gly Ser Lys Ser Val Asp Gly Ile Ile Asp Ser
385                 390                 395                 400

Gly Asp Gly Leu His Met Gly Thr Gln Lys Phe Lys Ala Ala Ile Asp
                405                 410                 415

Gly Asn Gly Phe Lys Gly Thr Trp Thr Glu Asn Gly Gly Gly Asp Val
            420                 425                 430

Ser Gly Lys Phe Tyr Gly Pro Ala Gly Glu Glu Val Ala Gly Lys Tyr
        435                 440                 445

Ser Tyr Arg Pro Thr Asp Ala Glu Lys Gly Gly Phe Gly Val Phe Ala
    450                 455                 460

Gly Lys Lys Glu Gln Asp Gly Ser Gly Gly Gly Gly Ala Thr Tyr Lys
465                 470                 475                 480

Val Asp Glu Tyr His Ala Asn Ala Arg Phe Ala Ile Asp His Phe Asn
                485                 490                 495

Thr Ser Thr Asn Val Gly Gly Phe Tyr Gly Leu Thr Gly Ser Val Glu
            500                 505                 510

Phe Asp Gln Ala Lys Arg Asp Gly Lys Ile Asp Ile Thr Ile Pro Val
        515                 520                 525

Ala Asn Leu Gln Ser Gly Ser Gln His Phe Thr Asp His Leu Lys Ser
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Ala Asp Ile Phe Asp Ala Ala Gln Tyr Pro Asp Ile Arg Phe Val Ser
545                 550                 555                 560

Thr Lys Phe Asn Phe Asn Gly Lys Lys Leu Val Ser Val Asp Gly Asn
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Leu Thr Met His Gly Lys Thr Ala Pro Val Lys Leu Lys Ala Glu Lys
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Phe Asn Cys Tyr Gln Ser Pro Met Ala Lys Thr Glu Val Cys Gly Gly
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        595                 600                 605

Asp Phe Ser Thr Thr Ile Asp Arg Thr Lys Trp Gly Val Asp Tyr Leu
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Val Asn Val Gly Met Thr Lys Ser Val Arg Ile Asp Ile Gln Ile Glu
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            20                  25                  30

Gln Ala Gly Ser Gln Gly Gln Gly Ala Pro Ser Ala Gln Gly Gly Gln
        35                  40                  45

Asp Met Ala Ala Val Ser Glu Glu Asn Thr Gly Asn Gly Gly Ala Ala
    50                  55                  60

Ala Thr Asp Lys Pro Lys Asn Glu Asp Glu Gly Ala Gln Asn Asp Met
65                  70                  75                  80

Pro Gln Asn Ala Ala Asp Thr Asp Ser Leu Thr Pro Asn His Thr Pro
                85                  90                  95

Ala Ser Asn Met Pro Ala Gly Asn Met Glu Asn Gln Ala Pro Asp Ala
            100                 105                 110

Gly Glu Ser Glu Gln Pro Ala Asn Gln Pro Asp Met Ala Asn Thr Ala
        115                 120                 125

Asp Gly Met Gln Gly Asp Asp Pro Ser Ala Gly Gly Glu Asn Ala Gly
    130                 135                 140

Asn Thr Ala Ala Gln Gly Thr Asn Gln Ala Glu Asn Asn Gln Thr Ala
145                 150                 155                 160

Gly Ser Gln Asn Pro Ala Ser Ser Thr Asn Pro Ser Ala Thr Asn Ser
                165                 170                 175

Gly Gly Asp Phe Gly Arg Thr Asn Val Gly Asn Ser Val Val Ile Asp
            180                 185                 190

Gly Pro Ser Gln Asn Ile Thr Leu Thr His Cys Lys Gly Asp Ser Cys
        195                 200                 205

Ser Gly Asn Asn Phe Leu Asp Glu Glu Val Gln Leu Lys Ser Glu Phe
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Glu Lys Leu Ser Asp Ala Asp Lys Ile Ser Asn Tyr Lys Lys Asp Gly
225                 230                 235                 240

Lys Asn Asp Gly Lys Asn Asp Lys Phe Val Gly Leu Val Ala Asp Ser
                245                 250                 255

Val Gln Met Lys Gly Ile Asn Gln Tyr Ile Ile Phe Tyr Lys Pro Lys
            260                 265                 270

Pro Thr Ser Phe Ala Arg Phe Arg Arg Ser Ala Arg Ser Arg Arg Ser
        275                 280                 285

Leu Pro Ala Glu Met Pro Leu Ile Pro Val Asn Gln Ala Asp Thr Leu
    290                 295                 300

Ile Val Asp Gly Glu Ala Val Ser Leu Thr Gly His Ser Gly Asn Ile
305                 310                 315                 320

Phe Ala Pro Glu Gly Asn Tyr Arg Tyr Leu Thr Tyr Gly Ala Glu Lys
                325                 330                 335

Leu Pro Gly Gly Ser Tyr Ala Leu Arg Val Gln Gly Glu Pro Ser Lys
            340                 345                 350

Gly Glu Met Leu Ala Gly Thr Ala Val Tyr Asn Gly Glu Val Leu His
        355                 360                 365

Phe His Thr Glu Asn Gly Arg Pro Ser Pro Ser Arg Gly Arg Phe Ala
    370                 375                 380

Ala Lys Val Asp Phe Gly Ser Lys Ser Val Asp Gly Ile Ile Asp Ser
385                 390                 395                 400

Gly Asp Gly Leu His Met Gly Thr Gln Lys Phe Lys Ala Ala Ile Asp
                405                 410                 415

Gly Asn Gly Phe Lys Gly Thr Trp Thr Glu Asn Gly Gly Gly Asp Val
            420                 425                 430

Ser Gly Lys Phe Tyr Gly Pro Ala Gly Glu Glu Val Ala Gly Lys Tyr
        435                 440                 445

Ser Tyr Arg Pro Thr Asp Ala Glu Lys Gly Gly Phe Gly Val Phe Ala
    450                 455                 460

Gly Lys Lys Glu Gln Asp Gly Ser Gly Gly Gly Gly Ala Thr Asn Asp
465                 470                 475                 480

Asp Asp Val Lys Lys Ala Ala Thr Val Ala Ile Ala Ala Ala Tyr Asn
                485                 490                 495

Asn Gly Gln Glu Ile Asn Gly Phe Lys Ala Gly Glu Thr Ile Tyr Asp
            500                 505                 510

Ile Asp Glu Asp Gly Thr Ile Thr Lys Lys Asp Ala Thr Ala Ala Asp
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Val Glu Ala Asp Asp Phe Lys Gly Leu Gly Leu Lys Lys Val Val Thr
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Val Lys Ala Ala Glu Ser Glu Ile Glu Lys Leu Thr Thr Lys Leu Ala
                565                 570                 575

Asp Thr Asp Ala Ala Leu Ala Asp Thr Asp Ala Ala Leu Asp Ala Thr
            580                 585                 590

Thr Asn Ala Leu Asn Lys Leu Gly Glu Asn Ile Thr Thr Phe Ala Glu
        595                 600                 605

Glu Thr Lys Thr Asn Ile Val Lys Ile Asp Glu Lys Leu Glu Ala Val
    610                 615                 620

Ala Asp Thr Val Asp Lys His Ala Glu Ala Phe Asn Asp Ile Ala Asp
625                 630                 635                 640

Ser Leu Asp Glu Thr Asn Thr Lys Ala Asp Glu Ala Val Lys Thr Ala
                645                 650                 655

Asn Glu Ala Lys Gln Thr Ala Glu Glu Thr Lys Gln Asn Val Asp Ala
            660                 665                 670

Lys Val Lys Ala Ala Glu Thr Ala Ala Gly Lys Ala Glu Ala Ala Ala
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Gly Thr Ala Asn Thr Ala Ala Asp Lys Ala Glu Ala Val Ala Ala Lys
    690                 695                 700

Val Thr Asp Ile Lys Ala Asp Ile Ala Thr Asn Lys Asp Asn Ile Ala
705                 710                 715                 720

Lys Lys Ala Asn Ser Ala Asp Val Tyr Thr Arg Glu Glu Ser Asp Ser
                725                 730                 735

Lys Phe Val Arg Ile Asp Gly Leu Asn Ala Thr Thr Glu Lys Leu Asp
            740                 745                 750

Thr Arg Leu Ala Ser Ala Glu Lys Ser Ile Ala Asp His Asp Thr Arg
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Leu Asn Gly Leu Asp Lys Thr Val Ser Asp Leu Arg Lys Glu Thr Arg
    770                 775                 780

Gln Gly Leu Ala Glu Gln Ala Ala Leu Ser Gly Leu Phe Gln Pro Tyr
785                 790                 795                 800

Asn Val Gly Arg Phe Asn Val Thr Ala Ala Val Gly Gly Tyr Lys Ser
                805                 810                 815

Glu Ser Ala Val Ala Ile Gly Thr Gly Phe Arg Phe Thr Glu Asn Phe
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Ile Lys Asn Glu Met Cys Lys Asp Arg Ser Met Leu Cys Ala Gly Arg
35 40 45

Asp Asp Val Ala Val Thr Asp Arg Asp Ala Lys Ile Asn Ala Pro Pro
50 55 60

Pro Asn Leu His Thr Gly Asp Phe Pro Asn Pro Asn Asp Ala Tyr Lys

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Asn Leu Ile Asn Leu Lys Pro Ala Ile Glu Ala Gly Tyr Thr Gly Arg
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Gly Val Glu Val Gly Ile Val Asp Thr Gly Glu Ser Val Gly Ser Ile
            100                 105                 110

Ser Phe Pro Glu Leu Tyr Gly Arg Lys Glu His Gly Tyr Asn Glu Asn
        115                 120                 125

Tyr Lys Asn Tyr Thr Ala Tyr Met Arg Lys Glu Ala Pro Glu Asp Gly
    130                 135                 140

Gly Gly Lys Asp Ile Glu Ala Ser Phe Asp Asp Glu Ala Val Ile Glu
145                 150                 155                 160

Thr Glu Ala Lys Pro Thr Asp Ile Arg His Val Lys Glu Ile Gly His
                165                 170                 175

Ile Asp Leu Val Ser His Ile Ile Gly Gly Arg Ser Val Asp Gly Arg
            180                 185                 190

Pro Ala Gly Gly Ile Ala Pro Asp Ala Thr Leu His Ile Met Asn Thr
        195                 200                 205

Asn Asp Glu Thr Lys Asn Glu Met Met Val Ala Ala Ile Arg Asn Ala
    210                 215                 220

Trp Val Lys Leu Gly Glu Arg Gly Val Arg Ile Val Asn Asn Ser Phe
225                 230                 235                 240

Gly Thr Thr Ser Arg Ala Gly Thr Ala Asp Leu Phe Gln Ile Ala Asn
                245                 250                 255

Ser Glu Glu Gln Tyr Arg Gln Ala Leu Leu Asp Tyr Ser Gly Gly Asp
            260                 265                 270

Lys Thr Asp Glu Gly Ile Arg Leu Met Gln Gln Ser Asp Tyr Gly Asn
        275                 280                 285

Leu Ser Tyr His Ile Arg Asn Lys Asn Met Leu Phe Ile Phe Ser Thr
    290                 295                 300

Gly Asn Asp Ala Gln Ala Gln Pro Asn Thr Tyr Ala Leu Leu Pro Phe
305                 310                 315                 320

Tyr Glu Lys Asp Ala Gln Lys Gly Ile Ile Thr Val Ala Gly Val Asp
                325                 330                 335

Arg Ser Gly Glu Lys Phe Lys Arg Glu Met Tyr Gly Glu Pro Gly Thr
            340                 345                 350

Glu Pro Leu Glu Tyr Gly Ser Asn His Cys Gly Ile Thr Ala Met Trp
        355                 360                 365

Cys Leu Ser Ala Pro Tyr Glu Ala Ser Val Arg Phe Thr Arg Thr Asn
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Leu Arg Thr Thr Leu Leu Thr Thr Ala Gln Asp Ile Gly Ala Val Gly
420 425 430

Val Asp Ser Lys Phe Gly Trp Gly Leu Leu Asp Ala Gly Lys Ala Met
435 440 445

Asn Gly Pro Ala Ser Phe Pro Phe Gly Asp Phe Thr Ala Asp Thr Lys
450 455 460

Gly Thr Ser Asp Ile Ala Tyr Ser Phe Arg Asn Asp Ile Ser Gly Thr
465 470 475 480

Gly Gly Leu Ile Lys Lys Gly Gly Ser Gln Leu Gln Leu His Gly Asn
485 490 495

Asn Thr Tyr Thr Gly Lys Thr Ile Ile Glu Gly Gly Ser Leu Val Leu
500 505 510

Tyr Gly Asn Asn Lys Ser Asp Met Arg Val Glu Thr Lys Gly Ala Leu
515 520 525

Ile Tyr Asn Gly Ala Ala Ser Gly Gly Ser Leu Asn Ser Asp Gly Ile
530 535 540

Val Tyr Leu Ala Asp Thr Asp Gln Ser Gly Ala Asn Glu Thr Val His
545 550 555 560

Ile Lys Gly Ser Leu Gln Leu Asp Gly Lys Gly Thr Leu Tyr Thr Arg
565 570 575

Leu Gly Lys Leu Leu Lys Val Asp Gly Thr Ala Ile Ile Gly Gly Lys
580 585 590

Leu Tyr Met Ser Ala Arg Gly Lys Gly Ala Gly Tyr Leu Asn Ser Thr
595 600 605

Gly Arg Arg Val Pro Phe Leu Ser Ala Ala Lys Ile Gly Gln Asp Tyr
610 615 620

Ser Phe Phe Thr Asn Ile Glu Thr Asp Gly Gly Leu Leu Ala Ser Leu
625 630 635 640

Asp Ser Val Glu Lys Thr Ala Gly Ser Glu Gly Asp Thr Leu Ser Tyr
645 650 655

Tyr Val Arg Arg Gly Asn Ala Ala Arg Thr Ala Ser Ala Ala Ala His
660 665 670

Ser Ala Pro Ala Gly Leu Lys His Ala Val Glu Gln Gly Gly Ser Asn

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        675                 680                 685

Leu Glu Asn Leu Met Val Glu Leu Asp Ala Ser Glu Ser Ser Ala Thr
    690                 695                 700

Pro Glu Thr Val Glu Thr Ala Ala Ala Asp Arg Thr Asp Met Pro Gly
705                 710                 715                 720

Ile Arg Pro Tyr Gly Ala Thr Phe Arg Ala Ala Ala Ala Val Gln His
                725                 730                 735

Ala Asn Ala Ala Asp Gly Val Arg Ile Phe Asn Ser Leu Ala Ala Thr
            740                 745                 750

Val Tyr Ala Asp Ser Thr Ala Ala His Ala Asp Met Gln Gly Arg Arg
        755                 760                 765

Leu Lys Ala Val Ser Asp Gly Leu Asp His Asn Gly Thr Gly Leu Arg
    770                 775                 780

Val Ile Ala Gln Thr Gln Gln Asp Gly Gly Thr Trp Glu Gln Gly Gly
785                 790                 795                 800

Val Glu Gly Lys Met Arg Gly Ser Thr Gln Thr Val Gly Ile Ala Ala
                805                 810                 815

Lys Thr Gly Glu Asn Thr Thr Ala Ala Ala Thr Leu Gly Met Gly Arg
            820                 825                 830

Ser Thr Trp Ser Glu Asn Ser Ala Asn Ala Lys Thr Asp Ser Ile Ser
        835                 840                 845

Leu Phe Ala Gly Ile Arg His Asp Ala Gly Asp Ile Gly Tyr Leu Lys
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Gly Leu Phe Ser Tyr Gly Arg Tyr Lys Asn Ser Ile Ser Arg Ser Thr
865                 870                 875                 880

Gly Ala Asp Glu His Ala Glu Gly Ser Val Asn Gly Thr Leu Met Gln
                885                 890                 895

Leu Gly Ala Leu Gly Gly Val Asn Val Pro Phe Ala Ala Thr Gly Asp
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Leu Thr Val Glu Gly Gly Leu Arg Tyr Asp Leu Leu Lys Gln Asp Ala
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Phe Ala Glu Lys Gly Ser Ala Leu Gly Trp Ser Gly Asn Ser Leu Thr
    930                 935                 940

Glu Gly Thr Leu Val Gly Leu Ala Gly Leu Lys Leu Ser Gln Pro Leu
945                 950                 955                 960

Ser Asp Lys Ala Val Leu Phe Ala Thr Ala Gly Val Glu Arg Asp Leu
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Asn Gly Arg Asp Tyr Thr Val Thr Gly Gly Phe Thr Gly Ala Thr Ala
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980 985 990

Ala Thr Gly Lys Thr Gly Ala Arg Asn Met Pro His Thr Arg Leu Val
995 1000 1005

Ala Gly Leu Gly Ala Asp Val Glu Phe Gly Asn Gly Trp Asn Gly Leu
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Ala Arg Tyr Ser Tyr Ala Gly Ser Lys Gln Tyr Gly Asn His Ser Gly
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Arg Val Gly Val Gly Tyr Arg Phe Leu Asp Gly Gly Gly Gly Thr Gly
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Ser Ser Asp Leu Ala Asn Asp Ser Phe Ile Arg Gln Val Leu Asp Arg
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Gln His Phe Glu Pro Asp Gly Lys Tyr His Leu Phe Gly Ser Arg Gly
1075 1080 1085

Glu Leu Ala Glu Arg Ser Gly His Ile Gly Leu Gly Lys Ile Gln Ser
1090 1095 1100

His Gln Leu Gly Asn Leu Met Ile Gln Gln Ala Ala Ile Lys Gly Asn
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Ile Gly Tyr Ile Val Arg Phe Ser Asp His Gly His Glu Val His Ser
1125 1130 1135

Pro Phe Asp Asn His Ala Ser His Ser Asp Ser Asp Glu Ala Gly Ser
1140 1145 1150

Pro Val Asp Gly Phe Ser Leu Tyr Arg Ile His Trp Asp Gly Tyr Glu
1155 1160 1165

His His Pro Ala Asp Gly Tyr Asp Gly Pro Gln Gly Gly Gly Tyr Pro
1170 1175 1180

Ala Pro Lys Gly Ala Arg Asp Ile Tyr Ser Tyr Asp Ile Lys Gly Val
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Ala Gln Asn Ile Arg Leu Asn Leu Thr Asp Asn Arg Ser Thr Gly Gln
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Arg Leu Ala Asp Arg Phe His Asn Ala Gly Ser Met Leu Thr Gln Gly
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Val Gly Asp Gly Phe Lys Arg Ala Thr Arg Tyr Ser Pro Glu Leu Asp
1235 1240 1245

Arg Ser Gly Asn Ala Ala Glu Ala Phe Asn Gly Thr Ala Asp Ile Val
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Lys Asn Ile Ile Gly Ala Ala Gly Glu Ile Val Gly Ala Gly Asp Ala
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Val Gln Gly Ile Ser Glu Gly Ser Asn Ile Ala Val Met His Gly Leu

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                1285                1290                1295

Gly Leu Leu Ser Thr Glu Asn Lys Met Ala Arg Ile Asn Asp Leu Ala
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Asp Met Ala Gln Leu Lys Asp Tyr Ala Ala Ala Ala Ile Arg Asp Trp
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Ala Val Gln Asn Pro Asn Ala Ala Gln Gly Ile Glu Ala Val Ser Asn
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Ile Phe Met Ala Ala Ile Pro Ile Lys Gly Ile Gly Ala Val Arg Gly
1345                1350                1355                1360

Lys Tyr Gly Leu Gly Gly Ile Thr Ala His Pro Ile Lys Arg Ser Gln
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Met Gly Ala Ile Ala Leu Pro Lys Gly Lys Ser Ala Val Ser Asp Asn
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Phe Ala Asp Ala Ala Tyr Ala Lys Tyr Pro Ser Pro Tyr His Ser Arg
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Asn Ile Arg Ser Asn Leu Glu Gln Arg Tyr Gly Lys Glu Asn Ile Thr
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Ser Ser Thr Val Pro Pro Ser Asn Gly Lys Asn Val Lys Leu Ala Asp
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Gln Arg His Pro Lys Thr Gly Val Pro Phe Asp Gly Lys Gly Phe Pro
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Asn Phe Glu Lys His Val Lys Tyr Asp Thr Leu Glu His His His His
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His His


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caggaagttg ccggcagcgc ggaagtgaaa accgtaaacg gcatacgcca tatcggcctt  3900
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Ile Lys Asn Glu Met Cys Lys Asp Arg Ser Met Leu Cys Ala Gly Arg
35 40 45

Asp Asp Val Ala Val Thr Asp Arg Asp Ala Lys Ile Asn Ala Pro Pro
50 55 60

Pro Asn Leu His Thr Gly Asp Phe Pro Asn Pro Asn Asp Ala Tyr Lys
65 70 75 80

Asn Leu Ile Asn Leu Lys Pro Ala Ile Glu Ala Gly Tyr Thr Gly Arg
85 90 95

Gly Val Glu Val Gly Ile Val Asp Thr Gly Glu Ser Val Gly Ser Ile
100 105 110

Ser Phe Pro Glu Leu Tyr Gly Arg Lys Glu His Gly Tyr Asn Glu Asn
115 120 125

Tyr Lys Asn Tyr Thr Ala Tyr Met Arg Lys Glu Ala Pro Glu Asp Gly
130 135 140

Gly Gly Lys Asp Ile Glu Ala Ser Phe Asp Asp Glu Ala Val Ile Glu
145 150 155 160

Thr Glu Ala Lys Pro Thr Asp Ile Arg His Val Lys Glu Ile Gly His
165 170 175

Ile Asp Leu Val Ser His Ile Ile Gly Gly Arg Ser Val Asp Gly Arg
180 185 190

Pro Ala Gly Gly Ile Ala Pro Asp Ala Thr Leu His Ile Met Asn Thr
195 200 205

Asn Asp Glu Thr Lys Asn Glu Met Met Val Ala Ala Ile Arg Asn Ala
210 215 220

Trp Val Lys Leu Gly Glu Arg Gly Val Arg Ile Val Asn Asn Ser Phe
225 230 235 240

Gly Thr Thr Ser Arg Ala Gly Thr Ala Asp Leu Phe Gln Ile Ala Asn
245 250 255

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Ser Glu Glu Gln Tyr Arg Gln Ala Leu Leu Asp Tyr Ser Gly Gly Asp
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Lys Thr Asp Glu Gly Ile Arg Leu Met Gln Gln Ser Asp Tyr Gly Asn
        275                 280                 285

Leu Ser Tyr His Ile Arg Asn Lys Asn Met Leu Phe Ile Phe Ser Thr
    290                 295                 300

Gly Asn Asp Ala Gln Ala Gln Pro Asn Thr Tyr Ala Leu Leu Pro Phe
305                 310                 315                 320

Tyr Glu Lys Asp Ala Gln Lys Gly Ile Ile Thr Val Ala Gly Val Asp
                325                 330                 335

Arg Ser Gly Glu Lys Phe Lys Arg Glu Met Tyr Gly Glu Pro Gly Thr
            340                 345                 350

Glu Pro Leu Glu Tyr Gly Ser Asn His Cys Gly Ile Thr Ala Met Trp
        355                 360                 365

Cys Leu Ser Ala Pro Tyr Glu Ala Ser Val Arg Phe Thr Arg Thr Asn
    370                 375                 380

Pro Ile Gln Ile Ala Gly Thr Ser Phe Ser Ala Pro Ile Val Thr Gly
385                 390                 395                 400

Thr Ala Ala Leu Leu Leu Gln Lys Tyr Pro Trp Met Ser Asn Asp Asn
                405                 410                 415

Leu Arg Thr Thr Leu Leu Thr Thr Ala Gln Asp Ile Gly Ala Val Gly
            420                 425                 430

Val Asp Ser Lys Phe Gly Trp Gly Leu Leu Asp Ala Gly Lys Ala Met
        435                 440                 445

Asn Gly Pro Ala Ser Phe Pro Phe Gly Asp Phe Thr Ala Asp Thr Lys
    450                 455                 460

Gly Thr Ser Asp Ile Ala Tyr Ser Phe Arg Asn Asp Ile Ser Gly Thr
465                 470                 475                 480

Gly Gly Leu Ile Lys Lys Gly Gly Ser Gln Leu Gln Leu His Gly Asn
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Asn Thr Tyr Thr Gly Lys Thr Ile Ile Glu Gly Gly Ser Leu Val Leu
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Tyr Gly Asn Asn Lys Ser Asp Met Arg Val Glu Thr Lys Gly Ala Leu
        515                 520                 525

Ile Tyr Asn Gly Ala Ala Ser Gly Gly Ser Leu Asn Ser Asp Gly Ile
    530                 535                 540

Val Tyr Leu Ala Asp Thr Asp Gln Ser Gly Ala Asn Glu Thr Val His
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Leu Gly Lys Leu Leu Lys Val Asp Gly Thr Ala Ile Ile Gly Gly Lys
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Leu Tyr Met Ser Ala Arg Gly Lys Gly Ala Gly Tyr Leu Asn Ser Thr
        595                 600                 605

Gly Arg Arg Val Pro Phe Leu Ser Ala Ala Lys Ile Gly Gln Asp Tyr
    610                 615                 620

Ser Phe Phe Thr Asn Ile Glu Thr Asp Gly Gly Leu Leu Ala Ser Leu
625                 630                 635                 640

Asp Ser Val Glu Lys Thr Ala Gly Ser Glu Gly Asp Thr Leu Ser Tyr
                645                 650                 655

Tyr Val Arg Arg Gly Asn Ala Ala Arg Thr Ala Ser Ala Ala Ala His
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Ser Ala Pro Ala Gly Leu Lys His Ala Val Glu Gln Gly Gly Ser Asn
        675                 680                 685

Leu Glu Asn Leu Met Val Glu Leu Asp Ala Ser Glu Ser Ser Ala Thr
    690                 695                 700

Pro Glu Thr Val Glu Thr Ala Ala Ala Asp Arg Thr Asp Met Pro Gly
705                 710                 715                 720

Ile Arg Pro Tyr Gly Ala Thr Phe Arg Ala Ala Ala Ala Val Gln His
                725                 730                 735

Ala Asn Ala Ala Asp Gly Val Arg Ile Phe Asn Ser Leu Ala Ala Thr
            740                 745                 750

Val Tyr Ala Asp Ser Thr Ala Ala His Ala Asp Met Gln Gly Arg Arg
        755                 760                 765

Leu Lys Ala Val Ser Asp Gly Leu Asp His Asn Gly Thr Gly Leu Arg
    770                 775                 780

Val Ile Ala Gln Thr Gln Gln Asp Gly Gly Thr Trp Glu Gln Gly Gly
785                 790                 795                 800

Val Glu Gly Lys Met Arg Gly Ser Thr Gln Thr Val Gly Ile Ala Ala
                805                 810                 815

Lys Thr Gly Glu Asn Thr Thr Ala Ala Ala Thr Leu Gly Met Gly Arg
            820                 825                 830

Ser Thr Trp Ser Glu Asn Ser Ala Asn Ala Lys Thr Asp Ser Ile Ser
        835                 840                 845

Leu Phe Ala Gly Ile Arg His Asp Ala Gly Asp Ile Gly Tyr Leu Lys
    850                 855                 860
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Leu Thr Val Glu Gly Gly Leu Arg Tyr Asp Leu Leu Lys Gln Asp Ala
915 920 925

Phe Ala Glu Lys Gly Ser Ala Leu Gly Trp Ser Gly Asn Ser Leu Thr
930 935 940

Glu Gly Thr Leu Val Gly Leu Ala Gly Leu Lys Leu Ser Gln Pro Leu
945 950 955 960

Ser Asp Lys Ala Val Leu Phe Ala Thr Ala Gly Val Glu Arg Asp Leu
965 970 975

Asn Gly Arg Asp Tyr Thr Val Thr Gly Gly Phe Thr Gly Ala Thr Ala
980 985 990

Ala Thr Gly Lys Thr Gly Ala Arg Asn Met Pro His Thr Arg Leu Val
995 1000 1005

Ala Gly Leu Gly Ala Asp Val Glu Phe Gly Asn Gly Trp Asn Gly Leu
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Ala Arg Tyr Ser Tyr Ala Gly Ser Lys Gln Tyr Gly Asn His Ser Gly
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Ser Ala Leu Thr Ala Phe Gln Thr Glu Gln Ile Gln Asp Ser Glu His
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Leu Lys Ser Pro Glu Leu Asn Val Asp Leu Ala Ala Ala Asp Ile Lys
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Pro Asp Gly Lys Arg His Ala Val Ile Ser Gly Ser Val Leu Tyr Asn
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tacaacgtgg gtcggttcaa tgtaacggct gcagtcggcg gctacaaatc cgaatcggca   4200
gtcgccatcg gtaccggctt ccgctttacc gaaaactttg ccgccaaagc aggcgtggca   4260
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            20                  25                  30

Ile Lys Asn Glu Met Cys Lys Asp Arg Ser Met Leu Cys Ala Gly Arg
        35                  40                  45

Asp Asp Val Ala Val Thr Asp Arg Asp Ala Lys Ile Asn Ala Pro Pro
    50                  55                  60

Pro Asn Leu His Thr Gly Asp Phe Pro Asn Pro Asn Asp Ala Tyr Lys
65                  70                  75                  80

Asn Leu Ile Asn Leu Lys Pro Ala Ile Glu Ala Gly Tyr Thr Gly Arg
                85                  90                  95

Gly Val Glu Val Gly Ile Val Asp Thr Gly Glu Ser Val Gly Ser Ile
            100                 105                 110

Ser Phe Pro Glu Leu Tyr Gly Arg Lys Glu His Gly Tyr Asn Glu Asn
        115                 120                 125

Tyr Lys Asn Tyr Thr Ala Tyr Met Arg Lys Glu Ala Pro Glu Asp Gly
    130                 135                 140

Gly Gly Lys Asp Ile Glu Ala Ser Phe Asp Asp Glu Ala Val Ile Glu
145                 150                 155                 160

Thr Glu Ala Lys Pro Thr Asp Ile Arg His Val Lys Glu Ile Gly His
                165                 170                 175

Ile Asp Leu Val Ser His Ile Ile Gly Gly Arg Ser Val Asp Gly Arg
            180                 185                 190

Pro Ala Gly Gly Ile Ala Pro Asp Ala Thr Leu His Ile Met Asn Thr
        195                 200                 205

Asn Asp Glu Thr Lys Asn Glu Met Met Val Ala Ala Ile Arg Asn Ala
    210                 215                 220

Trp Val Lys Leu Gly Glu Arg Gly Val Arg Ile Val Asn Asn Ser Phe
225                 230                 235                 240

Gly Thr Thr Ser Arg Ala Gly Thr Ala Asp Leu Phe Gln Ile Ala Asn
                245                 250                 255

Ser Glu Glu Gln Tyr Arg Gln Ala Leu Leu Asp Tyr Ser Gly Gly Asp
            260                 265                 270
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Lys Thr Asp Glu Gly Ile Arg Leu Met Gln Gln Ser Asp Tyr Gly Asn
        275                 280                 285

Leu Ser Tyr His Ile Arg Asn Lys Asn Met Leu Phe Ile Phe Ser Thr
    290                 295                 300

Gly Asn Asp Ala Gln Ala Gln Pro Asn Thr Tyr Ala Leu Leu Pro Phe
305                 310                 315                 320

Tyr Glu Lys Asp Ala Gln Lys Gly Ile Ile Thr Val Ala Gly Val Asp
                325                 330                 335

Arg Ser Gly Glu Lys Phe Lys Arg Glu Met Tyr Gly Glu Pro Gly Thr
            340                 345                 350

Glu Pro Leu Glu Tyr Gly Ser Asn His Cys Gly Ile Thr Ala Met Trp
        355                 360                 365

Cys Leu Ser Ala Pro Tyr Glu Ala Ser Val Arg Phe Thr Arg Thr Asn
    370                 375                 380

Pro Ile Gln Ile Ala Gly Thr Ser Phe Ser Ala Pro Ile Val Thr Gly
385                 390                 395                 400

Thr Ala Ala Leu Leu Leu Gln Lys Tyr Pro Trp Met Ser Asn Asp Asn
                405                 410                 415

Leu Arg Thr Thr Leu Leu Thr Thr Ala Gln Asp Ile Gly Ala Val Gly
            420                 425                 430

Val Asp Ser Lys Phe Gly Trp Gly Leu Leu Asp Ala Gly Lys Ala Met
        435                 440                 445

Asn Gly Pro Ala Ser Phe Pro Phe Gly Asp Phe Thr Ala Asp Thr Lys
    450                 455                 460

Gly Thr Ser Asp Ile Ala Tyr Ser Phe Arg Asn Asp Ile Ser Gly Thr
465                 470                 475                 480

Gly Gly Leu Ile Lys Lys Gly Gly Ser Gln Leu Gln Leu His Gly Asn
                485                 490                 495

Asn Thr Tyr Thr Gly Lys Thr Ile Ile Glu Gly Gly Ser Leu Val Leu
            500                 505                 510

Tyr Gly Asn Asn Lys Ser Asp Met Arg Val Glu Thr Lys Gly Ala Leu
        515                 520                 525

Ile Tyr Asn Gly Ala Ala Ser Gly Gly Ser Leu Asn Ser Asp Gly Ile
    530                 535                 540

Val Tyr Leu Ala Asp Thr Asp Gln Ser Gly Ala Asn Glu Thr Val His
545                 550                 555                 560

Ile Lys Gly Ser Leu Gln Leu Asp Gly Lys Gly Thr Leu Tyr Thr Arg
                565                 570                 575
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Leu Gly Lys Leu Leu Lys Val Asp Gly Thr Ala Ile Ile Gly Gly Lys
580 585 590

Leu Tyr Met Ser Ala Arg Gly Lys Gly Ala Gly Tyr Leu Asn Ser Thr
595 600 605

Gly Arg Arg Val Pro Phe Leu Ser Ala Ala Lys Ile Gly Gln Asp Tyr
610 615 620

Ser Phe Phe Thr Asn Ile Glu Thr Asp Gly Gly Leu Leu Ala Ser Leu
625 630 635 640

Asp Ser Val Glu Lys Thr Ala Gly Ser Glu Gly Asp Thr Leu Ser Tyr
645 650 655

Tyr Val Arg Arg Gly Asn Ala Ala Arg Thr Ala Ser Ala Ala Ala His
660 665 670

Ser Ala Pro Ala Gly Leu Lys His Ala Val Glu Gln Gly Gly Ser Asn
675 680 685

Leu Glu Asn Leu Met Val Glu Leu Asp Ala Ser Glu Ser Ser Ala Thr
690 695 700

Pro Glu Thr Val Glu Thr Ala Ala Ala Asp Arg Thr Asp Met Pro Gly
705 710 715 720

Ile Arg Pro Tyr Gly Ala Thr Phe Arg Ala Ala Ala Ala Val Gln His
725 730 735

Ala Asn Ala Ala Asp Gly Val Arg Ile Phe Asn Ser Leu Ala Ala Thr
740 745 750

Val Tyr Ala Asp Ser Thr Ala Ala His Ala Asp Met Gln Gly Arg Arg
755 760 765

Leu Lys Ala Val Ser Asp Gly Leu Asp His Asn Gly Thr Gly Leu Arg
770 775 780

Val Ile Ala Gln Thr Gln Gln Asp Gly Gly Thr Trp Glu Gln Gly Gly
785 790 795 800

Val Glu Gly Lys Met Arg Gly Ser Thr Gln Thr Val Gly Ile Ala Ala
805 810 815

Lys Thr Gly Glu Asn Thr Thr Ala Ala Ala Thr Leu Gly Met Gly Arg
820 825 830

Ser Thr Trp Ser Glu Asn Ser Ala Asn Ala Lys Thr Asp Ser Ile Ser
835 840 845

Leu Phe Ala Gly Ile Arg His Asp Ala Gly Asp Ile Gly Tyr Leu Lys
850 855 860

Gly Leu Phe Ser Tyr Gly Arg Tyr Lys Asn Ser Ile Ser Arg Ser Thr
865 870 875 880

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Gly Ala Asp Glu His Ala Glu Gly Ser Val Asn Gly Thr Leu Met Gln
                885                 890                 895

Leu Gly Ala Leu Gly Gly Val Asn Val Pro Phe Ala Ala Thr Gly Asp
            900                 905                 910

Leu Thr Val Glu Gly Gly Leu Arg Tyr Asp Leu Leu Lys Gln Asp Ala
        915                 920                 925

Phe Ala Glu Lys Gly Ser Ala Leu Gly Trp Ser Gly Asn Ser Leu Thr
    930                 935                 940

Glu Gly Thr Leu Val Gly Leu Ala Gly Leu Lys Leu Ser Gln Pro Leu
945                 950                 955                 960

Ser Asp Lys Ala Val Leu Phe Ala Thr Ala Gly Val Glu Arg Asp Leu
                965                 970                 975

Asn Gly Arg Asp Tyr Thr Val Thr Gly Gly Phe Thr Gly Ala Thr Ala
            980                 985                 990

Ala Thr Gly Lys Thr Gly Ala Arg Asn Met Pro His Thr Arg Leu Val
        995                 1000                1005

Ala Gly Leu Gly Ala Asp Val Glu Phe Gly Asn Gly Trp Asn Gly Leu
    1010                1015                1020

Ala Arg Tyr Ser Tyr Ala Gly Ser Lys Gln Tyr Gly Asn His Ser Gly
1025                1030                1035                1040

Arg Val Gly Val Gly Tyr Arg Phe Leu Glu Gly Gly Gly Gly Thr Gly
                1045                1050                1055

Ser Ala Thr Asn Asp Asp Asp Val Lys Lys Ala Ala Thr Val Ala Ile
            1060                1065                1070

Ala Ala Ala Tyr Asn Asn Gly Gln Glu Ile Asn Gly Phe Lys Ala Gly
        1075                1080                1085

Glu Thr Ile Tyr Asp Ile Asp Glu Asp Gly Thr Ile Thr Lys Lys Asp
    1090                1095                1100

Ala Thr Ala Ala Asp Val Glu Ala Asp Asp Phe Lys Gly Leu Gly Leu
1105                1110                1115                1120

Lys Lys Val Val Thr Asn Leu Thr Lys Thr Val Asn Glu Asn Lys Gln
                1125                1130                1135

Asn Val Asp Ala Lys Val Lys Ala Ala Glu Ser Glu Ile Glu Lys Leu
            1140                1145                1150

Thr Thr Lys Leu Ala Asp Thr Asp Ala Ala Leu Ala Asp Thr Asp Ala
        1155                1160                1165

Ala Leu Asp Ala Thr Thr Asn Ala Leu Asn Lys Leu Gly Glu Asn Ile
    1170                1175                1180
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Thr Thr Phe Ala Glu Glu Thr Lys Thr Asn Ile Val Lys Ile Asp Glu
1185 1190 1195 1200

Lys Leu Glu Ala Val Ala Asp Thr Val Asp Lys His Ala Glu Ala Phe
1205 1210 1215

Asn Asp Ile Ala Asp Ser Leu Asp Glu Thr Asn Thr Lys Ala Asp Glu
1220 1225 1230

Ala Val Lys Thr Ala Asn Glu Ala Lys Gln Thr Ala Glu Glu Thr Lys
1235 1240 1245

Gln Asn Val Asp Ala Lys Val Lys Ala Ala Glu Thr Ala Ala Gly Lys
1250 1255 1260

Ala Glu Ala Ala Ala Gly Thr Ala Asn Thr Ala Ala Asp Lys Ala Glu
1265 1270 1275 1280

Ala Val Ala Ala Lys Val Thr Asp Ile Lys Ala Asp Ile Ala Thr Asn
1285 1290 1295

Lys Asp Asn Ile Ala Lys Lys Ala Asn Ser Ala Asp Val Tyr Thr Arg
1300 1305 1310

Glu Glu Ser Asp Ser Lys Phe Val Arg Ile Asp Gly Leu Asn Ala Thr
1315 1320 1325

Thr Glu Lys Leu Asp Thr Arg Leu Ala Ser Ala Glu Lys Ser Ile Ala
1330 1335 1340

Asp His Asp Thr Arg Leu Asn Gly Leu Asp Lys Thr Val Ser Asp Leu
1345 1350 1355 1360

Arg Lys Glu Thr Arg Gln Gly Leu Ala Glu Gln Ala Ala Leu Ser Gly
1365 1370 1375

Leu Phe Gln Pro Tyr Asn Val Gly Arg Phe Asn Val Thr Ala Ala Val
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Gly Gly Tyr Lys Ser Glu Ser Ala Val Ala Ile Gly Thr Gly Phe Arg
1395 1400 1405

Phe Thr Glu Asn Phe Ala Ala Lys Ala Gly Val Ala Val Gly Thr Ser
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Ser Gly Ser Ser Ala Ala Tyr His Val Gly Val Asn Tyr Glu Trp Leu
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<212>   PRT
<213>   Artificial Sequence

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Asn Ser Arg Ala Thr Thr Ala Lys Ser Ala Ala Val Ser Tyr Ala Gly
            20                  25                  30

Ile Lys Asn Glu Met Cys Lys Asp Arg Ser Met Leu Cys Ala Gly Arg
        35                  40                  45

Asp Asp Val Ala Val Thr Asp Arg Asp Ala Lys Ile Asn Ala Pro Pro
    50                  55                  60

Pro Asn Leu His Thr Gly Asp Phe Pro Asn Pro Asn Asp Ala Tyr Lys
65                  70                  75                  80

Asn Leu Ile Asn Leu Lys Pro Ala Ile Glu Ala Gly Tyr Thr Gly Arg
                85                  90                  95

Gly Val Glu Val Gly Ile Val Asp Thr Gly Glu Ser Val Gly Ser Ile
            100                 105                 110

Ser Phe Pro Glu Leu Tyr Gly Arg Lys Glu His Gly Tyr Asn Glu Asn
        115                 120                 125

Tyr Lys Asn Tyr Thr Ala Tyr Met Arg Lys Glu Ala Pro Glu Asp Gly
    130                 135                 140

Gly Gly Lys Asp Ile Glu Ala Ser Phe Asp Asp Glu Ala Val Ile Glu
145                 150                 155                 160

Thr Glu Ala Lys Pro Thr Asp Ile Arg His Val Lys Glu Ile Gly His
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165 170 175

Ile Asp Leu Val Ser His Ile Ile Gly Gly Arg Ser Val Asp Gly Arg
180 185 190

Pro Ala Gly Gly Ile Ala Pro Asp Ala Thr Leu His Ile Met Asn Thr
195 200 205

Asn Asp Glu Thr Lys Asn Glu Met Met Val Ala Ala Ile Arg Asn Ala
210 215 220

Trp Val Lys Leu Gly Glu Arg Gly Val Arg Ile Val Asn Asn Ser Phe
225 230 235 240

Gly Thr Thr Ser Arg Ala Gly Thr Ala Asp Leu Phe Gln Ile Ala Asn
245 250 255

Ser Glu Glu Gln Tyr Arg Gln Ala Leu Leu Asp Tyr Ser Gly Gly Asp
260 265 270

Lys Thr Asp Glu Gly Ile Arg Leu Met Gln Gln Ser Asp Tyr Gly Asn
275 280 285

Leu Ser Tyr His Ile Arg Asn Lys Asn Met Leu Phe Ile Phe Ser Thr
290 295 300

Gly Asn Asp Ala Gln Ala Gln Pro Asn Thr Tyr Ala Leu Leu Pro Phe
305 310 315 320

Tyr Glu Lys Asp Ala Gln Lys Gly Ile Ile Thr Val Ala Gly Val Asp
325 330 335

Arg Ser Gly Glu Lys Phe Lys Arg Glu Met Tyr Gly Glu Pro Gly Thr
340 345 350

Glu Pro Leu Glu Tyr Gly Ser Asn His Cys Gly Ile Thr Ala Met Trp
355 360 365

Cys Leu Ser Ala Pro Tyr Glu Ala Ser Val Arg Phe Thr Arg Thr Asn
370 375 380

Pro Ile Gln Ile Ala Gly Thr Ser Phe Ser Ala Pro Ile Val Thr Gly
385 390 395 400

Thr Ala Ala Leu Leu Leu Gln Lys Tyr Pro Trp Met Ser Asn Asp Asn
405 410 415

Leu Arg Thr Thr Leu Leu Thr Thr Ala Gln Asp Ile Gly Ala Val Gly
420 425 430

Val Asp Ser Lys Phe Gly Trp Gly Leu Leu Asp Ala Gly Lys Ala Met
435 440 445

Asn Gly Pro Ala Ser Phe Pro Phe Gly Asp Phe Thr Ala Asp Thr Lys
450 455 460

Gly Thr Ser Asp Ile Ala Tyr Ser Phe Arg Asn Asp Ile Ser Gly Thr

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465                 470                 475                 480

Gly Gly Leu Ile Lys Lys Gly Gly Ser Gln Leu Gln Leu His Gly Asn
                485                 490                 495

Asn Thr Tyr Thr Gly Lys Thr Ile Ile Glu Gly Gly Ser Leu Val Leu
            500                 505                 510

Tyr Gly Asn Asn Lys Ser Asp Met Arg Val Glu Thr Lys Gly Ala Leu
        515                 520                 525

Ile Tyr Asn Gly Ala Ala Ser Gly Gly Ser Leu Asn Ser Asp Gly Ile
    530                 535                 540

Val Tyr Leu Ala Asp Thr Asp Gln Ser Gly Ala Asn Glu Thr Val His
545                 550                 555                 560

Ile Lys Gly Ser Leu Gln Leu Asp Gly Lys Gly Thr Leu Tyr Thr Arg
                565                 570                 575

Leu Gly Lys Leu Leu Lys Val Asp Gly Thr Ala Ile Ile Gly Gly Lys
            580                 585                 590

Leu Tyr Met Ser Ala Arg Gly Lys Gly Ala Gly Tyr Leu Asn Ser Thr
        595                 600                 605

Gly Arg Arg Val Pro Phe Leu Ser Ala Ala Lys Ile Gly Gln Asp Tyr
    610                 615                 620

Ser Phe Phe Thr Asn Ile Glu Thr Asp Gly Gly Leu Leu Ala Ser Leu
625                 630                 635                 640

Asp Ser Val Glu Lys Thr Ala Gly Ser Glu Gly Asp Thr Leu Ser Tyr
                645                 650                 655

Tyr Val Arg Arg Gly Asn Ala Ala Arg Thr Ala Ser Ala Ala Ala His
            660                 665                 670

Ser Ala Pro Ala Gly Leu Lys His Ala Val Glu Gln Gly Gly Ser Asn
        675                 680                 685

Leu Glu Asn Leu Met Val Glu Leu Asp Ala Ser Glu Ser Ser Ala Thr
    690                 695                 700

Pro Glu Thr Val Glu Thr Ala Ala Ala Asp Arg Thr Asp Met Pro Gly
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Ile Arg Pro Tyr Gly Ala Thr Phe Arg Ala Ala Ala Ala Val Gln His
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Ala Asn Ala Ala Asp Gly Val Arg Ile Phe Asn Ser Leu Ala Ala Thr
            740                 745                 750

Val Tyr Ala Asp Ser Thr Ala Ala His Ala Asp Met Gln Gly Arg Arg
        755                 760                 765

Leu Lys Ala Val Ser Asp Gly Leu Asp His Asn Gly Thr Gly Leu Arg
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770 775 780

Val Ile Ala Gln Thr Gln Gln Asp Gly Gly Thr Trp Glu Gln Gly Gly
785 790 795 800

Val Glu Gly Lys Met Arg Gly Ser Thr Gln Thr Val Gly Ile Ala Ala
805 810 815

Lys Thr Gly Glu Asn Thr Thr Ala Ala Ala Thr Leu Gly Met Gly Arg
820 825 830

Ser Thr Trp Ser Glu Asn Ser Ala Asn Ala Lys Thr Asp Ser Ile Ser
835 840 845

Leu Phe Ala Gly Ile Arg His Asp Ala Gly Asp Ile Gly Tyr Leu Lys
850 855 860

Gly Leu Phe Ser Tyr Gly Arg Tyr Lys Asn Ser Ile Ser Arg Ser Thr
865 870 875 880

Gly Ala Asp Glu His Ala Glu Gly Ser Val Asn Gly Thr Leu Met Gln
885 890 895

Leu Gly Ala Leu Gly Gly Val Asn Val Pro Phe Ala Ala Thr Gly Asp
900 905 910

Leu Thr Val Glu Gly Gly Leu Arg Tyr Asp Leu Leu Lys Gln Asp Ala
915 920 925

Phe Ala Glu Lys Gly Ser Ala Leu Gly Trp Ser Gly Asn Ser Leu Thr
930 935 940

Glu Gly Thr Leu Val Gly Leu Ala Gly Leu Lys Leu Ser Gln Pro Leu
945 950 955 960

Ser Asp Lys Ala Val Leu Phe Ala Thr Ala Gly Val Glu Arg Asp Leu
965 970 975

Asn Gly Arg Asp Tyr Thr Val Thr Gly Gly Phe Thr Gly Ala Thr Ala
980 985 990

Ala Thr Gly Lys Thr Gly Ala Arg Asn Met Pro His Thr Arg Leu Val
995 1000 1005

Ala Gly Leu Gly Ala Asp Val Glu Phe Gly Asn Gly Trp Asn Gly Leu
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Ala Arg Tyr Ser Tyr Ala Gly Ser Lys Gln Tyr Gly Asn His Ser Gly
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Arg Val Gly Val Gly Tyr Arg Phe Leu Glu Gly Gly Gly Gly Thr Gly
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Ser Ala Thr Asn Asp Asp Asp Val Lys Lys Ala Ala Thr Val Ala Ile
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Ala Ala Ala Tyr Asn Asn Gly Gln Glu Ile Asn Gly Phe Lys Ala Gly

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Glu Thr Ile Tyr Asp Ile Asp Glu Asp Gly Thr Ile Thr Lys Lys Asp
1090 1095 1100

Ala Thr Ala Ala Asp Val Glu Ala Asp Asp Phe Lys Gly Leu Gly Leu
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Lys Lys Val Val Thr Asn Leu Thr Lys Thr Val Asn Glu Asn Lys Gln
1125 1130 1135

Asn Val Asp Ala Lys Val Lys Ala Ala Glu Ser Glu Ile Glu Lys Leu
1140 1145 1150

Thr Thr Lys Leu Ala Asp Thr Asp Ala Ala Leu Ala Asp Thr Asp Ala
1155 1160 1165

Ala Leu Asp Ala Thr Thr Asn Ala Leu Asn Lys Leu Gly Glu Asn Ile
1170 1175 1180

Thr Thr Phe Ala Glu Glu Thr Lys Thr Asn Ile Val Lys Ile Asp Glu
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Lys Leu Glu Ala Val Ala Asp Thr Val Asp Lys His Ala Glu Ala Phe
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Asn Asp Ile Ala Asp Ser Leu Asp Glu Thr Asn Thr Lys Ala Asp Glu
1220 1225 1230

Ala Val Lys Thr Ala Asn Glu Ala Lys Gln Thr Ala Glu Glu Thr Lys
1235 1240 1245

Gln Asn Val Asp Ala Lys Val Lys Ala Ala Glu Thr Ala Ala Gly Lys
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Ala Glu Ala Ala Ala Gly Thr Ala Asn Thr Ala Ala Asp Lys Ala Glu
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Ala Val Ala Ala Lys Val Thr Asp Ile Lys Ala Asp Ile Ala Thr Asn
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Lys Asp Asn Ile Ala Lys Lys Ala Asn Ser Ala Asp Val Tyr Thr Arg
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Glu Glu Ser Asp Ser Lys Phe Val Arg Ile Asp Gly Leu Asn Ala Thr
1315 1320 1325

Thr Glu Lys Leu Asp Thr Arg Leu Ala Ser Ala Glu Lys Ser Ile Ala
1330 1335 1340

Asp His Asp Thr Arg Leu Asn Gly Leu Asp Lys Thr Val Ser Asp Leu
1345 1350 1355 1360

Arg Lys Glu Thr Arg Gln Gly Leu Ala Glu Gln Ala Ala Leu Ser Gly
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Leu Phe Gln Pro Tyr Asn Val Gly Leu Glu His His His His His His

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Ser Val Arg Lys Asn Glu Lys Leu Lys Leu Ala Ala Gln Gly Ala Glu
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Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn Thr Gly Lys Leu Lys Asn
    50                  55                  60

Asp Lys Val Ser Arg Phe Asp Phe Ile Arg Gln Ile Glu Val Asp Gly
65                  70                  75                  80

Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe Gln Val Tyr Lys Gln Ser
                85                  90                  95

His Ser Ala Leu Thr Ala Phe Gln Thr Glu Gln Ile Gln Asp Ser Glu
            100                 105                 110

His Ser Gly Lys Met Val Ala Lys Arg Gln Phe Arg Ile Gly Asp Ile
        115                 120                 125

Ala Gly Glu His Thr Ser Phe Asp Lys Leu Pro Glu Gly Gly Arg Ala
    130                 135                 140

Thr Tyr Arg Gly Thr Ala Phe Gly Ser Asp Asp Ala Gly Gly Lys Leu
145                 150                 155                 160

Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln Gly Asn Gly Lys Ile Glu
                165                 170                 175

His Leu Lys Ser Pro Glu Leu Asn Val Asp Leu Ala Ala Ala Asp Ile
            180                 185                 190

Lys Pro Asp Gly Lys Arg His Ala Val Ile Ser Gly Ser Val Leu Tyr
        195                 200                 205

Asn Gln Ala Glu Lys Gly Ser Tyr Ser Leu Gly Ile Phe Gly Gly Lys
    210                 215                 220

Ala Gln Glu Val Ala Gly Ser Ala Glu Val Lys Thr Val Asn Gly Ile
225                 230                 235                 240

Arg His Ile Gly Leu Ala Ala Lys Gln Leu Glu Gly Gly Gly Gly Thr
                245                 250                 255

Gly Ser Ala Thr Asn Asp Asp Asp Val Lys Lys Ala Ala Thr Val Ala
            260                 265                 270

Ile Ala Ala Ala Tyr Asn Asn Gly Gln Glu Ile Asn Gly Phe Lys Ala
        275                 280                 285

Gly Glu Thr Ile Tyr Asp Ile Asp Glu Asp Gly Thr Ile Thr Lys Lys
    290                 295                 300

Asp Ala Thr Ala Ala Asp Val Glu Ala Asp Asp Phe Lys Gly Leu Gly
305                 310                 315                 320
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Leu Lys Lys Val Val Thr Asn Leu Thr Lys Thr Val Asn Glu Asn Lys
                325                 330                 335

Gln Asn Val Asp Ala Lys Val Lys Ala Ala Glu Ser Glu Ile Glu Lys
            340                 345                 350

Leu Thr Thr Lys Leu Ala Asp Thr Asp Ala Ala Leu Ala Asp Thr Asp
        355                 360                 365

Ala Ala Leu Asp Ala Thr Thr Asn Ala Leu Asn Lys Leu Gly Glu Asn
    370                 375                 380

Ile Thr Thr Phe Ala Glu Glu Thr Lys Thr Asn Ile Val Lys Ile Asp
385                 390                 395                 400

Glu Lys Leu Glu Ala Val Ala Asp Thr Val Asp Lys His Ala Glu Ala
                405                 410                 415

Phe Asn Asp Ile Ala Asp Ser Leu Asp Glu Thr Asn Thr Lys Ala Asp
            420                 425                 430

Glu Ala Val Lys Thr Ala Asn Glu Ala Lys Gln Thr Ala Glu Glu Thr
        435                 440                 445

Lys Gln Asn Val Asp Ala Lys Val Lys Ala Ala Glu Thr Ala Ala Gly
    450                 455                 460

Lys Ala Glu Ala Ala Ala Gly Thr Ala Asn Thr Ala Ala Asp Lys Ala
465                 470                 475                 480

Glu Ala Val Ala Ala Lys Val Thr Asp Ile Lys Ala Asp Ile Ala Thr
                485                 490                 495

Asn Lys Asp Asn Ile Ala Lys Lys Ala Asn Ser Ala Asp Val Tyr Thr
            500                 505                 510

Arg Glu Glu Ser Asp Ser Lys Phe Val Arg Ile Asp Gly Leu Asn Ala
        515                 520                 525

Thr Thr Glu Lys Leu Asp Thr Arg Leu Ala Ser Ala Glu Lys Ser Ile
    530                 535                 540

Ala Asp His Asp Thr Arg Leu Asn Gly Leu Asp Lys Thr Val Ser Asp
545                 550                 555                 560

Leu Arg Lys Glu Thr Arg Gln Gly Leu Ala Glu Gln Ala Ala Leu Ser
                565                 570                 575

Gly Leu Phe Gln Pro Tyr Asn Val Gly Arg Phe Asn Val Thr Ala Ala
            580                 585                 590

Val Gly Gly Tyr Lys Ser Glu Ser Ala Val Ala Ile Gly Thr Gly Phe
        595                 600                 605

Arg Phe Thr Glu Asn Phe Ala Ala Lys Ala Gly Val Ala Val Gly Thr
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Leu Glu His His His His His His
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Ser Val Arg Lys Asn Glu Lys Leu Lys Leu Ala Ala Gln Gly Ala Glu
35 40 45

Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn Thr Gly Lys Leu Lys Asn
50 55 60

Asp Lys Val Ser Arg Phe Asp Phe Ile Arg Gln Ile Glu Val Asp Gly
65 70 75 80

Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe Gln Val Tyr Lys Gln Ser
85 90 95

His Ser Ala Leu Thr Ala Phe Gln Thr Glu Gln Ile Gln Asp Ser Glu
100 105 110

His Ser Gly Lys Met Val Ala Lys Arg Gln Phe Arg Ile Gly Asp Ile
115 120 125

Ala Gly Glu His Thr Ser Phe Asp Lys Leu Pro Glu Gly Gly Arg Ala
130 135 140

Thr Tyr Arg Gly Thr Ala Phe Gly Ser Asp Asp Ala Gly Gly Lys Leu
145 150 155 160

Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln Gly Asn Gly Lys Ile Glu
165 170 175

His Leu Lys Ser Pro Glu Leu Asn Val Asp Leu Ala Ala Ala Asp Ile
180 185 190

Lys Pro Asp Gly Lys Arg His Ala Val Ile Ser Gly Ser Val Leu Tyr
195 200 205

Asn Gln Ala Glu Lys Gly Ser Tyr Ser Leu Gly Ile Phe Gly Gly Lys
210 215 220

Ala Gln Glu Val Ala Gly Ser Ala Glu Val Lys Thr Val Asn Gly Ile
225 230 235 240

Arg His Ile Gly Leu Ala Ala Lys Gln Leu Glu Gly Gly Gly Gly Thr
245 250 255

Gly Ser Ala Thr Asn Asp Asp Asp Val Lys Lys Ala Ala Thr Val Ala
260 265 270

Ile Ala Ala Ala Tyr Asn Asn Gly Gln Glu Ile Asn Gly Phe Lys Ala
275 280 285

Gly Glu Thr Ile Tyr Asp Ile Asp Glu Asp Gly Thr Ile Thr Lys Lys
290 295 300

Asp Ala Thr Ala Ala Asp Val Glu Ala Asp Asp Phe Lys Gly Leu Gly

305 310 315 320

Leu Lys Lys Val Val Thr Asn Leu Thr Lys Thr Val Asn Glu Asn Lys
325 330 335

Gln Asn Val Asp Ala Lys Val Lys Ala Ala Glu Ser Glu Ile Glu Lys
340 345 350

Leu Thr Thr Lys Leu Ala Asp Thr Asp Ala Ala Leu Ala Asp Thr Asp
355 360 365

Ala Ala Leu Asp Ala Thr Thr Asn Ala Leu Asn Lys Leu Gly Glu Asn
370 375 380

Ile Thr Thr Phe Ala Glu Glu Thr Lys Thr Asn Ile Val Lys Ile Asp
385 390 395 400

Glu Lys Leu Glu Ala Val Ala Asp Thr Val Asp Lys His Ala Glu Ala
405 410 415

Phe Asn Asp Ile Ala Asp Ser Leu Asp Glu Thr Asn Thr Lys Ala Asp
420 425 430

Glu Ala Val Lys Thr Ala Asn Glu Ala Lys Gln Thr Ala Glu Glu Thr
435 440 445

Lys Gln Asn Val Asp Ala Lys Val Lys Ala Ala Glu Thr Ala Ala Gly
450 455 460

Lys Ala Glu Ala Ala Ala Gly Thr Ala Asn Thr Ala Ala Asp Lys Ala
465 470 475 480

Glu Ala Val Ala Ala Lys Val Thr Asp Ile Lys Ala Asp Ile Ala Thr
485 490 495

Asn Lys Asp Asn Ile Ala Lys Lys Ala Asn Ser Ala Asp Val Tyr Thr
500 505 510

Arg Glu Glu Ser Asp Ser Lys Phe Val Arg Ile Asp Gly Leu Asn Ala
515 520 525

Thr Thr Glu Lys Leu Asp Thr Arg Leu Ala Ser Ala Glu Lys Ser Ile
530 535 540

Ala Asp His Asp Thr Arg Leu Asn Gly Leu Asp Lys Thr Val Ser Asp
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gttccgtttg ccgcaacggg agatttgacg gtcgaaggcg gtctgcgcta cgacctgctc    3540
aaacaggatg cattcgccga aaaaggcagt gctttgggct ggagcggcaa cagcctcact    3600
gaaggcacgc tggtcggact cgcgggtctg aagctgtcgc aacccttgag cgataaagcc    3660
gtcctgtttg caacggcggg cgtggaacgc gacctgaacg gacgcgacta cacggtaacg    3720
ggcggcttta ccggcgcgac tgcagcaacc ggcaagacgg gggcacgcaa tatgccgcac    3780
acccgtctgg ttgccggcct gggcgcggat gtcgaattcg gcaacggctg gaacggcttg    3840
gcacgttaca gctacgccgg ttccaaacag tacggcaacc acagcggacg agtcggcgta    3900
ggctaccggt tcctcgagca ccaccaccac caccactga                            3939
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<210>   113
<211>   1312
<212>   PRT
<213>   Artificial Sequence

<220>
<223>   deltaG741-983

<400>   113
Met Val Ala Ala Asp Ile Gly Ala Gly Leu Ala Asp Ala Leu Thr Ala
1               5                   10                  15

Pro Leu Asp His Lys Asp Lys Gly Leu Gln Ser Leu Thr Leu Asp Gln
            20                  25                  30

Ser Val Arg Lys Asn Glu Lys Leu Lys Leu Ala Ala Gln Gly Ala Glu
        35                  40                  45

Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn Thr Gly Lys Leu Lys Asn
    50                  55                  60

Asp Lys Val Ser Arg Phe Asp Phe Ile Arg Gln Ile Glu Val Asp Gly
65                  70                  75                  80

Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe Gln Val Tyr Lys Gln Ser
                85                  90                  95

His Ser Ala Leu Thr Ala Phe Gln Thr Glu Gln Ile Gln Asp Ser Glu
            100                 105                 110

His Ser Gly Lys Met Val Ala Lys Arg Gln Phe Arg Ile Gly Asp Ile
        115                 120                 125

Ala Gly Glu His Thr Ser Phe Asp Lys Leu Pro Glu Gly Gly Arg Ala
    130                 135                 140

Thr Tyr Arg Gly Thr Ala Phe Gly Ser Asp Asp Ala Gly Gly Lys Leu
145                 150                 155                 160
```

```
Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln Gly Asn Gly Lys Ile Glu
                165                 170                 175

His Leu Lys Ser Pro Glu Leu Asn Val Asp Leu Ala Ala Ala Asp Ile
            180                 185                 190

Lys Pro Asp Gly Lys Arg His Ala Val Ile Ser Gly Ser Val Leu Tyr
        195                 200                 205

Asn Gln Ala Glu Lys Gly Ser Tyr Ser Leu Gly Ile Phe Gly Gly Lys
    210                 215                 220

Ala Gln Glu Val Ala Gly Ser Ala Glu Val Lys Thr Val Asn Gly Ile
225                 230                 235                 240

Arg His Ile Gly Leu Ala Ala Lys Gln Leu Glu Gly Ser Gly Gly Gly
                245                 250                 255

Gly Thr Ser Ala Pro Asp Phe Asn Ala Gly Gly Thr Gly Ile Gly Ser
            260                 265                 270

Asn Ser Arg Ala Thr Thr Ala Lys Ser Ala Ala Val Ser Tyr Ala Gly
        275                 280                 285

Ile Lys Asn Glu Met Cys Lys Asp Arg Ser Met Leu Cys Ala Gly Arg
    290                 295                 300

Asp Asp Val Ala Val Thr Asp Arg Asp Ala Lys Ile Asn Ala Pro Pro
305                 310                 315                 320

Pro Asn Leu His Thr Gly Asp Phe Pro Asn Pro Asn Asp Ala Tyr Lys
                325                 330                 335

Asn Leu Ile Asn Leu Lys Pro Ala Ile Glu Ala Gly Tyr Thr Gly Arg
            340                 345                 350

Gly Val Glu Val Gly Ile Val Asp Thr Gly Glu Ser Val Gly Ser Ile
        355                 360                 365

Ser Phe Pro Glu Leu Tyr Gly Arg Lys Glu His Gly Tyr Asn Glu Asn
    370                 375                 380

Tyr Lys Asn Tyr Thr Ala Tyr Met Arg Lys Glu Ala Pro Glu Asp Gly
385                 390                 395                 400

Gly Gly Lys Asp Ile Glu Ala Ser Phe Asp Asp Glu Ala Val Ile Glu
                405                 410                 415

Thr Glu Ala Lys Pro Thr Asp Ile Arg His Val Lys Glu Ile Gly His
            420                 425                 430

Ile Asp Leu Val Ser His Ile Ile Gly Gly Arg Ser Val Asp Gly Arg
        435                 440                 445

Pro Ala Gly Gly Ile Ala Pro Asp Ala Thr Leu His Ile Met Asn Thr
    450                 455                 460
```

```
Asn Asp Glu Thr Lys Asn Glu Met Met Val Ala Ala Ile Arg Asn Ala
465                 470                 475                 480

Trp Val Lys Leu Gly Glu Arg Gly Val Arg Ile Val Asn Asn Ser Phe
                485                 490                 495

Gly Thr Thr Ser Arg Ala Gly Thr Ala Asp Leu Phe Gln Ile Ala Asn
            500                 505                 510

Ser Glu Glu Gln Tyr Arg Gln Ala Leu Leu Asp Tyr Ser Gly Gly Asp
        515                 520                 525

Lys Thr Asp Glu Gly Ile Arg Leu Met Gln Gln Ser Asp Tyr Gly Asn
    530                 535                 540

Leu Ser Tyr His Ile Arg Asn Lys Asn Met Leu Phe Ile Phe Ser Thr
545                 550                 555                 560

Gly Asn Asp Ala Gln Ala Gln Pro Asn Thr Tyr Ala Leu Leu Pro Phe
                565                 570                 575

Tyr Glu Lys Asp Ala Gln Lys Gly Ile Ile Thr Val Ala Gly Val Asp
            580                 585                 590

Arg Ser Gly Glu Lys Phe Lys Arg Glu Met Tyr Gly Glu Pro Gly Thr
        595                 600                 605

Glu Pro Leu Glu Tyr Gly Ser Asn His Cys Gly Ile Thr Ala Met Trp
    610                 615                 620

Cys Leu Ser Ala Pro Tyr Glu Ala Ser Val Arg Phe Thr Arg Thr Asn
625                 630                 635                 640

Pro Ile Gln Ile Ala Gly Thr Ser Phe Ser Ala Pro Ile Val Thr Gly
                645                 650                 655

Thr Ala Ala Leu Leu Leu Gln Lys Tyr Pro Trp Met Ser Asn Asp Asn
            660                 665                 670

Leu Arg Thr Thr Leu Leu Thr Thr Ala Gln Asp Ile Gly Ala Val Gly
        675                 680                 685

Val Asp Ser Lys Phe Gly Trp Gly Leu Leu Asp Ala Gly Lys Ala Met
    690                 695                 700

Asn Gly Pro Ala Ser Phe Pro Phe Gly Asp Phe Thr Ala Asp Thr Lys
705                 710                 715                 720

Gly Thr Ser Asp Ile Ala Tyr Ser Phe Arg Asn Asp Ile Ser Gly Thr
                725                 730                 735

Gly Gly Leu Ile Lys Lys Gly Gly Ser Gln Leu Gln Leu His Gly Asn
            740                 745                 750

Asn Thr Tyr Thr Gly Lys Thr Ile Ile Glu Gly Gly Ser Leu Val Leu
        755                 760                 765
```

```
Tyr Gly Asn Asn Lys Ser Asp Met Arg Val Glu Thr Lys Gly Ala Leu
    770                 775                 780

Ile Tyr Asn Gly Ala Ala Ser Gly Gly Ser Leu Asn Ser Asp Gly Ile
785                 790                 795                 800

Val Tyr Leu Ala Asp Thr Asp Gln Ser Gly Ala Asn Glu Thr Val His
                805                 810                 815

Ile Lys Gly Ser Leu Gln Leu Asp Gly Lys Gly Thr Leu Tyr Thr Arg
            820                 825                 830

Leu Gly Lys Leu Leu Lys Val Asp Gly Thr Ala Ile Ile Gly Gly Lys
        835                 840                 845

Leu Tyr Met Ser Ala Arg Gly Lys Gly Ala Gly Tyr Leu Asn Ser Thr
    850                 855                 860

Gly Arg Arg Val Pro Phe Leu Ser Ala Ala Lys Ile Gly Gln Asp Tyr
865                 870                 875                 880

Ser Phe Phe Thr Asn Ile Glu Thr Asp Gly Gly Leu Leu Ala Ser Leu
                885                 890                 895

Asp Ser Val Glu Lys Thr Ala Gly Ser Glu Gly Asp Thr Leu Ser Tyr
            900                 905                 910

Tyr Val Arg Arg Gly Asn Ala Ala Arg Thr Ala Ser Ala Ala Ala His
        915                 920                 925

Ser Ala Pro Ala Gly Leu Lys His Ala Val Glu Gln Gly Gly Ser Asn
    930                 935                 940

Leu Glu Asn Leu Met Val Glu Leu Asp Ala Ser Glu Ser Ser Ala Thr
945                 950                 955                 960

Pro Glu Thr Val Glu Thr Ala Ala Ala Asp Arg Thr Asp Met Pro Gly
                965                 970                 975

Ile Arg Pro Tyr Gly Ala Thr Phe Arg Ala Ala Ala Ala Val Gln His
            980                 985                 990

Ala Asn Ala Ala Asp Gly Val Arg Ile Phe Asn Ser Leu Ala Ala Thr
        995                 1000                1005

Val Tyr Ala Asp Ser Thr Ala Ala His Ala Asp Met Gln Gly Arg Arg
    1010                1015                1020

Leu Lys Ala Val Ser Asp Gly Leu Asp His Asn Gly Thr Gly Leu Arg
1025                1030                1035                1040

Val Ile Ala Gln Thr Gln Gln Asp Gly Gly Thr Trp Glu Gln Gly Gly
                1045                1050                1055

Val Glu Gly Lys Met Arg Gly Ser Thr Gln Thr Val Gly Ile Ala Ala
            1060                1065                1070
```

```
Lys Thr Gly Glu Asn Thr Thr Ala Ala Ala Thr Leu Gly Met Gly Arg
        1075                1080                1085

Ser Thr Trp Ser Glu Asn Ser Ala Asn Ala Lys Thr Asp Ser Ile Ser
    1090                1095                1100

Leu Phe Ala Gly Ile Arg His Asp Ala Gly Asp Ile Gly Tyr Leu Lys
1105                1110                1115                1120

Gly Leu Phe Ser Tyr Gly Arg Tyr Lys Asn Ser Ile Ser Arg Ser Thr
                1125                1130                1135

Gly Ala Asp Glu His Ala Glu Gly Ser Val Asn Gly Thr Leu Met Gln
            1140                1145                1150

Leu Gly Ala Leu Gly Gly Val Asn Val Pro Phe Ala Ala Thr Gly Asp
        1155                1160                1165

Leu Thr Val Glu Gly Gly Leu Arg Tyr Asp Leu Leu Lys Gln Asp Ala
    1170                1175                1180

Phe Ala Glu Lys Gly Ser Ala Leu Gly Trp Ser Gly Asn Ser Leu Thr
1185                1190                1195                1200

Glu Gly Thr Leu Val Gly Leu Ala Gly Leu Lys Leu Ser Gln Pro Leu
                1205                1210                1215

Ser Asp Lys Ala Val Leu Phe Ala Thr Ala Gly Val Glu Arg Asp Leu
            1220                1225                1230

Asn Gly Arg Asp Tyr Thr Val Thr Gly Gly Phe Thr Gly Ala Thr Ala
        1235                1240                1245

Ala Thr Gly Lys Thr Gly Ala Arg Asn Met Pro His Thr Arg Leu Val
    1250                1255                1260

Ala Gly Leu Gly Ala Asp Val Glu Phe Gly Asn Gly Trp Asn Gly Leu
1265                1270                1275                1280

Ala Arg Tyr Ser Tyr Ala Gly Ser Lys Gln Tyr Gly Asn His Ser Gly
                1285                1290                1295

Arg Val Gly Val Gly Tyr Arg Phe Leu Glu His His His His His His
            1300                1305                1310


<210>   114
<211>   2028
<212>   DNA
<213>   Artificial Sequence

<220>
<223>   deltaG741-ORF46.1

<400>   114
atggtcgccg ccgacatcgg tgcggggctt gccgatgcac taaccgcacc gctcgaccat      60
aaagacaaag gtttgcagtc tttgacgctg gatcagtccg tcaggaaaaa cgagaaactg     120
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aagctggcgg cacaaggtgc ggaaaaaact tatggaaacg gtgacagcct caatacgggc   180
aaattgaaga acgacaaggt cagccgtttc gactttatcc gccaaatcga agtggacggg   240
cagctcatta ccttggagag tggagagttc caagtataca aacaaagcca ttccgcctta   300
accgcctttc agaccgagca aatacaagat tcggagcatt ccgggaagat ggttgcgaaa   360
cgccagttca gaatcggcga catagcgggc gaacatacat cttttgacaa gcttcccgaa   420
ggcggcaggg cgacatatcg cgggacggcg ttcggttcag acgatgccgg cggaaaactg   480
acctacacca tagatttcgc cgccaagcag ggaaacggca aaatcgaaca tttgaaatcg   540
ccagaactca atgtcgacct ggccgccgcc gatatcaagc cggatggaaa acgccatgcc   600
gtcatcagcg gttccgtcct ttacaaccaa gccgagaaag gcagttactc cctcggtatc   660
tttggcggaa aagcccagga agttgccggc agcgcggaag tgaaaaccgt aaacggcata   720
cgccatatcg gccttgccgc caagcaactc gacggtggcg gaggcactgg atcctcagat   780
ttggcaaacg attcttttat ccggcaggtt ctcgaccgtc agcatttcga acccgacggg   840
aaataccacc tattcggcag caggggggaa cttgccgagc gcagcggcca tatcggattg   900
ggaaaaatac aaagccatca gttgggcaac ctgatgattc aacaggcggc cattaaagga   960
aatatcggct acattgtccg cttttccgat cacgggcacg aagtccattc cccttcgac   1020
aaccatgcct cacattccga ttctgatgaa gccggtagtc ccgttgacgg atttagcctt  1080
taccgcatcc attgggacgg atacgaacac catcccgccg acggctatga cgggccacag  1140
ggcggcggct atcccgctcc caaaggcgcg agggatatat acagctacga cataaaaggc  1200
gttgcccaaa atatccgcct caacctgacc gacaaccgca gcaccggaca acggcttgcc  1260
gaccgtttcc acaatgccgg tagtatgctg acgcaaggag taggcgacgg attcaaacgc  1320
gccacccgat acagccccga gctggacaga tcgggcaatg ccgccgaagc cttcaacggc  1380
actgcagata tcgttaaaaa catcatcggc gcggcaggag aaattgtcgg cgcaggcgat  1440
gccgtgcagg gcataagcga aggctcaaac attgctgtca tgcacggctt gggtctgctt  1500
tccaccgaaa acaagatggc gcgcatcaac gatttggcag atatggcgca actcaaagac  1560
tatgccgcag cagccatccg cgattgggca gtccaaaacc ccaatgccgc acaaggcata  1620
gaagccgtca gcaatatctt tatggcagcc atccccatca aagggattgg agctgttcgg  1680
ggaaaatacg gcttgggcgg catcacggca catcctatca agcggtcgca gatgggcgcg  1740
atcgcattgc cgaaagggaa atccgccgtc agcgacaatt ttgccgatgc ggcatacgcc  1800
aaatacccgt ccccttacca ttcccgaaat atccgttcaa acttggagca gcgttacggc  1860
aaagaaaaca tcacctcctc aaccgtgccg ccgtcaaacg gcaaaaatgt caaactggca  1920
gaccaacgcc acccgaagac aggcgtaccg tttgacggta aagggtttcc gaattttgag  1980
aagcacgtga aatatgatac gctcgagcac caccaccacc accactga               2028
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<210>   115
<211>   675
<212>   PRT
<213>   Artificial Sequence

<220>
<223>   deltaG741-ORF46.1

<400>   115
Met Val Ala Ala Asp Ile Gly Ala Gly Leu Ala Asp Ala Leu Thr Ala
1               5                   10                  15

Pro Leu Asp His Lys Asp Lys Gly Leu Gln Ser Leu Thr Leu Asp Gln
            20                  25                  30

Ser Val Arg Lys Asn Glu Lys Leu Lys Leu Ala Ala Gln Gly Ala Glu
        35                  40                  45

Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn Thr Gly Lys Leu Lys Asn
    50                  55                  60

Asp Lys Val Ser Arg Phe Asp Phe Ile Arg Gln Ile Glu Val Asp Gly
65                  70                  75                  80
```

```
Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe Gln Val Tyr Lys Gln Ser
                85                  90                  95

His Ser Ala Leu Thr Ala Phe Gln Thr Glu Gln Ile Gln Asp Ser Glu
            100                 105                 110

His Ser Gly Lys Met Val Ala Lys Arg Gln Phe Arg Ile Gly Asp Ile
        115                 120                 125

Ala Gly Glu His Thr Ser Phe Asp Lys Leu Pro Glu Gly Gly Arg Ala
    130                 135                 140

Thr Tyr Arg Gly Thr Ala Phe Gly Ser Asp Asp Ala Gly Gly Lys Leu
145                 150                 155                 160

Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln Gly Asn Gly Lys Ile Glu
                165                 170                 175

His Leu Lys Ser Pro Glu Leu Asn Val Asp Leu Ala Ala Ala Asp Ile
            180                 185                 190

Lys Pro Asp Gly Lys Arg His Ala Val Ile Ser Gly Ser Val Leu Tyr
        195                 200                 205

Asn Gln Ala Glu Lys Gly Ser Tyr Ser Leu Gly Ile Phe Gly Gly Lys
    210                 215                 220

Ala Gln Glu Val Ala Gly Ser Ala Glu Val Lys Thr Val Asn Gly Ile
225                 230                 235                 240

Arg His Ile Gly Leu Ala Ala Lys Gln Leu Asp Gly Gly Gly Gly Thr
                245                 250                 255

Gly Ser Ser Asp Leu Ala Asn Asp Ser Phe Ile Arg Gln Val Leu Asp
            260                 265                 270

Arg Gln His Phe Glu Pro Asp Gly Lys Tyr His Leu Phe Gly Ser Arg
        275                 280                 285

Gly Glu Leu Ala Glu Arg Ser Gly His Ile Gly Leu Gly Lys Ile Gln
    290                 295                 300

Ser His Gln Leu Gly Asn Leu Met Ile Gln Gln Ala Ala Ile Lys Gly
305                 310                 315                 320

Asn Ile Gly Tyr Ile Val Arg Phe Ser Asp His Gly His Glu Val His
                325                 330                 335

Ser Pro Phe Asp Asn His Ala Ser His Ser Asp Ser Asp Glu Ala Gly
            340                 345                 350

Ser Pro Val Asp Gly Phe Ser Leu Tyr Arg Ile His Trp Asp Gly Tyr
        355                 360                 365

Glu His His Pro Ala Asp Gly Tyr Asp Gly Pro Gln Gly Gly Gly Tyr
    370                 375                 380
```

```
Pro Ala Pro Lys Gly Ala Arg Asp Ile Tyr Ser Tyr Asp Ile Lys Gly
385                 390                 395                 400

Val Ala Gln Asn Ile Arg Leu Asn Leu Thr Asp Asn Arg Ser Thr Gly
                405                 410                 415

Gln Arg Leu Ala Asp Arg Phe His Asn Ala Gly Ser Met Leu Thr Gln
            420                 425                 430

Gly Val Gly Asp Gly Phe Lys Arg Ala Thr Arg Tyr Ser Pro Glu Leu
        435                 440                 445

Asp Arg Ser Gly Asn Ala Ala Glu Ala Phe Asn Gly Thr Ala Asp Ile
    450                 455                 460

Val Lys Asn Ile Ile Gly Ala Ala Gly Glu Ile Val Gly Ala Gly Asp
465                 470                 475                 480

Ala Val Gln Gly Ile Ser Glu Gly Ser Asn Ile Ala Val Met His Gly
                485                 490                 495

Leu Gly Leu Leu Ser Thr Glu Asn Lys Met Ala Arg Ile Asn Asp Leu
            500                 505                 510

Ala Asp Met Ala Gln Leu Lys Asp Tyr Ala Ala Ala Ala Ile Arg Asp
        515                 520                 525

Trp Ala Val Gln Asn Pro Asn Ala Ala Gln Gly Ile Glu Ala Val Ser
    530                 535                 540

Asn Ile Phe Met Ala Ala Ile Pro Ile Lys Gly Ile Gly Ala Val Arg
545                 550                 555                 560

Gly Lys Tyr Gly Leu Gly Gly Ile Thr Ala His Pro Ile Lys Arg Ser
                565                 570                 575

Gln Met Gly Ala Ile Ala Leu Pro Lys Gly Lys Ser Ala Val Ser Asp
            580                 585                 590

Asn Phe Ala Asp Ala Ala Tyr Ala Lys Tyr Pro Ser Pro Tyr His Ser
        595                 600                 605

Arg Asn Ile Arg Ser Asn Leu Glu Gln Arg Tyr Gly Lys Glu Asn Ile
    610                 615                 620

Thr Ser Ser Thr Val Pro Pro Ser Asn Gly Lys Asn Val Lys Leu Ala
625                 630                 635                 640

Asp Gln Arg His Pro Lys Thr Gly Val Pro Phe Asp Gly Lys Gly Phe
                645                 650                 655

Pro Asn Phe Glu Lys His Val Lys Tyr Asp Thr Leu Glu His His His
            660                 665                 670

His His His
        675
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<210> 116
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Novel protein

<400> 116
Met Lys Lys Tyr Leu Phe Arg Ala Ala Leu Tyr Gly Ile Ala Ala Ala
1 5 10 15

Ile Leu Ala Ala Ala Ile Pro Ala Gly Asn Asp Ala Thr Thr Lys Pro
20 25 30

Asp Leu Tyr Tyr Leu Lys Asn Glu Gln Ala Ile Asp Ser Leu Lys Leu
35 40 45

Leu Pro Pro Pro Pro Glu Val Gly Ser Ile Gln Phe Leu Asn Asp Gln
50 55 60

Ala Met Tyr Glu Lys Gly Arg Met Leu Arg Asn Thr Glu Arg Gly Lys
65 70 75 80

Gln Ala Gln Ala Asp Ala Asp Leu Ala Ala Gly Gly Val Ala Thr Ala
85 90 95

Phe Ser Gly Ala Phe Gly Tyr Pro Ile Thr Glu Lys Asp Ser Pro Glu
100 105 110

Leu Tyr Lys Leu Leu Thr Asn Met Ile Glu Asp Ala Gly Asp Leu Ala
115 120 125

Thr Arg Ser Ala Lys Glu His Tyr Met Arg Ile Arg Pro Phe Ala Phe
130 135 140

Tyr Gly Thr Glu Thr Cys Asn Thr Lys Asp Gln Lys Lys Leu Ser Thr
145 150 155 160

Asn Gly Ser Tyr Pro Ser Gly His Thr Ser Ile Gly Trp Ala Thr Ala
165 170 175

Leu Val Leu Ala Glu Val Asn Pro Ala Asn Gln Asp Ala Ile Leu Glu
180 185 190

Arg Gly Tyr Gln Leu Gly Gln Ser Arg Val Ile Cys Gly Tyr His Trp
195 200 205

Gln Ser Asp Val Asp Ala Ala Arg Ile Val Gly Ser Ala Ala Val Ala
210 215 220

Thr Leu His Ser Asp Pro Ala Phe Gln Ala Gln Leu Ala Lys Ala Lys
225 230 235 240

Gln Glu Phe Ala Gln Lys Ser Gln Lys
245

<210> 117
<211> 66
<212> DNA
<213> Artificial Sequence

<220>
<223> L1 linker

<220>
<221> N
<222> 13
<223> A, T/U, G or C

<400> 117
tatgaartay ytnttymgcg ccgccctgta cggcatcgcc gccgccatcc tcgccgccgc 60
gatccc 66

<210> 118
<211> 69
<212> DNA
<213> Artificial Sequence

<220>
<223> S1 linker

<220>
<221> N
<222> 25, 28
<223> A, T/U, G or C

<400> 118
tatgaaaaaa tacctattcc grgcngcnyt rtayggsatc gccgccgcca tcctcgccgc 60
cgcgatccc 69

<210> 119
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> 9L1-a

<400> 119
atgaagaagt accttttcag cgccgcc 27

<210> 120
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> 9L1-e

<400> 120
atgaaaaaat actttttccg cgccgcc 27

<210> 121

<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> 9L1-d

<400> 121
atgaaaaaat actttttccg cgccgcc 27

<210> 122
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> 9L1-f

<400> 122
atgaaaaaat atctctttag cgccgccctg tacggcatcg ccgccgccat cctcgccgcc 60

<210> 123
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> 919sp

<400> 123
atgaaaaaat acctattccg cgccgccctg tacggcatcg ccgccgccat cctcgccgcc 60

<210> 124
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 9L1a

<400> 124
Met Lys Lys Tyr Leu Phe Ser Ala Ala
1 5

<210> 125
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 9L1e

<400> 125
Met Lys Lys Tyr Phe Phe Arg Ala Ala
1 5

<210> 126

<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 9L1d

<400> 126
Met Lys Lys Tyr Phe Phe Arg Ala Ala
1 5

<210> 127
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> 9L1f

<400> 127
Met Lys Lys Tyr Leu Phe Ser Ala Ala Leu Tyr Gly Ile Ala Ala Ala
1 5 10 15

Ile Leu Ala Ala
20

<210> 128
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> 9L1sp

<400> 128
Met Lys Lys Tyr Leu Phe Arg Ala Ala Leu Tyr Gly Ile Ala Ala Ala
1 5 10 15

Ile Leu Ala Ala
20

<210> 129
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
<223> 9S1-e

<400> 129
atgaaaaaat acctattcat cgccgccgcc atcctcgccg cc 42

<210> 130
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> 9S1-c

<400> 130
atgaaaaaat acctattccg agctgcccaa tacggcatcg ccgccgccat cctcgccgcc 60

<210> 131
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> 9S1-b

<400> 131
atgaaaaaat acctattccg ggccgcccaa tacggcatcg ccgccgccat cctcgccgcc 60

<210> 132
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> 9S1-i

<400> 132
atgaaaaaat acctattccg ggcggctttg tacgggatcg ccgccgccat cctcgccgcc 60

<210> 133
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 9S1e

<400> 133
Met Lys Lys Tyr Leu Phe Ile Ala Ala Ala Ile Leu Ala Ala
1 5 10

<210> 134
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> 9S1c

<400> 134
Met Lys Lys Tyr Leu Phe Arg Ala Ala Gln Tyr Gly Ile Ala Ala Ala
1 5 10 15

Ile Leu Ala Ala
20

<210> 135
<211> 20

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<212>   PRT
<213>   Artificial Sequence

<220>
<223>   9S1b

<400>   135
Met Lys Lys Tyr Leu Phe Arg Ala Ala Gln Tyr Gly Ile Ala Ala Ala
1               5                   10                  15

Ile Leu Ala Ala
            20

<210>   136
<211>   20
<212>   PRT
<213>   Artificial Sequence

<220>
<223>   9S1i

<400>   136
Met Lys Lys Tyr Leu Phe Arg Ala Ala Leu Tyr Gly Ile Ala Ala Ala
1               5                   10                  15

Ile Leu Ala Ala
            20

<210>   137
<211>   467
<212>   PRT
<213>   Artificial Sequence

<220>
<223>   730

<400>   137
Val Lys Pro Leu Arg Arg Leu Thr Asn Leu Leu Ala Ala Cys Ala Val
1               5                   10                  15

Ala Ala Ala Ala Leu Ile Gln Pro Ala Leu Ala Ala Asp Leu Ala Gln
            20                  25                  30

Asp Pro Phe Ile Thr Asp Asn Ala Gln Arg Gln His Tyr Glu Pro Gly
        35                  40                  45

Gly Lys Tyr His Leu Phe Gly Asp Pro Arg Gly Ser Val Ser Asp Arg
    50                  55                  60

Thr Gly Lys Ile Asn Val Ile Gln Asp Tyr Thr His Gln Met Gly Asn
65                  70                  75                  80

Leu Leu Ile Gln Gln Ala Asn Ile Asn Gly Thr Ile Gly Tyr His Thr
                85                  90                  95

Arg Phe Ser Gly His Gly His Glu Glu His Ala Pro Phe Asp Asn His
            100                 105                 110
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```
Ala Ala Asp Ser Ala Ser Glu Glu Lys Gly Asn Val Asp Glu Gly Phe
        115                 120                 125

Thr Val Tyr Arg Leu Asn Trp Glu Gly His Glu His His Pro Ala Asp
    130                 135                 140

Ala Tyr Asp Gly Pro Lys Gly Gly Asn Tyr Pro Lys Pro Thr Gly Ala
145                 150                 155                 160

Arg Asp Glu Tyr Thr Tyr His Val Asn Gly Thr Ala Arg Ser Ile Lys
                165                 170                 175

Leu Asn Pro Thr Asp Thr Arg Ser Ile Arg Gln Arg Ile Ser Asp Asn
            180                 185                 190

Tyr Ser Asn Leu Gly Ser Asn Phe Ser Asp Arg Ala Asp Glu Ala Asn
        195                 200                 205

Arg Lys Met Phe Glu His Asn Ala Lys Leu Asp Arg Trp Gly Asn Ser
    210                 215                 220

Met Glu Phe Ile Asn Gly Val Ala Ala Gly Ala Leu Asn Pro Phe Ile
225                 230                 235                 240

Ser Ala Gly Glu Ala Leu Gly Ile Gly Asp Ile Leu Tyr Gly Thr Arg
                245                 250                 255

Tyr Ala Ile Asp Lys Ala Ala Met Arg Asn Ile Ala Pro Leu Pro Ala
            260                 265                 270

Glu Gly Lys Phe Ala Val Ile Gly Gly Leu Gly Ser Val Ala Gly Phe
        275                 280                 285

Glu Lys Asn Thr Arg Glu Ala Val Asp Arg Trp Ile Gln Glu Asn Pro
    290                 295                 300

Asn Ala Ala Glu Thr Val Glu Ala Val Phe Asn Val Ala Ala Ala Ala
305                 310                 315                 320

Lys Val Ala Lys Leu Ala Lys Ala Ala Lys Pro Gly Lys Ala Ala Val
                325                 330                 335

Ser Gly Asp Phe Ala Asp Ser Tyr Lys Lys Lys Leu Ala Leu Ser Asp
            340                 345                 350

Ser Ala Arg Gln Leu Tyr Gln Asn Ala Lys Tyr Arg Glu Ala Leu Asp
        355                 360                 365

Ile His Tyr Glu Asp Leu Ile Arg Arg Lys Thr Asp Gly Ser Ser Lys
    370                 375                 380

Phe Ile Asn Gly Arg Glu Ile Asp Ala Val Thr Asn Asp Ala Leu Ile
385                 390                 395                 400

Gln Ala Lys Arg Thr Ile Ser Ala Ile Asp Lys Pro Lys Asn Phe Leu
                405                 410                 415
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Asn Gln Lys Asn Arg Lys Gln Ile Lys Ala Thr Ile Glu Ala Ala Asn
420 425 430

Gln Gln Gly Lys Arg Ala Glu Phe Trp Phe Lys Tyr Gly Val His Ser
435 440 445

Gln Val Lys Ser Tyr Ile Glu Ser Lys Gly Gly Ile Val Lys Thr Gly
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Leu Gly Asp
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Gln His Tyr Glu Pro Gly Gly Lys Tyr His Leu Phe Gly Asp Pro Arg
20 25 30

Gly Ser Val Ser Asp Arg Thr Gly Lys Ile Asn Val Ile Gln Asp Tyr
35 40 45

Thr His Gln Met Gly Asn Leu Leu Ile Gln Gln Ala Asn Ile Asn Gly
50 55 60

Thr Ile Gly Tyr His Thr Arg Phe Ser Gly His Gly His Glu Glu His
65 70 75 80

Ala Pro Phe Asp Asn His Ala Ala Asp Ser Ala Ser Glu Glu Lys Gly
85 90 95

Asn Val Asp Glu Gly Phe Thr Val Tyr Arg Leu Asn Trp Glu Gly His
100 105 110

Glu His His Pro Ala Asp Ala Tyr Asp Gly Pro Lys Gly Gly Asn Tyr
115 120 125

Pro Lys Pro Thr Gly Ala Arg Asp Glu Tyr Thr Tyr His Val Asn Gly
130 135 140

Thr Ala Arg Ser Ile Lys Leu Asn Pro Thr Asp Thr Arg Ser Ile Arg
145 150 155 160

Gln Arg Ile Ser Asp Asn Tyr Ser Asn Leu Gly Ser Asn Phe Ser Asp
165 170 175

Arg Ala Asp Glu Ala Asn Arg Lys Met Phe Glu His Asn Ala Lys Leu
180 185 190

```
Asp Arg Trp Gly Asn Ser Met Glu Phe Ile Asn Gly Val Ala Ala Gly
        195                 200                 205

Ala Leu Asn Pro Phe Ile Ser Ala Gly Glu Ala Leu Gly Ile Gly Asp
    210                 215                 220

Ile Leu Tyr Gly Thr Arg Tyr Ala Ile Asp Lys Ala Ala Met Arg Asn
225                 230                 235                 240

Ile Ala Pro Leu Pro Ala Glu Gly Lys Phe Ala Val Ile Gly Gly Leu
                245                 250                 255

Gly Ser Val Ala Gly Phe Glu Lys Asn Thr Arg Glu Ala Val Asp Arg
            260                 265                 270

Trp Ile Gln Glu Asn Pro Asn Ala Ala Glu Thr Val Glu Ala Val Phe
        275                 280                 285

Asn Val Ala Ala Ala Ala Lys Val Ala Lys Leu Ala Lys Ala Ala Lys
    290                 295                 300

Pro Gly Lys Ala Ala Val Ser Gly Asp Phe Ala Asp Ser Tyr Lys Lys
305                 310                 315                 320

Lys Leu Ala Leu Ser Asp Ser Ala Arg Gln Leu Tyr Gln Asn Ala Lys
                325                 330                 335

Tyr Arg Glu Ala Leu Asp Ile His Tyr Glu Asp Leu Ile Arg Arg Lys
            340                 345                 350

Thr Asp Gly Ser Ser Lys Phe Ile Asn Gly Arg Glu Ile Asp Ala Val
        355                 360                 365

Thr Asn Asp Ala Leu Ile Gln Ala Arg
    370                 375

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<212>   PRT
<213>   Artificial Sequence

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Met Ala Asp Leu Ala Gln Asp Pro Phe Ile Thr Asp Asn Ala Gln Arg
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Gln His Tyr Glu Pro Gly Gly Lys Tyr His Leu Phe Gly Asp Pro Arg
            20                  25                  30

Gly Ser Val Ser Asp Arg Thr Gly Lys Ile Asn Val Ile Gln Asp Tyr
        35                  40                  45

Thr His Gln Met Gly Asn Leu Leu Ile Gln Gln Ala Asn Ile Asn Gly
    50                  55                  60
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Thr Ile Gly Tyr His Thr Arg Phe Ser Gly His Gly His Glu Glu His
65                  70                  75                  80

Ala Pro Phe Asp Asn His Ala Ala Asp Ser Ala Ser Glu Glu Lys Gly
                85                  90                  95

Asn Val Asp Glu Gly Phe Thr Val Tyr Arg Leu Asn Trp Glu Gly His
            100                 105                 110

Glu His His Pro Ala Asp Ala Tyr Asp Gly Pro Lys Gly Gly Asn Tyr
        115                 120                 125

Pro Lys Pro Thr Gly Ala Arg Asp Glu Tyr Thr Tyr His Val Asn Gly
    130                 135                 140

Thr Ala Arg Ser Ile Lys Leu Asn Pro Thr Asp Thr Arg Ser Ile Arg
145                 150                 155                 160

Gln Arg Ile Ser Asp Asn Tyr Ser Asn Leu Gly Ser Asn Phe Ser Asp
                165                 170                 175

Arg Ala Asp Glu Ala Asn Arg Lys Met Phe Glu His Asn Ala Lys Leu
            180                 185                 190

Asp Arg Trp Gly Asn Ser Met Glu Phe Ile Asn Gly Val Ala Ala Gly
        195                 200                 205

Ala Leu Asn Pro Phe Ile Ser Ala Gly Glu Ala Leu Gly Ile Gly Asp
    210                 215                 220

Ile Leu Tyr Gly Thr Arg Tyr Ala Ile Asp Lys Ala Ala Met Arg Asn
225                 230                 235                 240

Ile Ala Pro Leu Pro Ala Glu Gly Lys Phe Ala Val Ile Gly Gly Leu
                245                 250                 255

Gly Ser Val Ala Gly Phe Glu Lys Asn Thr Arg Glu Ala Val Asp Arg
            260                 265                 270

Trp Ile Gln Glu Asn Pro Asn Ala Ala Glu Thr Val Glu Ala Val Phe
        275                 280                 285

Asn Val Ala Ala Ala Ala Lys Val Ala Lys Leu Ala Lys Ala Ala Lys
    290                 295                 300

Pro Gly Lys Ala Ala Val Ser Gly Asp Phe Ala Asp Ser Tyr Lys Lys
305                 310                 315                 320

Lys Leu Ala Leu Ser Asp Ser Ala Arg Gln Leu Tyr Gln Asn Ala Lys
                325                 330                 335

Tyr Arg Glu Ala Leu Gly Lys Val Arg Ile Ser Gly Glu Ile Leu Leu
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Gly
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<211>   2019
<212>   DNA
<213>   Artificial Sequence

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atcggattgg gaaaaataca aagccatcag ttgggcaacc tgatgattca acaggcggcc    180
attaaaggaa atatcggcta cattgtccgc ttttccgatc acgggcacga agtccattcc    240
cccttcgaca accatgcctc acattccgat tctgatgaag ccggtagtcc cgttgacgga    300
tttagccttt accgcatcca ttgggacgga tacgaacacc atcccgccga cggctatgac    360
gggccacagg gcggcggcta tcccgctccc aaaggcgcga gggatatata cagctacgac    420
ataaaaggcg ttgcccaaaa tatccgcctc aacctgaccg acaaccgcag caccggacaa    480
cggcttgccg accgtttcca caatgccggt agtatgctga cgcaaggagt aggcgacgga    540
ttcaaacgcg ccacccgata cagccccgag ctggacagat cgggcaatgc cgccgaagcc    600
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gcaggcgatg ccgtgcaggg cataagcgaa ggctcaaaca ttgctgtcat gcacggcttg    720
ggtctgcttt ccaccgaaaa caagatggcg cgcatcaacg atttggcaga tatggcgcaa    780
ctcaaagact atgccgcagc agccatccgc gattgggcag tccaaaaccc caatgccgca    840
caaggcatag aagccgtcag caatatcttt atggcagcca tccccatcaa agggattgga    900
gctgttcggg gaaaatacgg cttgggcggc atcacggcac atcctatcaa gcggtcgcag    960
atgggcgcga tcgcattgcc gaaagggaaa tccgccgtca gcgacaattt tgccgatgcg   1020
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cgttacggca aagaaaacat cacctcctca accgtgccgc cgtcaaacgg caaaaatgtc   1140
aaactggcag accaacgcca cccgaagaca ggcgtaccgt ttgacggtaa agggtttccg   1200
aattttgaga agcacgtgaa atatgatacg ggatccggag gggtggtgt cgccgccgac   1260
atcggtgcgg ggcttgccga tgcactaacc gcaccgctcg accataaaga caaaggtttg   1320
cagtctttga cgctggatca gtccgtcagg aaaaacgaga aactgaagct ggcggcacaa   1380
ggtgcggaaa aaacttatgg aaacggtgac agcctcaata cgggcaaatt gaagaacgac   1440
aaggtcagcc gtttcgactt tatccgccaa atcgaagtgg acgggcagct cattaccttg   1500
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gagcaaatac aagattcgga gcattccggg aagatggttg cgaaacgcca gttcagaatc   1620
ggcgacatag cgggcgaaca tacatctttt gacaagcttc ccgaaggcgg cagggcgaca   1680
tatcgcggga cggcgttcgg ttcagacgat gccggcggaa aactgaccta caccatagat   1740
ttcgccgcca agcagggaaa cggcaaaatc gaacatttga aatcgccaga actcaatgtc   1800
gacctggccg ccgccgatat caagccggat ggaaaacgcc atgccgtcat cagcggttcc   1860
gtcctttaca accaagccga gaaaggcagt tactccctcg gtatctttgg cggaaaagcc   1920
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<212>   PRT
<213>   Artificial Sequence

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1               5                   10                  15
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Gln His Phe Glu Pro Asp Gly Lys Tyr His Leu Phe Gly Ser Arg Gly
            20                  25                  30

Glu Leu Ala Glu Arg Ser Gly His Ile Gly Leu Gly Lys Ile Gln Ser
        35                  40                  45

His Gln Leu Gly Asn Leu Met Ile Gln Gln Ala Ala Ile Lys Gly Asn
    50                  55                  60

Ile Gly Tyr Ile Val Arg Phe Ser Asp His Gly His Glu Val His Ser
65                  70                  75                  80

Pro Phe Asp Asn His Ala Ser His Ser Asp Ser Asp Glu Ala Gly Ser
                85                  90                  95

Pro Val Asp Gly Phe Ser Leu Tyr Arg Ile His Trp Asp Gly Tyr Glu
            100                 105                 110

His His Pro Ala Asp Gly Tyr Asp Gly Pro Gln Gly Gly Gly Tyr Pro
        115                 120                 125

Ala Pro Lys Gly Ala Arg Asp Ile Tyr Ser Tyr Asp Ile Lys Gly Val
    130                 135                 140

Ala Gln Asn Ile Arg Leu Asn Leu Thr Asp Asn Arg Ser Thr Gly Gln
145                 150                 155                 160

Arg Leu Ala Asp Arg Phe His Asn Ala Gly Ser Met Leu Thr Gln Gly
                165                 170                 175

Val Gly Asp Gly Phe Lys Arg Ala Thr Arg Tyr Ser Pro Glu Leu Asp
            180                 185                 190

Arg Ser Gly Asn Ala Ala Glu Ala Phe Asn Gly Thr Ala Asp Ile Val
        195                 200                 205

Lys Asn Ile Ile Gly Ala Ala Gly Glu Ile Val Gly Ala Gly Asp Ala
    210                 215                 220

Val Gln Gly Ile Ser Glu Gly Ser Asn Ile Ala Val Met His Gly Leu
225                 230                 235                 240

Gly Leu Leu Ser Thr Glu Asn Lys Met Ala Arg Ile Asn Asp Leu Ala
                245                 250                 255

Asp Met Ala Gln Leu Lys Asp Tyr Ala Ala Ala Ala Ile Arg Asp Trp
            260                 265                 270

Ala Val Gln Asn Pro Asn Ala Ala Gln Gly Ile Glu Ala Val Ser Asn
        275                 280                 285

Ile Phe Met Ala Ala Ile Pro Ile Lys Gly Ile Gly Ala Val Arg Gly
    290                 295                 300

Lys Tyr Gly Leu Gly Gly Ile Thr Ala His Pro Ile Lys Arg Ser Gln
305                 310                 315                 320
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Met Gly Ala Ile Ala Leu Pro Lys Gly Lys Ser Ala Val Ser Asp Asn
325 330 335

Phe Ala Asp Ala Ala Tyr Ala Lys Tyr Pro Ser Pro Tyr His Ser Arg
340 345 350

Asn Ile Arg Ser Asn Leu Glu Gln Arg Tyr Gly Lys Glu Asn Ile Thr
355 360 365

Ser Ser Thr Val Pro Pro Ser Asn Gly Lys Asn Val Lys Leu Ala Asp
370 375 380

Gln Arg His Pro Lys Thr Gly Val Pro Phe Asp Gly Lys Gly Phe Pro
385 390 395 400

Asn Phe Glu Lys His Val Lys Tyr Asp Thr Gly Ser Gly Gly Gly Gly
405 410 415

Val Ala Ala Asp Ile Gly Ala Gly Leu Ala Asp Ala Leu Thr Ala Pro
420 425 430

Leu Asp His Lys Asp Lys Gly Leu Gln Ser Leu Thr Leu Asp Gln Ser
435 440 445

Val Arg Lys Asn Glu Lys Leu Lys Leu Ala Ala Gln Gly Ala Glu Lys
450 455 460

Thr Tyr Gly Asn Gly Asp Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp
465 470 475 480

Lys Val Ser Arg Phe Asp Phe Ile Arg Gln Ile Glu Val Asp Gly Gln
485 490 495

Leu Ile Thr Leu Glu Ser Gly Glu Phe Gln Val Tyr Lys Gln Ser His
500 505 510

Ser Ala Leu Thr Ala Phe Gln Thr Glu Gln Ile Gln Asp Ser Glu His
515 520 525

Ser Gly Lys Met Val Ala Lys Arg Gln Phe Arg Ile Gly Asp Ile Ala
530 535 540

Gly Glu His Thr Ser Phe Asp Lys Leu Pro Glu Gly Gly Arg Ala Thr
545 550 555 560

Tyr Arg Gly Thr Ala Phe Gly Ser Asp Asp Ala Gly Gly Lys Leu Thr
565 570 575

Tyr Thr Ile Asp Phe Ala Ala Lys Gln Gly Asn Gly Lys Ile Glu His
580 585 590

Leu Lys Ser Pro Glu Leu Asn Val Asp Leu Ala Ala Ala Asp Ile Lys
595 600 605

Pro Asp Gly Lys Arg His Ala Val Ile Ser Gly Ser Val Leu Tyr Asn
610 615 620

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Gln Ala Glu Lys Gly Ser Tyr Ser Leu Gly Ile Phe Gly Gly Lys Ala
625                 630                 635                 640

Gln Glu Val Ala Gly Ser Ala Glu Val Lys Thr Val Asn Gly Ile Arg
                645                 650                 655

His Ile Gly Leu Ala Ala Lys Gln Leu Glu His His His His His His
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<212> DNA
<213> Artificial Sequence

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attaaaggaa atatcggcta cattgtccgc ttttccgatc acgggcacga agtccattcc 240
cccttcgaca accatgcctc acattccgat tctgatgaag ccggtagtcc cgttgacgga 300
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gcaggcgatg ccgtgcaggg cataagcgaa ggctcaaaca ttgctgtcat gcacggcttg 720
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<212>  PRT
<213>  Artificial Sequence

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Gln His Phe Glu Pro Asp Gly Lys Tyr His Leu Phe Gly Ser Arg Gly
            20                  25                  30

Glu Leu Ala Glu Arg Ser Gly His Ile Gly Leu Gly Lys Ile Gln Ser
        35                  40                  45

His Gln Leu Gly Asn Leu Met Ile Gln Gln Ala Ala Ile Lys Gly Asn
    50                  55                  60

Ile Gly Tyr Ile Val Arg Phe Ser Asp His Gly His Glu Val His Ser
65                  70                  75                  80

Pro Phe Asp Asn His Ala Ser His Ser Asp Ser Asp Glu Ala Gly Ser
                85                  90                  95

Pro Val Asp Gly Phe Ser Leu Tyr Arg Ile His Trp Asp Gly Tyr Glu
            100                 105                 110

His His Pro Ala Asp Gly Tyr Asp Gly Pro Gln Gly Gly Gly Tyr Pro
        115                 120                 125

Ala Pro Lys Gly Ala Arg Asp Ile Tyr Ser Tyr Asp Ile Lys Gly Val
    130                 135                 140

Ala Gln Asn Ile Arg Leu Asn Leu Thr Asp Asn Arg Ser Thr Gly Gln
145                 150                 155                 160

Arg Leu Ala Asp Arg Phe His Asn Ala Gly Ser Met Leu Thr Gln Gly
                165                 170                 175

Val Gly Asp Gly Phe Lys Arg Ala Thr Arg Tyr Ser Pro Glu Leu Asp
            180                 185                 190

Arg Ser Gly Asn Ala Ala Glu Ala Phe Asn Gly Thr Ala Asp Ile Val
        195                 200                 205

Lys Asn Ile Ile Gly Ala Ala Gly Glu Ile Val Gly Ala Gly Asp Ala
    210                 215                 220

Val Gln Gly Ile Ser Glu Gly Ser Asn Ile Ala Val Met His Gly Leu
225                 230                 235                 240
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Gly Leu Leu Ser Thr Glu Asn Lys Met Ala Arg Ile Asn Asp Leu Ala
                245                 250                 255

Asp Met Ala Gln Leu Lys Asp Tyr Ala Ala Ala Ala Ile Arg Asp Trp
            260                 265                 270

Ala Val Gln Asn Pro Asn Ala Ala Gln Gly Ile Glu Ala Val Ser Asn
        275                 280                 285

Ile Phe Met Ala Ala Ile Pro Ile Lys Gly Ile Gly Ala Val Arg Gly
    290                 295                 300

Lys Tyr Gly Leu Gly Gly Ile Thr Ala His Pro Ile Lys Arg Ser Gln
305                 310                 315                 320

Met Gly Ala Ile Ala Leu Pro Lys Gly Lys Ser Ala Val Ser Asp Asn
                325                 330                 335

Phe Ala Asp Ala Ala Tyr Ala Lys Tyr Pro Ser Pro Tyr His Ser Arg
            340                 345                 350

Asn Ile Arg Ser Asn Leu Glu Gln Arg Tyr Gly Lys Glu Asn Ile Thr
        355                 360                 365

Ser Ser Thr Val Pro Pro Ser Asn Gly Lys Asn Val Lys Leu Ala Asp
    370                 375                 380

Gln Arg His Pro Lys Thr Gly Val Pro Phe Asp Gly Lys Gly Phe Pro
385                 390                 395                 400

Asn Phe Glu Lys His Val Lys Tyr Asp Thr Gly Ser Gly Gly Gly Gly
                405                 410                 415

Ala Thr Asn Asp Asp Asp Val Lys Lys Ala Ala Thr Val Ala Ile Ala
            420                 425                 430

Ala Ala Tyr Asn Asn Gly Gln Glu Ile Asn Gly Phe Lys Ala Gly Glu
        435                 440                 445

Thr Ile Tyr Asp Ile Asp Glu Asp Gly Thr Ile Thr Lys Lys Asp Ala
    450                 455                 460

Thr Ala Ala Asp Val Glu Ala Asp Asp Phe Lys Gly Leu Gly Leu Lys
465                 470                 475                 480

Lys Val Val Thr Asn Leu Thr Lys Thr Val Asn Glu Asn Lys Gln Asn
                485                 490                 495

Val Asp Ala Lys Val Lys Ala Ala Glu Ser Glu Ile Glu Lys Leu Thr
            500                 505                 510

Thr Lys Leu Ala Asp Thr Asp Ala Ala Leu Ala Asp Thr Asp Ala Ala
        515                 520                 525

Leu Asp Ala Thr Thr Asn Ala Leu Asn Lys Leu Gly Glu Asn Ile Thr
    530                 535                 540
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Thr Phe Ala Glu Glu Thr Lys Thr Asn Ile Val Lys Ile Asp Glu Lys
545 550 555 560

Leu Glu Ala Val Ala Asp Thr Val Asp Lys His Ala Glu Ala Phe Asn
565 570 575

Asp Ile Ala Asp Ser Leu Asp Glu Thr Asn Thr Lys Ala Asp Glu Ala
580 585 590

Val Lys Thr Ala Asn Glu Ala Lys Gln Thr Ala Glu Glu Thr Lys Gln
595 600 605

Asn Val Asp Ala Lys Val Lys Ala Ala Glu Thr Ala Ala Gly Lys Ala
610 615 620

Glu Ala Ala Ala Gly Thr Ala Asn Thr Ala Ala Asp Lys Ala Glu Ala
625 630 635 640

Val Ala Ala Lys Val Thr Asp Ile Lys Ala Asp Ile Ala Thr Asn Lys
645 650 655

Asp Asn Ile Ala Lys Lys Ala Asn Ser Ala Asp Val Tyr Thr Arg Glu
660 665 670

Glu Ser Asp Ser Lys Phe Val Arg Ile Asp Gly Leu Asn Ala Thr Thr
675 680 685

Glu Lys Leu Asp Thr Arg Leu Ala Ser Ala Glu Lys Ser Ile Ala Asp
690 695 700

His Asp Thr Arg Leu Asn Gly Leu Asp Lys Thr Val Ser Asp Leu Arg
705 710 715 720

Lys Glu Thr Arg Gln Gly Leu Ala Glu Gln Ala Ala Leu Ser Gly Leu
725 730 735

Phe Gln Pro Tyr Asn Val Gly Arg Phe Asn Val Thr Ala Ala Val Gly
740 745 750

Gly Tyr Lys Ser Glu Ser Ala Val Ala Ile Gly Thr Gly Phe Arg Phe
755 760 765

Thr Glu Asn Phe Ala Ala Lys Ala Gly Val Ala Val Gly Thr Ser Ser
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Gly Ser Ser Ala Ala Tyr His Val Gly Val Asn Tyr Glu Trp Leu Glu
785 790 795 800

His His His His His His
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<210> 144
<211> 2256
<212> DNA
<213> Artificial Sequence

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<223> ORF46.1-961c

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attaaaggaa atatcggcta cattgtccgc ttttccgatc acgggcacga agtccattcc 240
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<212> PRT
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Gln His Phe Glu Pro Asp Gly Lys Tyr His Leu Phe Gly Ser Arg Gly
20 25 30

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Glu Leu Ala Glu Arg Ser Gly His Ile Gly Leu Gly Lys Ile Gln Ser
        35                  40                  45

His Gln Leu Gly Asn Leu Met Ile Gln Gln Ala Ala Ile Lys Gly Asn
    50                  55                  60

Ile Gly Tyr Ile Val Arg Phe Ser Asp His Gly His Glu Val His Ser
65                  70                  75                  80

Pro Phe Asp Asn His Ala Ser His Ser Asp Ser Asp Glu Ala Gly Ser
                85                  90                  95

Pro Val Asp Gly Phe Ser Leu Tyr Arg Ile His Trp Asp Gly Tyr Glu
            100                 105                 110

His His Pro Ala Asp Gly Tyr Asp Gly Pro Gln Gly Gly Gly Tyr Pro
        115                 120                 125

Ala Pro Lys Gly Ala Arg Asp Ile Tyr Ser Tyr Asp Ile Lys Gly Val
    130                 135                 140

Ala Gln Asn Ile Arg Leu Asn Leu Thr Asp Asn Arg Ser Thr Gly Gln
145                 150                 155                 160

Arg Leu Ala Asp Arg Phe His Asn Ala Gly Ser Met Leu Thr Gln Gly
                165                 170                 175

Val Gly Asp Gly Phe Lys Arg Ala Thr Arg Tyr Ser Pro Glu Leu Asp
            180                 185                 190

Arg Ser Gly Asn Ala Ala Glu Ala Phe Asn Gly Thr Ala Asp Ile Val
        195                 200                 205

Lys Asn Ile Ile Gly Ala Ala Gly Glu Ile Val Gly Ala Gly Asp Ala
    210                 215                 220

Val Gln Gly Ile Ser Glu Gly Ser Asn Ile Ala Val Met His Gly Leu
225                 230                 235                 240

Gly Leu Leu Ser Thr Glu Asn Lys Met Ala Arg Ile Asn Asp Leu Ala
                245                 250                 255

Asp Met Ala Gln Leu Lys Asp Tyr Ala Ala Ala Ala Ile Arg Asp Trp
            260                 265                 270

Ala Val Gln Asn Pro Asn Ala Ala Gln Gly Ile Glu Ala Val Ser Asn
        275                 280                 285

Ile Phe Met Ala Ala Ile Pro Ile Lys Gly Ile Gly Ala Val Arg Gly
    290                 295                 300

Lys Tyr Gly Leu Gly Gly Ile Thr Ala His Pro Ile Lys Arg Ser Gln
305                 310                 315                 320

Met Gly Ala Ile Ala Leu Pro Lys Gly Lys Ser Ala Val Ser Asp Asn
                325                 330                 335
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Phe Ala Asp Ala Ala Tyr Ala Lys Tyr Pro Ser Pro Tyr His Ser Arg
            340                 345                 350

Asn Ile Arg Ser Asn Leu Glu Gln Arg Tyr Gly Lys Glu Asn Ile Thr
        355                 360                 365

Ser Ser Thr Val Pro Pro Ser Asn Gly Lys Asn Val Lys Leu Ala Asp
    370                 375                 380

Gln Arg His Pro Lys Thr Gly Val Pro Phe Asp Gly Lys Gly Phe Pro
385                 390                 395                 400

Asn Phe Glu Lys His Val Lys Tyr Asp Thr Gly Ser Gly Gly Gly Gly
                405                 410                 415

Ala Thr Asn Asp Asp Asp Val Lys Lys Ala Ala Thr Val Ala Ile Ala
            420                 425                 430

Ala Ala Tyr Asn Asn Gly Gln Glu Ile Asn Gly Phe Lys Ala Gly Glu
        435                 440                 445

Thr Ile Tyr Asp Ile Asp Glu Asp Gly Thr Ile Thr Lys Lys Asp Ala
    450                 455                 460

Thr Ala Ala Asp Val Glu Ala Asp Asp Phe Lys Gly Leu Gly Leu Lys
465                 470                 475                 480

Lys Val Val Thr Asn Leu Thr Lys Thr Val Asn Glu Asn Lys Gln Asn
                485                 490                 495

Val Asp Ala Lys Val Lys Ala Ala Glu Ser Glu Ile Glu Lys Leu Thr
            500                 505                 510

Thr Lys Leu Ala Asp Thr Asp Ala Ala Leu Ala Asp Thr Asp Ala Ala
        515                 520                 525

Leu Asp Ala Thr Thr Asn Ala Leu Asn Lys Leu Gly Glu Asn Ile Thr
    530                 535                 540

Thr Phe Ala Glu Glu Thr Lys Thr Asn Ile Val Lys Ile Asp Glu Lys
545                 550                 555                 560

Leu Glu Ala Val Ala Asp Thr Val Asp Lys His Ala Glu Ala Phe Asn
                565                 570                 575

Asp Ile Ala Asp Ser Leu Asp Glu Thr Asn Thr Lys Ala Asp Glu Ala
            580                 585                 590

Val Lys Thr Ala Asn Glu Ala Lys Gln Thr Ala Glu Glu Thr Lys Gln
        595                 600                 605

Asn Val Asp Ala Lys Val Lys Ala Ala Glu Thr Ala Ala Gly Lys Ala
    610                 615                 620

Glu Ala Ala Ala Gly Thr Ala Asn Thr Ala Ala Asp Lys Ala Glu Ala
625                 630                 635                 640
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Val Ala Ala Lys Val Thr Asp Ile Lys Ala Asp Ile Ala Thr Asn Lys
645 650 655

Asp Asn Ile Ala Lys Lys Ala Asn Ser Ala Asp Val Tyr Thr Arg Glu
660 665 670

Glu Ser Asp Ser Lys Phe Val Arg Ile Asp Gly Leu Asn Ala Thr Thr
675 680 685

Glu Lys Leu Asp Thr Arg Leu Ala Ser Ala Glu Lys Ser Ile Ala Asp
690 695 700

His Asp Thr Arg Leu Asn Gly Leu Asp Lys Thr Val Ser Asp Leu Arg
705 710 715 720

Lys Glu Thr Arg Gln Gly Leu Ala Glu Gln Ala Ala Leu Ser Gly Leu
725 730 735

Phe Gln Pro Tyr Asn Val Gly Leu Glu His His His His His His
740 745 750

<210> 146
<211> 2421
<212> DNA
<213> Artificial Sequence

<220>
<223> 961-ORF46.1

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gacggcacaa ttaccaaaaa agacgcaact gcagccgatg ttgaagccga cgactttaaa 180
ggtctgggtc tgaaaaaagt cgtgactaac ctgaccaaaa ccgtcaatga aaacaaacaa 240
aacgtcgatg ccaaagtaaa agctgcagaa tctgaaatag aaaagttaac aaccaagtta 300
gcagacactg atgccgcttt agcagatact gatgccgctc tggatgcaac caccaacgcc 360
ttgaataaat tgggagaaaa tataacgaca tttgctgaag agactaagac aaatatcgta 420
aaaattgatg aaaaattaga agccgtggct gataccgtcg acaagcatgc cgaagcattc 480
aacgatatcg ccgattcatt ggatgaaacc aacactaagg cagacgaagc cgtcaaaacc 540
gccaatgaag ccaaacagac ggccgaagaa accaaacaaa acgtcgatgc caaagtaaaa 600
gctgcagaaa ctgcagcagg caaagccgaa gctgccgctg gcacagctaa tactgcagcc 660
gacaaggccg aagctgtcgc tgcaaaagtt accgacatca aagctgatat cgctacgaac 720
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gttctcgacc gtcagcattt cgaacccgac gggaaatacc acctattcgg cagcaggggg 1260
gaacttgccg agcgcagcgg ccatatcgga ttgggaaaaa tacaaagcca tcagttgggc 1320
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gatcacgggc acgaagtcca ttcccccttc gacaaccatg cctcacattc cgattctgat 1440
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aacgatttgg cagatatggc gcaactcaaa gactatgccg cagcagccat ccgcgattgg   1980
gcagtccaaa accccaatgc cgcacaaggc atagaagccg tcagcaatat ctttatggca   2040
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gtcagcgaca attttgccga tgcggcatac gccaaatacc cgtcccctta ccattcccga   2220
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ccgccgtcaa acggcaaaaa tgtcaaactg gcagaccaac gccacccgaa gacaggcgta   2340
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<212>   PRT
<213>   Artificial Sequence

<220>
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Ala Ala Ala Tyr Asn Asn Gly Gln Glu Ile Asn Gly Phe Lys Ala Gly
            20                  25                  30

Glu Thr Ile Tyr Asp Ile Asp Glu Asp Gly Thr Ile Thr Lys Lys Asp
        35                  40                  45

Ala Thr Ala Ala Asp Val Glu Ala Asp Asp Phe Lys Gly Leu Gly Leu
    50                  55                  60

Lys Lys Val Val Thr Asn Leu Thr Lys Thr Val Asn Glu Asn Lys Gln
65                  70                  75                  80

Asn Val Asp Ala Lys Val Lys Ala Ala Glu Ser Glu Ile Glu Lys Leu
                85                  90                  95

Thr Thr Lys Leu Ala Asp Thr Asp Ala Ala Leu Ala Asp Thr Asp Ala
            100                 105                 110

Ala Leu Asp Ala Thr Thr Asn Ala Leu Asn Lys Leu Gly Glu Asn Ile
        115                 120                 125

Thr Thr Phe Ala Glu Glu Thr Lys Thr Asn Ile Val Lys Ile Asp Glu
    130                 135                 140

Lys Leu Glu Ala Val Ala Asp Thr Val Asp Lys His Ala Glu Ala Phe
145                 150                 155                 160

Asn Asp Ile Ala Asp Ser Leu Asp Glu Thr Asn Thr Lys Ala Asp Glu
                165                 170                 175
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Ala Val Lys Thr Ala Asn Glu Ala Lys Gln Thr Ala Glu Glu Thr Lys
180 185 190

Gln Asn Val Asp Ala Lys Val Lys Ala Ala Glu Thr Ala Ala Gly Lys
195 200 205

Ala Glu Ala Ala Ala Gly Thr Ala Asn Thr Ala Ala Asp Lys Ala Glu
210 215 220

Ala Val Ala Ala Lys Val Thr Asp Ile Lys Ala Asp Ile Ala Thr Asn
225 230 235 240

Lys Asp Asn Ile Ala Lys Lys Ala Asn Ser Ala Asp Val Tyr Thr Arg
245 250 255

Glu Glu Ser Asp Ser Lys Phe Val Arg Ile Asp Gly Leu Asn Ala Thr
260 265 270

Thr Glu Lys Leu Asp Thr Arg Leu Ala Ser Ala Glu Lys Ser Ile Ala
275 280 285

Asp His Asp Thr Arg Leu Asn Gly Leu Asp Lys Thr Val Ser Asp Leu
290 295 300

Arg Lys Glu Thr Arg Gln Gly Leu Ala Glu Gln Ala Ala Leu Ser Gly
305 310 315 320

Leu Phe Gln Pro Tyr Asn Val Gly Arg Phe Asn Val Thr Ala Ala Val
325 330 335

Gly Gly Tyr Lys Ser Glu Ser Ala Val Ala Ile Gly Thr Gly Phe Arg
340 345 350

Phe Thr Glu Asn Phe Ala Ala Lys Ala Gly Val Ala Val Gly Thr Ser
355 360 365

Ser Gly Ser Ser Ala Ala Tyr His Val Gly Val Asn Tyr Glu Trp Gly
370 375 380

Ser Gly Gly Gly Gly Ser Asp Leu Ala Asn Asp Ser Phe Ile Arg Gln
385 390 395 400

Val Leu Asp Arg Gln His Phe Glu Pro Asp Gly Lys Tyr His Leu Phe
405 410 415

Gly Ser Arg Gly Glu Leu Ala Glu Arg Ser Gly His Ile Gly Leu Gly
420 425 430

Lys Ile Gln Ser His Gln Leu Gly Asn Leu Met Ile Gln Gln Ala Ala
435 440 445

Ile Lys Gly Asn Ile Gly Tyr Ile Val Arg Phe Ser Asp His Gly His
450 455 460

Glu Val His Ser Pro Phe Asp Asn His Ala Ser His Ser Asp Ser Asp
465 470 475 480

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Glu Ala Gly Ser Pro Val Asp Gly Phe Ser Leu Tyr Arg Ile His Trp
                485                 490                 495

Asp Gly Tyr Glu His His Pro Ala Asp Gly Tyr Asp Gly Pro Gln Gly
            500                 505                 510

Gly Gly Tyr Pro Ala Pro Lys Gly Ala Arg Asp Ile Tyr Ser Tyr Asp
    515                 520                 525

Ile Lys Gly Val Ala Gln Asn Ile Arg Leu Asn Leu Thr Asp Asn Arg
    530                 535                 540

Ser Thr Gly Gln Arg Leu Ala Asp Arg Phe His Asn Ala Gly Ser Met
545                 550                 555                 560

Leu Thr Gln Gly Val Gly Asp Gly Phe Lys Arg Ala Thr Arg Tyr Ser
                565                 570                 575

Pro Glu Leu Asp Arg Ser Gly Asn Ala Ala Glu Ala Phe Asn Gly Thr
            580                 585                 590

Ala Asp Ile Val Lys Asn Ile Ile Gly Ala Ala Gly Glu Ile Val Gly
        595                 600                 605

Ala Gly Asp Ala Val Gln Gly Ile Ser Glu Gly Ser Asn Ile Ala Val
    610                 615                 620

Met His Gly Leu Gly Leu Leu Ser Thr Glu Asn Lys Met Ala Arg Ile
625                 630                 635                 640

Asn Asp Leu Ala Asp Met Ala Gln Leu Lys Asp Tyr Ala Ala Ala Ala
                645                 650                 655

Ile Arg Asp Trp Ala Val Gln Asn Pro Asn Ala Ala Gln Gly Ile Glu
            660                 665                 670

Ala Val Ser Asn Ile Phe Met Ala Ala Ile Pro Ile Lys Gly Ile Gly
        675                 680                 685

Ala Val Arg Gly Lys Tyr Gly Leu Gly Gly Ile Thr Ala His Pro Ile
    690                 695                 700

Lys Arg Ser Gln Met Gly Ala Ile Ala Leu Pro Lys Gly Lys Ser Ala
705                 710                 715                 720

Val Ser Asp Asn Phe Ala Asp Ala Ala Tyr Ala Lys Tyr Pro Ser Pro
                725                 730                 735

Tyr His Ser Arg Asn Ile Arg Ser Asn Leu Glu Gln Arg Tyr Gly Lys
            740                 745                 750

Glu Asn Ile Thr Ser Ser Thr Val Pro Pro Ser Asn Gly Lys Asn Val
        755                 760                 765

Lys Leu Ala Asp Gln Arg His Pro Lys Thr Gly Val Pro Phe Asp Gly
    770                 775                 780
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Lys Gly Phe Pro Asn Phe Glu Lys His Val Lys Tyr Asp Thr Leu Glu
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His His His His His His
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<211>  1938
<212>  DNA
<213>  Artificial Sequence

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<223>  961-741

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gacggcacaa ttaccaaaaa agacgcaact gcagccgatg ttgaagccga cgactttaaa   180
ggtctgggtc tgaaaaaagt cgtgactaac ctgaccaaaa ccgtcaatga aaacaaacaa   240
aacgtcgatg ccaaagtaaa agctgcagaa tctgaaatag aaaagttaac aaccaagtta   300
gcagacactg atgccgcttt agcagatact gatgccgctc tggatgcaac caccaacgcc   360
ttgaataaat tgggagaaaa tataacgaca tttgctgaag agactaagac aaatatcgta   420
aaaattgatg aaaaattaga agccgtggct gataccgtcg acaagcatgc cgaagcattc   480
aacgatatcg ccgattcatt ggatgaaacc aacactaagg cagacgaagc cgtcaaaacc   540
gccaatgaag ccaaacagac ggccgaagaa accaaacaaa acgtcgatgc caaagtaaaa   600
gctgcagaaa ctgcagcagg caaagccgaa gctgccgctg gcacagctaa tactgcagcc   660
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gtgtcagacc tgcgcaaaga aacccgccaa ggccttgcag aacaagccgc gctctccggt   960
ctgttccaac cttacaacgt gggtcggttc aatgtaacgg ctgcagtcgg cggctacaaa  1020
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gcaggcgtgg cagtcggcac ttcgtccggt tcttccgcag cctaccatgt cggcgtcaat  1140
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aaaggcagtt actccctcgg tatctttggc ggaaaagccc aggaagttgc cggcagcgcg  1860
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<210>  149
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<212>  PRT
<213>  Artificial Sequence

<220>
<223>  961-741
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Ala Ala Ala Tyr Asn Asn Gly Gln Glu Ile Asn Gly Phe Lys Ala Gly
            20                  25                  30

Glu Thr Ile Tyr Asp Ile Asp Glu Asp Gly Thr Ile Thr Lys Lys Asp
        35                  40                  45

Ala Thr Ala Ala Asp Val Glu Ala Asp Asp Phe Lys Gly Leu Gly Leu
    50                  55                  60

Lys Lys Val Val Thr Asn Leu Thr Lys Thr Val Asn Glu Asn Lys Gln
65                  70                  75                  80

Asn Val Asp Ala Lys Val Lys Ala Ala Glu Ser Glu Ile Glu Lys Leu
                85                  90                  95

Thr Thr Lys Leu Ala Asp Thr Asp Ala Ala Leu Ala Asp Thr Asp Ala
            100                 105                 110

Ala Leu Asp Ala Thr Thr Asn Ala Leu Asn Lys Leu Gly Glu Asn Ile
        115                 120                 125

Thr Thr Phe Ala Glu Glu Thr Lys Thr Asn Ile Val Lys Ile Asp Glu
    130                 135                 140

Lys Leu Glu Ala Val Ala Asp Thr Val Asp Lys His Ala Glu Ala Phe
145                 150                 155                 160

Asn Asp Ile Ala Asp Ser Leu Asp Glu Thr Asn Thr Lys Ala Asp Glu
                165                 170                 175

Ala Val Lys Thr Ala Asn Glu Ala Lys Gln Thr Ala Glu Glu Thr Lys
            180                 185                 190

Gln Asn Val Asp Ala Lys Val Lys Ala Ala Glu Thr Ala Ala Gly Lys
        195                 200                 205

Ala Glu Ala Ala Ala Gly Thr Ala Asn Thr Ala Ala Asp Lys Ala Glu
    210                 215                 220

Ala Val Ala Ala Lys Val Thr Asp Ile Lys Ala Asp Ile Ala Thr Asn
225                 230                 235                 240

Lys Asp Asn Ile Ala Lys Lys Ala Asn Ser Ala Asp Val Tyr Thr Arg
                245                 250                 255

Glu Glu Ser Asp Ser Lys Phe Val Arg Ile Asp Gly Leu Asn Ala Thr
            260                 265                 270

Thr Glu Lys Leu Asp Thr Arg Leu Ala Ser Ala Glu Lys Ser Ile Ala
        275                 280                 285

Asp His Asp Thr Arg Leu Asn Gly Leu Asp Lys Thr Val Ser Asp Leu
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    290                 295                 300

Arg Lys Glu Thr Arg Gln Gly Leu Ala Glu Gln Ala Ala Leu Ser Gly
305                 310                 315                 320

Leu Phe Gln Pro Tyr Asn Val Gly Arg Phe Asn Val Thr Ala Ala Val
                325                 330                 335

Gly Gly Tyr Lys Ser Glu Ser Ala Val Ala Ile Gly Thr Gly Phe Arg
            340                 345                 350

Phe Thr Glu Asn Phe Ala Ala Lys Ala Gly Val Ala Val Gly Thr Ser
        355                 360                 365

Ser Gly Ser Ser Ala Ala Tyr His Val Gly Val Asn Tyr Glu Trp Gly
    370                 375                 380

Ser Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu Ala Asp
385                 390                 395                 400

Ala Leu Thr Ala Pro Leu Asp His Lys Asp Lys Gly Leu Gln Ser Leu
                405                 410                 415

Thr Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu Ala Ala
            420                 425                 430

Gln Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn Thr Gly
        435                 440                 445

Lys Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg Gln Ile
    450                 455                 460

Glu Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe Gln Val
465                 470                 475                 480

Tyr Lys Gln Ser His Ser Ala Leu Thr Ala Phe Gln Thr Glu Gln Ile
                485                 490                 495

Gln Asp Ser Glu His Ser Gly Lys Met Val Ala Lys Arg Gln Phe Arg
            500                 505                 510

Ile Gly Asp Ile Ala Gly Glu His Thr Ser Phe Asp Lys Leu Pro Glu
        515                 520                 525

Gly Gly Arg Ala Thr Tyr Arg Gly Thr Ala Phe Gly Ser Asp Asp Ala
    530                 535                 540

Gly Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln Gly Asn
545                 550                 555                 560

Gly Lys Ile Glu His Leu Lys Ser Pro Glu Leu Asn Val Asp Leu Ala
                565                 570                 575

Ala Ala Asp Ile Lys Pro Asp Gly Lys Arg His Ala Val Ile Ser Gly
            580                 585                 590

Ser Val Leu Tyr Asn Gln Ala Glu Lys Gly Ser Tyr Ser Leu Gly Ile
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595 600 605

Phe Gly Gly Lys Ala Gln Glu Val Ala Gly Ser Ala Glu Val Lys Thr
610 615 620

Val Asn Gly Ile Arg His Ile Gly Leu Ala Ala Lys Gln Leu Glu His
625 630 635 640

His His His His His
645

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<211> 4335
<212> DNA
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<220>
<223> 961-983

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gacggcacaa ttaccaaaaa agacgcaact gcagccgatg ttgaagccga cgactttaaa 180
ggtctgggtc tgaaaaaagt cgtgactaac ctgaccaaaa ccgtcaatga aaacaaacaa 240
aacgtcgatg ccaaagtaaa agctgcagaa tctgaaatag aaaagttaac aaccaagtta 300
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Glu Thr Ile Tyr Asp Ile Asp Glu Asp Gly Thr Ile Thr Lys Lys Asp
        35                  40                  45

Ala Thr Ala Ala Asp Val Glu Ala Asp Asp Phe Lys Gly Leu Gly Leu
    50                  55                  60
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Lys Lys Val Val Thr Asn Leu Thr Lys Thr Val Asn Glu Asn Lys Gln
65 70 75 80

Asn Val Asp Ala Lys Val Lys Ala Ala Glu Ser Glu Ile Glu Lys Leu
85 90 95

Thr Thr Lys Leu Ala Asp Thr Asp Ala Ala Leu Ala Asp Thr Asp Ala
100 105 110

Ala Leu Asp Ala Thr Thr Asn Ala Leu Asn Lys Leu Gly Glu Asn Ile
115 120 125

Thr Thr Phe Ala Glu Glu Thr Lys Thr Asn Ile Val Lys Ile Asp Glu
130 135 140

Lys Leu Glu Ala Val Ala Asp Thr Val Asp Lys His Ala Glu Ala Phe
145 150 155 160

Asn Asp Ile Ala Asp Ser Leu Asp Glu Thr Asn Thr Lys Ala Asp Glu
165 170 175

Ala Val Lys Thr Ala Asn Glu Ala Lys Gln Thr Ala Glu Glu Thr Lys
180 185 190

Gln Asn Val Asp Ala Lys Val Lys Ala Ala Glu Thr Ala Ala Gly Lys
195 200 205

Ala Glu Ala Ala Ala Gly Thr Ala Asn Thr Ala Ala Asp Lys Ala Glu
210 215 220

Ala Val Ala Ala Lys Val Thr Asp Ile Lys Ala Asp Ile Ala Thr Asn
225 230 235 240

Lys Asp Asn Ile Ala Lys Lys Ala Asn Ser Ala Asp Val Tyr Thr Arg
245 250 255

Glu Glu Ser Asp Ser Lys Phe Val Arg Ile Asp Gly Leu Asn Ala Thr
260 265 270

Thr Glu Lys Leu Asp Thr Arg Leu Ala Ser Ala Glu Lys Ser Ile Ala
275 280 285

Asp His Asp Thr Arg Leu Asn Gly Leu Asp Lys Thr Val Ser Asp Leu
290 295 300

Arg Lys Glu Thr Arg Gln Gly Leu Ala Glu Gln Ala Ala Leu Ser Gly
305 310 315 320

Leu Phe Gln Pro Tyr Asn Val Gly Arg Phe Asn Val Thr Ala Ala Val
325 330 335

Gly Gly Tyr Lys Ser Glu Ser Ala Val Ala Ile Gly Thr Gly Phe Arg
340 345 350

Phe Thr Glu Asn Phe Ala Ala Lys Ala Gly Val Ala Val Gly Thr Ser
355 360 365

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Ser Gly Ser Ser Ala Ala Tyr His Val Gly Val Asn Tyr Glu Trp Gly
    370                 375                 380

Ser Gly Gly Gly Gly Thr Ser Ala Pro Asp Phe Asn Ala Gly Gly Thr
385                 390                 395                 400

Gly Ile Gly Ser Asn Ser Arg Ala Thr Thr Ala Lys Ser Ala Ala Val
                405                 410                 415

Ser Tyr Ala Gly Ile Lys Asn Glu Met Cys Lys Asp Arg Ser Met Leu
            420                 425                 430

Cys Ala Gly Arg Asp Asp Val Ala Val Thr Asp Arg Asp Ala Lys Ile
        435                 440                 445

Asn Ala Pro Pro Pro Asn Leu His Thr Gly Asp Phe Pro Asn Pro Asn
    450                 455                 460

Asp Ala Tyr Lys Asn Leu Ile Asn Leu Lys Pro Ala Ile Glu Ala Gly
465                 470                 475                 480

Tyr Thr Gly Arg Gly Val Glu Val Gly Ile Val Asp Thr Gly Glu Ser
                485                 490                 495

Val Gly Ser Ile Ser Phe Pro Glu Leu Tyr Gly Arg Lys Glu His Gly
            500                 505                 510

Tyr Asn Glu Asn Tyr Lys Asn Tyr Thr Ala Tyr Met Arg Lys Glu Ala
        515                 520                 525

Pro Glu Asp Gly Gly Gly Lys Asp Ile Glu Ala Ser Phe Asp Asp Glu
    530                 535                 540

Ala Val Ile Glu Thr Glu Ala Lys Pro Thr Asp Ile Arg His Val Lys
545                 550                 555                 560

Glu Ile Gly His Ile Asp Leu Val Ser His Ile Ile Gly Gly Arg Ser
                565                 570                 575

Val Asp Gly Arg Pro Ala Gly Gly Ile Ala Pro Asp Ala Thr Leu His
            580                 585                 590

Ile Met Asn Thr Asn Asp Glu Thr Lys Asn Glu Met Met Val Ala Ala
        595                 600                 605

Ile Arg Asn Ala Trp Val Lys Leu Gly Glu Arg Gly Val Arg Ile Val
    610                 615                 620

Asn Asn Ser Phe Gly Thr Thr Ser Arg Ala Gly Thr Ala Asp Leu Phe
625                 630                 635                 640

Gln Ile Ala Asn Ser Glu Glu Gln Tyr Arg Gln Ala Leu Leu Asp Tyr
                645                 650                 655

Ser Gly Gly Asp Lys Thr Asp Glu Gly Ile Arg Leu Met Gln Gln Ser
            660                 665                 670
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Asp Tyr Gly Asn Leu Ser Tyr His Ile Arg Asn Lys Asn Met Leu Phe
        675                 680                 685

Ile Phe Ser Thr Gly Asn Asp Ala Gln Ala Gln Pro Asn Thr Tyr Ala
    690                 695                 700

Leu Leu Pro Phe Tyr Glu Lys Asp Ala Gln Lys Gly Ile Ile Thr Val
705                 710                 715                 720

Ala Gly Val Asp Arg Ser Gly Glu Lys Phe Lys Arg Glu Met Tyr Gly
                725                 730                 735

Glu Pro Gly Thr Glu Pro Leu Glu Tyr Gly Ser Asn His Cys Gly Ile
            740                 745                 750

Thr Ala Met Trp Cys Leu Ser Ala Pro Tyr Glu Ala Ser Val Arg Phe
        755                 760                 765

Thr Arg Thr Asn Pro Ile Gln Ile Ala Gly Thr Ser Phe Ser Ala Pro
    770                 775                 780

Ile Val Thr Gly Thr Ala Ala Leu Leu Leu Gln Lys Tyr Pro Trp Met
785                 790                 795                 800

Ser Asn Asp Asn Leu Arg Thr Thr Leu Leu Thr Thr Ala Gln Asp Ile
                805                 810                 815

Gly Ala Val Gly Val Asp Ser Lys Phe Gly Trp Gly Leu Leu Asp Ala
            820                 825                 830

Gly Lys Ala Met Asn Gly Pro Ala Ser Phe Pro Phe Gly Asp Phe Thr
        835                 840                 845

Ala Asp Thr Lys Gly Thr Ser Asp Ile Ala Tyr Ser Phe Arg Asn Asp
    850                 855                 860

Ile Ser Gly Thr Gly Gly Leu Ile Lys Lys Gly Gly Ser Gln Leu Gln
865                 870                 875                 880

Leu His Gly Asn Asn Thr Tyr Thr Gly Lys Thr Ile Ile Glu Gly Gly
                885                 890                 895

Ser Leu Val Leu Tyr Gly Asn Asn Lys Ser Asp Met Arg Val Glu Thr
            900                 905                 910

Lys Gly Ala Leu Ile Tyr Asn Gly Ala Ala Ser Gly Gly Ser Leu Asn
        915                 920                 925

Ser Asp Gly Ile Val Tyr Leu Ala Asp Thr Asp Gln Ser Gly Ala Asn
    930                 935                 940

Glu Thr Val His Ile Lys Gly Ser Leu Gln Leu Asp Gly Lys Gly Thr
945                 950                 955                 960

Leu Tyr Thr Arg Leu Gly Lys Leu Leu Lys Val Asp Gly Thr Ala Ile
                965                 970                 975
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Ile Gly Gly Lys Leu Tyr Met Ser Ala Arg Gly Lys Gly Ala Gly Tyr
            980                 985                 990

Leu Asn Ser Thr Gly Arg Arg Val Pro Phe Leu Ser Ala Ala Lys Ile
        995                 1000                1005

Gly Gln Asp Tyr Ser Phe Phe Thr Asn Ile Glu Thr Asp Gly Gly Leu
    1010                1015                1020

Leu Ala Ser Leu Asp Ser Val Glu Lys Thr Ala Gly Ser Glu Gly Asp
1025                1030                1035                1040

Thr Leu Ser Tyr Tyr Val Arg Arg Gly Asn Ala Ala Arg Thr Ala Ser
                1045                1050                1055

Ala Ala Ala His Ser Ala Pro Ala Gly Leu Lys His Ala Val Glu Gln
            1060                1065                1070

Gly Gly Ser Asn Leu Glu Asn Leu Met Val Glu Leu Asp Ala Ser Glu
        1075                1080                1085

Ser Ser Ala Thr Pro Glu Thr Val Glu Thr Ala Ala Ala Asp Arg Thr
    1090                1095                1100

Asp Met Pro Gly Ile Arg Pro Tyr Gly Ala Thr Phe Arg Ala Ala Ala
1105                1110                1115                1120

Ala Val Gln His Ala Asn Ala Ala Asp Gly Val Arg Ile Phe Asn Ser
                1125                1130                1135

Leu Ala Ala Thr Val Tyr Ala Asp Ser Thr Ala Ala His Ala Asp Met
            1140                1145                1150

Gln Gly Arg Arg Leu Lys Ala Val Ser Asp Gly Leu Asp His Asn Gly
        1155                1160                1165

Thr Gly Leu Arg Val Ile Ala Gln Thr Gln Gln Asp Gly Gly Thr Trp
    1170                1175                1180

Glu Gln Gly Gly Val Glu Gly Lys Met Arg Gly Ser Thr Gln Thr Val
1185                1190                1195                1200

Gly Ile Ala Ala Lys Thr Gly Glu Asn Thr Thr Ala Ala Ala Thr Leu
                1205                1210                1215

Gly Met Gly Arg Ser Thr Trp Ser Glu Asn Ser Ala Asn Ala Lys Thr
            1220                1225                1230

Asp Ser Ile Ser Leu Phe Ala Gly Ile Arg His Asp Ala Gly Asp Ile
        1235                1240                1245

Gly Tyr Leu Lys Gly Leu Phe Ser Tyr Gly Arg Tyr Lys Asn Ser Ile
    1250                1255                1260

Ser Arg Ser Thr Gly Ala Asp Glu His Ala Glu Gly Ser Val Asn Gly
1265                1270                1275                1280
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Thr Leu Met Gln Leu Gly Ala Leu Gly Gly Val Asn Val Pro Phe Ala
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Ala Thr Gly Asp Leu Thr Val Glu Gly Gly Leu Arg Tyr Asp Leu Leu
            1300                1305                1310

Lys Gln Asp Ala Phe Ala Glu Lys Gly Ser Ala Leu Gly Trp Ser Gly
        1315                1320                1325

Asn Ser Leu Thr Glu Gly Thr Leu Val Gly Leu Ala Gly Leu Lys Leu
    1330                1335                1340

Ser Gln Pro Leu Ser Asp Lys Ala Val Leu Phe Ala Thr Ala Gly Val
1345                1350                1355                1360

Glu Arg Asp Leu Asn Gly Arg Asp Tyr Thr Val Thr Gly Gly Phe Thr
                1365                1370                1375

Gly Ala Thr Ala Ala Thr Gly Lys Thr Gly Ala Arg Asn Met Pro His
            1380                1385                1390

Thr Arg Leu Val Ala Gly Leu Gly Ala Asp Val Glu Phe Gly Asn Gly
        1395                1400                1405

Trp Asn Gly Leu Ala Arg Tyr Ser Tyr Ala Gly Ser Lys Gln Tyr Gly
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Asn His Ser Gly Arg Val Gly Val Gly Tyr Arg Phe Leu Glu His His
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His His His His


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gccaatgaag ccaaacagac ggccgaagaa accaaacaaa acgtcgatgc caaagtaaaa     600
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20 25 30

Glu Thr Ile Tyr Asp Ile Asp Glu Asp Gly Thr Ile Thr Lys Lys Asp
35 40 45

Ala Thr Ala Ala Asp Val Glu Ala Asp Asp Phe Lys Gly Leu Gly Leu
50 55 60

Lys Lys Val Val Thr Asn Leu Thr Lys Thr Val Asn Glu Asn Lys Gln
65 70 75 80

Asn Val Asp Ala Lys Val Lys Ala Ala Glu Ser Glu Ile Glu Lys Leu
85 90 95

Thr Thr Lys Leu Ala Asp Thr Asp Ala Ala Leu Ala Asp Thr Asp Ala
100 105 110

Ala Leu Asp Ala Thr Thr Asn Ala Leu Asn Lys Leu Gly Glu Asn Ile
115 120 125

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Thr Thr Phe Ala Glu Glu Thr Lys Thr Asn Ile Val Lys Ile Asp Glu
    130                 135                 140

Lys Leu Glu Ala Val Ala Asp Thr Val Asp Lys His Ala Glu Ala Phe
145                 150                 155                 160

Asn Asp Ile Ala Asp Ser Leu Asp Glu Thr Asn Thr Lys Ala Asp Glu
                165                 170                 175

Ala Val Lys Thr Ala Asn Glu Ala Lys Gln Thr Ala Glu Glu Thr Lys
            180                 185                 190

Gln Asn Val Asp Ala Lys Val Lys Ala Ala Glu Thr Ala Ala Gly Lys
        195                 200                 205

Ala Glu Ala Ala Ala Gly Thr Ala Asn Thr Ala Ala Asp Lys Ala Glu
    210                 215                 220

Ala Val Ala Ala Lys Val Thr Asp Ile Lys Ala Asp Ile Ala Thr Asn
225                 230                 235                 240

Lys Asp Asn Ile Ala Lys Lys Ala Asn Ser Ala Asp Val Tyr Thr Arg
                245                 250                 255

Glu Glu Ser Asp Ser Lys Phe Val Arg Ile Asp Gly Leu Asn Ala Thr
            260                 265                 270

Thr Glu Lys Leu Asp Thr Arg Leu Ala Ser Ala Glu Lys Ser Ile Ala
        275                 280                 285

Asp His Asp Thr Arg Leu Asn Gly Leu Asp Lys Thr Val Ser Asp Leu
    290                 295                 300

Arg Lys Glu Thr Arg Gln Gly Leu Ala Glu Gln Ala Ala Leu Ser Gly
305                 310                 315                 320

Leu Phe Gln Pro Tyr Asn Val Gly Gly Ser Gly Gly Gly Gly Ser Asp
                325                 330                 335

Leu Ala Asn Asp Ser Phe Ile Arg Gln Val Leu Asp Arg Gln His Phe
            340                 345                 350

Glu Pro Asp Gly Lys Tyr His Leu Phe Gly Ser Arg Gly Glu Leu Ala
        355                 360                 365

Glu Arg Ser Gly His Ile Gly Leu Gly Lys Ile Gln Ser His Gln Leu
    370                 375                 380

Gly Asn Leu Met Ile Gln Gln Ala Ala Ile Lys Gly Asn Ile Gly Tyr
385                 390                 395                 400

Ile Val Arg Phe Ser Asp His Gly His Glu Val His Ser Pro Phe Asp
                405                 410                 415

Asn His Ala Ser His Ser Asp Ser Asp Glu Ala Gly Ser Pro Val Asp
            420                 425                 430
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Gly Phe Ser Leu Tyr Arg Ile His Trp Asp Gly Tyr Glu His His Pro
        435                 440                 445

Ala Asp Gly Tyr Asp Gly Pro Gln Gly Gly Gly Tyr Pro Ala Pro Lys
    450                 455                 460

Gly Ala Arg Asp Ile Tyr Ser Tyr Asp Ile Lys Gly Val Ala Gln Asn
465                 470                 475                 480

Ile Arg Leu Asn Leu Thr Asp Asn Arg Ser Thr Gly Gln Arg Leu Ala
                485                 490                 495

Asp Arg Phe His Asn Ala Gly Ser Met Leu Thr Gln Gly Val Gly Asp
            500                 505                 510

Gly Phe Lys Arg Ala Thr Arg Tyr Ser Pro Glu Leu Asp Arg Ser Gly
        515                 520                 525

Asn Ala Ala Glu Ala Phe Asn Gly Thr Ala Asp Ile Val Lys Asn Ile
    530                 535                 540

Ile Gly Ala Ala Gly Glu Ile Val Gly Ala Gly Asp Ala Val Gln Gly
545                 550                 555                 560

Ile Ser Glu Gly Ser Asn Ile Ala Val Met His Gly Leu Gly Leu Leu
                565                 570                 575

Ser Thr Glu Asn Lys Met Ala Arg Ile Asn Asp Leu Ala Asp Met Ala
            580                 585                 590

Gln Leu Lys Asp Tyr Ala Ala Ala Ala Ile Arg Asp Trp Ala Val Gln
        595                 600                 605

Asn Pro Asn Ala Ala Gln Gly Ile Glu Ala Val Ser Asn Ile Phe Met
    610                 615                 620

Ala Ala Ile Pro Ile Lys Gly Ile Gly Ala Val Arg Gly Lys Tyr Gly
625                 630                 635                 640

Leu Gly Gly Ile Thr Ala His Pro Ile Lys Arg Ser Gln Met Gly Ala
                645                 650                 655

Ile Ala Leu Pro Lys Gly Lys Ser Ala Val Ser Asp Asn Phe Ala Asp
            660                 665                 670

Ala Ala Tyr Ala Lys Tyr Pro Ser Pro Tyr His Ser Arg Asn Ile Arg
        675                 680                 685

Ser Asn Leu Glu Gln Arg Tyr Gly Lys Glu Asn Ile Thr Ser Ser Thr
    690                 695                 700

Val Pro Pro Ser Asn Gly Lys Asn Val Lys Leu Ala Asp Gln Arg His
705                 710                 715                 720

Pro Lys Thr Gly Val Pro Phe Asp Gly Lys Gly Phe Pro Asn Phe Glu
                725                 730                 735
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Lys His Val Lys Tyr Asp Thr Leu Glu His His His His His His
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                20                  25                  30

Glu Thr Ile Tyr Asp Ile Asp Glu Asp Gly Thr Ile Thr Lys Lys Asp
        35                  40                  45

Ala Thr Ala Ala Asp Val Glu Ala Asp Asp Phe Lys Gly Leu Gly Leu
    50                  55                  60

Lys Lys Val Val Thr Asn Leu Thr Lys Thr Val Asn Glu Asn Lys Gln
65                  70                  75                  80

Asn Val Asp Ala Lys Val Lys Ala Ala Glu Ser Glu Ile Glu Lys Leu
                85                  90                  95

Thr Thr Lys Leu Ala Asp Thr Asp Ala Ala Leu Ala Asp Thr Asp Ala
            100                 105                 110

Ala Leu Asp Ala Thr Thr Asn Ala Leu Asn Lys Leu Gly Glu Asn Ile
        115                 120                 125

Thr Thr Phe Ala Glu Glu Thr Lys Thr Asn Ile Val Lys Ile Asp Glu
    130                 135                 140

Lys Leu Glu Ala Val Ala Asp Thr Val Asp Lys His Ala Glu Ala Phe
145                 150                 155                 160

Asn Asp Ile Ala Asp Ser Leu Asp Glu Thr Asn Thr Lys Ala Asp Glu
                165                 170                 175

Ala Val Lys Thr Ala Asn Glu Ala Lys Gln Thr Ala Glu Glu Thr Lys
            180                 185                 190

Gln Asn Val Asp Ala Lys Val Lys Ala Ala Glu Thr Ala Ala Gly Lys
        195                 200                 205

Ala Glu Ala Ala Ala Gly Thr Ala Asn Thr Ala Ala Asp Lys Ala Glu
    210                 215                 220

Ala Val Ala Ala Lys Val Thr Asp Ile Lys Ala Asp Ile Ala Thr Asn
225                 230                 235                 240

Lys Asp Asn Ile Ala Lys Lys Ala Asn Ser Ala Asp Val Tyr Thr Arg
                245                 250                 255

Glu Glu Ser Asp Ser Lys Phe Val Arg Ile Asp Gly Leu Asn Ala Thr
            260                 265                 270

Thr Glu Lys Leu Asp Thr Arg Leu Ala Ser Ala Glu Lys Ser Ile Ala
        275                 280                 285

Asp His Asp Thr Arg Leu Asn Gly Leu Asp Lys Thr Val Ser Asp Leu
    290                 295                 300

Arg Lys Glu Thr Arg Gln Gly Leu Ala Glu Gln Ala Ala Leu Ser Gly
305                 310                 315                 320

Leu Phe Gln Pro Tyr Asn Val Gly Gly Ser Gly Gly Gly Gly Val Ala
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325 330 335

Ala Asp Ile Gly Ala Gly Leu Ala Asp Ala Leu Thr Ala Pro Leu Asp
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His Lys Asp Lys Gly Leu Gln Ser Leu Thr Leu Asp Gln Ser Val Arg
355 360 365

Lys Asn Glu Lys Leu Lys Leu Ala Ala Gln Gly Ala Glu Lys Thr Tyr
370 375 380

Gly Asn Gly Asp Ser Leu Asn Thr Gly Lys Leu Lys Asn Asp Lys Val
385 390 395 400

Ser Arg Phe Asp Phe Ile Arg Gln Ile Glu Val Asp Gly Gln Leu Ile
405 410 415

Thr Leu Glu Ser Gly Glu Phe Gln Val Tyr Lys Gln Ser His Ser Ala
420 425 430

Leu Thr Ala Phe Gln Thr Glu Gln Ile Gln Asp Ser Glu His Ser Gly
435 440 445

Lys Met Val Ala Lys Arg Gln Phe Arg Ile Gly Asp Ile Ala Gly Glu
450 455 460

His Thr Ser Phe Asp Lys Leu Pro Glu Gly Gly Arg Ala Thr Tyr Arg
465 470 475 480

Gly Thr Ala Phe Gly Ser Asp Asp Ala Gly Gly Lys Leu Thr Tyr Thr
485 490 495

Ile Asp Phe Ala Ala Lys Gln Gly Asn Gly Lys Ile Glu His Leu Lys
500 505 510

Ser Pro Glu Leu Asn Val Asp Leu Ala Ala Ala Asp Ile Lys Pro Asp
515 520 525

Gly Lys Arg His Ala Val Ile Ser Gly Ser Val Leu Tyr Asn Gln Ala
530 535 540

Glu Lys Gly Ser Tyr Ser Leu Gly Ile Phe Gly Gly Lys Ala Gln Glu
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<400> 157

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Glu Thr Ile Tyr Asp Ile Asp Glu Asp Gly Thr Ile Thr Lys Lys Asp
        35                  40                  45

Ala Thr Ala Ala Asp Val Glu Ala Asp Asp Phe Lys Gly Leu Gly Leu
    50                  55                  60

Lys Lys Val Val Thr Asn Leu Thr Lys Thr Val Asn Glu Asn Lys Gln
65                  70                  75                  80

Asn Val Asp Ala Lys Val Lys Ala Ala Glu Ser Glu Ile Glu Lys Leu
                85                  90                  95

Thr Thr Lys Leu Ala Asp Thr Asp Ala Ala Leu Ala Asp Thr Asp Ala
            100                 105                 110

Ala Leu Asp Ala Thr Thr Asn Ala Leu Asn Lys Leu Gly Glu Asn Ile
        115                 120                 125

Thr Thr Phe Ala Glu Glu Thr Lys Thr Asn Ile Val Lys Ile Asp Glu
    130                 135                 140

Lys Leu Glu Ala Val Ala Asp Thr Val Asp Lys His Ala Glu Ala Phe
145                 150                 155                 160

Asn Asp Ile Ala Asp Ser Leu Asp Glu Thr Asn Thr Lys Ala Asp Glu
                165                 170                 175
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Ala Val Lys Thr Ala Asn Glu Ala Lys Gln Thr Ala Glu Glu Thr Lys
            180                 185                 190

Gln Asn Val Asp Ala Lys Val Lys Ala Ala Glu Thr Ala Ala Gly Lys
        195                 200                 205

Ala Glu Ala Ala Ala Gly Thr Ala Asn Thr Ala Ala Asp Lys Ala Glu
    210                 215                 220

Ala Val Ala Ala Lys Val Thr Asp Ile Lys Ala Asp Ile Ala Thr Asn
225                 230                 235                 240

Lys Asp Asn Ile Ala Lys Lys Ala Asn Ser Ala Asp Val Tyr Thr Arg
                245                 250                 255

Glu Glu Ser Asp Ser Lys Phe Val Arg Ile Asp Gly Leu Asn Ala Thr
            260                 265                 270

Thr Glu Lys Leu Asp Thr Arg Leu Ala Ser Ala Glu Lys Ser Ile Ala
        275                 280                 285

Asp His Asp Thr Arg Leu Asn Gly Leu Asp Lys Thr Val Ser Asp Leu
    290                 295                 300

Arg Lys Glu Thr Arg Gln Gly Leu Ala Glu Gln Ala Ala Leu Ser Gly
305                 310                 315                 320

Leu Phe Gln Pro Tyr Asn Val Gly Gly Ser Gly Gly Gly Gly Thr Ser
                325                 330                 335

Ala Pro Asp Phe Asn Ala Gly Gly Thr Gly Ile Gly Ser Asn Ser Arg
            340                 345                 350

Ala Thr Thr Ala Lys Ser Ala Ala Val Ser Tyr Ala Gly Ile Lys Asn
        355                 360                 365

Glu Met Cys Lys Asp Arg Ser Met Leu Cys Ala Gly Arg Asp Asp Val
    370                 375                 380

Ala Val Thr Asp Arg Asp Ala Lys Ile Asn Ala Pro Pro Pro Asn Leu
385                 390                 395                 400

His Thr Gly Asp Phe Pro Asn Pro Asn Asp Ala Tyr Lys Asn Leu Ile
                405                 410                 415

Asn Leu Lys Pro Ala Ile Glu Ala Gly Tyr Thr Gly Arg Gly Val Glu
            420                 425                 430

Val Gly Ile Val Asp Thr Gly Glu Ser Val Gly Ser Ile Ser Phe Pro
        435                 440                 445

Glu Leu Tyr Gly Arg Lys Glu His Gly Tyr Asn Glu Asn Tyr Lys Asn
    450                 455                 460

Tyr Thr Ala Tyr Met Arg Lys Glu Ala Pro Glu Asp Gly Gly Gly Lys
465                 470                 475                 480
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Asp Ile Glu Ala Ser Phe Asp Asp Glu Ala Val Ile Glu Thr Glu Ala
                485                 490                 495

Lys Pro Thr Asp Ile Arg His Val Lys Glu Ile Gly His Ile Asp Leu
            500                 505                 510

Val Ser His Ile Ile Gly Gly Arg Ser Val Asp Gly Arg Pro Ala Gly
        515                 520                 525

Gly Ile Ala Pro Asp Ala Thr Leu His Ile Met Asn Thr Asn Asp Glu
    530                 535                 540

Thr Lys Asn Glu Met Met Val Ala Ala Ile Arg Asn Ala Trp Val Lys
545                 550                 555                 560

Leu Gly Glu Arg Gly Val Arg Ile Val Asn Asn Ser Phe Gly Thr Thr
                565                 570                 575

Ser Arg Ala Gly Thr Ala Asp Leu Phe Gln Ile Ala Asn Ser Glu Glu
            580                 585                 590

Gln Tyr Arg Gln Ala Leu Leu Asp Tyr Ser Gly Gly Asp Lys Thr Asp
        595                 600                 605

Glu Gly Ile Arg Leu Met Gln Gln Ser Asp Tyr Gly Asn Leu Ser Tyr
    610                 615                 620

His Ile Arg Asn Lys Asn Met Leu Phe Ile Phe Ser Thr Gly Asn Asp
625                 630                 635                 640

Ala Gln Ala Gln Pro Asn Thr Tyr Ala Leu Leu Pro Phe Tyr Glu Lys
                645                 650                 655

Asp Ala Gln Lys Gly Ile Ile Thr Val Ala Gly Val Asp Arg Ser Gly
            660                 665                 670

Glu Lys Phe Lys Arg Glu Met Tyr Gly Glu Pro Gly Thr Glu Pro Leu
        675                 680                 685

Glu Tyr Gly Ser Asn His Cys Gly Ile Thr Ala Met Trp Cys Leu Ser
    690                 695                 700

Ala Pro Tyr Glu Ala Ser Val Arg Phe Thr Arg Thr Asn Pro Ile Gln
705                 710                 715                 720

Ile Ala Gly Thr Ser Phe Ser Ala Pro Ile Val Thr Gly Thr Ala Ala
                725                 730                 735

Leu Leu Leu Gln Lys Tyr Pro Trp Met Ser Asn Asp Asn Leu Arg Thr
            740                 745                 750

Thr Leu Leu Thr Thr Ala Gln Asp Ile Gly Ala Val Gly Val Asp Ser
        755                 760                 765

Lys Phe Gly Trp Gly Leu Leu Asp Ala Gly Lys Ala Met Asn Gly Pro
    770                 775                 780
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Ala Ser Phe Pro Phe Gly Asp Phe Thr Ala Asp Thr Lys Gly Thr Ser
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Asp Ile Ala Tyr Ser Phe Arg Asn Asp Ile Ser Gly Thr Gly Gly Leu
                805                 810                 815

Ile Lys Lys Gly Gly Ser Gln Leu Gln Leu His Gly Asn Asn Thr Tyr
            820                 825                 830

Thr Gly Lys Thr Ile Ile Glu Gly Gly Ser Leu Val Leu Tyr Gly Asn
        835                 840                 845

Asn Lys Ser Asp Met Arg Val Glu Thr Lys Gly Ala Leu Ile Tyr Asn
    850                 855                 860

Gly Ala Ala Ser Gly Gly Ser Leu Asn Ser Asp Gly Ile Val Tyr Leu
865                 870                 875                 880

Ala Asp Thr Asp Gln Ser Gly Ala Asn Glu Thr Val His Ile Lys Gly
                885                 890                 895

Ser Leu Gln Leu Asp Gly Lys Gly Thr Leu Tyr Thr Arg Leu Gly Lys
            900                 905                 910

Leu Leu Lys Val Asp Gly Thr Ala Ile Ile Gly Gly Lys Leu Tyr Met
        915                 920                 925

Ser Ala Arg Gly Lys Gly Ala Gly Tyr Leu Asn Ser Thr Gly Arg Arg
    930                 935                 940

Val Pro Phe Leu Ser Ala Ala Lys Ile Gly Gln Asp Tyr Ser Phe Phe
945                 950                 955                 960

Thr Asn Ile Glu Thr Asp Gly Gly Leu Leu Ala Ser Leu Asp Ser Val
                965                 970                 975

Glu Lys Thr Ala Gly Ser Glu Gly Asp Thr Leu Ser Tyr Tyr Val Arg
            980                 985                 990

Arg Gly Asn Ala Ala Arg Thr Ala Ser Ala Ala Ala His Ser Ala Pro
        995                 1000                1005

Ala Gly Leu Lys His Ala Val Glu Gln Gly Gly Ser Asn Leu Glu Asn
    1010                1015                1020

Leu Met Val Glu Leu Asp Ala Ser Glu Ser Ser Ala Thr Pro Glu Thr
1025                1030                1035                1040

Val Glu Thr Ala Ala Ala Asp Arg Thr Asp Met Pro Gly Ile Arg Pro
                1045                1050                1055

Tyr Gly Ala Thr Phe Arg Ala Ala Ala Ala Val Gln His Ala Asn Ala
            1060                1065                1070

Ala Asp Gly Val Arg Ile Phe Asn Ser Leu Ala Ala Thr Val Tyr Ala
        1075                1080                1085
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Asp Ser Thr Ala Ala His Ala Asp Met Gln Gly Arg Arg Leu Lys Ala
    1090                1095                1100

Val Ser Asp Gly Leu Asp His Asn Gly Thr Gly Leu Arg Val Ile Ala
1105                1110                1115                1120

Gln Thr Gln Gln Asp Gly Gly Thr Trp Glu Gln Gly Gly Val Glu Gly
                1125                1130                1135

Lys Met Arg Gly Ser Thr Gln Thr Val Gly Ile Ala Ala Lys Thr Gly
            1140                1145                1150

Glu Asn Thr Thr Ala Ala Ala Thr Leu Gly Met Gly Arg Ser Thr Trp
        1155                1160                1165

Ser Glu Asn Ser Ala Asn Ala Lys Thr Asp Ser Ile Ser Leu Phe Ala
    1170                1175                1180

Gly Ile Arg His Asp Ala Gly Asp Ile Gly Tyr Leu Lys Gly Leu Phe
1185                1190                1195                1200

Ser Tyr Gly Arg Tyr Lys Asn Ser Ile Ser Arg Ser Thr Gly Ala Asp
                1205                1210                1215

Glu His Ala Glu Gly Ser Val Asn Gly Thr Leu Met Gln Leu Gly Ala
            1220                1225                1230

Leu Gly Gly Val Asn Val Pro Phe Ala Ala Thr Gly Asp Leu Thr Val
        1235                1240                1245

Glu Gly Gly Leu Arg Tyr Asp Leu Leu Lys Gln Asp Ala Phe Ala Glu
    1250                1255                1260

Lys Gly Ser Ala Leu Gly Trp Ser Gly Asn Ser Leu Thr Glu Gly Thr
1265                1270                1275                1280

Leu Val Gly Leu Ala Gly Leu Lys Leu Ser Gln Pro Leu Ser Asp Lys
                1285                1290                1295

Ala Val Leu Phe Ala Thr Ala Gly Val Glu Arg Asp Leu Asn Gly Arg
            1300                1305                1310

Asp Tyr Thr Val Thr Gly Gly Phe Thr Gly Ala Thr Ala Ala Thr Gly
        1315                1320                1325

Lys Thr Gly Ala Arg Asn Met Pro His Thr Arg Leu Val Ala Gly Leu
    1330                1335                1340

Gly Ala Asp Val Glu Phe Gly Asn Gly Trp Asn Gly Leu Ala Arg Tyr
1345                1350                1355                1360

Ser Tyr Ala Gly Ser Lys Gln Tyr Gly Asn His Ser Gly Arg Val Gly
                1365                1370                1375

Val Gly Tyr Arg Phe Leu Glu His His His His His His
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35 40 45

Asn Gly Phe Lys Ala Gly Glu Thr Ile Tyr Asp Ile Asp Glu Asp Gly
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Thr Ile Thr Lys Lys Asp Ala Thr Ala Ala Asp Val Glu Ala Asp Asp
65 70 75 80

Phe Lys Gly Leu Gly Leu Lys Lys Val Val Thr Asn Leu Thr Lys Thr
85 90 95

Val Asn Glu Asn Lys Gln Asn Val Asp Ala Lys Val Lys Ala Ala Glu
100 105 110

Ser Glu Ile Glu Lys Leu Thr Thr Lys Leu Ala Asp Thr Asp Ala Ala
115 120 125

Leu Ala Asp Thr Asp Ala Ala Leu Asp Ala Thr Thr Asn Ala Leu Asn
130 135 140

Lys Leu Gly Glu Asn Ile Thr Thr Phe Ala Glu Glu Thr Lys Thr Asn
145 150 155 160

Ile Val Lys Ile Asp Glu Lys Leu Glu Ala Val Ala Asp Thr Val Asp
165 170 175

Lys His Ala Glu Ala Phe Asn Asp Ile Ala Asp Ser Leu Asp Glu Thr
180 185 190

Asn Thr Lys Ala Asp Glu Ala Val Lys Thr Ala Asn Glu Ala Lys Gln
195 200 205

Thr Ala Glu Glu Thr Lys Gln Asn Val Asp Ala Lys Val Lys Ala Ala
210 215 220

Glu Thr Ala Ala Gly Lys Ala Glu Ala Ala Ala Gly Thr Ala Asn Thr
225 230 235 240

Ala Ala Asp Lys Ala Glu Ala Val Ala Ala Lys Val Thr Asp Ile Lys
245 250 255

Ala Asp Ile Ala Thr Asn Lys Asp Asn Ile Ala Lys Lys Ala Asn Ser
260 265 270

Ala Asp Val Tyr Thr Arg Glu Glu Ser Asp Ser Lys Phe Val Arg Ile
275 280 285

Asp Gly Leu Asn Ala Thr Thr Glu Lys Leu Asp Thr Arg Leu Ala Ser

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Ala Glu Lys Ser Ile Ala Asp His Asp Thr Arg Leu Asn Gly Leu Asp
305                 310                 315                 320

Lys Thr Val Ser Asp Leu Arg Lys Glu Thr Arg Gln Gly Leu Ala Glu
                325                 330                 335

Gln Ala Ala Leu Ser Gly Leu Phe Gln Pro Tyr Asn Val Gly Gly Ser
            340                 345                 350

Gly Gly Gly Gly Ser Asp Leu Ala Asn Asp Ser Phe Ile Arg Gln Val
        355                 360                 365

Leu Asp Arg Gln His Phe Glu Pro Asp Gly Lys Tyr His Leu Phe Gly
    370                 375                 380

Ser Arg Gly Glu Leu Ala Glu Arg Ser Gly His Ile Gly Leu Gly Lys
385                 390                 395                 400

Ile Gln Ser His Gln Leu Gly Asn Leu Met Ile Gln Gln Ala Ala Ile
                405                 410                 415

Lys Gly Asn Ile Gly Tyr Ile Val Arg Phe Ser Asp His Gly His Glu
            420                 425                 430

Val His Ser Pro Phe Asp Asn His Ala Ser His Ser Asp Ser Asp Glu
        435                 440                 445

Ala Gly Ser Pro Val Asp Gly Phe Ser Leu Tyr Arg Ile His Trp Asp
    450                 455                 460

Gly Tyr Glu His His Pro Ala Asp Gly Tyr Asp Gly Pro Gln Gly Gly
465                 470                 475                 480

Gly Tyr Pro Ala Pro Lys Gly Ala Arg Asp Ile Tyr Ser Tyr Asp Ile
                485                 490                 495

Lys Gly Val Ala Gln Asn Ile Arg Leu Asn Leu Thr Asp Asn Arg Ser
            500                 505                 510

Thr Gly Gln Arg Leu Ala Asp Arg Phe His Asn Ala Gly Ser Met Leu
        515                 520                 525

Thr Gln Gly Val Gly Asp Gly Phe Lys Arg Ala Thr Arg Tyr Ser Pro
    530                 535                 540

Glu Leu Asp Arg Ser Gly Asn Ala Ala Glu Ala Phe Asn Gly Thr Ala
545                 550                 555                 560

Asp Ile Val Lys Asn Ile Ile Gly Ala Ala Gly Glu Ile Val Gly Ala
                565                 570                 575

Gly Asp Ala Val Gln Gly Ile Ser Glu Gly Ser Asn Ile Ala Val Met
            580                 585                 590

His Gly Leu Gly Leu Leu Ser Thr Glu Asn Lys Met Ala Arg Ile Asn
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595 600 605

Asp Leu Ala Asp Met Ala Gln Leu Lys Asp Tyr Ala Ala Ala Ala Ile
610 615 620

Arg Asp Trp Ala Val Gln Asn Pro Asn Ala Ala Gln Gly Ile Glu Ala
625 630 635 640

Val Ser Asn Ile Phe Met Ala Ala Ile Pro Ile Lys Gly Ile Gly Ala
645 650 655

Val Arg Gly Lys Tyr Gly Leu Gly Gly Ile Thr Ala His Pro Ile Lys
660 665 670

Arg Ser Gln Met Gly Ala Ile Ala Leu Pro Lys Gly Lys Ser Ala Val
675 680 685

Ser Asp Asn Phe Ala Asp Ala Ala Tyr Ala Lys Tyr Pro Ser Pro Tyr
690 695 700

His Ser Arg Asn Ile Arg Ser Asn Leu Glu Gln Arg Tyr Gly Lys Glu
705 710 715 720

Asn Ile Thr Ser Ser Thr Val Pro Pro Ser Asn Gly Lys Asn Val Lys
725 730 735

Leu Ala Asp Gln Arg His Pro Lys Thr Gly Val Pro Phe Asp Gly Lys
740 745 750

Gly Phe Pro Asn Phe Glu Lys His Val Lys Tyr Asp Thr
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gcctacaaca atggccaaga aatcaacggt ttcaaagctg gagagaccat ctacgacatt 180
gatgaagacg gcacaattac caaaaaagac gcaactgcag ccgatgttga agccgacgac 240
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aaacaaaacg tcgatgccaa agtaaaagct gcagaatctg aaatagaaaa gttaacaacc 360
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aacgccttga ataaattggg agaaaatata acgacatttg ctgaagagac taagacaaat 480
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gcattcaacg atatcgccga ttcattggat gaaaccaaca ctaaggcaga cgaagccgtc 600
aaaaccgcca atgaagccaa acagacggcc gaagaaacca aacaaaacgt cgatgccaaa 660
gtaaaagctg cagaaactgc agcaggcaaa gccgaagctg ccgctggcac agctaatact 720
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cgcttggctt ctgctgaaaa atccattgcc gatcacgata ctcgcctgaa cggtttggat 960

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ggtgcggaaa aaacttatgg aaacggtgac agcctcaata cgggcaaatt gaagaacgac   1260
aaggtcagcc gtttcgactt tatccgccaa atcgaagtgg acgggcagct cattaccttg   1320
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tatcgcggga cggcgttcgg ttcagacgat gccggcggaa aactgaccta caccatagat   1560
ttcgccgcca agcagggaaa cggcaaaatc gaacatttga aatcgccaga actcaatgtc   1620
gacctggccg ccgccgatat caagccggat ggaaaacgcc atgccgtcat cagcggttcc   1680
gtcctttaca accaagccga gaaaggcagt tactccctcg gtatctttgg cggaaaagcc   1740
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Phe Cys Ser Gly Ala Leu Ala Ala Thr Asn Asp Asp Asp Val Lys Lys
            20                  25                  30

Ala Ala Thr Val Ala Ile Ala Ala Ala Tyr Asn Asn Gly Gln Glu Ile
        35                  40                  45

Asn Gly Phe Lys Ala Gly Glu Thr Ile Tyr Asp Ile Asp Glu Asp Gly
    50                  55                  60

Thr Ile Thr Lys Lys Asp Ala Thr Ala Ala Asp Val Glu Ala Asp Asp
65                  70                  75                  80

Phe Lys Gly Leu Gly Leu Lys Lys Val Val Thr Asn Leu Thr Lys Thr
                85                  90                  95

Val Asn Glu Asn Lys Gln Asn Val Asp Ala Lys Val Lys Ala Ala Glu
            100                 105                 110

Ser Glu Ile Glu Lys Leu Thr Thr Lys Leu Ala Asp Thr Asp Ala Ala
        115                 120                 125

Leu Ala Asp Thr Asp Ala Ala Leu Asp Ala Thr Thr Asn Ala Leu Asn
    130                 135                 140

Lys Leu Gly Glu Asn Ile Thr Thr Phe Ala Glu Glu Thr Lys Thr Asn
145                 150                 155                 160

Ile Val Lys Ile Asp Glu Lys Leu Glu Ala Val Ala Asp Thr Val Asp
                165                 170                 175
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Lys His Ala Glu Ala Phe Asn Asp Ile Ala Asp Ser Leu Asp Glu Thr
            180                 185                 190

Asn Thr Lys Ala Asp Glu Ala Val Lys Thr Ala Asn Glu Ala Lys Gln
        195                 200                 205

Thr Ala Glu Glu Thr Lys Gln Asn Val Asp Ala Lys Val Lys Ala Ala
    210                 215                 220

Glu Thr Ala Ala Gly Lys Ala Glu Ala Ala Ala Gly Thr Ala Asn Thr
225                 230                 235                 240

Ala Ala Asp Lys Ala Glu Ala Val Ala Ala Lys Val Thr Asp Ile Lys
                245                 250                 255

Ala Asp Ile Ala Thr Asn Lys Asp Asn Ile Ala Lys Lys Ala Asn Ser
            260                 265                 270

Ala Asp Val Tyr Thr Arg Glu Glu Ser Asp Ser Lys Phe Val Arg Ile
        275                 280                 285

Asp Gly Leu Asn Ala Thr Thr Glu Lys Leu Asp Thr Arg Leu Ala Ser
    290                 295                 300

Ala Glu Lys Ser Ile Ala Asp His Asp Thr Arg Leu Asn Gly Leu Asp
305                 310                 315                 320

Lys Thr Val Ser Asp Leu Arg Lys Glu Thr Arg Gln Gly Leu Ala Glu
                325                 330                 335

Gln Ala Ala Leu Ser Gly Leu Phe Gln Pro Tyr Asn Val Gly Gly Ser
            340                 345                 350

Gly Gly Gly Gly Val Ala Ala Asp Ile Gly Ala Gly Leu Ala Asp Ala
        355                 360                 365

Leu Thr Ala Pro Leu Asp His Lys Asp Lys Gly Leu Gln Ser Leu Thr
    370                 375                 380

Leu Asp Gln Ser Val Arg Lys Asn Glu Lys Leu Lys Leu Ala Ala Gln
385                 390                 395                 400

Gly Ala Glu Lys Thr Tyr Gly Asn Gly Asp Ser Leu Asn Thr Gly Lys
                405                 410                 415

Leu Lys Asn Asp Lys Val Ser Arg Phe Asp Phe Ile Arg Gln Ile Glu
            420                 425                 430

Val Asp Gly Gln Leu Ile Thr Leu Glu Ser Gly Glu Phe Gln Val Tyr
        435                 440                 445

Lys Gln Ser His Ser Ala Leu Thr Ala Phe Gln Thr Glu Gln Ile Gln
    450                 455                 460

Asp Ser Glu His Ser Gly Lys Met Val Ala Lys Arg Gln Phe Arg Ile
465                 470                 475                 480
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Gly Asp Ile Ala Gly Glu His Thr Ser Phe Asp Lys Leu Pro Glu Gly
485 490 495

Gly Arg Ala Thr Tyr Arg Gly Thr Ala Phe Gly Ser Asp Asp Ala Gly
500 505 510

Gly Lys Leu Thr Tyr Thr Ile Asp Phe Ala Ala Lys Gln Gly Asn Gly
515 520 525

Lys Ile Glu His Leu Lys Ser Pro Glu Leu Asn Val Asp Leu Ala Ala
530 535 540

Ala Asp Ile Lys Pro Asp Gly Lys Arg His Ala Val Ile Ser Gly Ser
545 550 555 560

Val Leu Tyr Asn Gln Ala Glu Lys Gly Ser Tyr Ser Leu Gly Ile Phe
565 570 575

Gly Gly Lys Ala Gln Glu Val Ala Gly Ser Ala Glu Val Lys Thr Val
580 585 590

Asn Gly Ile Arg His Ile Gly Leu Ala Ala Lys Gln Leu Glu His His
595 600 605

His His His His
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            20                  25                  30

Ala Ala Thr Val Ala Ile Ala Ala Ala Tyr Asn Asn Gly Gln Glu Ile
        35                  40                  45

Asn Gly Phe Lys Ala Gly Glu Thr Ile Tyr Asp Ile Asp Glu Asp Gly
    50                  55                  60

Thr Ile Thr Lys Lys Asp Ala Thr Ala Ala Asp Val Glu Ala Asp Asp
65                  70                  75                  80

Phe Lys Gly Leu Gly Leu Lys Lys Val Val Thr Asn Leu Thr Lys Thr
                85                  90                  95

Val Asn Glu Asn Lys Gln Asn Val Asp Ala Lys Val Lys Ala Ala Glu
            100                 105                 110

Ser Glu Ile Glu Lys Leu Thr Thr Lys Leu Ala Asp Thr Asp Ala Ala
        115                 120                 125

Leu Ala Asp Thr Asp Ala Ala Leu Asp Ala Thr Thr Asn Ala Leu Asn
    130                 135                 140

Lys Leu Gly Glu Asn Ile Thr Thr Phe Ala Glu Glu Thr Lys Thr Asn
145                 150                 155                 160

Ile Val Lys Ile Asp Glu Lys Leu Glu Ala Val Ala Asp Thr Val Asp
                165                 170                 175

Lys His Ala Glu Ala Phe Asn Asp Ile Ala Asp Ser Leu Asp Glu Thr
            180                 185                 190

Asn Thr Lys Ala Asp Glu Ala Val Lys Thr Ala Asn Glu Ala Lys Gln
        195                 200                 205

Thr Ala Glu Glu Thr Lys Gln Asn Val Asp Ala Lys Val Lys Ala Ala
    210                 215                 220

Glu Thr Ala Ala Gly Lys Ala Glu Ala Ala Ala Gly Thr Ala Asn Thr
225                 230                 235                 240

Ala Ala Asp Lys Ala Glu Ala Val Ala Ala Lys Val Thr Asp Ile Lys
                245                 250                 255

Ala Asp Ile Ala Thr Asn Lys Asp Asn Ile Ala Lys Lys Ala Asn Ser
            260                 265                 270

Ala Asp Val Tyr Thr Arg Glu Glu Ser Asp Ser Lys Phe Val Arg Ile
        275                 280                 285
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Asp Gly Leu Asn Ala Thr Thr Glu Lys Leu Asp Thr Arg Leu Ala Ser
    290                 295                 300

Ala Glu Lys Ser Ile Ala Asp His Asp Thr Arg Leu Asn Gly Leu Asp
305                 310                 315                 320

Lys Thr Val Ser Asp Leu Arg Lys Glu Thr Arg Gln Gly Leu Ala Glu
                325                 330                 335

Gln Ala Ala Leu Ser Gly Leu Phe Gln Pro Tyr Asn Val Gly Gly Ser
            340                 345                 350

Gly Gly Gly Gly Thr Ser Ala Pro Asp Phe Asn Ala Gly Gly Thr Gly
        355                 360                 365

Ile Gly Ser Asn Ser Arg Ala Thr Thr Ala Lys Ser Ala Ala Val Ser
    370                 375                 380

Tyr Ala Gly Ile Lys Asn Glu Met Cys Lys Asp Arg Ser Met Leu Cys
385                 390                 395                 400

Ala Gly Arg Asp Asp Val Ala Val Thr Asp Arg Asp Ala Lys Ile Asn
                405                 410                 415

Ala Pro Pro Pro Asn Leu His Thr Gly Asp Phe Pro Asn Pro Asn Asp
            420                 425                 430

Ala Tyr Lys Asn Leu Ile Asn Leu Lys Pro Ala Ile Glu Ala Gly Tyr
        435                 440                 445

Thr Gly Arg Gly Val Glu Val Gly Ile Val Asp Thr Gly Glu Ser Val
    450                 455                 460

Gly Ser Ile Ser Phe Pro Glu Leu Tyr Gly Arg Lys Glu His Gly Tyr
465                 470                 475                 480

Asn Glu Asn Tyr Lys Asn Tyr Thr Ala Tyr Met Arg Lys Glu Ala Pro
                485                 490                 495

Glu Asp Gly Gly Gly Lys Asp Ile Glu Ala Ser Phe Asp Asp Glu Ala
            500                 505                 510

Val Ile Glu Thr Glu Ala Lys Pro Thr Asp Ile Arg His Val Lys Glu
        515                 520                 525

Ile Gly His Ile Asp Leu Val Ser His Ile Ile Gly Gly Arg Ser Val
    530                 535                 540

Asp Gly Arg Pro Ala Gly Gly Ile Ala Pro Asp Ala Thr Leu His Ile
545                 550                 555                 560

Met Asn Thr Asn Asp Glu Thr Lys Asn Glu Met Met Val Ala Ala Ile
                565                 570                 575

Arg Asn Ala Trp Val Lys Leu Gly Glu Arg Gly Val Arg Ile Val Asn
            580                 585                 590
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Asn Ser Phe Gly Thr Thr Ser Arg Ala Gly Thr Ala Asp Leu Phe Gln
        595                 600                 605

Ile Ala Asn Ser Glu Glu Gln Tyr Arg Gln Ala Leu Leu Asp Tyr Ser
    610                 615                 620

Gly Gly Asp Lys Thr Asp Glu Gly Ile Arg Leu Met Gln Gln Ser Asp
625                 630                 635                 640

Tyr Gly Asn Leu Ser Tyr His Ile Arg Asn Lys Asn Met Leu Phe Ile
                645                 650                 655

Phe Ser Thr Gly Asn Asp Ala Gln Ala Gln Pro Asn Thr Tyr Ala Leu
            660                 665                 670

Leu Pro Phe Tyr Glu Lys Asp Ala Gln Lys Gly Ile Ile Thr Val Ala
        675                 680                 685

Gly Val Asp Arg Ser Gly Glu Lys Phe Lys Arg Glu Met Tyr Gly Glu
    690                 695                 700

Pro Gly Thr Glu Pro Leu Glu Tyr Gly Ser Asn His Cys Gly Ile Thr
705                 710                 715                 720

Ala Met Trp Cys Leu Ser Ala Pro Tyr Glu Ala Ser Val Arg Phe Thr
                725                 730                 735

Arg Thr Asn Pro Ile Gln Ile Ala Gly Thr Ser Phe Ser Ala Pro Ile
            740                 745                 750

Val Thr Gly Thr Ala Ala Leu Leu Leu Gln Lys Tyr Pro Trp Met Ser
        755                 760                 765

Asn Asp Asn Leu Arg Thr Thr Leu Leu Thr Thr Ala Gln Asp Ile Gly
    770                 775                 780

Ala Val Gly Val Asp Ser Lys Phe Gly Trp Gly Leu Leu Asp Ala Gly
785                 790                 795                 800

Lys Ala Met Asn Gly Pro Ala Ser Phe Pro Phe Gly Asp Phe Thr Ala
                805                 810                 815

Asp Thr Lys Gly Thr Ser Asp Ile Ala Tyr Ser Phe Arg Asn Asp Ile
            820                 825                 830

Ser Gly Thr Gly Gly Leu Ile Lys Lys Gly Gly Ser Gln Leu Gln Leu
        835                 840                 845

His Gly Asn Asn Thr Tyr Thr Gly Lys Thr Ile Ile Glu Gly Gly Ser
    850                 855                 860

Leu Val Leu Tyr Gly Asn Asn Lys Ser Asp Met Arg Val Glu Thr Lys
865                 870                 875                 880

Gly Ala Leu Ile Tyr Asn Gly Ala Ala Ser Gly Gly Ser Leu Asn Ser
                885                 890                 895
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Asp Gly Ile Val Tyr Leu Ala Asp Thr Asp Gln Ser Gly Ala Asn Glu
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Thr Val His Ile Lys Gly Ser Leu Gln Leu Asp Gly Lys Gly Thr Leu
        915                 920                 925

Tyr Thr Arg Leu Gly Lys Leu Leu Lys Val Asp Gly Thr Ala Ile Ile
    930                 935                 940

Gly Gly Lys Leu Tyr Met Ser Ala Arg Gly Lys Gly Ala Gly Tyr Leu
945                 950                 955                 960

Asn Ser Thr Gly Arg Arg Val Pro Phe Leu Ser Ala Ala Lys Ile Gly
                965                 970                 975

Gln Asp Tyr Ser Phe Phe Thr Asn Ile Glu Thr Asp Gly Gly Leu Leu
            980                 985                 990

Ala Ser Leu Asp Ser Val Glu Lys Thr Ala Gly Ser Glu Gly Asp Thr
        995                 1000                1005

Leu Ser Tyr Tyr Val Arg Arg Gly Asn Ala Ala Arg Thr Ala Ser Ala
    1010                1015                1020

Ala Ala His Ser Ala Pro Ala Gly Leu Lys His Ala Val Glu Gln Gly
1025                1030                1035                1040

Gly Ser Asn Leu Glu Asn Leu Met Val Glu Leu Asp Ala Ser Glu Ser
                1045                1050                1055

Ser Ala Thr Pro Glu Thr Val Glu Thr Ala Ala Ala Asp Arg Thr Asp
            1060                1065                1070

Met Pro Gly Ile Arg Pro Tyr Gly Ala Thr Phe Arg Ala Ala Ala Ala
        1075                1080                1085

Val Gln His Ala Asn Ala Ala Asp Gly Val Arg Ile Phe Asn Ser Leu
    1090                1095                1100

Ala Ala Thr Val Tyr Ala Asp Ser Thr Ala Ala His Ala Asp Met Gln
1105                1110                1115                1120

Gly Arg Arg Leu Lys Ala Val Ser Asp Gly Leu Asp His Asn Gly Thr
                1125                1130                1135

Gly Leu Arg Val Ile Ala Gln Thr Gln Gln Asp Gly Gly Thr Trp Glu
            1140                1145                1150

Gln Gly Gly Val Glu Gly Lys Met Arg Gly Ser Thr Gln Thr Val Gly
        1155                1160                1165

Ile Ala Ala Lys Thr Gly Glu Asn Thr Thr Ala Ala Ala Thr Leu Gly
    1170                1175                1180

Met Gly Arg Ser Thr Trp Ser Glu Asn Ser Ala Asn Ala Lys Thr Asp
1185                1190                1195                1200
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Ser Ile Ser Leu Phe Ala Gly Ile Arg His Asp Ala Gly Asp Ile Gly
1205 1210 1215

Tyr Leu Lys Gly Leu Phe Ser Tyr Gly Arg Tyr Lys Asn Ser Ile Ser
1220 1225 1230

Arg Ser Thr Gly Ala Asp Glu His Ala Glu Gly Ser Val Asn Gly Thr
1235 1240 1245

Leu Met Gln Leu Gly Ala Leu Gly Gly Val Asn Val Pro Phe Ala Ala
1250 1255 1260

Thr Gly Asp Leu Thr Val Glu Gly Gly Leu Arg Tyr Asp Leu Leu Lys
1265 1270 1275 1280

Gln Asp Ala Phe Ala Glu Lys Gly Ser Ala Leu Gly Trp Ser Gly Asn
1285 1290 1295

Ser Leu Thr Glu Gly Thr Leu Val Gly Leu Ala Gly Leu Lys Leu Ser
1300 1305 1310

Gln Pro Leu Ser Asp Lys Ala Val Leu Phe Ala Thr Ala Gly Val Glu
1315 1320 1325

Arg Asp Leu Asn Gly Arg Asp Tyr Thr Val Thr Gly Gly Phe Thr Gly
1330 1335 1340

Ala Thr Ala Ala Thr Gly Lys Thr Gly Ala Arg Asn Met Pro His Thr
1345 1350 1355 1360

Arg Leu Val Ala Gly Leu Gly Ala Asp Val Glu Phe Gly Asn Gly Trp
1365 1370 1375

Asn Gly Leu Ala Arg Tyr Ser Tyr Ala Gly Ser Lys Gln Tyr Gly Asn
1380 1385 1390

His Ser Gly Arg Val Gly Val Gly Tyr Arg Phe
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cccgctcgag ttaccagcgg tagccta 27

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cccgctcgag 10

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cccgctcgag ttaaagccgg gtaacgc 27

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<220>
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cccgctcgag ccactcgtaa ttgacgcc 28

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<220>
<223> Oligonucleotide

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<211> 37
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 617
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<210> 618
<211> 29
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<220>
<223> Oligonucleotide

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cccgctcgag cgtatcatat ttcacgtgc 29

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<211> 488
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1 5 10 15

Ala Cys Gly Gly Gly Gly Gly Gly Ser Pro Asp Val Lys Ser Ala Asp
20 25 30

Thr Leu Ser Lys Pro Ala Ala Pro Val Val Ser Glu Lys Glu Thr Glu
35 40 45

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Ala Lys Glu Asp Ala Pro Gln Ala Gly Ser Gln Gly Gln Gly Ala Pro
    50                  55                  60

Ser Ala Gln Gly Ser Gln Asp Met Ala Ala Val Ser Glu Glu Asn Thr
65                  70                  75                  80

Gly Asn Gly Gly Ala Val Thr Ala Asp Asn Pro Lys Asn Glu Asp Glu
                85                  90                  95

Val Ala Gln Asn Asp Met Pro Gln Asn Ala Ala Gly Thr Asp Ser Ser
            100                 105                 110

Thr Pro Asn His Thr Pro Asp Pro Asn Met Leu Ala Gly Asn Met Glu
        115                 120                 125

Asn Gln Ala Thr Asp Ala Gly Glu Ser Ser Gln Pro Ala Asn Gln Pro
    130                 135                 140

Asp Met Ala Asn Ala Ala Asp Gly Met Gln Gly Asp Asp Pro Ser Ala
145                 150                 155                 160

Gly Gly Gln Asn Ala Gly Asn Thr Ala Ala Gln Gly Ala Asn Gln Ala
                165                 170                 175

Gly Asn Asn Gln Ala Ala Gly Ser Ser Asp Pro Ile Pro Ala Ser Asn
            180                 185                 190

Pro Ala Pro Ala Asn Gly Gly Ser Asn Phe Gly Arg Val Asp Leu Ala
        195                 200                 205

Asn Gly Val Leu Ile Asp Gly Pro Ser Gln Asn Ile Thr Leu Thr His
    210                 215                 220

Cys Lys Gly Asp Ser Cys Ser Gly Asn Asn Phe Leu Asp Glu Glu Val
225                 230                 235                 240

Gln Leu Lys Ser Glu Phe Glu Lys Leu Ser Asp Ala Asp Lys Ile Ser
                245                 250                 255

Asn Tyr Lys Lys Asp Gly Lys Asn Asp Lys Phe Val Gly Leu Val Ala
            260                 265                 270

Asp Ser Val Gln Met Lys Gly Ile Asn Gln Tyr Ile Ile Phe Tyr Lys
        275                 280                 285

Pro Lys Pro Thr Ser Phe Ala Arg Phe Arg Arg Ser Ala Arg Ser Arg
    290                 295                 300

Arg Ser Leu Pro Ala Glu Met Pro Leu Ile Pro Val Asn Gln Ala Asp
305                 310                 315                 320

Thr Leu Ile Val Asp Gly Glu Ala Val Ser Leu Thr Gly His Ser Gly
                325                 330                 335

Asn Ile Phe Ala Pro Glu Gly Asn Tyr Arg Tyr Leu Thr Tyr Gly Ala
            340                 345                 350
```

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Glu Lys Leu Pro Gly Gly Ser Tyr Ala Leu Arg Val Gln Gly Glu Pro
        355                 360                 365

Ala Lys Gly Glu Met Leu Ala Gly Ala Ala Val Tyr Asn Gly Glu Val
    370                 375                 380

Leu His Phe His Thr Glu Asn Gly Arg Pro Tyr Pro Thr Arg Gly Arg
385                 390                 395                 400

Phe Ala Ala Lys Val Asp Phe Gly Ser Lys Ser Val Asp Gly Ile Ile
                405                 410                 415

Asp Ser Gly Asp Asp Leu His Met Gly Thr Gln Lys Phe Lys Ala Ala
            420                 425                 430

Ile Asp Gly Asn Gly Phe Lys Gly Thr Trp Thr Glu Asn Gly Ser Gly
        435                 440                 445

Asp Val Ser Gly Lys Phe Tyr Gly Pro Ala Gly Glu Glu Val Ala Gly
    450                 455                 460

Lys Tyr Ser Tyr Arg Pro Thr Asp Ala Glu Lys Gly Gly Phe Gly Val
465                 470                 475                 480

Phe Ala Gly Lys Lys Glu Gln Asp
                485

<210>   620
<211>   427
<212>   PRT
<213>   Artificial Sequence

<220>
<223>   2996

<400>   620
Met Phe Glu Arg Ser Val Ile Ala Met Ala Cys Ile Phe Ala Leu Ser
1               5                   10                  15

Ala Cys Gly Gly Gly Gly Gly Gly Ser Pro Asp Val Lys Ser Ala Asp
            20                  25                  30

Thr Leu Ser Lys Pro Ala Ala Pro Val Val Ala Glu Lys Glu Thr Glu
        35                  40                  45

Val Lys Glu Asp Ala Pro Gln Ala Gly Ser Gln Gly Gln Gly Ala Pro
    50                  55                  60

Ser Thr Gln Gly Ser Gln Asp Met Ala Ala Val Ser Ala Glu Asn Thr
65                  70                  75                  80

Gly Asn Gly Gly Ala Ala Thr Thr Asp Lys Pro Lys Asn Glu Asp Glu
                85                  90                  95

Gly Pro Gln Asn Asp Met Pro Gln Asn Ser Ala Glu Ser Ala Asn Gln
            100                 105                 110
```

Thr Gly Asn Asn Gln Pro Ala Asp Ser Ser Asp Ser Ala Pro Ala Ser
115 120 125

Asn Pro Ala Pro Ala Asn Gly Gly Ser Asn Phe Gly Arg Val Asp Leu
130 135 140

Ala Asn Gly Val Leu Ile Asp Gly Pro Ser Gln Asn Ile Thr Leu Thr
145 150 155 160

His Cys Lys Gly Asp Ser Cys Asn Gly Asp Asn Leu Leu Asp Glu Glu
165 170 175

Ala Pro Ser Lys Ser Glu Phe Glu Asn Leu Asn Glu Ser Glu Arg Ile
180 185 190

Glu Lys Tyr Lys Lys Asp Gly Lys Ser Asp Lys Phe Thr Asn Leu Val
195 200 205

Ala Thr Ala Val Gln Ala Asn Gly Thr Asn Lys Tyr Val Ile Ile Tyr
210 215 220

Lys Asp Lys Ser Ala Ser Ser Ser Ser Ala Arg Phe Arg Arg Ser Ala
225 230 235 240

Arg Ser Arg Arg Ser Leu Pro Ala Glu Met Pro Leu Ile Pro Val Asn
245 250 255

Gln Ala Asp Thr Leu Ile Val Asp Gly Glu Ala Val Ser Leu Thr Gly
260 265 270

His Ser Gly Asn Ile Phe Ala Pro Glu Gly Asn Tyr Arg Tyr Leu Thr
275 280 285

Tyr Gly Ala Glu Lys Leu Pro Gly Gly Ser Tyr Ala Leu Arg Val Gln
290 295 300

Gly Glu Pro Ala Lys Gly Glu Met Leu Ala Gly Thr Ala Val Tyr Asn
305 310 315 320

Gly Glu Val Leu His Phe His Thr Glu Asn Gly Arg Pro Tyr Pro Thr
325 330 335

Arg Gly Arg Phe Ala Ala Lys Val Asp Phe Gly Ser Lys Ser Val Asp
340 345 350

Gly Ile Ile Asp Ser Gly Asp Asp Leu His Met Gly Thr Gln Lys Phe
355 360 365

Lys Ala Ala Ile Asp Gly Asn Gly Phe Lys Gly Thr Trp Thr Glu Asn
370 375 380

Gly Gly Gly Asp Val Ser Gly Arg Phe Tyr Gly Pro Ala Gly Glu Glu
385 390 395 400

Val Ala Gly Lys Tyr Ser Tyr Arg Pro Thr Asp Ala Glu Lys Gly Gly
405 410 415

Phe Gly Val Phe Ala Gly Lys Lys Glu Gln Asp
420 425

Patentansprüche

1. Verfahren zur heterologen Expression von N. meningitidis-Protein ‚961', wobei:
(a) Protein 961 die Aminosäuresequenz ‚961' in Stamm MC58 hat:

MSMKHFPAKVLTTAILATFCSGALAATSDDDVKKAATVAIVAAYNNGQEINGFKAGETIYDIGE
DGTITQKDATAADVEADDFKGLGLKKVVTNLTKTVNENKQNVDAKVKAAESEIEKLTTKLADTD
AALADTDAALDETTNALNKLGENITTFAEETKTNIVKIDEKLEAVADTVDKHAEAFNDIADSLD
ETNTKADEAVKTANEAKQTAEETKQNVDAKVKAAETAAGKAEAAAGTANTAADKAEAVAAKVTD
IKADIATNKADIAKNSARIDSLDKNVANLRKETRQGLAEQAALSGLFQPYNVGRFNVTAAVGGY
KSESAVAIGTGFRFTENFAAKAGVAVGTSSGSSAAYHVGVNYEW

und wobei
(b) zumindest eine Domäne des Proteins deletiert wurde, wobei die Domänen von ‚961' in Stamm MC58 folgendermaßen sind: (1) Aminosäuren 1 bis 23; (2) Aminosäuren 24 bis 268; (3) Aminosäuren 269 bis 307; und (4) Aminosäuren 308 bis 364,
und wobei das ‚961'-Protein in einer Wirtszelle exprimiert wird.

2. Verfahren nach Anspruch 1, wobei kein Fusionspartner zur Proteinexpression verwendet wird.

3. Verfahren nach Anspruch 1, wobei das Protein eine C-terminale His-Markierung umfasst.

4. Verfahren nach Anspruch 1, wobei das Protein eine N-terminale GST umfasst.

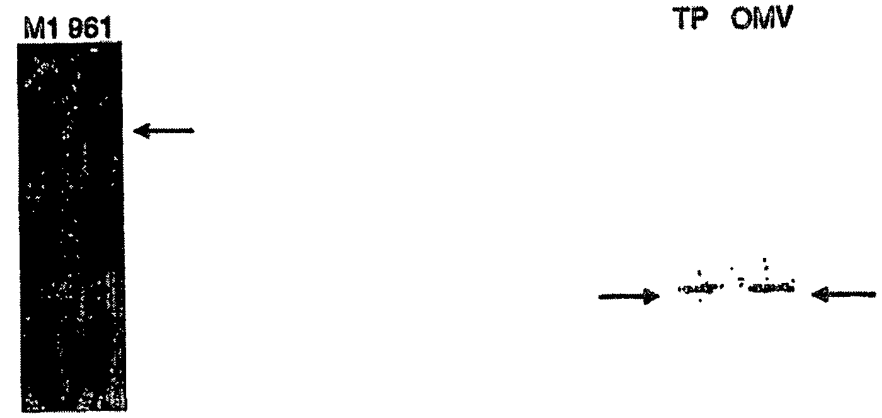
5. Verfahren nach Anspruch 1, wobei das Protein ‚961' der N-terminale Teil eines Hybridproteins ist.

6. Protein, exprimiert durch das Verfahren nach einem der vorhergehenden Ansprüche.

Es folgen 8 Blatt Zeichnungen

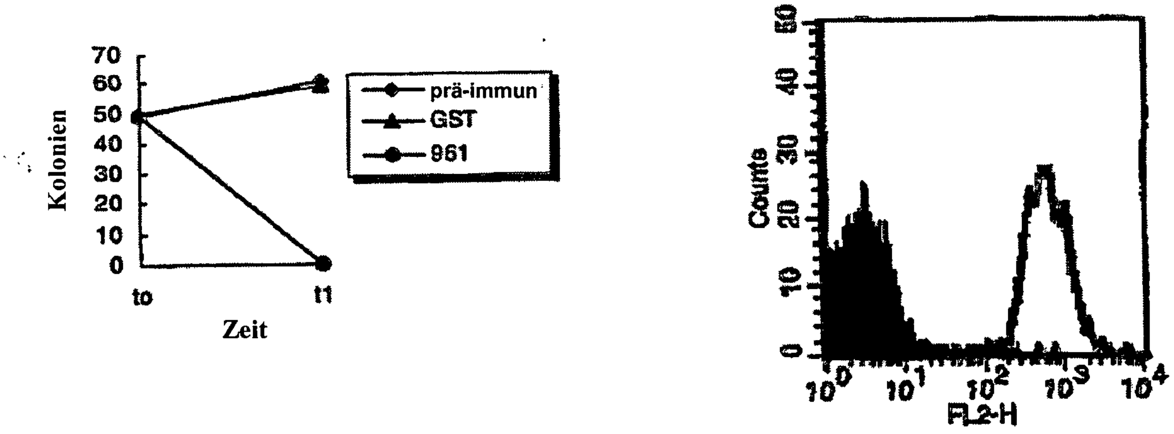
Anhängende Zeichnungen

FIGUR 4



AUFREINIGUNG

WESTERN BLOT

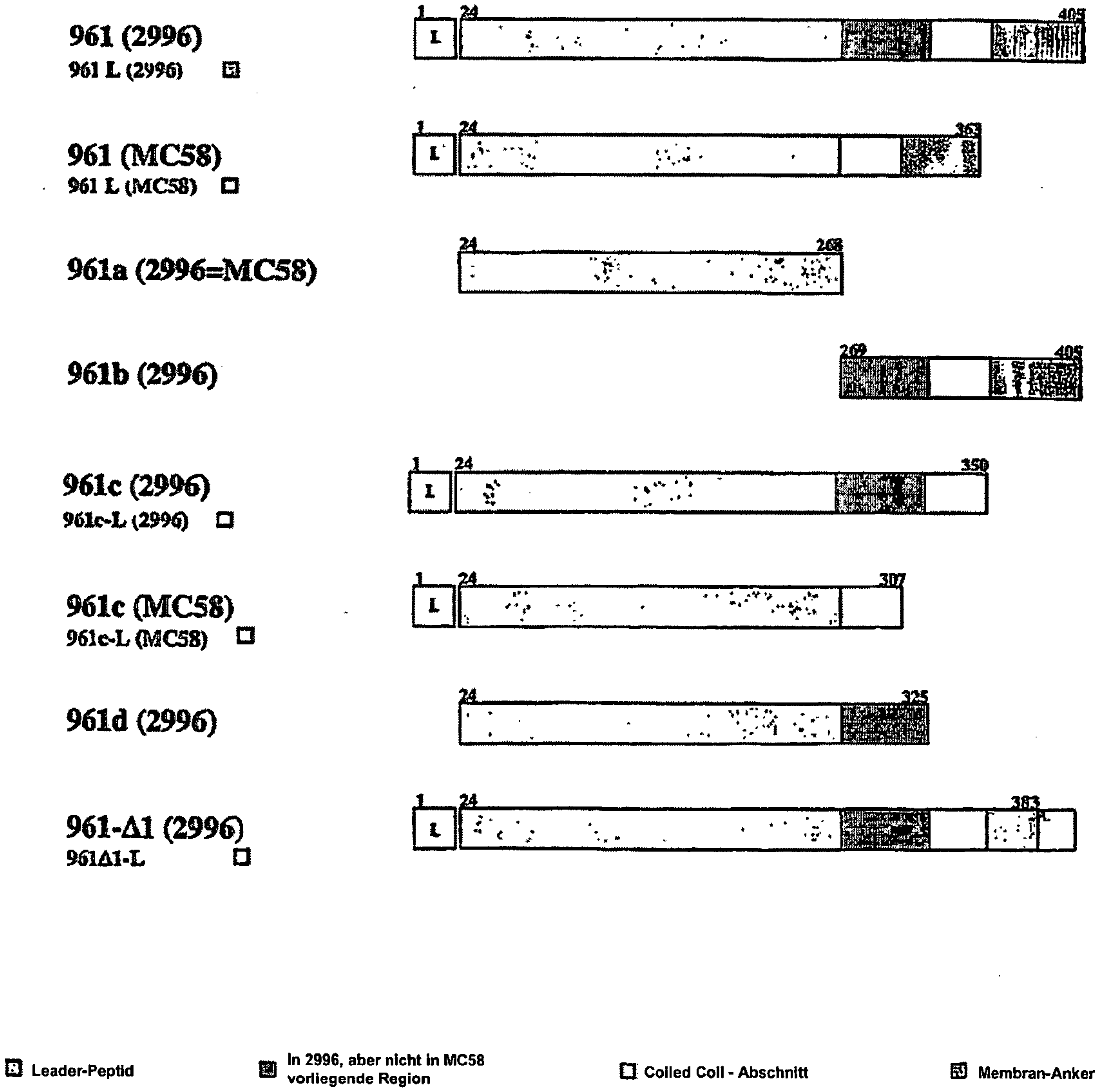


BAKTERIZIDIE - ASSAY

FACS

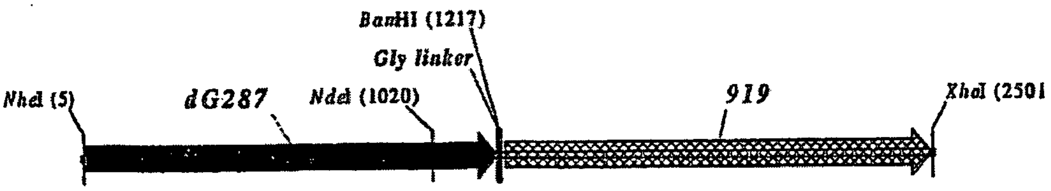
ELISA: *positiv*

FIGUR 12

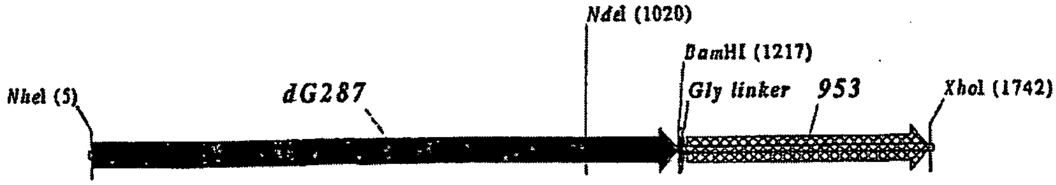

961 (2996)
961 L (2996)
1
24
L
405
961 (MC58)
961 L (MC58)
1
24
L
363
961a (2996=MC58)
24
268
961b (2996)
269
405
961c (2996)
961c-L (2996)
1
24
L
350
961c (MC58)
961c-L (MC58)
1
24
L
307
961d (2996)
24
325
961-Δ1 (2996)
961Δ1-L
1
24
L
383
Leader-Peptid
In 2996, aber nicht in MC58 vorliegende Region
Coiled Coil - Abschnitt
Membran-Anker

FIGUR 14

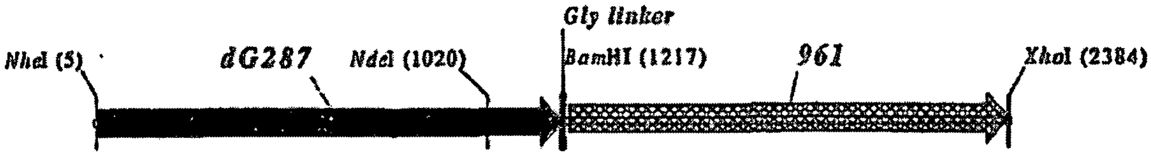
FIGUR 14A — ΔG287—919



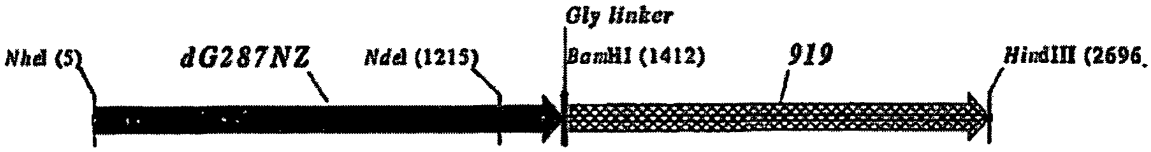
FIGUR 14B — ΔG287—953



FIGUR 14C — ΔG287—961

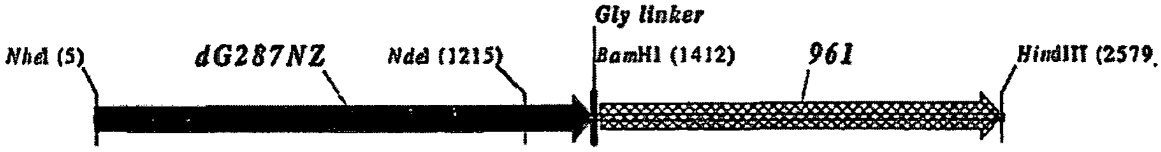


FIGUR 14D — ΔG287NZ—919



FIGUR 14E — ΔG287NZ—953

FIGUR 14F — ΔG287NZ—961



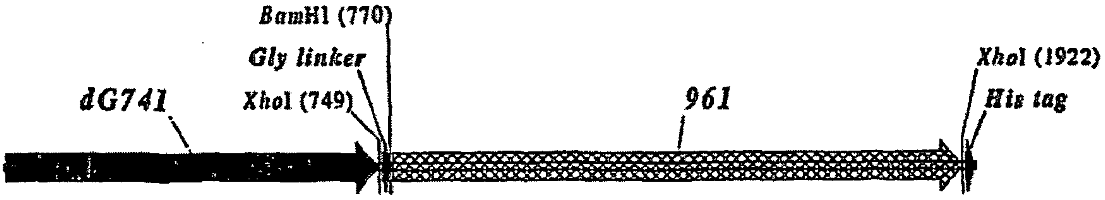
FIGUR 14G — ΔG983-ORF46.1

FIGUR 14H — ΔG983-741

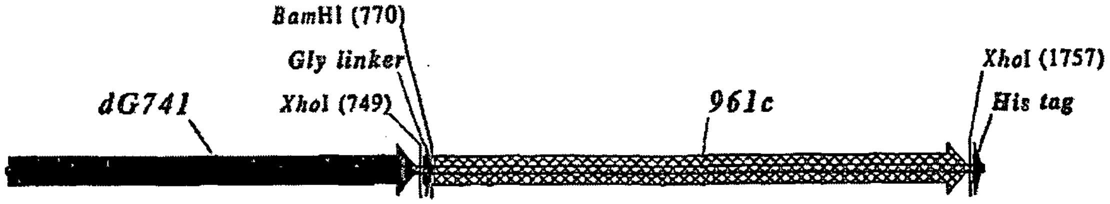
FIGUR 14I — ΔG983-961

FIGUR 14J — ΔG983-961c

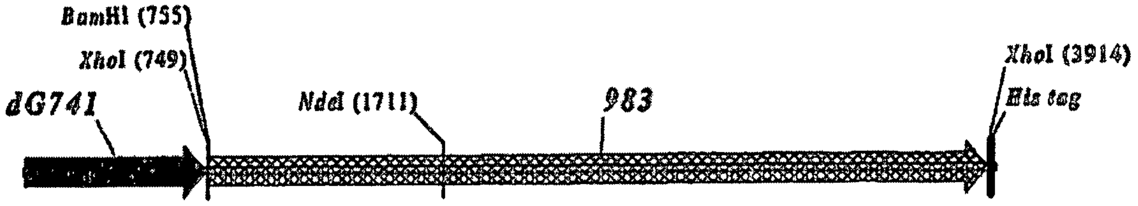
FIGUR 14K — ΔG741-961



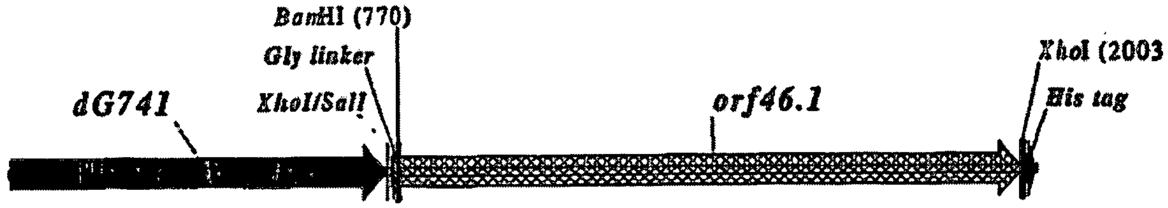
FIGUR 14L — ΔG741-961c



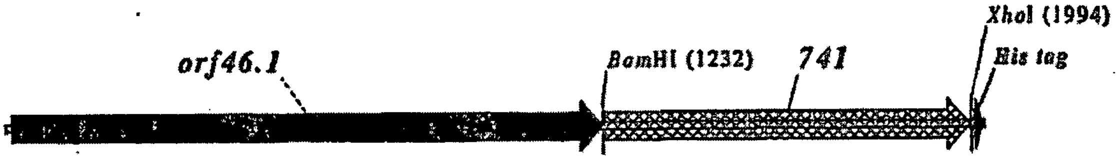
FIGUR 14M — ΔG741-983



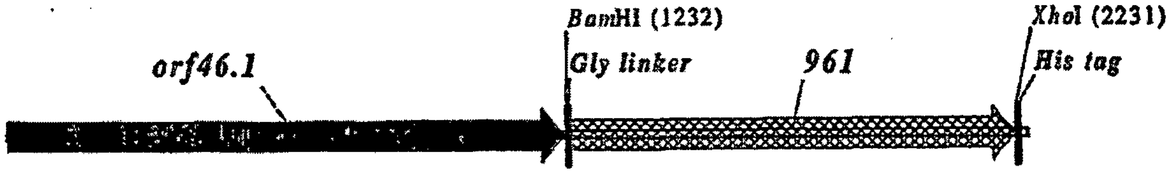
FIGUR 14N — ΔG741-ORF46.1



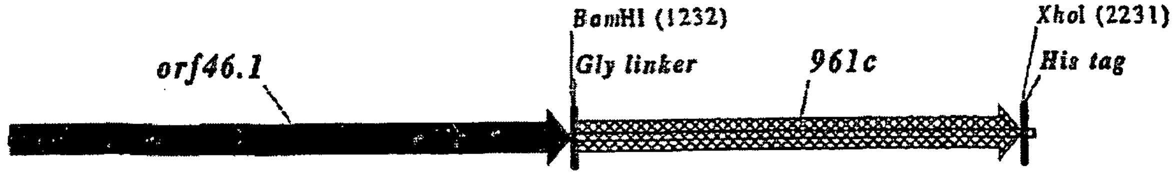
FIGUR 14O — ORF46.1-741



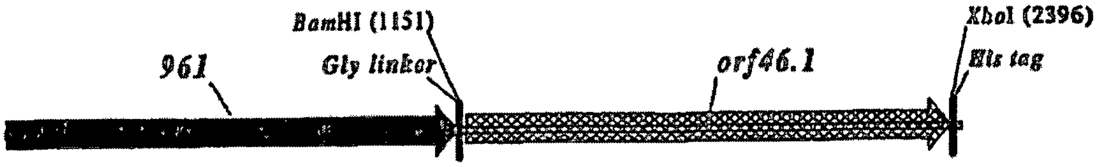
FIGUR 14P — ORF46.1-961



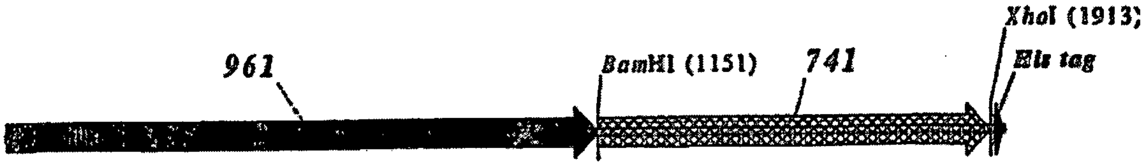
FIGUR 14Q — ORF46.1—961c



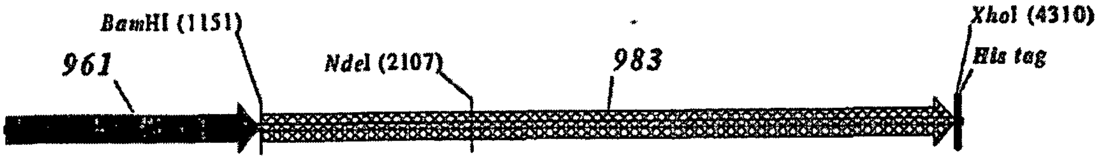
FIGUR 14R — 961-ORF46.1



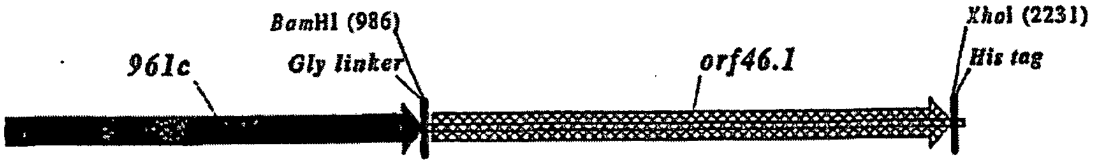
FIGUR 14S — 961-741



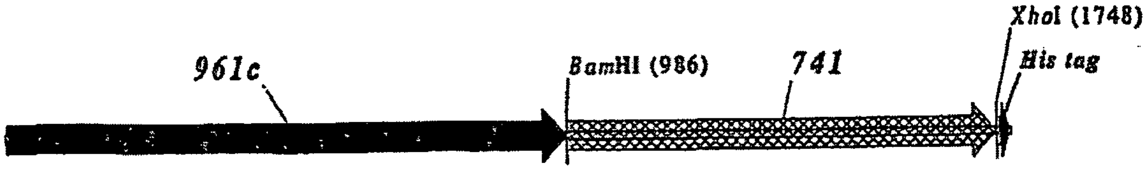
FIGUR 14T — 961-983



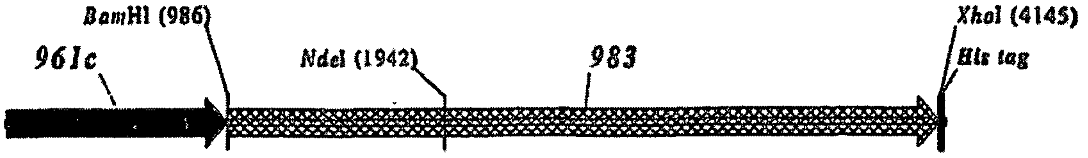
FIGUR 14U — 961c-ORF46.1



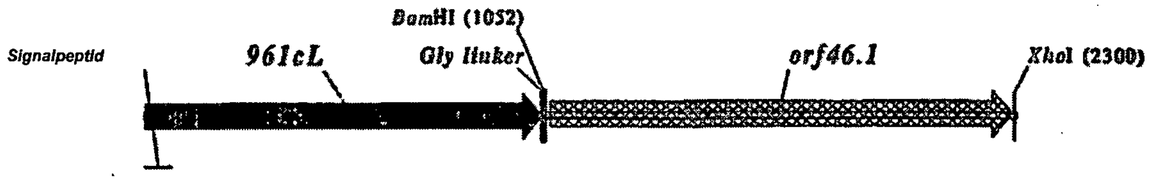
FIGUR 14V — 961c-741



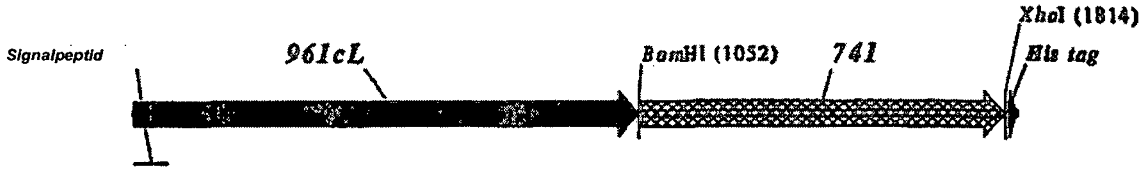
FIGUR 14W — 961c-983



FIGUR 14X — 961cL-ORF46.1



FIGUR 14Y — 961cL-741



FIGUR 14Z — 961cL-983