

(19) **DANMARK**



Patent- og
Varemærkestyrelsen

(10) **DK/EP 3283520 T3**

(12) Oversættelse af
europæisk patentskrift

-
- (51) Int.Cl.: **C 07 K 16/28 (2006.01)** **A 61 K 35/17 (2015.01)** **A 61 K 39/395 (2006.01)**
A 61 P 35/00 (2006.01) **C 07 K 19/00 (2006.01)**
- (45) Oversættelsen bekendtgjort den: **2020-07-20**
- (80) Dato for Den Europæiske Patentmyndigheds
bekendtgørelse om meddelelse af patentet: **2020-05-06**
- (86) Europæisk ansøgning nr.: **16714020.1**
- (86) Europæisk indleveringsdag: **2016-03-30**
- (87) Den europæiske ansøgnings publiceringsdag: **2018-02-21**
- (86) International ansøgning nr.: **IB2016051808**
- (87) Internationalt publikationsnr.: **WO2016166630**
- (30) Prioritet: **2015-04-13 US 201562146825 P** **2016-01-25 US 201662286473 P**
2016-02-29 US 201662301177 P
- (84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV
MC MK MT NL NO PL PT RO RS SE SI SK SM TR**
- (73) Patenthaver: **Pfizer Inc, 235 East 42nd Street, New York, NY 10017, USA**
- (72) Opfinder: **KUO, Tracy Chia-Chien, 225 9th Avenue 307, San Mateo, CA 94401, USA**
CHAPARRO RIGGERS, Javier Fernando, 904 Peninsula Avenue, San Mateo, CA 94401, USA
SASU, Barbra Johnson, 2125 Bryant Street 316, San Francisco, CA 94110, USA
GALETTI, Roman, 12 Rue Ernest Cresson, 75014 Paris, Frankrig
BOLDAJIPOUR, Bijan Andre, 860 14th Street Apt. 3, San Francisco, CA 94114, USA
SOMMER, Cesar Adolfo, 155 N El Camino Real Apt. 31, San Mateo, CA 94401, USA
VAN BLARCOM, Thomas John, 6415 Chelton Drive, Oakland, CA 94611, USA
PERTEL, Thomas Charles, 29 Creekridge Court, San Mateo, CA 94402, USA
RAJPAL, Arvind, 519 Foerster Street, San Francisco, CA 94127, USA
DUCHATEAU, Philippe, Bateau Fawen, Quai des Dames, 91210 Draveil, Frankrig
JUILLERAT, Alexandre, 38 rue de l'Amiral Mouchez, 75014 Paris, Frankrig
VALTON, Julien, 19 rue Victor Hugo, 94220 Charenton le Pont, Frankrig
- (74) Fuldmægtig i Danmark: **NORDIC PATENT SERVICE A/S, Bredgade 30, 1260 København K, Danmark**
- (54) Benævnelse: **KIMÆRISKE ANTIGENRECEPTORER MÅLRETTET B-CELLE- MODNINGSANTIGEN**
- (56) Fremdragne publikationer:
WO-A1-2013/154760
WO-A1-2014/068079
WO-A1-2014/122143
WO-A1-2014/140248
WO-A1-2014/152177
WO-A1-2015/158671

Fortsættes ...

WO-A2-2014/089335

WO-A2-2016/014565

US-A1- 2013 280 280

US-A1- 2014 161 828

TORIKAI HIROKI ET AL: "A foundation for universal T-cell based immunotherapy: T cells engineered to express a CD19-specific chimeric-antigen-receptor and eliminate expression of endogenous TCR", BLOOD, AMERICAN SOCIETY OF HEMATOLOGY, UNITED STATES, vol. 119, no. 24, 14 June 2012 (2012-06-14), pages 5697-5705, XP002752739, ISSN: 1528-0020

"9.8.3 Automated Modeling Tools" In: Dübel et al: "Handbook of Therapeutic Antibodies - Volume 3 (2nd ed)", 2014, Wiley Blackwell, Weinheim (Germany) ISBN: 978-3-527-32937-3 page 217,

Accelrys Software, Inc: ""Abm" 0 results found", Accelrys.com Search Tool , 10 August 2018 (2018-08-10),

Retrieved from the Internet: URL:<http://search.accelrys.com/solr/collection1/browse?fq=url%3A%22http%3A%2F%2Faccelrys.com%22&q=Abm&btnG=Search> [retrieved on 2018-08-

10]

DESCRIPTION

Field

[0001] The invention relates to chimeric antigen receptors (CAR). CARs are able to redirect immune cell specificity and reactivity toward a selected target exploiting the ligand-binding domain properties. The invention relates to CARs that specifically bind to B-Cell Maturation Antigen (BCMA specific CARs). The invention further relates to polynucleotides encoding BCMA specific CAR and isolated cells expressing BCMA specific CARs at their surface. The invention further relates to *in vitro* methods for engineering immune cells expressing BCMA specific CARs at their surface. The invention is particularly useful for the treatment of B-cell lymphomas and leukemia. The invention further relates to immune cells comprising the BCMA specific CARs (BCMA specific CAR-T cells), compositions comprising the BCMA specific CAR-T cells, and the BCMA specific CAR-T cells for use in treating conditions associated with malignant cells expressing BCMA (e.g., cancer).

Background

[0002] Multiple myeloma is a malignancy characterized by an accumulation of clonal plasma cells (see, e.g., Lonial et al., Clinical Cancer Res., 77(6): 1264-1277 (2011)). Current therapies for MM often cause remissions, but nearly all patients eventually relapse and die (see, e.g., Rajkumar, Nature Rev. Clinical Oncol, 5(8): 479-491 (2011)).

[0003] Adoptive transfer of T cells genetically modified to recognize malignancy-associated antigens is showing promise as a new approach to treating cancer (see, e.g., Brenner et al., Current Opinion in Immunology, 22(2): 251-257 (2010); Rosenberg et al., Nature Reviews Cancer, 8(4): 299-308 (2008)). T cells can be genetically modified to express chimeric antigen receptors (CARs), which are fusion proteins comprised of an antigen recognition moiety and T cell activation domains (see, e.g., Eshhar et al., Proc. Natl. Acad. Sci. USA, 90(2): 720-724 (1993), and Sadelain et al., Curr. Opin. Immunol, 21(2): 215-223 (2009)).

[0004] B-cell maturation antigen (BCMA, CD269, or TNFRSF17) is a member of the tumor necrosis factor receptor (TNFR) superfamily. BCMA was identified in a malignant human T cell lymphoma containing a t(4;16) translocation. The gene is selectively expressed in the B-cell lineage with the highest expression in plasmablasts and plasma cells, antibody secreting cells. BCMA binds two ligands, B-cell activation factor (BAFF) (also called B-lymphocyte stimulator (BLyS) and APOL-related leukocyte expressed ligand (TALL-1)) and a proliferation-inducing ligand (APRIL) with affinity of 1 μ M and 16 nM, respectively. Binding of APRIL or BAFF to BCMA promotes a signaling cascade involving NF-kappa B, Elk-1, c-Jun N-terminal kinase and the p38 mitogen-activated protein kinase, which produce signals for cell survival and proliferation. BCMA is also expressed on malignant B cells and several cancers that involve B lymphocytes including multiple myeloma, plasmacytoma, Hodgkin's Lymphoma, and chronic lymphocytic leukemia. In autoimmune diseases where plasmablasts are involved such as systemic lupus erythematosus (SLE) and rheumatoid arthritis, BCMA expressing antibody-producing cells secrete autoantibodies that attack self.

[0005] In the case of multiple myeloma, about 24,000 new cases are newly diagnosed in the United States each year, and this number represents about 15% of the newly diagnosed hematological cancers in the United States. An average of 11,000 deaths result from multiple myeloma each year, and the average 5-year survival rate is about 44%, with median survival of 50-55 months. Current treatment for multiple myeloma is focused on plasma cells apoptosis and/or decreasing osteoclast activity (e.g., chemotherapy, thalidomide, lenalidomide, bisphosphonates, and/or proteasome inhibitors such as bortezomib (VELCADE®) or carfilzomib). However, multiple myeloma remains an incurable disease, and almost all patients have developed resistance to these agents and eventually relapse. Accordingly, an alternative treatment to multiple myeloma, such as using an anti-BCMA antagonist including BCMA specific CARs and BCMA specific CAR-T cells, would make a superior therapeutic agent.

[0006] WO 2013/154760 reports an isolated and purified nucleic acid sequence encoding a CAR directed against BCMA, as well as host cells and methods for destroying multiple myeloma cells.

Summary

[0007] Chimeric antigen receptors (CARs) that bind to BCMA are provided. It is demonstrated that certain BCMA specific CARs are effective when expressed in T cells to activate T cells upon contact with BCMA. Advantageously, the BCMA specific CARs provided herein bind human and cynomolgous monkey BCMA. Also advantageously, the BCMA specific CAR-T cells provided herein exhibit degranulation activity, increased interferon gamma production, and/or cytotoxic activity upon contact with BCMA-expressing cells.

[0008] In a first aspect of the invention, there is provided a BCMA specific CAR according to claim 1.

[0009] Disclosed herein is a BCMA specific CAR comprising an extracellular ligand-binding domain, a first transmembrane domain, and

an intracellular signaling domain, wherein the extracellular ligand-binding domain comprises (a) a heavy chain variable (VH) region comprising (i) a VH complementarity determining region one (CDR1) comprising the sequence SYX₁MX₂, wherein X₁ is A or P; and X₂ is T, N, or S (SEQ ID NO: 301), GFTFX₁SY, wherein X₁ is G or S (SEQ ID NO: 302), or GFTFX₁SYX₂MX₃, wherein X₁ is G or S, X₂ is A or P; and X₃ is T, N, or S (SEQ ID NO: 303); (ii) a VH CDR2 comprising the sequence AX₁X₂X₃X₄GX₅X₆X₇X₈YADX₉X₁₀KG, wherein X₁ is I, V, T, H, L, A, or C; X₂ is S, D, G, T, I, L, F, M, or V; X₃ is G, Y, L, H, D, A, S, or M; X₄ is S, Q, T, A, F, or W; X₅ is G or T; X₆ is N, S, P, Y, W, or F; X₇ is S, T, I, L, T, A, R, V, K, G, or C; X₈ is F, Y, P, W, H, or G; X₉ is V, R, or L; and X₁₀ is G or T (SEQ ID NO: 305), or X₁X₂X₃X₄X₅X₆, wherein X₁ is S, V, I, D, G, T, L, F, or M; X₂ is G, Y, L, H, D, A, S, or M; X₃ is S, G, F, or W; X₄ is G or S; X₅ is G or T; and X₆ is N, S, P, Y, or W (SEQ ID NO: 306); and (iii) a VH CDR3 comprising the sequence VSPIX₁X₂X₃X₄, wherein X₁ is A or Y; X₂ is A or S; and X₃ is G, Q, L, P, or E (SEQ ID NO: 307), or YWPMX₁X₂, wherein X₁ is D, S, T, or A; and X₂ is I, S, L, P, or D (SEQ ID NO: 308); and/or (b) a light chain variable (VL) region comprising (i) a VL CDR1 comprising the sequence X₁X₂X₃X₄X₅X₆X₇X₈X₉X₁₀X₁₁X₁₂, wherein X₁ is R, G, W, A, or C; X₂ is A, P, G, L, C, or S; X₃ is S, G, or R; X₄ is Q, C, E, V, or I; X₅ is S, L, P, G, A, R, or D; X₆ is V, G, or I; X₇ is S, E, D, or P; X₈ is S, P, F, A, M, E, V, N, D, or Y; X₉ is I, T, V, E, S, A, M, Q, Y, H, or R; X₁₀ is Y or F; X₁₁ is L, W, or P; and X₁₂ is A, S, or G (SEQ ID NO: 309); (ii) a VL CDR2 comprising the sequence X₁ASX₂RAX₃, wherein X₁ is G or D; X₂ is S or I; and X₃ is T or P (SEQ ID NO: 310); and (iii) a VL CDR3 comprising the sequence QQYX₁X₂X₃PX₄T, wherein X₁ is G, Q, E, L, F, A, S, M, K, R, or Y; X₂ is S, R, T, G, V, F, Y, D, A, H, V, E, K, or C; X₃ is W, F, or S; and X₄ is L or I (SEQ ID NO: 311), or QQYX₁X₂X₃PX₄, wherein X₁ is G, Q, E, L, F, A, S, M, R, K, or Y; X₂ is S, R, T, G, R, V, D, A, H, E, K, C, F, or Y; X₃ is W, S, or F; and X₄ is L or I (SEQ ID NO: 312).

[0010] Disclosed herein is a BCMA specific CAR comprising an extracellular ligand-binding domain, a first transmembrane domain, and an intracellular signaling domain, wherein the extracellular domain comprises a single chain Fv fragment (scFv) comprising a heavy chain variable (VH) region comprising three CDRs from the VH region comprising the sequence shown in SEQ ID NO: 33, 72, 39, 76, 83, 92, 25, or 8; and a light chain variable (VL) region comprising three CDRs from the VL region shown in SEQ ID NO: 34, 73, 40, 77, 84, 93, 18, or 80. In some examples, the VH region can comprise the sequence shown in SEQ ID NO: 33, 72, 39, 76, 83, 92, 25, or 8, or a variant thereof with one or several conservative amino acid substitutions in residues that are not within a CDR and/or the VL region can comprise the amino acid sequence shown in SEQ ID NO: 34, 73, 40, 77, 84, 93, 18, or 80, or a variant thereof with one or several amino acid substitutions in amino acids that are not within a CDR.

[0011] In some examples, the extracellular ligand-binding domain of a BCMA specific CAR provided herein comprises (a) a heavy chain variable (VH) region comprising (i) a VH complementarity determining region one (CDR1) comprising the sequence shown in SEQ ID NO: 150, 151, 152, 156, 157, 129, 130, or 131; (ii) a VH CDR2 comprising the sequence shown in 153, 154, 187, 188, 165, 166, 162, 159, 190, 191, 169, 154, 139, 140, 132, or 133; and (iii) a VH CD3 comprising the sequence shown in 155, 161, 134, or 137; and/or (b) a light chain variable region (VL) comprising (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 209, 249, 226, 251, 262, 271, 217, or 377; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 221, 252, or 210; and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 222, 225, 227, 253, 263, 272, 216, or 214.

[0012] In some embodiments, the extracellular ligand-binding domain of a BCMA specific CAR provided herein comprises (a) a heavy chain variable (VH) region comprising (i) a VH complementarity determining region one (CDR1) comprising the sequence shown in SEQ ID NO: 150, 151, or 152; (ii) a VH CDR2 comprising the sequence shown in 153 or 154; and (iii) a VH CD3 comprising the sequence shown in 155; and/or (b) a light chain variable region (VL) comprising (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 209; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 221, and (iii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 222.

[0013] In some embodiments, the extracellular ligand-binding domain of a BCMA specific CAR provided herein comprises (a) a heavy chain variable (VH) region comprising (i) a VH complementarity determining region one (CDR1) comprising the sequence shown in SEQ ID NO: 150, 151, or 152; (ii) a VH CDR2 comprising the sequence shown in 187 or 188; and (iii) a VH CD3 comprising the sequence shown in 155; and/or (b) a light chain variable region (VL) comprising (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 249; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 221, and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 225.

[0014] In some embodiments, the extracellular ligand-binding domain of a BCMA specific CAR provided herein comprises (a) a heavy chain variable (VH) region comprising (i) a VH complementarity determining region one (CDR1) comprising the sequence shown in SEQ ID NO: 150, 151, or 152; (ii) a VH CDR2 comprising the sequence shown in 165 or 166; and (iii) a VH CD3 comprising the sequence shown in 155; and/or (b) a light chain variable region (VL) comprising (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 226; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 221, and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 227.

[0015] In some embodiments, the extracellular ligand-binding domain of a BCMA specific CAR provided herein comprises (a) a heavy chain variable (VH) region comprising (i) a VH complementarity determining region one (CDR1) comprising the sequence shown in SEQ ID NO: 156, 151, or 157; (ii) a VH CDR2 comprising the sequence shown in 162 or 159; and (iii) a VH CD3 comprising the sequence shown in 161; and/or (b) a light chain variable region (VL) comprising (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 251; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 252, and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 253.

[0016] In some embodiments, the extracellular ligand-binding domain domain of a BCMA specific CAR provided herein comprises (a) a heavy chain variable (VH) region comprising (i) a VH complementarity determining region one (CDR1) comprising the sequence shown in SEQ ID NO: 156, 151, or 157; (ii) a VH CDR2 comprising the sequence shown in 190 or 191; and (iii) a VH CD3 comprising the sequence shown in 161; and/or (b) a light chain variable region (VL) comprising (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 262; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 252, and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 263.

[0017] In some embodiments, the extracellular ligand-binding domain domain of a BCMA specific CAR provided herein comprises (a) a heavy chain variable (VH) region comprising (i) a VH complementarity determining region one (CDR1) comprising the sequence shown in SEQ ID NO: 150, 151, or 152; (ii) a VH CDR2 comprising the sequence shown in 169 or 154; and (iii) a VH CD3 comprising the sequence shown in 155; and/or (b) a light chain variable region (VL) comprising (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 271; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 221, and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 272.

[0018] In some embodiments, the extracellular ligand-binding domain domain of a BCMA specific CAR provided herein comprises (a) a heavy chain variable (VH) region comprising (i) a VH complementarity determining region one (CDR1) comprising the sequence shown in SEQ ID NO: 129, 130, or 131; (ii) a VH CDR2 comprising the sequence shown in 139 or 140; and (iii) a VH CD3 comprising the sequence shown in 134; and/or (b) a light chain variable region (VL) comprising (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 217; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 210, and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 216.

[0019] In some examples, the extracellular ligand-binding domain domain of a BCMA specific CAR provided herein comprises (a) a heavy chain variable (VH) region comprising (i) a VH complementarity determining region one (CDR1) comprising the sequence shown in SEQ ID NO: 129, 130, or 131; (ii) a VH CDR2 comprising the sequence shown in 132 or 133; and (iii) a VH CD3 comprising the sequence shown in 137; and/or (b) a light chain variable region (VL) comprising (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 377; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 210, and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 214.

[0020] In some embodiments, the intracellular signaling domain comprises a CD3 ζ signalling domain. In some embodiments, the intracellular signaling domain comprises a 4-1BB domain. In some embodiments, the CAR can further comprise another intracellular signaling domain. In some embodiments, the additional intracellular signaling domain can comprise a 4-1BB domain.

[0021] In some embodiments, the CAR can comprise a stalk domain between the extracellular ligand-binding domain and the first transmembrane domain. In some embodiments, the stalk domain can be selected from the group consisting of: a human CD8 α hinge, an IgG1 hinge, and an Fc γ R1IIa hinge.

[0022] In some embodiments, the first transmembrane domain can comprise a CD8 α chain transmembrane domain.

[0023] In some embodiments, the CAR can comprise a CD20 epitope.

[0024] In some embodiments, the CAR can comprise another extracellular ligand-binding domain which is not specific for BCMA.

[0025] In some embodiments, the BCMA specific CAR can comprise the amino acid sequence shown in SEQ ID NO: 396.

[0026] In some embodiments of a CAR, the extracellular ligand-binding domain(s), the first transmembrane domain, and intracellular signaling domain(s) are on a single polypeptide.

[0027] In some embodiments, the CAR can comprise a second transmembrane domain, wherein the first transmembrane domain and the extracellular ligand-binding domain(s) are on a first polypeptide, and wherein the second transmembrane domain and the intracellular signaling domain(s) are on a second polypeptide, wherein the first transmembrane domain comprises a transmembrane domain from the α chain of the high-affinity IgE receptor (Fc ϵ RI) and the second transmembrane domain comprises a transmembrane domain from the γ or β chain of Fc ϵ RI. In some embodiments, the CAR can comprise a third polypeptide comprising a third transmembrane domain fused to an intracellular signaling domain from a co-stimulatory molecule, wherein the third transmembrane domain comprises a transmembrane domain from the γ or β chain of Fc ϵ RI.

[0028] In another aspect, the invention provides an isolated polynucleotide comprising a nucleic acid sequence encoding a BCMA specific CAR of the first aspect of the invention.

[0029] In another aspect, the invention provides an expression vector comprising a nucleic acid sequence encoding a BCMA specific CAR of the first aspect of the invention.

[0030] In another aspect, the invention provides engineered immune cell expressing at its cell surface membrane a BCMA specific CAR of the first aspect of the invention. In some embodiments, the engineered immune cell can comprise another CAR which is not specific for BCMA. In some embodiments, the engineered immune cell can comprise a polynucleotide encoding a suicide polypeptide. In some embodiments, the suicide polypeptide is RQR8.

[0031] In some embodiments, the immune cell can be derived from an inflammatory T-lymphocyte, a cytotoxic T-lymphocyte, a regulatory T- lymphocyte, or a helper T-lymphocyte.

[0032] In some embodiments, the engineered immune cell can comprise a disruption one or more endogenous genes, wherein the endogenous gene encodes TCR α , TCR β , CD52, glucocorticoid receptor (GR), deoxycytidine kinase (DCK), or an immune checkpoint protein such as for example programmed death-1 (PD-1).

[0033] In some embodiments, immune cell is obtained from a healthy donor. In some embodiments, the immune cell is obtained from a patient.

[0034] In another aspect, the invention provides an engineered immune cell expressing at its cell surface membrane a BCMA specific CAR of the first aspect of the invention, for use as a medicament. In some embodiments, the medicament is for use in treatment of a B-cell related cancer selecting from the group consisting of multiple myeloma, malignant plasma cell neoplasm, Hodgkin's lymphoma, nodular lymphocyte predominant Hodgkin's lymphoma, Kahler's disease and Myelomatosis, plasma cell leukemia, plasmacytoma, B-cell prolymphocytic leukemia, hairy cell leukemia, B-cell non-Hodgkin's lymphoma (NHL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), follicular lymphoma, Burkitt's lymphoma, marginal zone lymphoma, mantle cell lymphoma, large cell lymphoma, precursor B-lymphoblastic lymphoma, myeloid leukemia, Waldenstrom's macroglobulinemia, diffuse large B cell lymphoma, follicular lymphoma, marginal zone lymphoma, mucosa-associated lymphatic tissue lymphoma, small cell lymphocytic lymphoma, mantle cell lymphoma, Burkitt lymphoma, primary mediastinal (thymic) large B-cell lymphoma, lymphoplasmacytic lymphoma, Waldenstrom macroglobulinemia, nodal marginal zone B cell lymphoma, splenic marginal zone lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, lymphomatoid granulomatosis, T cell/histiocyte-rich large B-cell lymphoma, primary central nervous system lymphoma, primary cutaneous diffuse large B-cell lymphoma (leg type), EBV positive diffuse large B-cell lymphoma of the elderly, diffuse large B-cell lymphoma associated with inflammation, intravascular large B-cell lymphoma, ALK-positive large B-cell lymphoma, plasmablastic lymphoma, large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease, B-cell lymphoma unclassified with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma, B-cell lymphoma unclassified with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma, and other B-cell related lymphoma.

[0035] In another aspect, the invention provides an *in vitro* method of engineering an immune cell comprising: providing an immune cell; and expressing at the surface of the cell at least one BCMA specific CAR of the first aspect of the invention.

[0036] In some embodiments, the method comprises: providing an immune cell; introducing into the cell at least one polynucleotide encoding said BCMA specific CAR; and expressing said polynucleotide into the cell.

[0037] In some embodiments, the method comprises providing an immune cell; introducing into the cell at least one polynucleotide encoding said BCMA specific CAR; and introducing at least one other CAR which is not specific for BCMA.

[0038] Provided herein is a method of treating a subject suffering from a condition associated with malignant cells, the method comprising: providing a immune cell expressing at the surface a BCMA specific CAR as described herein; and administering said immune cells to said patient.

[0039] In another aspect, the invention provides a pharmaceutical composition comprising an engineered immune cell of the invention.

[0040] Provided herein is a method of treating a condition associated with malignant cells expressing BCMA in a subject comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition of as described herein, comprising an engineered immune cell as described herein. In some examples, the condition is a cancer. In some examples, the cancer is a B-cell related cancer selecting from the group consisting of multiple myeloma, malignant plasma cell neoplasm, Hodgkin's lymphoma, nodular lymphocyte predominant Hodgkin's lymphoma, Kahler's disease and Myelomatosis, plasma cell leukemia, plasmacytoma, B-cell prolymphocytic leukemia, hairy cell leukemia, B-cell non-Hodgkin's lymphoma (NHL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), follicular lymphoma, Burkitt's lymphoma, marginal zone lymphoma, mantle cell lymphoma, large cell lymphoma, precursor B-lymphoblastic lymphoma, myeloid leukemia, Waldenstrom's macroglobulinemia, diffuse large B cell lymphoma, follicular lymphoma, marginal zone lymphoma, mucosa-associated lymphatic tissue lymphoma, small cell lymphocytic lymphoma, mantle cell lymphoma, Burkitt lymphoma, primary mediastinal (thymic) large B-cell lymphoma, lymphoplasmacytic lymphoma, Waldenstrom macroglobulinemia, nodal marginal zone B cell lymphoma, splenic marginal zone lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, lymphomatoid granulomatosis, T cell/histiocyte-rich large B-cell lymphoma, primary central nervous system lymphoma, primary cutaneous diffuse large B-cell lymphoma (leg type), EBV positive diffuse large B-cell lymphoma of the elderly, diffuse large B-cell lymphoma associated with inflammation, intravascular large B-cell lymphoma, ALK-positive large B-cell lymphoma, plasmablastic lymphoma, large B-cell

lymphoma arising in HHV8-associated multicentric Castleman disease, B-cell lymphoma unclassified with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma, B-cell lymphoma unclassified with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma, and other B-cell related lymphoma.

[0041] Provided herein is a method of inhibiting tumor growth or progression in a subject who has malignant cells expressing BCMA, comprising administering to the subject in need thereof an effective amount of a pharmaceutical composition comprising an engineered immune cell as described herein.

[0042] Provided herein is a method of inhibiting metastasis of malignant cells expressing BCMA in a subject, comprising administering to the subject in need thereof an effective amount of the pharmaceutical composition comprising an engineered immune cell as described herein.

[0043] Provided herein is a method of inducing tumor regression in a subject who has malignant cells expressing BCMA, comprising administering to the subject in need thereof an effective amount of the pharmaceutical composition of a pharmaceutical composition comprising an engineered immune cell as described herein.

[0044] In some examples, any of the above methods further comprises administering one or more additional therapies, such as for example, a monoclonal antibody and/or a chemotherapeutic. In some examples, the monoclonal antibody can be, for example, an antibody that binds to a checkpoint inhibitor such as, for example, an anti-PD-1 antibody or an anti-PD-L1 antibody. In some examples, any of the above methods further comprises administering a nucleoside analog therapy, such as for example fludarabine or clofarabine, to the subject.

Brief Description of the Drawings

[0045]

FIG. 1 depicts a graph summarizing the results of treatment with BCMA specific CAR-T in the MM1.S tumor model.

FIG. 2 depicts a graph summarizing the results of treatment with BCMA specific CAR-T in the Molp8 tumor model.

Detailed Description

[0046] The invention disclosed herein provides chimeric antigen receptors (CARs) and immune cells comprising CARs (CAR-T cells) that specifically bind to BCMA (e.g., human BCMA). The invention also provides polynucleotides encoding these CARs, compositions comprising these CAR-T cells, and methods of making and using these CARs and CAR-T cells. The disclosure also provides methods for treating a condition associated with malignant BCMA expression in a subject, such as cancer.

General Techniques

[0047] The practice of the invention will employ, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry and immunology, which are within the skill of the art. Such techniques are explained fully in the literature, such as, Molecular Cloning: A Laboratory Manual, second edition (Sambrook et al., 1989) Cold Spring Harbor Press; Oligonucleotide Synthesis (M.J. Gait, ed., 1984); Methods in Molecular Biology, Humana Press; Cell Biology: A Laboratory Notebook (J.E. Cellis, ed., 1998) Academic Press; Animal Cell Culture (R.I. Freshney, ed., 1987); Introduction to Cell and Tissue Culture (J.P. Mather and P.E. Roberts, 1998) Plenum Press; Cell and Tissue Culture: Laboratory Procedures (A. Doyle, J.B. Griffiths, and D.G. Newell, eds., 1993-1998) J. Wiley and Sons; Methods in Enzymology (Academic Press, Inc.); Handbook of Experimental Immunology (D.M. Weir and C.C. Blackwell, eds.); Gene Transfer Vectors for Mammalian Cells (J.M. Miller and M.P. Calos, eds., 1987); Current Protocols in Molecular Biology (F.M. Ausubel et al., eds., 1987); PCR: The Polymerase Chain Reaction, (Mullis et al., eds., 1994); Current Protocols in Immunology (J.E. Coligan et al., eds., 1991); Short Protocols in Molecular Biology (Wiley and Sons, 1999); Immunobiology (C.A. Janeway and P. Travers, 1997); Antibodies (P. Finch, 1997); Antibodies: a practical approach (D. Catty, ed., IRL Press, 1988-1989); Monoclonal antibodies: a practical approach (P. Shepherd and C. Dean, eds., Oxford University Press, 2000); Using antibodies: a laboratory manual (E. Harlow and D. Lane (Cold Spring Harbor Laboratory Press, 1999); The Antibodies (M. Zanetti and J.D. Capra, eds., Harwood Academic Publishers, 1995).

Definitions

[0048] The term "extracellular ligand-binding domain" as used herein refers to an oligo- or polypeptide that is capable of binding a ligand. Preferably, the domain will be capable of interacting with a cell surface molecule. For example, the extracellular ligand-binding domain may be chosen to recognize a ligand that acts as a cell surface marker on target cells associated with a particular disease state.

[0049] The term "stalk domain" or "hinge domain" are used interchangeably herein to refer to any oligo- or polypeptide that functions to link the transmembrane domain to the extracellular ligand-binding domain. In particular, stalk domains are used to provide more flexibility and accessibility for the extracellular ligand-binding domain.

[0050] The term "intracellular signaling domain" refers to the portion of a protein which transduces the effector signal function signal and directs the cell to perform a specialized function.

[0051] A "co-stimulatory molecule" as used herein refers to the cognate binding partner on a T cell that specifically binds with a co-stimulatory ligand, thereby mediating a co-stimulatory response by the cell, such as, but not limited to proliferation. Co-stimulatory molecules include, but are not limited to an MHC class I molecule, BTLA and Toll ligand receptor. Examples of costimulatory molecules include CD27, CD28, CD8, 4-1BB (CD137), OX40, CD30, CD40, PD-1, ICOS, lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, B7-H3 and a ligand that specifically binds with CD83 and the like.

[0052] A "co-stimulatory ligand" refers to a molecule on an antigen presenting cell that specifically binds a cognate co-stimulatory signal molecule on a T cell, thereby providing a signal which, in addition to the primary signal provided by, for instance, binding of a TCR/CD3 complex with an MHC molecule loaded with peptide, mediates a T cell response, including, but not limited to, proliferation activation, differentiation and the like. A co-stimulatory ligand can include but is not limited to CD7, B7-1 (CD80), B7-2 (CD86), PD-L1, PD-L2, 4-1BBL, OX40L, inducible costimulatory ligand (ICOS-L), intercellular adhesion molecule (ICAM, CD30L, CD40, CD70, CD83, HLA-G, MICA, M1CB, HVEM, lymphotoxin β receptor, 3/TR6, ILT3, ILT4, an agonist or antibody that binds Toll ligand receptor and a ligand that specifically binds with B7-H3. A co-stimulatory ligand also encompasses, inter alia, an antibody that specifically binds with a co-stimulatory molecule present on a T cell, such as but not limited to, CD27, CD28, 4-1BB, OX40, CD30, CD40, PD-1, ICOS, lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LTGHT, NKG2C, B7-H3, a ligand that specifically binds with CD83.

[0053] An "antibody" is an immunoglobulin molecule capable of specific binding to a target, such as a carbohydrate, polynucleotide, lipid, polypeptide, etc., through at least one antigen recognition site, located in the variable region of the immunoglobulin molecule. As used herein, the term encompasses not only intact polyclonal or monoclonal antibodies, but also fragments thereof (such as Fab, Fab', F(ab')₂, Fv), single chain (scFv) and domain antibodies (including, for example, shark and camelid antibodies), and fusion proteins comprising an antibody, and any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site. An antibody includes an antibody of any class, such as IgG, IgA, or IgM (or sub-class thereof), and the antibody need not be of any particular class. Depending on the antibody amino acid sequence of the constant region of its heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2. The heavy-chain constant regions that correspond to the different classes of immunoglobulins are called alpha, delta, epsilon, gamma, and mu, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

[0054] The term "antigen binding fragment" or "antigen binding portion" of an antibody, as used herein, refers to one or more fragments of an intact antibody that retain the ability to specifically bind to a given antigen (e.g., BCMA). Antigen binding functions of an antibody can be performed by fragments of an intact antibody. Examples of binding fragments encompassed within the term "antigen binding fragment" of an antibody include Fab; Fab'; F(ab')₂; an Fd fragment consisting of the VH and CH1 domains; an Fv fragment consisting of the VL and VH domains of a single arm of an antibody; a single domain antibody (dAb) fragment (Ward et al., Nature 341:544-546, 1989), and an isolated complementarity determining region (CDR).

[0055] An antibody, an antibody conjugate, or a polypeptide that "preferentially binds" or "specifically binds" (used interchangeably herein) to a target (e.g., BCMA protein) is a term well understood in the art, and methods to determine such specific or preferential binding are also well known in the art. A molecule is said to exhibit "specific binding" or "preferential binding" if it reacts or associates more frequently, more rapidly, with greater duration and/or with greater affinity with a particular cell or substance than it does with alternative cells or substances. An antibody "specifically binds" or "preferentially binds" to a target if it binds with greater affinity, avidity, more readily, and/or with greater duration than it binds to other substances. For example, an antibody that specifically or preferentially binds to a BCMA epitope is an antibody that binds this epitope with greater affinity, avidity, more readily, and/or with greater duration than it binds to other BCMA epitopes or non-BCMA epitopes. It is also understood that by reading this definition, for example, an antibody (or moiety or epitope) that specifically or preferentially binds to a first target may or may not specifically or preferentially bind to a second target. As such, "specific binding" or "preferential binding" does not necessarily require (although it can include) exclusive binding. Generally, but not necessarily, reference to binding means preferential binding.

[0056] A "variable region" of an antibody refers to the variable region of the antibody light chain or the variable region of the antibody heavy chain, either alone or in combination. As known in the art, the variable regions of the heavy and light chain each consist of four framework regions (FR) connected by three complementarity determining regions (CDRs) also known as hypervariable regions. The

CDRs in each chain are held together in close proximity by the FRs and, with the CDRs from the other chain, contribute to the formation of the antigen binding site of antibodies. There are at least two techniques for determining CDRs: (1) an approach based on cross-species sequence variability (i.e., Kabat et al. Sequences of Proteins of Immunological Interest, (5th ed., 1991, National Institutes of Health, Bethesda MD)); and (2) an approach based on crystallographic studies of antigen-antibody complexes (Al-lazikani et al., 1997, J. Molec. Biol. 273:927-948). As used herein, a CDR may refer to CDRs defined by either approach or by a combination of both approaches.

[0057] A "CDR" of a variable domain are amino acid residues within the variable region that are identified in accordance with the definitions of the Kabat, Chothia, the accumulation of both Kabat and Chothia, AbM, contact, and/or conformational definitions or any method of CDR determination well known in the art. Antibody CDRs may be identified as the hypervariable regions originally defined by Kabat et al. See, e.g., Kabat et al., 1992, Sequences of Proteins of Immunological Interest, 5th ed., Public Health Service, NIH, Washington D.C. The positions of the CDRs may also be identified as the structural loop structures originally described by Chothia and others. See, e.g., Chothia et al., Nature 342:877-883, 1989. Other approaches to CDR identification include the "AbM definition," which is a compromise between Kabat and Chothia and is derived using Oxford Molecular's AbM antibody modeling software (now Accelrys®), or the "contact definition" of CDRs based on observed antigen contacts, set forth in MacCallum et al., J. Mol. Biol., 262:732-745, 1996. In another approach, referred to herein as the "conformational definition" of CDRs, the positions of the CDRs may be identified as the residues that make enthalpic contributions to antigen binding. See, e.g., Makabe et al., Journal of Biological Chemistry, 283:1156-1166, 2008. Still other CDR boundary definitions may not strictly follow one of the above approaches, but will nonetheless overlap with at least a portion of the Kabat CDRs, although they may be shortened or lengthened in light of prediction or experimental findings that particular residues or groups of residues or even entire CDRs do not significantly impact antigen binding. As used herein, a CDR may refer to CDRs defined by any approach known in the art, including combinations of approaches. The methods used herein may utilize CDRs defined according to any of these approaches. For any given embodiment containing more than one CDR, the CDRs may be defined in accordance with any of Kabat, Chothia, extended, AbM, contact, and/or conformational definitions.

[0058] As used herein, "monoclonal antibody" refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to polyclonal antibody preparations, which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the disclosure may be made by the hybridoma method first described by Kohler and Milstein, Nature 256:495, 1975, or may be made by recombinant DNA methods such as described in U.S. Pat. No. 4,816,567. The monoclonal antibodies may also be isolated from phage libraries generated using the techniques described in McCafferty et al., Nature 348:552-554, 1990, for example.

[0059] As used herein, "humanized" antibody refers to forms of non-human (e.g. murine) antibodies that are chimeric immunoglobulins, immunoglobulin chains, or fragments thereof (such as Fv, Fab, Fab', F(ab')₂ or other antigen binding subsequences of antibodies) that contain minimal sequence derived from non-human immunoglobulin. Preferably, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementarity determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, the humanized antibody may comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences, but are included to further refine and optimize antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region or domain (Fc), typically that of a human immunoglobulin. Preferred are antibodies having Fc regions modified as described in WO 99/58572. Other forms of humanized antibodies have one or more CDRs (CDR L1, CDR L2, CDR L3, CDR H1, CDR H2, or CDR H3) which are altered with respect to the original antibody, which are also termed one or more CDRs "derived from" one or more CDRs from the original antibody.

[0060] As used herein, "human antibody" means an antibody having an amino acid sequence corresponding to that of an antibody produced by a human and/or which has been made using any of the techniques for making human antibodies known to those skilled in the art or disclosed herein. This definition of a human antibody includes antibodies comprising at least one human heavy chain polypeptide or at least one human light chain polypeptide. One such example is an antibody comprising murine light chain and human heavy chain polypeptides. Human antibodies can be produced using various techniques known in the art. In one example, the human antibody is selected from a phage library, where that phage library expresses human antibodies (Vaughan et al., Nature Biotechnology, 14:309-314, 1996; Sheets et al., Proc. Natl. Acad. Sci. (USA) 95:6157-6162, 1998; Hoogenboom and Winter, J. Mol. Biol., 227:381, 1991; Marks et al., J. Mol. Biol., 222:581, 1991). Human antibodies can also be made by immunization of animals into which human immunoglobulin loci have been transgenically introduced in place of the endogenous loci, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. This approach is described in U.S. Pat. Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and 5,661,016. Alternatively, the human antibody may be prepared by immortalizing human B lymphocytes that produce an antibody directed against a target antigen (such B lymphocytes may be recovered from an

individual or from single cell cloning of the cDNA, or may have been immunized *in vitro*). See, e.g., Cole et al. Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77, 1985; Boerner et al., J. Immunol., 147 (1):86-95, 1991; and U.S. Pat. No. 5,750,373.

[0061] The term "chimeric antibody" is intended to refer to antibodies in which the variable region sequences are derived from one species and the constant region sequences are derived from another species, such as an antibody in which the variable region sequences are derived from a mouse antibody and the constant region sequences are derived from a human antibody.

[0062] The terms "polypeptide", "oligopeptide", "peptide" and "protein" are used interchangeably herein to refer to chains of amino acids of any length, preferably, relatively short (e.g., 10-100 amino acids). The chain may be linear or branched, it may comprise modified amino acids, and/or may be interrupted by non-amino acids. The terms also encompass an amino acid chain that has been modified naturally or by intervention; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification, such as conjugation with a labeling component. Also included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), as well as other modifications known in the art. It is understood that the polypeptides can occur as single chains or associated chains.

[0063] A "monovalent antibody" comprises one antigen binding site per molecule (e.g., IgG or Fab). In some instances, a monovalent antibody can have more than one antigen binding sites, but the binding sites are from different antigens.

[0064] A "bivalent antibody" comprises two antigen binding sites per molecule (e.g., IgG). In some instances, the two binding sites have the same antigen specificities. However, bivalent antibodies may be bispecific.

[0065] A "bispecific," "dual-specific" or "bifunctional" antibody is a hybrid antibody having two different antigen binding sites. The two antigen binding sites of a bispecific antibody bind to two different epitopes, which may reside on the same or different protein targets.

[0066] Antibodies of the disclosure can be produced using techniques well known in the art, e.g., recombinant technologies, phage display technologies, synthetic technologies or combinations of such technologies or other technologies readily known in the art (see, for example, Jayasena, S.D., Clin. Chem., 45: 1628-50, 1999 and Fellouse, F.A., et al, J. Mol. Biol., 373(4):924-40, 2007).

[0067] As known in the art, "polynucleotide," or "nucleic acid," as used interchangeably herein, refer to chains of nucleotides of any length, and include DNA and RNA. The nucleotides can be deoxyribonucleotides, ribonucleotides, modified nucleotides or bases, and/or their analogs, or any substrate that can be incorporated into a chain by DNA or RNA polymerase. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and their analogs. If present, modification to the nucleotide structure may be imparted before or after assembly of the chain. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after polymerization, such as by conjugation with a labeling component. Other types of modifications include, for example, "caps", substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as, for example, those with uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoamidates, carbamates, etc.) and with charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.), those containing pendant moieties, such as, for example, proteins (e.g., nucleases, toxins, antibodies, signal peptides, poly-L-lysine, etc.), those with intercalators (e.g., acridine, psoralen, etc.), those containing chelators (e.g., metals, radioactive metals, boron, oxidative metals, etc.), those containing alkylators, those with modified linkages (e.g., alpha anomeric nucleic acids, etc.), as well as unmodified forms of the polynucleotide(s). Further, any of the hydroxyl groups ordinarily present in the sugars may be replaced, for example, by phosphonate groups, phosphate groups, protected by standard protecting groups, or activated to prepare additional linkages to additional nucleotides, or may be conjugated to solid supports. The 5' and 3' terminal OH can be phosphorylated or substituted with amines or organic capping group moieties of from 1 to 20 carbon atoms. Other hydroxyls may also be derivatized to standard protecting groups. Polynucleotides can also contain analogous forms of ribose or deoxyribose sugars that are generally known in the art, including, for example, 2'-O-methyl-, 2'-O-allyl, 2'-fluoro- or 2'-azido-ribose, carbocyclic sugar analogs, alpha- or beta-anomeric sugars, epimeric sugars such as arabinose, xyloses or lyxoses, pyranose sugars, furanose sugars, sedoheptuloses, acyclic analogs and abasic nucleoside analogs such as methyl riboside. One or more phosphodiester linkages may be replaced by alternative linking groups. These alternative linking groups include, but are not limited to, embodiments wherein phosphate is replaced by P(O)S("thioate"), P(S)S("dithioate"), (O)NR₂ ("amidate"), P(O)R, P(O)OR', CO or CH₂ ("formacetal"), in which each R or R' is independently H or substituted or unsubstituted alkyl (1-20 C) optionally containing an ether (-O-) linkage, aryl, alkenyl, cycloalkyl, cycloalkenyl or araldyl. Not all linkages in a polynucleotide need be identical. The preceding description applies to all polynucleotides referred to herein, including RNA and DNA.

[0068] As known in the art a "constant region" of an antibody refers to the constant region of the antibody light chain or the constant region of the antibody heavy chain, either alone or in combination.

[0069] As used herein, "substantially pure" refers to material which is at least 50% pure (i.e., free from contaminants), more preferably, at least 90% pure, more preferably, at least 95% pure, yet more preferably, at least 98% pure, and most preferably, at least 99% pure.

[0070] A "host cell" includes an individual cell or cell culture that can be or has been a recipient for vector(s) for incorporation of polynucleotide inserts. Host cells include progeny of a single host cell, and the progeny may not necessarily be completely identical (in

morphology or in genomic DNA complement) to the original parent cell due to natural, accidental, or deliberate mutation. A host cell includes cells transfected in vivo with a polynucleotide(s) of this invention.

[0071] As used herein, "immune cell" refers to a cell of hematopoietic origin functionally involved in the initiation and/or execution of innate and/or adaptative immune response.

[0072] As known in the art, the term "Fc region" is used to define a C-terminal region of an immunoglobulin heavy chain. The "Fc region" may be a native sequence Fc region or a variant Fc region. Although the boundaries of the Fc region of an immunoglobulin heavy chain might vary, the human IgG heavy chain Fc region is usually defined to stretch from an amino acid residue at position Cys226, or from Pro230, to the carboxyl-terminus thereof. The numbering of the residues in the Fc region is that of the EU index as in Kabat. Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991. The Fc region of an immunoglobulin generally comprises two constant regions, CH2 and CH3.

[0073] As used in the art, "Fc receptor" and "FcR" describe a receptor that binds to the Fc region of an antibody. The preferred FcR is a native sequence human FcR. Moreover, a preferred FcR is one which binds an IgG antibody (a gamma receptor) and includes receptors of the FcγRI, FcγRII, and FcγRIII subclasses, including allelic variants and alternatively spliced forms of these receptors. FcγRII receptors include FcγRIIA (an "activating receptor") and FcγRIIB (an "inhibiting receptor"), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. FcRs are reviewed in Ravetch and Kinet, Ann. Rev. Immunol., 9:457-92, 1991; Capel et al., Immunomethods, 4:25-34, 1994; and de Haas et al., J. Lab. Clin. Med., 126:330-41, 1995. "FcR" also includes the neonatal receptor, FcRn, which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al., J. Immunol., 117:587, 1976; and Kim et al., J. Immunol., 24:249, 1994).

[0074] The term "compete", as used herein with regard to an antibody, means that a first antibody, or an antigen binding fragment (or portion) thereof, binds to an epitope in a manner sufficiently similar to the binding of a second antibody, or an antigen binding portion thereof, such that the result of binding of the first antibody with its cognate epitope is detectably decreased in the presence of the second antibody compared to the binding of the first antibody in the absence of the second antibody. The alternative, where the binding of the second antibody to its epitope is also detectably decreased in the presence of the first antibody, can, but need not be the case. That is, a first antibody can inhibit the binding of a second antibody to its epitope without that second antibody inhibiting the binding of the first antibody to its respective epitope. However, where each antibody detectably inhibits the binding of the other antibody with its cognate epitope or ligand, whether to the same, greater, or lesser extent, the antibodies are said to "cross-compete" with each other for binding of their respective epitope(s). Both competing and cross-competing antibodies are encompassed by the disclosure. Regardless of the mechanism by which such competition or cross-competition occurs (e.g., steric hindrance, conformational change, or binding to a common epitope, or portion thereof), the skilled artisan would appreciate, based upon the teachings provided herein, that such competing and/or cross-competing antibodies are encompassed and can be useful for the methods disclosed herein.

[0075] As used herein "autologous" means that cells, a cell line, or population of cells used for treating patients are originating from said patient or from a Human Leucocyte Antigen (HLA) compatible donor.

[0076] As used herein "allogeneic" means that cells or population of cells used for treating patients are not originating from said patient but from a donor.

[0077] As used herein, "treatment" is an approach for obtaining beneficial or desired clinical results. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, one or more of the following: reducing the proliferation of (or destroying) neoplastic or cancerous cells, inhibiting metastasis of neoplastic cells, shrinking or decreasing the size of BCMA expressing tumor, remission of a BCMA associated disease (e.g., cancer), decreasing symptoms resulting from a BCMA associated disease (e.g., cancer), increasing the quality of life of those suffering from a BCMA associated disease (e.g., cancer), decreasing the dose of other medications required to treat a BCMA associated disease (e.g., cancer), delaying the progression of a BCMA associated disease (e.g., cancer), curing a BCMA associated disease (e.g., cancer), and/or prolong survival of patients having a BCMA associated disease (e.g., cancer).

[0078] "Ameliorating" means a lessening or improvement of one or more symptoms as compared to not administering a BCMA antibody or a BCMA antibody conjugate. "Ameliorating" also includes shortening or reduction in duration of a symptom.

[0079] As used herein, an "effective dosage" or "effective amount" of drug, compound, or pharmaceutical composition is an amount sufficient to effect any one or more beneficial or desired results. For prophylactic use, beneficial or desired results include eliminating or reducing the risk, lessening the severity, or delaying the outset of the disease, including biochemical, histological and/or behavioral symptoms of the disease, its complications and intermediate pathological phenotypes presenting during development of the disease. For therapeutic use, beneficial or desired results include clinical results such as reducing incidence or amelioration of one or more symptoms of various BCMA associated diseases or conditions (such as for example multiple myeloma), decreasing the dose of other medications required to treat the disease, enhancing the effect of another medication, and/or delaying the progression of the BCMA associated disease of patients. An effective dosage can be administered in one or more administrations. For purposes of this invention, an effective dosage of drug, compound, or pharmaceutical composition is an amount sufficient to accomplish prophylactic or therapeutic treatment either directly or indirectly. As is understood in the clinical context, an effective dosage of a drug, compound, or

pharmaceutical composition may or may not be achieved in conjunction with another drug, compound, or pharmaceutical composition. Thus, an "effective dosage" may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable result may be or is achieved.

[0080] An "individual" or a "subject" is a mammal, more preferably, a human. Mammals also include, but are not limited to, farm animals, sport animals, pets, primates, horses, dogs, cats, mice and rats.

[0081] As used herein, "vector" means a construct, which is capable of delivering, and, preferably, expressing, one or more gene(s) or sequence(s) of interest in a host cell. Examples of vectors include, but are not limited to, viral vectors, naked DNA or RNA expression vectors, plasmid, cosmid or phage vectors, DNA or RNA expression vectors associated with cationic condensing agents, DNA or RNA expression vectors encapsulated in liposomes, and certain eukaryotic cells, such as producer cells.

[0082] As used herein, "expression control sequence" means a nucleic acid sequence that directs transcription of a nucleic acid. An expression control sequence can be a promoter, such as a constitutive or an inducible promoter, or an enhancer. The expression control sequence is operably linked to the nucleic acid sequence to be transcribed.

[0083] As used herein, "pharmaceutically acceptable carrier" or "pharmaceutical acceptable excipient" includes any material which, when combined with an active ingredient, allows the ingredient to retain biological activity and is non-reactive with the subject's immune system. Examples include, but are not limited to, any of the standard pharmaceutical carriers such as a phosphate buffered saline solution, water, emulsions such as oil/water emulsion, and various types of wetting agents. Preferred diluents for aerosol or parenteral administration are phosphate buffered saline (PBS) or normal (0.9%) saline. Compositions comprising such carriers are formulated by well known conventional methods (see, for example, Remington's Pharmaceutical Sciences, 18th edition, A. Gennaro, ed., Mack Publishing Co., Easton, PA, 1990; and Remington, The Science and Practice of Pharmacy 21st Ed. Mack Publishing, 2005).

[0084] The term " k_{on} ", as used herein, refers to the rate constant for association of an antibody to an antigen.

[0085] The term " k_{off} ", as used herein, refers to the rate constant for dissociation of an antibody from the antibody/antigen complex.

[0086] The term " K_D ", as used herein, refers to the equilibrium dissociation constant of an antibody-antigen interaction.

[0087] Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to "about X" includes description of "X." Numeric ranges are inclusive of the numbers defining the range.

[0088] It is understood that wherever embodiments are described herein with the language "comprising," otherwise analogous embodiments described in terms of "consisting of" and/or "consisting essentially of" are also provided.

[0089] Where examples are described in terms of a Markush group or other grouping of alternatives, the disclosure encompasses not only the entire group listed as a whole, but each member of the group individually and all possible subgroups of the main group, but also the main group absent one or more of the group members. The disclosure also envisages the explicit exclusion of one or more of any of the group members.

[0090] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In case of conflict, the present specification, including definitions, will control. Throughout this specification and claims, the word "comprise," or variations such as "comprises" or "comprising" will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

[0091] Exemplary methods and materials are described herein, although methods and materials similar or equivalent to those described herein can also be used. The materials, methods, and examples are illustrative only.

BCMA specific CARs and Methods of Making Thereof

[0092] The invention provides CARs that bind to BCMA (e.g., human BCMA (e.g., SEQ ID NO: 354 or accession number: Q02223-2). BCMA specific CARs provided herein include single chain CARs and multichain CARs. The CARs have the ability to redirect T cell specificity and reactivity toward BCMA in a non-MHC-restricted manner, exploiting the antigen-binding properties of monoclonal antibodies. The non-MHC-restricted antigen recognition gives T cells expressing CARs the ability to recognize an antigen independent of antigen processing, thus bypassing a major mechanism of tumor escape.

[0093] In some embodiments, CARs provided herein comprise an extracellular ligand-binding domain (e.g., a single chain variable

fragment (scFv)), a transmembrane domain, and an intracellular signaling domain. In some embodiments, the extracellular ligand-binding domain, transmembrane domain, and intracellular signaling domain are in one polypeptide, i.e., in a single chain. Multichain CARs and polypeptides are also provided herein. In some embodiments, the multichain CARs comprise: a first polypeptide comprising a transmembrane domain and at least one extracellular ligand-binding domain, and a second polypeptide comprising a transmembrane domain and at least one intracellular signaling domain, wherein the polypeptides assemble together to form a multichain CAR.

[0094] In some embodiments, a BCMA specific multichain CAR is based on the high affinity receptor for IgE (FcεRI). The FcεRI expressed on mast cells and basophiles triggers allergic reactions. FcεRI is a tetrameric complex composed of a single α subunit, a single β subunit, and two disulfide-linked γ subunits. The α subunit contains the IgE-binding domain. The β and γ subunits contain ITAMs that mediate signal transduction. In some embodiments, the extracellular domain of the FcRα chain is deleted and replaced by a BCMA specific extracellular ligand-binding domain. In some embodiments, the multichain BCMA specific CAR comprises an scFv that binds specifically to BCMA, the CD8α hinge, and the ITAM of the FCRβ chain. In some embodiments, the CAR may or may not comprise the FcRγ chain.

[0095] In some embodiments, the extracellular ligand-binding domain comprises an scFv comprising the light chain variable (VL) region and the heavy chain variable (VH) region of a target antigen specific monoclonal antibody joined by a flexible linker. Single chain variable region fragments are made by linking light and/or heavy chain variable regions by using a short linking peptide (Bird et al., Science 242:423-426, 1988). An example of a linking peptide is the GS linker having the amino acid sequence (GGGGS)₃ (SEQ ID NO: 333), which bridges approximately 3.5 nm between the carboxy terminus of one variable region and the amino terminus of the other variable region. Linkers of other sequences have been designed and used (Bird et al., 1988, supra). In general, linkers can be short, flexible polypeptides and preferably comprised of about 20 or fewer amino acid residues. Linkers can in turn be modified for additional functions, such as attachment of drugs or attachment to solid supports. The single chain variants can be produced either recombinantly or synthetically. For synthetic production of scFv, an automated synthesizer can be used. For recombinant production of scFv, a suitable plasmid containing polynucleotide that encodes the scFv can be introduced into a suitable host cell, either eukaryotic, such as yeast, plant, insect or mammalian cells, or prokaryotic, such as E. coli. Polynucleotides encoding the scFv of interest can be made by routine manipulations such as ligation of polynucleotides. The resultant scFv can be isolated using standard protein purification techniques known in the art.

[0096] In some examples, the extracellular ligand-binding domain comprises (a) a VH region comprising (i) a VH complementarity determining region one (CDR1) comprising the sequence SYX₁MX₂, wherein X₁ is A or P; and X₂ is T, N, or S (SEQ ID NO: 301), GFTFX₁SY, wherein X₁ is G or S (SEQ ID NO: 302), or GFTFX₁SYX₂MX₃, wherein X₁ is G or S, X₂ is A or P; and X₃ is T, N, or S (SEQ ID NO: 303); (ii) a VH CDR2 comprising the sequence AX₁X₂X₃X₄GX₅X₆X₇X₈YADX₉X₁₀KG, wherein X₁ is I, V, T, H, L, A, or C; X₂ is S, D, G, T, I, L, F, M, or V; X₃ is G, Y, L, H, D, A, S, or M; X₄ is S, Q, T, A, F, or W; X₅ is G or T; X₆ is N, S, P, Y, W, or F; X₇ is S, T, I, L, T, A, R, V, K, G, or C; X₈ is F, Y, P, W, H, or G; X₉ is V, R, or L; and X₁₀ is G or T (SEQ ID NO: 305), or X₁X₂X₃X₄X₅X₆, wherein X₁ is S, V, I, D, G, T, L, F, or M; X₂ is G, Y, L, H, D, A, S, or M; X₃ is S, G, F, or W; X₄ is G or S; X₅ is G or T; and X₆ is N, S, P, Y, or W (SEQ ID NO: 306); and (iii) a VH CDR3 comprising the sequence VSPIX₁X₂X₃X₄, wherein X₁ is A or Y; X₂ is A or S; and X₃ is G, Q, L, P, or E (SEQ ID NO: 307), or YWPMX₁X₂, wherein X₁ is D, S, T, or A; and X₂ is I, S, L, P, or D (SEQ ID NO: 308); and a VL region comprising (i) a VL CDR1 comprising the sequence X₁X₂X₃X₄X₅X₆X₇X₈X₉X₁₀X₁₁X₁₂, wherein X₁ is R, G, W, A, or C; X₂ is A, P, G, L, C, or S; X₃ is S, G, or R; X₄ is Q, C, E, V, or I; X₅ is S, L, P, G, A, R, or D; X₆ is V, G, or I; X₇ is S, E, D, or P; X₈ is S, P, F, A, M, E, V, N, D, or Y; X₉ is I, T, V, E, S, A, M, Q, Y, H, or R; X₁₀ is Y or F; X₁₁ is L, W, or P; and X₁₂ is A, S, or G (SEQ ID NO: 309); (ii) a VL CDR2 comprising the sequence X₁ASX₂RAX₃, wherein X₁ is G or D; X₂ is S or I; and X₃ is T or P (SEQ ID NO: 310); and (iii) a VL CDR3 comprising the sequence QQYX₁X₂X₃PX₄T, wherein X₁ is G, Q, E, L, F, A, S, M, K, R, or Y; X₂ is S, R, T, G, V, F, Y, D, A, H, V, E, K, or C; X₃ is W, F, or S; and X₄ is L or I (SEQ ID NO: 311), or QQYX₁X₂X₃PX₄, wherein X₁ is G, Q, E, L, F, A, S, M, R, K, or Y; X₂ is S, R, T, G, R, V, D, A, H, E, K, C, F, or Y; X₃ is W, S, or F; and X₄ is L or I (SEQ ID NO: 312). In some embodiments, the VH and VL are linked together by a flexible linker. In some embodiments a flexible linker comprises the amino acid sequence shown in SEQ ID NO: 333.

[0097] In another aspect, provided is CAR, which specifically binds to BCMA, wherein the CAR comprises an extracellular ligand-binding domain comprising: a VH region comprising a VH CDR1, VH CDR2, and VH CDR3 of the VH sequence shown in SEQ ID NO: 2, 3, 7, 8, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 35, 37, 39, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 83, 87, 92, 78, 95, 97, 99, 101, 104, 106, 110, 112, 114, 76, 118, 120, 122, 112, 125, 127, 313, or 314; and/or a VL region comprising VL CDR1, VL CDR2, and VL CDR3 of the VL sequence shown in SEQ ID NO: 1, 4, 5, 6, 9, 10, 11, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 34, 36, 38, 40, 41, 43, 45, 47, 49, 51, 53, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 317, 81, 82, 84, 85, 86, 88, 89, 90, 91, 93, 94, 96, 98, 100, 102, 103, 105, 107, 108, 109, 111, 113, 115, 116, 117, 119, 121, 123, 124, 126, 128, 315, or 316. In some embodiments, the VH and VL are linked together by a flexible linker. In some embodiments a flexible linker comprises the amino acid sequence shown in SEQ ID NO: 333.

[0098] In some example, a CAR of the disclosure comprises an extracellular ligand-binding domain having any one of partial light chain sequence as listed in Table 1 and/or any one of partial heavy chain sequence as listed in Table 1. In Table 1, the underlined sequences are CDR sequences according to Kabat and in bold according to Chothia, except for the heavy chain CDR2 sequences, the Chothia

CDR sequence is underlined and the Kabat CDR sequence is in bold.

Table 1

mAb	Light Chain	Heavy Chain
P6E01/P6E01	EIVLTQSPGTL ^S SLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYGSPPSFT</u> FGQGTKVEIK (SEQ ID NO: 1)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>ISGSGGNT</u> <u>FYADSVKGR</u> FTISRDN ^S SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGT ^L VT VSS (SEQ ID NO: 2)
P6E01/H3.AQ	EIVLTQSPGTL ^S SLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYGSPPSFT</u> FGQGTKVEIK (SEQ ID NO: 1)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>ISGSGGNT</u> <u>FYADSVKGR</u> FTISRDN ^S SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIAAQMDY</u> WGQGT ^L VT VSS (SEQ ID NO: 3)
L1.LGF/L3.KW/P6E01	EIVLTQSPGTL ^S SLSPGERATLSC <u>RASQSLGSFYLA</u> WYQQKPGQAPRLLIY <u>G</u> <u>ASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC EDFAVYYC <u>KHYGWPPSFT</u> FGQGTKVEIK (SEQ ID NO: 4)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>ISGSGGNT</u> <u>FYADSVKGR</u> FTISRDN ^S SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGT ^L VT VSS (SEQ ID NO: 2)
L1.LGF/L3.NY/P6E01	EIVLTQSPGTL ^S SLSPGERATLSC <u>RASQSLG</u> <u>SFYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYNYPSPST</u> FGQGTKVEIK (SEQ ID NO: 5)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>ISGSGGNT</u> <u>FYADSVKGR</u> FTISRDN ^S SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGT ^L VT VSS (SEQ ID NO: 2)
L1.GDF/L3.NY/P6E01	EIVLTQSPGTL ^S SLSPGERATLSC <u>RASQSVG</u>	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u>
	<u>DFYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> G IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYNYPSPST</u> FGQGTKVEIK (SEQ ID NO: 6)	<u>SYAMT</u> WVRQAPGKGLEWVSAI <u>ISGSGGNT</u> <u>FYADSVKGR</u> FTISRDN ^S SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGT ^L VT VSS (SEQ ID NO: 2)
L1.LGF/L3.KW/H3.AL	EIVLTQSPGTL ^S SLSPGERATLSC <u>RASQSLG</u> <u>SFYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>KHYGWPPSFT</u> FGQGTKVEIK (SEQ ID NO: 4)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>ISGSGGNT</u> <u>FYADSVKGR</u> FTISRDN ^S SKNTLYLQMNSLRA EDTAVYYCAR <u>ARVSPIAALMDY</u> WGQGT ^L VT VSS (SEQ ID NO: 7)
L1.LGF/L3.KW/H3.AP	EIVLTQSPGTL ^S SLSPGERATLSC <u>RASQSLG</u> <u>SFYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>KHYGWPPSFT</u> FGQGTKVEIK (SEQ ID NO: 4)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>ISGSGGNT</u> <u>FYADSVKGR</u> FTISRDN ^S SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIAAPMDY</u> WGQGT ^L VT VSS (SEQ ID NO: 8)
L1.LGF/ L3.KW/ H3.AQ	EIVLTQSPGTL ^S SLSPGERATLSC <u>RASQSLG</u> <u>SFYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>KHYGWPPSFT</u> FGQGTKVEIK (SEQ ID	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>ISGSGGNT</u> <u>FYADSVKGR</u> FTISRDN ^S SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIAAQMDY</u> WGQGT ^L VT

mAb	Light Chain	Heavy Chain
	NO: 4)	VSS (SEQ ID NO: 3)
L1.LGF/ L3.PY/H 3.AP	EIVLTQSPGTLSSLSPGERATLSC <u>RASQSLG</u> <u>SFYLA</u> WYQQKPGQAPRLLIY <u>GASSRATGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSFT</u> FGQGTKVEIK (SEQ ID NO: 9)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIAAPMDY</u> WGQGTLTVT VSS (SEQ ID NO: 8)
L1.LGF/ L3.PY/H 3.AQ	EIVLTQSPGTLSSLSPGERATLSC <u>RASQSLG</u> <u>SFYLA</u> WYQQKPGQAPRLLIY <u>GASSRATGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSFT</u> FGQGTKVEIK (SEQ ID NO: 9)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIAAQMDY</u> WGQGTLTVT
	NO: 9)	VSS (SEQ ID NO: 3)
L1.LGF/L3.NY/H3.AL	EIVLTQSPGTLSSLSPGERATLSC <u>RASQSLG</u> <u>SFYLA</u> WYQQKPGQAPRLLIY <u>GASSRATGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYNYPSPFT</u> FGQGTKVEIK (SEQ ID NO: 10)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIAALMDY</u> WGQGTLTVT VSS (SEQ ID NO: 7)
L1.LGF/L3.NY/H3.AP	EIVLTQSPGTLSSLSPGERATLSC <u>RASQSLG</u> <u>SFYLA</u> WYQQKPGQAPRLLIY <u>GASSRATGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYNYPSPFT</u> FGQGTKVEIK (SEQ ID NO: 10)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIAAPMDY</u> WGQGTLTVT VSS (SEQ ID NO: 8)
L1.LGF/L3.NY/H3.AQ	EIVLTQSPGTLSSLSPGERATLSC <u>RASQSLG</u> <u>SFYLA</u> WYQQKPGQAPRLLIY <u>GASSRATGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYNYPSPFT</u> FGQGTKVEIK (SEQ ID NO: 10)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIAAQMDY</u> WGQGTLTVT VSS (SEQ ID NO: 3)
L1.GDF/L3.KW/H3.AL	EIVLTQSPGTLSSLSPGERATLSC <u>RASQSVG</u> <u>DFYLA</u> WYQQKPGQAPRLLIY <u>GASSRATG</u> IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>KHYGWPPSFT</u> FGQGTKVEIK (SEQ ID NO: 11)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIAALMDY</u> WGQGTLTVT VSS (SEQ ID NO: 7)
L1.GDF/L3.KW/H3.AP	EIVLTQSPGTLSSLSPGERATLSC <u>RASQSVG</u> <u>DFYLA</u> WYQQKPGQAPRLLIY <u>GASSRATG</u> IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>KHYGWPPSFT</u> FGQGTKVEIK (SEQ ID NO: 11)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIAAPMDY</u> WGQGTLTVT VSS (SEQ ID NO: 8)
L1.GDF/L3.KW/H3.AQ	EIVLTQSPGTLSSLSPGERATLSC <u>RASQSVG</u> <u>DFYLA</u> WYQQKPGQAPRLLIY <u>GASSRATG</u> IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA

mAb	Light Chain	Heavy Chain
	<u>KHYGWPPSFT</u> FGQGTKVEIK (SEQ ID NO: 11)	EDTAVYYCAR <u>VSPIAAQMDY</u> WGQGTLT VSS (SEQ ID NO: 3)
L1.GDF/L3.PY/H3.AQ	EIVLTQSPGTLSLSPGERATLSC <u>RASQSVG</u> <u>DFYLA</u> WYQQKPGQAPRLLIY <u>GASSRATG</u> IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSFT</u> FGQGTKVEIK (SEQ ID NO: 12)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> FYADSVKGRFTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIAAQMDY</u> WGQGTLT VSS (SEQ ID NO: 3)
L1.GDF/L3.NY/H3.AL	EIVLTQSPGTLSLSPGERATLSC <u>RASQSVG</u> <u>DFYLA</u> WYQQKPGQAPRLLIY <u>GASSRATG</u> IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYNYP SFT</u> FGQGTKVEIK (SEQ ID NO: 13)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> FYADSVKGRFTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIAALMDY</u> WGQGTLT VSS (SEQ ID NO: 7)
L1.GDF/L3.NY/H3.AP	EIVLTQSPGTLSLSPGERATLSC <u>RASQSVG</u> <u>DFYLA</u> WYQQKPGQAPRLLIY <u>GASSRATG</u> IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYNYP SFT</u> FGQGTKVEIK (SEQ ID NO: 13)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> FYADSVKGRFTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIAAPMDY</u> WGQGTLT VSS (SEQ ID NO: 8)
L1.GDF/L3.NY/H3.AQ	EIVLTQSPGTLSLSPGERATLSC <u>RASQSVG</u> <u>DFYLA</u> WYQQKPGQAPRLLIY <u>GASSRATG</u> IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYNYP SFT</u> FGQGTKVEIK (SEQ ID NO: 14)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> FYADSVKGRFTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIAAQMDY</u> WGQGTLT VSS (SEQ ID NO: 3)
L3.KW/P6E01	EIVLTQSPGTLSLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRATGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>KHYGWPPSFT</u> FGQGTKVEIK (SEQ ID NO: 15)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> FYADSVKGRFTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGTLT VSS (SEQ ID NO: 2)
L3.PY/P6E01	EIVLTQSPGTLSLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRATGI</u>	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u>
	PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSFT</u> FGQGTKVEIK (SEQ ID NO: 16)	FYADSVKGRFTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGTLT VSS (SEQ ID NO: 2)
L3.NY/P6E01	EIVLTQSPGTLSLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRATGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYNYP SFT</u> FGQGTKVEIK (SEQ ID NO: 17)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> FYADSVKGRFTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGTLT VSS (SEQ ID NO: 2)
L3.PY/L1.PS/P6E01	EIVLTQSPGTLSLSPGERATLSC <u>RASQSVS</u> <u>SSYP S</u> WYQQKPGQAPRLLIY <u>GASSRATGI</u>	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u>

mAb	Light Chain	Heavy Chain
	PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 18)	<u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGLVT VSS (SEQ ID NO: 2)
L3.PY/L 1.AH/P6E01	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>AHYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> G IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGLVT VSS (SEQ ID NO: 2)
L3.PY/L 1.FF/P6 E01	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SFFLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGLVT VSS (SEQ ID NO: 2)
L3.PY/L 1.PH/P 6E01	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>PHYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> G IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 21)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGLVT VSS (SEQ ID NO: 2)
L3.PY/L3.KY/P6E01	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u>	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u>
	<u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>KYYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 22)	<u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGLVT VSS (SEQ ID NO: 2)
L3.PY/L3.KF/P6E01	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>KFYPPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 23)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGLVT VSS (SEQ ID NO: 2)
L3.PY/H2.QR	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADQRKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGLVT VSS (SEQ ID NO: 24)
L3.PY/H2.DY	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>IDYSGGN</u> <u>TFYADSVKGR</u> FTISRDN SKNTLYLQMNSLR AEDTAVYYCAR <u>VSPIASGMDY</u> WGQGLTV TVSS (SEQ ID NO: 25)
L3.PY/H2.YQ	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SYQGGN</u>

mAb	Light Chain	Heavy Chain
	PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 16)	<u>TFYADSVKGR</u> FTISRDN SKNTLYLQMNSLR AEDTAVYYCAR <u>VSPIASGMDY</u> WGQGLTV TVSS (SEQ ID NO: 26)
L3.PY/H2.LT	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SLTGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGLTV VSS (SEQ ID NO: 27)
L3.PY/H2.HA	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SHAGGN</u> <u>TFYADSVKGR</u> FTISRDN SKNTLYLQMNSLR AEDTAVYYCAR <u>VSPIASGMDY</u> WGQGLTV TVSS (SEQ ID NO: 28)
L3.PY/H2.QL	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADQLKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGLTV VSS (SEQ ID NO: 29)
L3.PY/H3.YA	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIAAGMDY</u> WGQGLTV VSS (SEQ ID NO: 30)
L3.PY/H3.AE	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIAAEMDY</u> WGQGLTV VSS (SEQ ID NO: 31)
L3.PY/H3.AQ	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIAAQMDY</u> WGQGLTV VSS (SEQ ID NO: 3)
L3.PY/H3.TAQ	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCTR <u>VSPIAAQMDY</u> WGQGLTV
	NO: 16)	VSS (SEQ ID NO: 32)
L3.PY/P6E01	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u>

mAb	Light Chain	Heavy Chain
	PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSFT</u>FGQGTKVEIK (SEQ ID NO: 16)	FYADSVKGRFTISRDN SKNTLYLQMNSLRA EDTAVYYCAR<u>VSPIASGMDY</u>WGQGT LVT VSS (SEQ ID NO: 2)
L3.PY/L1.PS/H2.QR	EIVLTQSPGTLSPGERATLSC<u>RASQSVS</u> <u>SSYP</u>SWYQQKPGQAPRLLIY<u>GASSRAT</u>GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSFT</u>FGQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCAAS<u>GFTFG</u> <u>SYAM</u>TWVRQAPGKGLEWVSAI<u>SGSGGNT</u> FYADQRKGRFTISRDN SKNTLYLQMNSLRA EDTAVYYCAR<u>VSPIASGMDY</u>WGQGT LVT VSS (SEQ ID NO: 24)
L3.PY/L1.PS/H2.DY	EIVLTQSPGTLSPGERATLSC<u>RASQSVS</u> <u>SSYP</u>SWYQQKPGQAPRLLIY<u>GASSRAT</u>GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSFT</u>FGQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCAAS<u>GFTFG</u> <u>SYAM</u>TWVRQAPGKGLEWVSAI<u>DYSGGNT</u> FYADSVKGRFTISRDN SKNTLYLQMNSLRA EDTAVYYCAR<u>VSPIASGMDY</u>WGQGT LVT VSS (SEQ ID NO: 25)
L3.PY/L1.PS/H2.YQ	EIVLTQSPGTLSPGERATLSC<u>RASQSVS</u> <u>SSYP</u>SWYQQKPGQAPRLLIY<u>GASSRAT</u>GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSFT</u>FGQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCAAS<u>GFTFG</u> <u>SYAM</u>TWVRQAPGKGLEWVSAI<u>SYQGGN</u> TFYADSVKGRFTISRDN SKNTLYLQMNSLR AEDTAVYYCAR<u>VSPIASGMDY</u>WGQGT LV TVSS (SEQ ID NO: 26)
L3.PY/L1.PS/H2.LT	EIVLTQSPGTLSPGERATLSC<u>RASQSVS</u> <u>SSYP</u>SWYQQKPGQAPRLLIY<u>GASSRAT</u>GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSFT</u>FGQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCAAS<u>GFTFG</u> <u>SYAM</u>TWVRQAPGKGLEWVSAI<u>SLTGGNT</u> FYADSVKGRFTISRDN SKNTLYLQMNSLRA EDTAVYYCAR<u>VSPIASGMDY</u>WGQGT LVT VSS (SEQ ID NO: 27)
L3.PY/L1.PS/H2.HA	EIVLTQSPGTLSPGERATLSC<u>RASQSVS</u> <u>SSYP</u>SWYQQKPGQAPRLLIY<u>GASSRAT</u>GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSFT</u>FGQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCAAS<u>GFTFG</u> <u>SYAM</u>TWVRQAPGKGLEWVSAI<u>SHAGGN</u> TFYADSVKGRFTISRDN SKNTLYLQMNSLR AEDTAVYYCAR<u>VSPIASGMDY</u>WGQGT LV TVSS (SEQ ID NO: 28)
L3.PY/L1.PS/H2.QL	EIVLTQSPGTLSPGERATLSC<u>RASQSVS</u> <u>SSYP</u>SWYQQKPGQAPRLLIY<u>GASSRAT</u>GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSFT</u>FGQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCAAS<u>GFTFG</u> <u>SYAM</u>TWVRQAPGKGLEWVSAI<u>SGSGGNT</u> FYADQLKGRFTISRDN SKNTLYLQMNSLRA EDTAVYYCAR<u>VSPIASGMDY</u>WGQGT LVT VSS (SEQ ID NO: 29)
L3.PY/L1.PS/H3.YA	EIVLTQSPGTLSPGERATLSC<u>RASQSVS</u> <u>SSYP</u>SWYQQKPGQAPRLLIY<u>GASSRAT</u>GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSFT</u>FGQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCAAS<u>GFTFG</u> <u>SYAM</u>TWVRQAPGKGLEWVSAI<u>SGSGGNT</u> FYADSVKGRFTISRDN SKNTLYLQMNSLRA EDTAVYYCAR<u>VSPIYAGMDY</u>WGQGT LVT VSS (SEQ ID NO: 30)
L3.PY/L1.PS/H3.AE	EIVLTQSPGTLSPGERATLSC<u>RASQSVS</u> <u>SSYP</u>SWYQQKPGQAPRLLIY<u>GASSRAT</u>GI	EVQLLESGGGLVQPGGSLRLSCAAS<u>GFTFG</u> <u>SYAM</u>TWVRQAPGKGLEWVSAI<u>SGSGGNT</u>

mAb	Light Chain	Heavy Chain
	PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u>TFGQGTKVEIK (SEQ ID NO: 18)	<u>FYADSVKGR</u>FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR<u>VSPIAAEMDY</u>WGQGLVT VSS (SEQ ID NO: 31)
L3.PY/L1.PS/H3.AQ	EIVLTQSPGTLSPGERATLSC<u>RASQSVS</u> <u>SSYP</u>SWYQQKPGQAPRLLIY<u>GASSRATG</u>I PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u>TFGQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLS CAAS<u>GFTFG</u> <u>SYAMT</u>WVRQAPGKGLEWVSAI<u>SGSGGNT</u> <u>FYADSVKGR</u>FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR<u>VSPIAAQMDY</u>WGQGLVT VSS (SEQ ID NO: 3)
L3.PY/L1.PS/H3.TAQ	EIVLTQSPGTLSPGERATLSC<u>RASQSVS</u> <u>SSYP</u>SWYQQKPGQAPRLLIY<u>GASSRATG</u>I PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u>TFGQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLS CAAS<u>GFTFG</u> <u>SYAMT</u>WVRQAPGKGLEWVSAI<u>SGSGGNT</u> <u>FYADSVKGR</u>FTISRDN SKNTLYLQMNSLRA EDTAVYYCTR<u>VSPIAAQMDY</u>WGQGLVT VSS (SEQ ID NO: 32)
L3.PY/L1.AH/H2.QR	EIVLTQSPGTLSPGERATLSC<u>RASQSVS</u> <u>AHYLA</u>WYQQKPGQAPRLLIY<u>GASSRATG</u>	EVQLLESGGGLVQPGGSLRLS CAAS<u>GFTFG</u> <u>SYAMT</u>WVRQAPGKGLEWVSAI<u>SGSGGNT</u>
	IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u>TFGQGTKVEIK (SEQ ID NO: 19)	<u>FYADQRKGR</u>FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR<u>VSPIASGMDY</u>WGQGLVT VSS (SEQ ID NO: 24)
L3.PY/L1.AH/H2.DY	EIVLTQSPGTLSPGERATLSC<u>RASQSVS</u> <u>AHYLA</u>WYQQKPGQAPRLLIY<u>GASSRATG</u> IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u>TFGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLS CAAS<u>GFTFG</u> <u>SYAMT</u>WVRQAPGKGLEWVSAI<u>DYSGGNT</u> <u>FYADSVKGR</u>FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR<u>VSPIASGMDY</u>WGQGLVT VSS (SEQ ID NO: 25)
L3.PY/L1.AH/H2.YQ	EIVLTQSPGTLSPGERATLSC<u>RASQSVS</u> <u>AHYLA</u>WYQQKPGQAPRLLIY<u>GASSRATG</u> IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u>TFGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLS CAAS<u>GFTFG</u> <u>SYAMT</u>WVRQAPGKGLEWVSAI<u>SYQGGN</u> <u>TFYADSVKGR</u>FTISRDN SKNTLYLQMNSLR AEDTAVYYCAR<u>VSPIASGMDY</u>WGQGLV TVSS (SEQ ID NO: 26)
L3.PY/L1.AH/H2.LT	EIVLTQSPGTLSPGERATLSC<u>RASQSVS</u> <u>AHYLA</u>WYQQKPGQAPRLLIY<u>GASSRATG</u> IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u>TFGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLS CAAS<u>GFTFG</u> <u>SYAMT</u>WVRQAPGKGLEWVSAI<u>SLTGNT</u> <u>FYADSVKGR</u>FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR<u>VSPIASGMDY</u>WGQGLVT VSS (SEQ ID NO: 27)
L3.PY/L1.AH/H2.HA	EIVLTQSPGTLSPGERATLSC<u>RASQSVS</u> <u>AHYLA</u>WYQQKPGQAPRLLIY<u>GASSRATG</u> IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u>TFGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLS CAAS<u>GFTFG</u> <u>SYAMT</u>WVRQAPGKGLEWVSAI<u>SHAGGN</u> <u>TFYADSVKGR</u>FTISRDN SKNTLYLQMNSLR AEDTAVYYCAR<u>VSPIASGMDY</u>WGQGLV TVSS (SEQ ID NO: 28)
L3.PY/L1.AH/H2.QL	EIVLTQSPGTLSPGERATLSC<u>RASQSVS</u> <u>AHYLA</u>WYQQKPGQAPRLLIY<u>GASSRATG</u>	EVQLLESGGGLVQPGGSLRLS CAAS<u>GFTFG</u> <u>SYAMT</u>WVRQAPGKGLEWVSAI<u>SGSGGNT</u>

mAb	Light Chain	Heavy Chain
	IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSFT</u> FGQGTKVEIK (SEQ ID NO: 19)	<u>FYADQLKGRFTISRDNSKNTLYLQMNSLRA</u> EDTAVYYCAR <u>VSPIASGMDY</u> WGQGTLT VSS (SEQ ID NO: 29)
L3.PY/L1.AH/H3.YA	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u>	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u>
	<u>AHYLA</u> WYQQKPGQAPRLLIY <u>GASSRATG</u> IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSFT</u> FGQGTKVEIK (SEQ ID NO: 19)	<u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGRFTISRDNSKNTLYLQMNSLRA</u> EDTAVYYCAR <u>VSPIYAGMDY</u> WGQGTLT VSS (SEQ ID NO: 30)
L3.PY/L1.AH/H3.AE	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>AHYLA</u> WYQQKPGQAPRLLIY <u>GASSRATG</u> IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSFT</u> FGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGRFTISRDNSKNTLYLQMNSLRA</u> EDTAVYYCAR <u>VSPIAAEMDY</u> WGQGTLT VSS (SEQ ID NO: 31)
L3.PY/L1.AH/H3.AQ	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>AHYLA</u> WYQQKPGQAPRLLIY <u>GASSRATG</u> IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSFT</u> FGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGRFTISRDNSKNTLYLQMNSLRA</u> EDTAVYYCAR <u>VSPIAAQMDY</u> WGQGTLT VSS (SEQ ID NO: 3)
L3.PY/L1.AH/H3.TAQ	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>AHYLA</u> WYQQKPGQAPRLLIY <u>GASSRATG</u> IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSFT</u> FGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGRFTISRDNSKNTLYLQMNSLRA</u> EDTAVYYCTR <u>VSPIAAQMDY</u> WGQGTLT VSS (SEQ ID NO: 32)
L3.PY/L1.FF/H2.QR	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SFFLA</u> WYQQKPGQAPRLLIY <u>GASSRATGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSFT</u> FGQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADQRKGRFTISRDNSKNTLYLQMNSLRA</u> EDTAVYYCAR <u>VSPIASGMDY</u> WGQGTLT VSS (SEQ ID NO: 24)
L3.PY/L1.FF/H2.DY	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SFFLA</u> WYQQKPGQAPRLLIY <u>GASSRATGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSFT</u> FGQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAIDYSGGNT <u>FYADSVKGRFTISRDNSKNTLYLQMNSLRA</u> EDTAVYYCAR <u>VSPIASGMDY</u> WGQGTLT
		VSS (SEQ ID NO: 25)
L3.PY/L1.FF/H2.YQ	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SFFLA</u> WYQQKPGQAPRLLIY <u>GASSRATGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSFT</u> FGQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SYQGGN</u> <u>TFYADSVKGRFTISRDNSKNTLYLQMNSLR</u> AEDTAVYYCAR <u>VSPIASGMDY</u> WGQGTLV TVSS (SEQ ID NO: 26)

mAb	Light Chain	Heavy Chain
L3.PY/L1.FF/H2.LT	EIVLTQSPGTL ~~SL~~ SPGERATLSC <u>RASQSVS</u> <u>SFFLA</u> WYQQKPGQAPRLLIY <u>GASSRATGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SLTGGNT</u> FYADSVKGRFTISRDN ~~SKNTLYLQ~~ MNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGT ~~LV~~ T VSS (SEQ ID NO: 27)
L3.PY/L1.FF/H2.HA	EIVLTQSPGTL ~~SL~~ SPGERATLSC <u>RASQSVS</u> <u>SFFLA</u> WYQQKPGQAPRLLIY <u>GASSRATGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SHAGGN</u> <u>TFYADSVKGRFTISRDN</u> SKNTLYLQMN ~~SLR~~ AEDTAVYYCAR <u>VSPIASGMDY</u> WGQGT ~~LV~~ T TVSS (SEQ ID NO: 28)
L3.PY/L1.FF/H2.QL	EIVLTQSPGTL ~~SL~~ SPGERATLSC <u>RASQSVS</u> <u>SFFLA</u> WYQQKPGQAPRLLIY <u>GASSRATGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADQLKGRFTISRDN</u> SKNTLYLQMN ~~SLR~~ EDTAVYYCAR <u>VSPIASGMDY</u> WGQGT ~~LV~~ T VSS (SEQ ID NO: 29)
L3.PY/L1.FF/H3.YA	EIVLTQSPGTL ~~SL~~ SPGERATLSC <u>RASQSVS</u> <u>SFFLA</u> WYQQKPGQAPRLLIY <u>GASSRATGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGRFTISRDN</u> SKNTLYLQMN ~~SLR~~ EDTAVYYCAR <u>VSPIYAGMDY</u> WGQGT ~~LV~~ T VSS (SEQ ID NO: 30)
L3.PY/L1.FF/H3.AE	EIVLTQSPGTL ~~SL~~ SPGERATLSC <u>RASQSVS</u> <u>SFFLA</u> WYQQKPGQAPRLLIY <u>GASSRATGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGRFTISRDN</u> SKNTLYLQMN ~~SLR~~
	<u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 20)	EDTAVYYCAR <u>VSPIAAEMDY</u> WGQGT ~~LV~~ T VSS (SEQ ID NO: 31)
L3.PY/L1.FF/H3.AQ	EIVLTQSPGTL ~~SL~~ SPGERATLSC <u>RASQSVS</u> <u>SFFLA</u> WYQQKPGQAPRLLIY <u>GASSRATGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGRFTISRDN</u> SKNTLYLQMN ~~SLR~~ EDTAVYYCAR <u>VSPIAAQMDY</u> WGQGT ~~LV~~ T VSS (SEQ ID NO: 3)
L3.PY/L1.FF/H3.TAQ	EIVLTQSPGTL ~~SL~~ SPGERATLSC <u>RASQSVS</u> <u>SFFLA</u> WYQQKPGQAPRLLIY <u>GASSRATGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGRFTISRDN</u> SKNTLYLQMN ~~SLR~~ EDTAVYYCTR <u>VSPIAAQMDY</u> WGQGT ~~LV~~ T VSS (SEQ ID NO: 32)
L3.PY/L1.PH/H2.QR	EIVLTQSPGTL ~~SL~~ SPGERATLSC <u>RASQSVS</u> <u>PHYLA</u> WYQQKPGQAPRLLIY <u>GASSRATG</u> IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 21)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADQRKGRFTISRDN</u> SKNTLYLQMN ~~SLR~~ EDTAVYYCAR <u>VSPIASGMDY</u> WGQGT ~~LV~~ T VSS (SEQ ID NO: 24)

mAb	Light Chain	Heavy Chain
L3.PY/L1.PH/H2.HA	EIVLTQSPGTL ^S SLSPGERATLSC <u>RASQSVS</u> <u>PHYLA</u> WYQQKPGQAPRLLIY <u>GASSRATG</u> IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 21)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SHAGGN</u> <u>TFYADSVKGR</u> FTISRDN ^S SKNTLYLQMNSLR AEDTAVYYCAR <u>VSPIASGMDY</u> WGQGLTV TVSS (SEQ ID NO: 28)
L3.PY/L1.PH/H3.AE	EIVLTQSPGTL ^S SLSPGERATLSC <u>RASQSVS</u> <u>PHYLA</u> WYQQKPGQAPRLLIY <u>GASSRATG</u> IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 21)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN ^S SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIAAEMDY</u> WGQGLTV VSS (SEQ ID NO: 31)
L3.PY/L1.PH/H3.AQ	EIVLTQSPGTL ^S SLSPGERATLSC <u>RASQSVS</u> <u>PHYLA</u> WYQQKPGQAPRLLIY <u>GASSRATG</u>	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u>
	IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 21)	<u>FYADSVKGR</u> FTISRDN ^S SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIAAQMDY</u> WGQGLTV VSS (SEQ ID NO: 3)
L3.PY/L1.PH/H3.TAQ	EIVLTQSPGTL ^S SLSPGERATLSC <u>RASQSVS</u> <u>PHYLA</u> WYQQKPGQAPRLLIY <u>GASSRATG</u> IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 21)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN ^S SKNTLYLQMNSLRA EDTAVYYCTR <u>VSPIAAQMDY</u> WGQGLTV VSS (SEQ ID NO: 32)
L3.PY/L3.KY/H2.QR	EIVLTQSPGTL ^S SLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRATGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>KYYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 22)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADQRKGR</u> FTISRDN ^S SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGLTV VSS (SEQ ID NO: 24)
L3.PY/L3.KY/H2.DY	EIVLTQSPGTL ^S SLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRATGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>KYYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 22)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>DYSGGNT</u> <u>FYADSVKGR</u> FTISRDN ^S SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGLTV VSS (SEQ ID NO: 25)
L3.PY/L3.KY/H2.YQ	EIVLTQSPGTL ^S SLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRATGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>KYYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 22)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SYQGGN</u> <u>TFYADSVKGR</u> FTISRDN ^S SKNTLYLQMNSLR AEDTAVYYCAR <u>VSPIASGMDY</u> WGQGLTV TVSS (SEQ ID NO: 26)
L3.PY/L3.KY/H2.LT	EIVLTQSPGTL ^S SLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRATGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>KYYPYPPSF</u> TFGQGTKVEIK (SEQ ID NO: 22)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SLTGGNT</u> <u>FYADSVKGR</u> FTISRDN ^S SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGLTV VSS (SEQ ID NO: 27)

mAb	Light Chain	Heavy Chain
L3.PY/L3.KY/H2.HA	EIVLTQSPGTLSLSPGERATLSC <u>RASQSVS</u>	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u>
	<u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>KYYPPPSFT</u> FGQGTKVEIK (SEQ ID NO: 22)	<u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SHAGGN</u> <u>TFYADSVKGR</u> FTISRDN SKNTLYLQMNSLR AEDTAVYYCAR <u>VSPIASGMDY</u> WGQGTLV TVSS (SEQ ID NO: 28)
L3.PY/L3.KY/H2.QL	EIVLTQSPGTLSLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>KYYPPPSFT</u> FGQGTKVEIK (SEQ ID NO: 22)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADQLKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGTLV VSS (SEQ ID NO: 29)
L3.PY/L3.KY/H3.YA	EIVLTQSPGTLSLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>KYYPPPSFT</u> FGQGTKVEIK (SEQ ID NO: 22)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIYAGMDY</u> WGQGTLV VSS (SEQ ID NO: 30)
L3.PY/L3.KY/H3.TAQ	EIVLTQSPGTLSLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>KYYPPPSFT</u> FGQGTKVEIK (SEQ ID NO: 22)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCTR <u>VSPIAAQMDY</u> WGQGTLV VSS (SEQ ID NO: 32)
L3.PY/L3.KF/H2.DY	EIVLTQSPGTLSLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>KFYPPPSFT</u> FGQGTKVEIK (SEQ ID NO: 23)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>DYSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGTLV VSS (SEQ ID NO: 25)
L3.PY/L3.KF/H2.YQ	EIVLTQSPGTLSLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>KFYPPPSFT</u> FGQGTKVEIK (SEQ ID NO: 23)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SYQGGN</u> <u>TFYADSVKGR</u> FTISRDN SKNTLYLQMNSLR AEDTAVYYCAR <u>VSPIASGMDY</u> WGQGTLV
	23)	TVSS (SEQ ID NO: 26)
L3.PY/L3.KF/H2.LT	EIVLTQSPGTLSLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>KFYPPPSFT</u> FGQGTKVEIK (SEQ ID NO: 23)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SLTGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGTLV VSS (SEQ ID NO: 27)
L3.PY/L3.KF/H2.QL	EIVLTQSPGTLSLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>KFYPPPSFT</u> FGQGTKVEIK (SEQ ID NO: 23)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADQLKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGTLV

mAb	Light Chain	Heavy Chain
	23)	VSS (SEQ ID NO: 29)
L3.PY/L3.KF/H3.YA	EIVLTQSPGTLSSLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>KFYPPPSFT</u> FGQGTKVEIK (SEQ ID NO: 23)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIYAGMDY</u> WGQGT LVT VSS (SEQ ID NO: 30)
L3.PY/L3.KF/H3.AE	EIVLTQSPGTLSSLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>KFYPPPSFT</u> FGQGTKVEIK (SEQ ID NO: 23)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIAAEMDY</u> WGQGT LVT VSS (SEQ ID NO: 31)
L3.PY/L3.KF/H3.AQ	EIVLTQSPGTLSSLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>KFYPPPSFT</u> FGQGTKVEIK (SEQ ID NO: 23)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIAAQMDY</u> WGQGT LVT VSS (SEQ ID NO: 3)
L3.PY/L3.KF/H3.TAQ	EIVLTQSPGTLSSLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAMT</u> WVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA
	<u>KFYPPPSFT</u> FGQGTKVEIK (SEQ ID NO: 23)	EDTAVYYCTR <u>VSPIAAQMDY</u> WGQGT LVT VSS (SEQ ID NO: 32)
P5A2_VHVL	EIVLTQSPGTLSSLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYGSWPLT</u> FGQGTKVEIK (SEQ ID NO: 34)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYAMN</u> WVRQAPGKGLEWVSAI <u>SDSGGS</u> <u>YYADSVKGR</u> FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>WPMDI</u> WGQGT LTVSS (SEQ ID NO: 33)
A02_Rd4_0.6nM_C06	EIVLTQSPGTLSSLSPGERATLSC <u>RASQSVS</u> <u>VIYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQYQRWPLT</u> FGQGTKVEIK (SEQ ID NO: 36)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYAMN</u> WVRQAPGKGLEWVSAI <u>SDSGGS</u> <u>AWYADSVKGR</u> FTISRDN SKNTLYLQMNSL RAEDTAVYYCARY <u>WPMSL</u> WGQGT LTVSS (SEQ ID NO: 35)
A02_Rd4_0.6nM_C09	EIVLTQSPGTLSSLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYQSWPLT</u> FGQGTKVEIK (SEQ ID NO: 38)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYAMN</u> WVRQAPGKGLEWVSAI <u>SDSGGS</u> <u>MWYADSVKGR</u> FTISRDN SKNTLYLQMNS LRAEDTAVYYCARY <u>WPMSL</u> WGQGT LTVSS (SEQ ID NO: 37)
A02_Rd4_6nM_C16 (P5AC16)	EIVLTQSPGTLSSLSPGERATLSC <u>RASQSVS</u> <u>DIYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYQSWPLT</u> FGQGTKVEIK (SEQ ID NO: 39)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYAMN</u> WVRQAPGKGLEWVSAI <u>SD</u> EGGST <u>YYADSVKGR</u> FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>WPMDI</u> WGQGT LTVSS (SEQ ID NO: 40)

mAb	Light Chain	Heavy Chain
	YC <u>QQYQTWPLT</u> FGQGTKVEIK (SEQ ID NO: 40)	AEDTAVYYCARY <u>WPMDI</u> WGQGTLVTVSS (SEQ ID NO: 39)
A02_Rd4_6nM_C03	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>NLYL</u> AWYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYQGWPLT</u> FGQGTKVEIK (SEQ ID NO: 41)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYAMN</u> WVRQAPGKGLEWVSA <u>ISDSGGST</u> <u>YYADSVKGR</u> FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>WPMDI</u> WGQGTLVTVSS (SEQ ID NO: 33)
A02_Rd4_6nM_C01	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>AYYL</u> AWYQQKPGQAPRLLMY <u>DASIRAT</u>	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYAMN</u> WVRQAPGKGLEWVSA <u>ITASGGST</u>
	GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYERWPLT</u> FGQGTKVEIK (SEQ ID NO: 43)	<u>YYADSVKGR</u> FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>WPMSL</u> WGQGTLVTVSS (SEQ ID NO: 42)
A02_Rd4_6nM_C26	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SLYL</u> AWYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYQVWPLT</u> FGQGTKVEIK (SEQ ID NO: 45)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYAMN</u> WVRQAPGKGLEWVSA <u>ISDSGGST</u> <u>YYADSVKGR</u> FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>WPMSL</u> WGQGTLVTVSS (SEQ ID NO: 44)
A02_Rd4_6nM_C25	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SSYL</u> AWYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYLDWPLT</u> FGQGTKVEIK (SEQ ID NO: 47)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYAMN</u> WVRQAPGKGLEWVSA <u>ISdSGGSR</u> <u>WYADSVKGR</u> FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>WPMT</u> PWGQGTLVTVSS (SEQ ID NO: 46)
A02_Rd4_6nM_C22	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SSYL</u> AWYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYQVWPLT</u> FGQGTKVEIK (SEQ ID NO: 49)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYAMN</u> WVRQAPGKGLEWVSA <u>AVLdSGGS</u> <u>TYADSVKGR</u> FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>WPMT</u> PWGQGTLVTVSS (SEQ ID NO: 48)
A02_Rd4_6nM_C19	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>VIYL</u> AWYQQKPGQAPRLLMY <u>DASIRAT</u> G IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQYLAWPLT</u> FGQGTKVEIK (SEQ ID NO: 51)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYAMN</u> WVRQAPGKGLEWVSA <u>ISdSGGSR</u> <u>WYADSVKGR</u> FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>WPMSD</u> WGQGTLVTVSS (SEQ ID NO: 50)
A02_Rd4_0.6nM_C03	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SSYL</u> AWYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYFTWPLT</u> FGQGTKVEIK (SEQ ID NO: 53)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYAMN</u> WVRQAPGKGLEWVSA <u>ISdSGGSK</u> <u>WYADSVKGR</u> FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>WPMSL</u> WGQGTLVTVSS (SEQ ID NO: 52)
A02_Rd4_6nM_C07	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u>	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u>
	<u>PyYL</u> AWYQQKPGQAPRLLMY <u>DASIRAT</u>	<u>SYAMN</u> WVRQAPGKGLEWVSA <u>IGGGSGGS</u>

mAb	Light Chain	Heavy Chain
	GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYERWPLT</u> FGQGGTKVEIK (SEQ ID NO: 55)	LPYADSVKGR FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>WPMD</u> SWGQGLTVTS S (SEQ ID NO: 54)
A02_Rd4_6nM_C23	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>VEYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYARWPLT</u> FGQGGTKVEIK (SEQ ID NO: 57)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYAMN</u> WVRQAPGKGLEWVSA <u>ISdSGGS</u> GWYADSVKGR FTISRDN SKNTLYLQMNSLR RAEDTAVYYCARY <u>WPMSL</u> WGQGLTVTS S (SEQ ID NO: 56)
A02_Rd4_0.6nM_C18	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>EIYLA</u> WYQQKPGQAPRLLMY <u>DASIRATG</u> IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQYFGWPLT</u> FGQGGTKVEIK (SEQ ID NO: 59)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYAMN</u> WVRQAPGKGLEWVSA <u>AVLdSGGS</u> TYYADSVKGR FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>WPMSL</u> WGQGLTVTVSS (SEQ ID NO: 58)
A02_Rd4_6nM_C10	EIVLTQSPGTLSPGERATLSC <u>RASQSV</u> <u>MSYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYAHWPLT</u> FGQGGTKVEIK (SEQ ID NO: 61)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYAMN</u> WVRQAPGKGLEWVSA <u>ISdSGGS</u> WYADSVKGR FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>WPMT</u> PWGQGLTVTVSS (SEQ ID NO: 60)
A02_Rd4_6nM_C05	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYQRWPLT</u> FGQGGTKVEIK (SEQ ID NO: 63)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYAMN</u> WVRQAPGKGLEWVSA <u>IFaSGGST</u> YYADSVKGR FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>WPMT</u> PWGQGLTVTVSS (SEQ ID NO: 62)
A02_Rd4_0.6nM_C10	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>AQYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYQRWPLT</u> FGQGGTKVEIK (SEQ ID NO: 65)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYAMN</u> WVRQAPGKGLEWVSA <u>ISgWGG</u> S LPYADSVKGR FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>WPMD</u> SWGQGLTVTS S (SEQ ID NO: 64)
A02_Rd4_6nM_C04	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>AIYLA</u> WYQQKPGQAPRLLMY <u>DASIRATG</u> IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQYQVWPLT</u> FGQGGTKVEIK (SEQ ID NO: 67)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYAMN</u> WVRQAPGKGLEWVSA <u>IMsSGGP</u> LYYADSVKGR FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>WPMAL</u> WGQGLTVTVSS (SEQ ID NO: 66)
A02_Rd4_0.6nM_C26	EIVLTQSPGTLSPGERATLSC <u>GPSQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYQSWPLT</u> FGQGGTKVEIK (SEQ ID NO: 69)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYAMN</u> WVRQAPGKGLEWVSA <u>ILmSGGS</u> TYYADSVKGR FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>WPMSL</u> WGQGLTVTVSS (SEQ ID NO: 68)
A02_Rd4_0.6nM_C13	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SSYWA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYAMN</u> WVRQAPGKGLEWVSA <u>ISdSGGY</u> RYYADSVKGR FTISRDN SKNTLYLQMNSLR

mAb	Light Chain	Heavy Chain
	YC <u>QQYESWPLT</u> FGQGTKVEIK (SEQ ID NO: 71)	AEDTAVYYCARY <u>YWPM</u> SLWGQGLTVTVSS (SEQ ID NO: 70)
A02_Rd4_0.6nM_C01 (P5AC1)	EIVLTQSPGTLSSLSPGERATLSC <u>RAGQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYQSWPLT</u> FGQGTKVEIK (SEQ ID NO: 73)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYAMN</u> WVRQAPGKGLEWVSA <u>ILsSGGST</u> YYADSVKGR FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>YWPM</u> DIWGQGLTVTVSS (SEQ ID NO: 72)
A02_Rd4_6nM_C08	EIVLTQSPGTLSSLSPGERATLSC <u>RASQSVS</u> <u>FIYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> G IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQYGSWPLT</u> FGQGTKVEIK (SEQ ID NO: 75)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYAMN</u> WVRQAPGKGLEWVSA <u>ILdSGGST</u> YYADSVKGR FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>YWPM</u> SPWGQGLTVTVSS (SEQ ID NO: 74)
P5C1_VHVL (PC1)	EIVLTQSPGTLSSLSPGERATLSC <u>RASQSVS</u> <u>STYLA</u> WYQQKPGQAPRLLIY <u>DASSRAP</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQYSTSPLT</u> FGQGTKVEIK (SEQ ID NO: 77)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYPMS</u> WVRQAPGKGLEWVSA <u>IGGS</u> GGST YYADSVKGR FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>YWPM</u> DSWGQGLTVTVS (SEQ ID NO: 76)
C01_Rd4_6nM_C24	EIVLTQSPGTLSSLSPGERATLSC <u>RASQSVS</u> <u>PEYLA</u> WYQQKPGQAPRLLIY <u>DASSRAP</u> G IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQYSVWPLT</u> FGQGTKVEIK (SEQ ID NO: 79)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYPMS</u> WVRQAPGKGLEWVSA <u>IGGS</u> GGSL PYADSVKGR FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>YWPM</u> DSWGQGLTVTVS (SEQ ID NO: 78)
C01_Rd4_6nM_C26	EIVLTQSPGTLSSLSPGERATLSC <u>RASQSVS</u> <u>AIYLA</u> WYQQKPGQAPRLLIY <u>DASSRAP</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQYSAWPLT</u> FGQGTKVEIK (SEQ ID NO: 317)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYPMS</u> WVRQAPGKGLEWVSA <u>IGGS</u> GGSL PYADSVKGR FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>YWPM</u> DSWGQGLTVTVS (SEQ ID NO: 78)
C01_Rd4_6nM_C10	EIVLTQSPGTLSSLSPGERATLSC <u>RASQSVS</u> <u>SvYLA</u> WYQQKPGQAPRLLIY <u>DASSRAP</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQYSTWPLT</u> FGQGTKVEIK (SEQ ID NO: 79)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYPMS</u> WVRQAPGKGLEWVSA <u>IGgSGGSL</u> PYADSVKGR FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>YWPM</u> DSWGQGLTVTVS (SEQ ID NO: 78)
C01_Rd4_0.6n M_C27	EIVLTQSPGTLSSLSPGERATLSC <u>RASQSVS</u> <u>STYLA</u> WYQQKPGQAPRLLIY <u>DASSRAP</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQYSRWPLT</u> FGQGTKVEIK (SEQ ID NO: 81)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYPMS</u> WVRQAPGKGLEWVSA <u>IGgSGGSL</u> PYADSVKGR FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>YWPM</u> DSWGQGLTVTVS (SEQ ID NO: 78)
C01_Rd4_6nM_C20	EIVLTQSPGTLSSLSPGERATLSC <u>RASQSVS</u> <u>PIYLA</u> WYQOKPGQAPRLLIY <u>DASSRAP</u> GI	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYPMS</u> WVRQAPGKGLEWVSA <u>IGgSGGSL</u>

mAb	Light Chain	Heavy Chain
	PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQYSAFPLT</u>FGQGTKVEIK (SEQ ID NO: 82)	PYADSVKGRFTISRDN SKNTLYLQMNSLR AEDTAVYYCARY<u>YWPMD</u>SWGQGLTVTS S (SEQ ID NO: 78)
C01_Rd4_6nM_C12 (PC1C1 2)	EIVLTQSPGTLSPGERATLSC<u>WLSQSVS</u> <u>STYLA</u>WYQQKPGQAPRLLIY<u>DASSRAPGI</u>	EVQLLESGGGLVQPGGSLRLSCAASGFTFS <u>SYPM</u>SWVRQAPGKGLEWVSAIGgSGGW
	PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQYSEWPLT</u>FGQGTKVEIK (SEQ ID NO: 84)	SYADSVKGRFTISRDN SKNTLYLQMNSLR AEDTAVYYCARY<u>YWPMD</u>SWGQGLTVTS S (SEQ ID NO: 83)
C01_Rd4_0.6nM_C16	EIVLTQSPGTLSPGERATLSC<u>RASQSVS</u> <u>STYLA</u>WYQQKPGQAPRLLIY<u>DASSRAPGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQYSSWPLT</u>FGQGTKVEIK (SEQ ID NO: 85)	EVQLLESGGGLVQPGGSLRLSCAASGFTFS <u>SYPM</u>SWVRQAPGKGLEWVSAIGgSGGSL PYADSVKGRFTISRDN SKNTLYLQMNSLR AEDTAVYYCARY<u>YWPMD</u>SWGQGLTVTS S (SEQ ID NO: 78)
C01_Rd4_0.6nM_C09	EIVLTQSPGTLSPGERATLSC<u>RASQSVS</u> <u>SIFLA</u>WYQQKPGQAPRLLIY<u>DASSRAPGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQYSAWPLT</u>FGQGTKVEIK (SEQ ID NO: 86)	EVQLLESGGGLVQPGGSLRLSCAASGFTFS <u>SYPM</u>SWVRQAPGKGLEWVSAIGgSGGSL PYADSVKGRFTISRDN SKNTLYLQMNSLR AEDTAVYYCARY<u>YWPMD</u>SWGQGLTVTS S (SEQ ID NO: 78)
C01_Rd4_6nM_C09	EIVLTQSPGTLSPGERATLSC<u>ACSQSVS</u> <u>STYLA</u>WYQQKPGQAPRLLIY<u>DASSRAPGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQYSAWPLT</u>FGQGTKVEIK (SEQ ID NO: 88)	EVQLLESGGGLVQPGGSLRLSCAASGFTFS <u>SYPM</u>SWVRQAPGKGLEWVSATvgSGGSI GYADSVKGRFTISRDN SKNTLYLQMNSLR AEDTAVYYCARY<u>YWPMD</u>SWGQGLTVTS S (SEQ ID NO: 87)
C01_Rd4_0.6nM_C03	EIVLTQSPGTLSPGERATLSC<u>RASCDVS</u> <u>STYLA</u>WYQQKPGQAPRLLIY<u>DASSRAPGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQYMRSPLT</u>FGQGTKVEIK (SEQ ID NO: 89)	EVQLLESGGGLVQPGGSLRLSCAASGFTFS <u>SYPM</u>SWVRQAPGKGLEWVSAIGgSGGSL PYADSVKGRFTISRDN SKNTLYLQMNSLR AEDTAVYYCARY<u>YWPMD</u>SWGQGLTVTS S (SEQ ID NO: 78)
C01_Rd4_0.6nM_C06	EIVLTQSPGTLSPGERATLSC<u>RASEAVP</u> <u>STYLA</u>WYQQKPGQAPRLLIY<u>DASSRAPGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQYSAFPLT</u>FGQGTKVEIK (SEQ ID NO: 90)	EVQLLESGGGLVQPGGSLRLSCAASGFTFS <u>SYPM</u>SWVRQAPGKGLEWVSAIGgSGGSL PYADSVKGTISRDN SKNTLYLQMNSLRAE DTAVYYCARY<u>YWPMD</u>SWGQGLTVTS (SEQ ID NO: 78)
C01_Rd4_6nM_C04	EIVLTQSPGTLSPGERATLSC<u>CSQSVSS</u>	EVQLLESGGGLVQPGGSLRLSCAASGFTFS
	<u>TYLA</u>WYQQKPGQAPRLLIY<u>DASSRAPGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQYSAFPLT</u>FGQGTKVEIK (SEQ ID NO: 91)	<u>SYPM</u>SWVRQAPGKGLEWVSAIGgSGGSL PYADSVKGRFTISRDN SKNTLYLQMNSLR AEDTAVYYCARY<u>YWPMD</u>SWGQGLTVTS S (SEQ ID NO: 78)

mAb	Light Chain	Heavy Chain
COMBO_Rd4_0.6nM_C22 (COM22)	EIVLTQSPGTLSPGERATLSC <u>RASVRVS</u> <u>STYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYMKWPLT</u> FGQGTKVEIK (SEQ ID NO: 93)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYAMN</u> WVRQAPGKGLEWVSA <u>ISdSGGSR</u> WYADSVKGR FTISRDN SKNTLYLQMNSLR AEDTAVYYCTRY <u>YWPMDI</u> WGQGT LTVSS (SEQ ID NO: 92)
COMBO_Rd4_6nM_C21	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>AAYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYMCWPLT</u> FGQGTKVEIK (SEQ ID NO: 94)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYPMS</u> WVRQAPGKGLEWVSA <u>IGgSGGSL</u> PYADSVKGR FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>YWPMDs</u> WGQGT LTVS S (SEQ ID NO: 78)
COMBO_Rd4_6nM_C10	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SSYWG</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYQCWPLT</u> FGQGTKVEIK (SEQ ID NO: 96)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYPMS</u> WVRQAPGKGLEWVSA <u>IGgSGGSI</u> HYADSVKGR FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>YWPMDs</u> WGQGT LTVS S (SEQ ID NO: 95)
COMBO_Rd4_0.6nM_C04	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>STYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYQSWPLT</u> FGQGTKVEIK (SEQ ID NO: 98)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYPMS</u> WVRQAPGKGLEWVSA <u>HIgSGGST</u> YYADSVKGR FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>YWPMDs</u> WGQGT LTVS S (SEQ ID NO: 97)
COMBO_Rd4_6nM_C25	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SpYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYQSWPLT</u> FGQGTKVEIK (SEQ ID NO: 100)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYPMS</u> WVRQAPGKGLEWVSA <u>IGgSGGST</u> YYADSVKGR FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>YWPMDP</u> WGQGT LTVS S (SEQ ID NO: 99)
COMBO_Rd4_0.6nM_C21	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYQSWPLT</u> FGQGTKVEIK (SEQ ID NO: 38)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYPMS</u> WVRQAPGKGLEWVSA <u>IGgSGGSL</u> PYADSVKGR FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>YWPMDs</u> WGQGT LTVS S (SEQ ID NO: 78)
COMBO_Rd4_6nM_C11	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>PIYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> G IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQYKAWPLT</u> FGQGTKVEIK (SEQ ID NO: 102)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYPMS</u> WVRQAPGKGLEWVSA <u>IGGSGGSL</u> GYADSVKGR FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>YWPMDs</u> WGQGT LTVS S (SEQ ID NO: 101)
COMBO_Rd4_0.6nM_C20	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>YLYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYMEWPLT</u> FGQGTKVEIK (SEQ ID NO: 103)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYPMS</u> WVRQAPGKGLEWVSA <u>IGGSGGSL</u> PYADSVKGR FTISRDN SKNTLYLQMNSLR AEDTAVYYCARY <u>YWPMDs</u> WGQGT LTVS S (SEQ ID NO: 78)

mAb	Light Chain	Heavy Chain
COMBO_Rd4_6nM_C09	EIVLTQSPGTL ~~SL~~ SPGERATLSC <u>RASQSVS</u> <u>AQYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYQAWPLT</u> FGQG ~~TK~~ VEIK (SEQ ID NO: 105)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYPMS</u> WVRQAPGKGLEWVSA <u>IFASGGST</u> YYADSVKGR FTISRDN ~~SKNTLYLQMN~~ SLR AEDTAVYYCARY <u>WPMD</u> SWGQGLTVTS S (SEQ ID NO: 104)
COMBO_Rd4_6nM_C08	EIVLTQSPGTL ~~SL~~ SPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYQKWPLT</u> FGQG ~~TK~~ VEIK (SEQ ID NO: 107)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYPMS</u> WVRQAPGKGLEWVSA <u>IGGGGTW</u> TYYADSVKGR FTISRDN ~~SKNTLYLQMN~~ SLR AEDTAVYYCARY <u>WPMD</u> SWGQGLTVTS S (SEQ ID NO: 106)
COMBO_Rd4_0.6nM_C19	EIVLTQSPGTL ~~SL~~ SPGERATLSC <u>RASQSVS</u> <u>AVYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYPMS</u> WVRQAPGKGLEWVSA <u>IGGGGGSL</u> PYADSVKGR FTISRDN ~~SKNTLYLQMN~~ SLR
	YC <u>QQYRAWPLT</u> FGQG ~~TK~~ VEIK (SEQ ID NO: 108)	AEDTAVYYCARY <u>WPMD</u> SWGQGLTVTS S (SEQ ID NO: 78)
COMBO_Rd4_0.6nM_C02	EIVLTQSPGTL ~~SL~~ SPGERATLSC <u>RASIAVSS</u> <u>TYLA</u> WYQQKPGQAPRLLMY <u>DASIRATGI</u> PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQYMWVPLT</u> FGQG ~~TK~~ VEIK (SEQ ID NO: 109)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYPMS</u> WVRQAPGKGLEWVSA <u>IGGGGGSL</u> PYADSVKGR FTISRDN ~~SKNTLYLQMN~~ SLR AEDTAVYYCARY <u>WPMD</u> SWGQGLTVTS S (SEQ ID NO: 78)
COMBO_Rd4_0.6nM_C23	EIVLTQSPGTL ~~SL~~ SPGERATLSC <u>RPROQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYQDWPLT</u> FGQG ~~TK~~ VEIK (SEQ ID NO: 111)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYPMS</u> WVRQAPGKGLEWVSA <u>IFGSGGST</u> YYADSVKGR FTISRDN ~~SKNTLYLQMN~~ SLR AEDTAVYYCARY <u>WPMD</u> SWGQGLTVTS S (SEQ ID NO: 110)
COMBO_Rd4_0.6nM_C29	EIVLTQSPGTL ~~SL~~ SPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYQSWPLT</u> FGQG ~~TK~~ VEIK (SEQ ID NO: 38)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYPMS</u> WVRQAPGKGLEWVSA <u>IGGGGGSL</u> PYADSVKGR FTISRDN ~~SKNTLYLQMN~~ SLR AEDTAVYYCARY <u>WPMDI</u> WGQGLTVTVSS (SEQ ID NO: 112)
COMBO_Rd4_0.6nM_C09	EIVLTQSPGTL ~~SL~~ SPGERATLSC <u>RASQSVS</u> <u>STYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYQEWPLT</u> FGQG ~~TK~~ VEIK (SEQ ID NO: 113)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYPMS</u> WVRQAPGKGLEWVSA <u>IGGGGGSL</u> PYADSVKGR FTISRDN ~~SKNTLYLQMN~~ SLR AEDTAVYYCARY <u>WPMDI</u> WGQGLTVTVSS (SEQ ID NO: 112)
COMBO_Rd4_6 nM_C1 2	EIVLTQSPGTL ~~SL~~ SPGERATLSC <u>RASQSVS</u> <u>ASYLA</u> WYQQKPGQAPRLLMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYMSWPLT</u> FGQG ~~TK~~ VEIK (SEQ ID NO: 115)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYPMS</u> WVRQAPGKGLEWVSA <u>ALGSGGS</u> TYYADSVKGR FTISRDN ~~SKNTLYLQMN~~ SLR AEDTAVYYCARY <u>WPMD</u> SWGQGLTVTS S (SEQ ID NO: 114)

mAb	Light Chain	Heavy Chain
COMBO_Rd4_0.6nM_C30	EIVLTQSPGTL ^S SLSPGERATLSC <u>RASQSVS</u> <u>YMYLA</u> WYQQKPGQAPRLLIY <u>DASIRAT</u> G	EVQLLESGGGLVQPGGSLRLSCAASGFTFS <u>SYPMS</u> WVRQAPGKGLEWVSA <u>IGGSGGST</u>
	IPDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQYKSWPLT</u> FGQGTKVEIK (SEQ ID NO: 116)	YYADSVKGR FTISRDN ^S SKNTLYLQMNSLR AEDTAVYYCARY <u>YWPMDS</u> WGQGLTVTS S (SEQ ID NO: 76)
COMBO_Rd4_0.6nM_C14	EIVLTQSPGTL ^S SLSPGERATLSC <u>RASQSVS</u> <u>ALYLA</u> WYQQKPGQAPRLIMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYYGWPLT</u> FGQGTKVEIK (SEQ ID NO: 117)	EVQLLESGGGLVQPGGSLRLSCAASGFTFS <u>SYPMS</u> WVRQAPGKGLEWVSA <u>IGGSGGSL</u> PYADSVKGR FTISRDN ^S SKNTLYLQMNSLR AEDTAVYYCARY <u>YWPMDI</u> WGQGLTVTVSS (SEQ ID NO: 112)
COMBO_Rd4_6nM_C07	EIVLTQSPGTL ^S SLSPGERATLSC <u>RASQPISS</u> <u>SYLA</u> WYQQKPGQAPRLIMY <u>DASIRAT</u> GI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QQYQGWPLT</u> FGQGTKVEIK (SEQ ID NO: 119)	EVQLLESGGGLVQPGGSLRLSCAASGFTFS <u>SYPMS</u> WVRQAPGKGLEWVSA <u>IGGSGGSL</u> PYADSVKGR FTISRDN ^S SKNTLYLQMNSLR AEDTAVYYCARY <u>YWPMAD</u> WGQGLTVTVS S (SEQ ID NO: 118)
COMBO_Rd4_6nM_C02	EIVLTQSPGTL ^S SLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLIMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYEFWPLT</u> FGQGTKVEIK (SEQ ID NO: 121)	EVQLLESGGGLVQPGGSLRLSCAASGFTFS <u>SYAMN</u> WVRQAPGKGLEWVSA <u>ISDSGGF</u> VYYADSVKGR FTISRDN ^S SKNTLYLQMNSL RAEDTAVYYCARY <u>YWPMDS</u> WGQGLTVTV SS (SEQ ID NO: 120)
COMBO_Rd4_0.6nM_C05	EIVLTQSPGTL ^S SLSPGERATLSC <u>RASQSVS</u> <u>STYLA</u> WYQQKPGQAPRLIMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYMSWPLT</u> FGQGTKVEIK (SEQ ID NO: 123)	EVQLLESGGGLVQPGGSLRLSCAASGFTFS <u>SYAMN</u> WVRQAPGKGLEWVSA <u>IGGSGGS</u> TYYADSVKGR FTISRDN ^S SKNTLYLQMNSLR AEDTAVYYCARY <u>YWPMSL</u> WGQGLTVTVSS (SEQ ID NO: 122)
COMBO_Rd4_0.6nM_C17	EIVLTQSPGTL ^S SLSPGERATLSC <u>RASQGIS</u> <u>STYLA</u> WYQQKPGQAPRLIMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYAYWPLT</u> FGQGTKVEIK (SEQ ID NO: 124)	EVQLLESGGGLVQPGGSLRLSCAASGFTFS <u>SYPMS</u> WVRQAPGKGLEWVSA <u>IGGSGGSL</u> PYADSVKGR FTISRDN ^S SKNTLYLQMNSLR AEDTAVYYCARY <u>YWPMDI</u> WGQGLTVTVSS (SEQ ID NO: 112)
COMBO_Rd4_6nM_C22	EIVLTQSPGTL ^S SLSPGERATLSC <u>RASQSVS</u>	EVQLLESGGGLVQPGGSLRLSCAASGFTFS
	<u>SSYLA</u> WYQQKPGQAPRLIMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYQGWPLT</u> FGQGTKVEIK (SEQ ID NO: 126)	<u>SYAMN</u> WVRQAPGKGLEWVSA <u>CLDSGGS</u> TYYADSVKGR FTISRDN ^S SKNTLYLQMNSLR AEDTAVYYCARY <u>YWPMDS</u> WGQGLTVTS S (SEQ ID NO: 125)
COMBO_Rd4_0.6nM_C11	EIVLTQSPGTL ^S SLSPGERATLSC <u>RASQSVS</u> <u>VRYLAW</u> YQQKPGQAPRLIMY <u>DASIRAT</u> GIPDRFSGSGSGTDFTLTISRLEPEDFAVY YC <u>QQYGSWPIT</u> FGQGTKVEIK (SEQ ID	EVQLLESGGGLVQPGGSLRLSCAASGFTFS <u>SYPMS</u> WVRQAPGKGLEWVSA <u>ALGSGGS</u> TYYADSVKGR FTISRDN ^S SKNTLYLQMNSLR AEDTAVYYCARY <u>YWPMSL</u> WGQGLTVTVSS

mAb	Light Chain	Heavy Chain
	NO: 128)	(SEQ ID NO: 127)
P6DY	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SSYP</u> SWYQQKPGQAPRLLIY <u>GASSR</u> ATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYP</u> PPSFTFGQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAM</u> TWVRQAPGKGLEWVSAIDYSGGNT <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIASGMDY</u> WGQGTLTVT VSS (SEQ ID NO: 25)
P6AP	EIVLTQSPGTLSPGERATLSC <u>RASQLGS</u> <u>FYLA</u> WYQQKPGQAPRLLIY <u>GASSR</u> ATGIP DRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>Q</u> <u>HYNYP</u> PSFTFGQGTKVEIK (SEQ ID NO: 80)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFG</u> <u>SYAM</u> TWVRQAPGKGLEWVSAI <u>SGSGGNT</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>VSPIAAPMDY</u> WGQGTLTVT VSS (SEQ ID NO: 8)
Consensus	EIVLTQSPGTLSPGERATLSC X ₁ X ₂ X ₃ X ₄ X ₅ X ₆ X ₇ X ₈ X ₉ X ₁₀ X ₁₁ X ₁₂ WYQQKP GQAPRLLMYX ₁₃ ASX ₁₄ RAX ₁₅ GIPDRFSGS GSGTDFTLTISRLEPEDFAVYYCX ₁₆ X ₁₇ YX ₁₈ X ₁₉ PPSFTFGQGTKVEIK, wherein X ₁ is R, G, W, A, or C; X ₂ is A, P, G, L, C, or S; X ₃ is S, G, or R; X ₄ is Q, C, E, V, or I; X ₅ is S, P, G, A, R, or D; X ₆ is V, G, I, or L; X ₇ is S, E, D, P, or G; X ₈ is S, P, F, A, M, E, V, N, D, or Y; X ₉ is I, T, V, E, S, A, M, Q, Y, H, R, or F; X ₁₀ is Y or F; X ₁₁ is L, W, or P; X ₁₂ is A, S, or G, X ₁₃ is G or D; X ₁₄ is S or I; X ₁₅ is T or P; X ₁₆ is Q or K; X ₁₇ is H or Y; X ₁₈ is G, N, or P; and X ₁₉ is S, W, or Y (SEQ ID NO: 315); or EIVLTQSPGTLSPGERATLSC X ₁ X ₂ X ₃ X ₄ X ₅ X ₆ X ₇ X ₈ X ₉ X ₁₀ X ₁₁ X ₁₂ WYQQKP GQAPRLLMYX ₁₃ ASX ₁₄ RAX ₁₅ GIPDRFSGS GSGTDFTLTISRLEPEDFAVYYCQQYX ₁₆ X ₁₇ X ₁₈ PX ₁₉ FGQGTKVEIK, wherein X ₁ is R, G, W, A, or C; X ₂ is A, P, G, L, C, or S; X ₃ is S, G, or R; X ₄ is Q, C, E, V, or I; X ₅ is S, L, P, G, A, R, or D; X ₆ is V, G, or I; X ₇ is S, E, D, or P; X ₈ is S, P, F, A, M, E, V, N, D, or Y; X ₉ is I, T, V, E, S, A, M, Q, Y, H, or R; X ₁₀ is Y or F; X ₁₁ is L, W, or P; X ₁₂ is A, S, or G, X ₁₃ is G or D; X ₁₄ is S or I; X ₁₅ is T or P; X ₁₆ is G, Q, E, L, F, A, S, M, R, K, or Y; X ₁₇ is S, R, T, G, R, V, D, A, H, E, K, C, F, or Y; X ₁₈ is W, S, or F; and X ₁₉ is L or I (SEQ ID NO: 316)	EVQLLESGGGLVQPGGSLRLSCAASGFTFX 1SYX2MX3WVRQAPGKGLEWWSAX4X5X6X 7GX8X9X10X11YADX12X13KGRFTISRDN SKN TLYLQMNSLRAEDTAVYYCARVSPIX14X15X 16MDYWGQGTTLVTVSS, wherein X ₁ is G or S, X ₂ is A or P; X ₃ is T, N, or S; X ₄ is I, V, T, H, L, A, or C; X ₅ is S, D, G, T, I, L, F, M, or V; X ₆ is G, Y, L, H, D, A, S, or M; X ₇ is S, Q, T, A, F, or W; X ₈ is G or T; X ₉ is N, S, P, Y, W, or F; X ₁₀ is S, T, I, L, T, A, R, V, K, G, or C; X ₁₁ is F, Y, P, W, H, or G; X ₁₂ is V, R, or L; X ₁₃ is G or T; X ₁₄ is A or Y; X ₁₅ is A or S; and X ₁₆ is G, Q, L, P, or E (SEQ ID NO: 313); or EVQLLESGGGLVQPGGSLRLSCAASGFTFX 1SYX2MX3WVRQAPGKGLEWWSAX4X5X6X 7GX8X9X10X11YADX12X13KGRFTISRDN SKN TLYLQMNSLRAEDTAVYYCARYWPMX14X 15WGQGTTLVTVSS, wherein X ₁ is G or S, X ₂ is A or P; X ₃ is T, N, or S; X ₄ is I, V, T, H, L, A, or C; X ₅ is S, D, G, T, I, L, F, M, or V; X ₆ is G, Y, L, H, D, A, S, or M; X ₇ is S, Q, T, A, F, or W; X ₈ is G or T; X ₉ is N, S, P, Y, W, or F; X ₁₀ is S, T, I, L, T, A, R, V, K, G, or C; X ₁₁ is F, Y, P, W, H, or G; X ₁₂ is V, R, or L; X ₁₃ is G or T; X ₁₄ is D, S, T, or A; and X ₁₅ is I, S, L, P, or D (SEQ ID NO: 314)
P4G4	EIVLTQSPGTLSPGERATLSC <u>RASQSVS</u> <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASSR</u> AYGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYGSPPLFT</u> FGQGTKVEIK (SEQ ID NO: 401)	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFS</u> <u>SYAMS</u> WVRQAPGKGLEWVSAI <u>SASGGST</u> <u>YYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAR <u>LSWSGAFDN</u> WGQGTTLVTV SS (SEQ ID NO: 378)
P1A11	EIVLTQSPGTLSPGERATLSC <u>RASQNV</u> S <u>SSYLA</u> WYQQKPGQAPRLLIY <u>GASYR</u> ATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYC <u>QHYGSPPSFT</u> FGQGTKVEIK (SEQ ID	EVQLLESGGGLVQPGGSLRLSCAAS <u>GFTFR</u> <u>SYAMS</u> WVRQAPGKGLEWVSAI <u>SGSGGST</u> <u>FYADSVKGR</u> FTISRDN SKNTLYLQMNSLRA EDTAVYYCAT <u>VGTSGAFGI</u> WGQGTTLTVS

mAb	Light Chain	Heavy Chain
	NO: 379)	S (SEQ ID NO: 380)

[0099] Also provided herein are CDR portions of extracellular ligand-binding domains of CARs to BCMA (including Chothia, Kabat CDRs, and CDR contact regions). Determination of CDR regions is well within the skill of the art. It is understood that in some embodiments, CDRs can be a combination of the Kabat and Chothia CDR (also termed "combined CRs" or "extended CDRs"). In some embodiments, the CDRs are the Kabat CDRs. In other embodiments, the CDRs are the Chothia CDRs. In other words, in embodiments with more than one CDR, the CDRs may be any of Kabat, Chothia, combination CDRs, or combinations thereof. Table 2 provides examples of CDR sequences provided herein.

Table 2

Heavy Chain			
mAb	CDRH1	CDRH2	CDRH3
P6E01	SYAMT (SEQ ID NO: 129) (Kabat);	AISGSGGNTFYADSV	VSPIASGMDY (SEQ ID NO: 134)
For the following mAbs:		KG (SEQ ID NO: 132) (Chothia)	
P6E01/P6E01;L1.LGF/L3.KW/P6E01;	GFTFGSY (SEQ ID NO: 130) (Chothia);		
L1.LGF/L3.NY/P6E01;		SGSGGN (SEQ ID NO:133) (Kabat)	
L1.GDF/L3.NY/P6E01;	GFTFGSYAMT (SEQ ID NO: 131) (extended)		
L3.KW/P6E01;			
L3.PY/P6E01;			
L3.NY/P6E01;			
L3.PY/L1.PS/P6E01;			
L3.PY/L1.AH/P6E01;			
L3.PY/L1.FF/P6E01;			
L3.PY/L1.PH/P6E01;			
L3.PY/L3.KY/P6E01;			
L3.PY/L3.KF/P6E01; and			
L3.PY/P6E01.			
H3.AQ	SYAMT (SEQ ID NO: 129) (Kabat);	AISGSGGNTFYADSV	VSPIAAQMDY (SEQ ID NO: 135)
For the following mAbs:		KG (SEQ ID NO: 132) (Chothia)	
P6E01/H3.AQ;	GFTFGSY (SEQ ID NO: 130) (Chothia);	SGSGGN (SEQ ID NO:133) (Kabat)	
L1.LGF/L3.KW/H3.AQ;			
L1.LGF/L3.PY/H3.AQ	GFTFGSYAMT (SEQ ID NO: 131) (extended)		
H3.AL	SYAMT (SEQ ID NO: 129) (Kabat);	AISGSGGNTFYADSV	VSPIAALMDY (SEQ ID NO: 136)
For the following mAbs:		KG (SEQ ID NO: 132) (Chothia)	
L1.LGF/L3.KW/H3.AL;	GFTFGSY (SEQ ID NO:130) (Chothia);	SGSGGN (SEQ ID NO:133) (Kabat)	
L1.LGF/L3.NY/H3.AL; and			
L1.GDF/L3.NY/H3.AL.	GFTFGSYAMT (SEQ ID NO: 131) (extended)		
H3.AP	SYAMT (SEQ ID NO: 129) (Kabat);	AISGSGGNTFYADSV	VSPIAAPMDY (SEQ ID NO: 137)
For the following mAbs:		KG (SEQ ID NO: 132) (Chothia)	
L1.LGF/L3.KW/H3.AP;	GFTFGSY (SEQ ID NO: 130) (Chothia);	SGSGGN (SEQ ID NO:133) (Kabat)	
L1.LGF/L3.PY/H3.AP;			
L1.LGF/L3NY/H3.AP;	GFTFGSYAMT (SEQ ID NO: 131) (extended)		
L1.GDF/L3.KW/H3.AP;			

Heavy Chain			
mAb	CDRH1	CDRH2	CDRH3
L1.GDF/L3.NY /H3.AP; P6AP.			
H2.QR	SYAMT (SEQ ID NO: 129) (Kabat);	AISGSGGNTFYADQ	VSPIASGMDY (SEQ ID NO: 134)
For the following mAbs:		RKG (SEQ ID NO: 138) (Chothia)	
L3.PY/H2.QR;	GFTFGSY (SEQ ID NO: 130) (Chothia);	SGSGGN (SEQ ID	
L3.PY/L1.PS/H2.QR;		NO:133) (KABAT)	
L3.PY/L1.AH/H2.QR;	GFTFGSYAMT (SEQ ID NO: 131) (extended)		
L3.PY/L1.FF/H2.QR;			
L3.PY/L1.PH/H2.QR; and			
L3.PY/L3.KY/H2.QR.			
H2.DY	SYAMT (SEQ ID NO: 129) (Kabat);	AIDYSGGNTFYADSV	VSPIASGMDY (SEQ ID NO: 134)
For the following mAbs:		KG (SEQ ID NO: 139) (Chothia)	
L3.PY/H2.DY; P6DY;	GFTFGSY (SEQ ID NO: 130) (Chothia);	DYSSGN (SEQ ID NO:140) (KABAT)	
L3.PY/L1.PS/H2.DY;			
L3.PY/L1.AH/H2.DY;	GFTFGSYAMT (SEQ ID NO: 131) (extended)		
L3.PY/L1.FF/H2.DY;			
L3.PY/L3.KY/H2.DY; and			
L3.PY/L3.KF/H2.DY.			
H2.YQ	SYAMT (SEQ ID NO: 129) (Kabat);	AISYQGGNTFYADSV	VSPIASGMDY (SEQ ID NO: 134)
For the following mAbs:		KG (SEQ ID NO: 141) (Chothia)	
L3.PY/H2.YQ;	GFTFGSY (SEQ ID NO: 130) (Chothia);	SYQGGN (SEQ ID NO:142) (KABAT)	
L3.PY/L1.PS/H2.YQ;			
L3.PY/L1.AH/H2.YQ;	GFTFGSYAMT (SEQ ID NO: 131) (extended)		
L3.PY/L1.FF/H2.YQ;			
L3.PY/L3.KY/H2.YQ; and			
L3.PY/L3.KF/H2.YQ.			
H2.LT	SYAMT (SEQ ID NO: 129) (Kabat);	AISLTGGNTFYADSV	VSPIASGMDY (SEQ ID NO: 134)
For the following mAbs:		KG (SEQ ID NO: 143) (Chothia)	
L3.PY/H2.LT;	GFTFGSY (SEQ ID NO: 130) (Chothia);	SLTGGN (SEQ ID NO:144) (KABAT)	
L3.PY/L1.PS/H2.LT;			
L3.PY/L1.AH/H2.LT;	GFTFGSYAMT (SEQ ID NO: 131) (extended)		
L3.PY/L1.FF/H2.LT;			
L3.PY/L3.KY/H2.LT; and			
L3.PY/L3.KF/H2.LT.			
H2.HA	SYAMT (SEQ ID NO: 129) (Kabat);	AISHAGGNTFYADSV	VSPIASGMDY (SEQ ID NO: 134)
For the following mAbs:		KG (SEQ ID NO: 145) (Chothia)	
L3.PY/H2.HA;	GFTFGSY (SEQ ID NO: 130) (Chothia);	SHAGGN (SEQ ID NO:146) (KABAT)	
L3.PY/L1.AH/H2.HA;			
L3.PY/L1.FF/H2.HA;	GFTFGSYAMT (SEQ ID NO: 131) (extended)		
L3.PY/L1.PH/H2.HA; and			
L3.PY/L3.KY/H2.HA.			
H2.QL	SYAMT (SEQ ID NO: 129) (Kabat);	AISGSGGNTFYADQL	VSPIASGMDY (SEQ ID NO: 134)

Heavy Chain			
mAb	CDRH1	CDRH2	CDRH3
For the following mAbs:		KG (SEQ ID NO: 147) (Chothia)	
L3.PY/H2.QL;	GFTFGSY (SEQ ID NO: 130) (Chothia);		
L3.PY/L1.PS/H2.QL;		SGSGGN (SEQ ID NO:133) (KABAT)	
L3.PY/L1.AH/H2.QL;	GFTFGSYAMT (SEQ ID NO: 131) (extended)		
L3.PY/L1.FF/H2.QL;			
L3.PY/L3.KY/H2.QL; and			
L3.PY/L3.KF/H2.QL.			
H3.YA	SYAMT (SEQ ID NO: 129) (Kabat);	AISGSGGNTFYADSV	VSPIYAGMDY (SEQ ID NO: 148)
For the following mAbs:		KG (SEQ ID NO: 132) (Chothia)	
L3.PY/H3.YA;	GFTFGSY (SEQ ID NO: 130) (Chothia);		
L3.PY/L1.PS/H3.YA;		SGSGGN (SEQ ID NO:133) (Kabat)	
L3.PY/L1.AH/H3.YA;	GFTFGSYAMT (SEQ ID NO: 131) (extended)		
L3.PY/L1.FF/H3.YA;			
L3.PY/L3.KY/H3.YA; and			
L3.PY/L3.KF/H3.YA.			
H3.AE	SYAMT (SEQ ID NO: 129) (Kabat);	AISGSGGNTFYADSV	VSPIAAEMDY (SEQ ID NO: 149)
For the following mAbs:		KG (SEQ ID NO: 132) (Chothia)	
L3.PY/H3.AE;	GFTFGSY (SEQ ID NO: 130) (Chothia);		
L3.PY/L1.AH/H3.AE;		SGSGGN (SEQ ID NO:133) (Kabat)	
L3.PY/L1.FF/H3.AE;	GFTFGSYAMT (SEQ ID NO: 131) (extended)		
L3.PY/L1.PH/H3.AE; and			
L3.PY/L3.KF/H3.AE.			
H3.TAQ	SYAMT (SEQ ID NO: 129) (Kabat);	AISGSGGNTFYADSV	VSPIAAQMDY (SEQ ID NO: 135)
For the following mAbs:		KG (SEQ ID NO: 132) (Chothia)	
L3.PY/H3.TAQ;	GFTFGSY (SEQ ID NO: 130) (Chothia);		
L3.PY/L1.PS/H3.TAQ;		SGSGGN (SEQ ID NO:133) (Kabat)	
L3.PY/L1.AH/H3.TAQ;	GFTFGSYAMT (SEQ ID NO: 131) (extended)		
L3.PY/L1.FF/H3.TAQ;			
L3.PY/L1.PH/H3.TAQ; and			
L3.PY/L3.KF/H3.TAQ.			
P5A2_VHVL and	SYAMN (SEQ ID NO: 150) (Kabat);	AISDSGGSTYYADSV	YWPMIDI (SEQ ID NO: 155)
A02_Rd4_6nM_C03		KG (SEQ ID NO: 153) (Chothia)	
	GFTFSSY (SEQ ID NO: 151) (Chothia);		
	GFTFSSYAMN (SEQ ID NO: 152) (extended)	SDSGGS (SEQ ID NO: 154) (Kabat)	
COMBO_Rd4_0.6nM_C17;	SYPMS (SEQ ID NO: 156) (Kabat);	AIGGSGGSLPYADSV	YWPMIDI (SEQ ID NO: 155)
COMBO_Rd4_0.6nM_C14;		KG (SEQ ID NO: 158) (Chothia)	
COMBO_Rd4_0.6nM_C29;	GFTFSSY (SEQ ID NO: 151) (Chothia);		
and			
COMBO_Rd4_0.6nM_C09	GFTFSSYPMS (SEQ ID NO: 159)	GGSGGS (SEQ ID NO: 159)	

Heavy Chain			
mAb	CDRH1	CDRH2	CDRH3
	157) (extended)	(Kabat)	
C01_Rd4_6nM_C04; C01_Rd4_0.6nM_C03; C01_Rd4_0.6nM_C06; COMBO_Rd4_0.6nM_C02;	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia);	AIGGSGGSLPYADSV KG (SEQ ID NO: 158) (Chothia)	YWPMDS (SEQ ID NO: 161)
COMBO_Rd4_6nM_C21; C01_Rd4_6nM_C26; COMBO_Rd4_0.6nM_C19; C01_Rd4_6nM_C24; C01_Rd4_6nM_C20; C01_Rd4_0.6nM_C09; COMBO_Rd4_0.6nM_C21; C01_Rd4_0.6nM_C04_C27; C01_Rd4_0.6nM_C16; C01_Rd4_6nM_C10; COMBO_Rd4_0.6nM_C20	GFTFSSYPMS (SEQ ID NO: 157) (extended)	GGSGGS (SEQ ID NO: 159) (Kabat)	
P5C1_VHVL (PC1) and	SYPMS (SEQ ID NO: 156) (Kabat);	AIGGSGGSTYYADSV KG	
COMBO_Rd4_0.6nM_C30	GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	(SEQ ID NO: 162) (Chothia) GGSGGS (SEQ ID NO: 159) (Kabat)	
A02_Rd4_0.6nM_C06	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AISDSGGSAWYADS VKG (SEQ ID NO: 163) (Chothia) SDSGGS (SEQ ID NO: 154) (Kabat)	YWPMDS (SEQ ID NO: 164)
A02_Rd4_0.6nM_C09	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia);	AISDSGGSAWYADS VKG (SEQ ID NO: 163)	
		(Chothia) GFTFSSYAMN (SEQ ID NO: 152) (extended)	
A02_Rd4_0.6nM_C16; A02_Rd4_6nM_C16	SYAMN (SEQ ID NO: 150) (Kabat);	AISDFGGSTYYADSV KG	YWPMDS (SEQ ID NO: 165)
(P5A16)	GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	(SEQ ID NO: 165) (Chothia) SDFGGS (SEQ ID NO: 166) (Kabat)	
A02_Rd4_6nM_C01	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151)	AITASGGSTYYADSV KG (SEQ ID NO: 167)	

Heavy Chain			
mAb	CDRH1	CDRH2	CDRH3
	(Chothia);	(Chothia)	
	GFTFSSYAMN (SEQ ID NO: 152) (extended)	TASGGS (SEQ ID NO: 168) (Kabat)	
A02_Rd4_6nM_C26	SYAMN (SEQ ID NO: 150) (Kabat);	AISDSGGSTYYADSV KG	YWPM SL (SEQ ID NO: 164)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	(SEQ ID NO: 153) (Chothia)	
	GFTFSSYAMN (SEQ ID NO: 152) (extended)	SDSGGS (SEQ ID NO: 154) (Kabat)	
A02_Rd4_6nM_C25	SYAMN (SEQ ID NO: 150) (Kabat);	AISDSGGSRWYADS VKG	YWPM TP (SEQ ID NO: 170)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	(SEQ ID NO: 169) (Chothia)	
	GFTFSSYAMN (SEQ ID NO: 152) (extended)	SDSGGS (SEQ ID NO: 154) (Kabat)	
A02_Rd4_6nM_C22	SYAMN (SEQ ID NO: 150) (Kabat);	AVLDSGGSTYYADSV KG	YWPM TP (SEQ ID NO: 170)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	(SEQ ID NO: 171) (Chothia)	
		(Chothia)	
	GFTFSSYAMN (SEQ ID NO: 152) (extended)	LDSGGS (SEQ ID NO: 172) (Kabat)	
A02_Rd4_6nM_C19	SYAMN (SEQ ID NO: 150) (Kabat);	AISDSGGSRWYADS VKG	YWPM SD (SEQ ID NO: 173)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	(SEQ ID NO: 169) (Chothia)	
	GFTFSSYAMN (SEQ ID NO: 152) (extended)	SDSGGS (SEQ ID NO: 154) (Kabat)	
A02_Rd4_0.6nM_C03	SYAMN (SEQ ID NO: 150) (Kabat);	AISDSGGSKWYADS VKG (SEQ ID NO: 174) (Chothia)	YWPM SL (SEQ ID NO: 164)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	SDSGGS (SEQ ID	
	GFTFSSYAMN (SEQ ID NO: 152) (extended)	NO: 154) (Kabat)	
A02_Rd4_6nM_C07	SYAMN (SEQ ID NO: 150) (Kabat);	AIGSGGSLPYADSV KG(SEQ ID NO: 158) (Chothia)	YWPM DS (SEQ ID NO: 161)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	GGSGGS (SEQ ID NO: 159) (Kabat)	
	GFTFSSYAMN (SEQ ID NO: 152) (extended)		
A02_Rd4_6nM_C23	SYAMN (SEQ ID NO: 150)		YWPM SL (SEQ ID NO: 164)

Heavy Chain			
mAb	CDRH1	CDRH2	CDRH3
	(Kabat);	AISDSGGSGWYADS	164)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	VKG (SEQ ID NO: 175) (Chothia)	
	GFTFSSYAMN (SEQ ID NO: 152) (extended)	SDSGGS (SEQ ID NO: 154) (Kabat)	
A02_Rd4_0.6nM_C18	SYAMN (SEQ ID NO: 150) (Kabat);	AVLDSGGSTYYADSV	YWPM SL (SEQ ID NO: 164)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	KG (SEQ ID NO: 171)	
		(Chothia)	
	GFTFSSYAMN (SEQ ID NO: 152) (extended)	LD SGGS (SEQ ID NO: 172) (Kabat)	
A02_Rd4_6nM_C10	SYAMN (SEQ ID NO: 150) (Kabat);	AISDSGGSCWYADS	YWPM TP (SEQ ID NO: 170)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	VKG (SEQ ID NO: 176) (Chothia)	
	GFTFSSYAMN (SEQ ID NO: 152) (extended)	SDSGGS (SEQ ID NO: 154) (Kabat)	
A02_Rd4_6nM_C05	SYAMN (SEQ ID NO: 150) (Kabat);	AIFASGGSTYYADSV	YWPM TP (SEQ ID NO: 170)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	KG (SEQ ID NO: 177) (Chothia)	
	GFTFSSYAMN (SEQ ID NO: 152) (extended)	FASGGS (SEQ ID NO: 178) (Kabat)	
A02_Rd4_0.6nM_C10	SYAMN (SEQ ID NO: 150) (Kabat);	AISGWGGSLPYADS	YWPM DS (SEQ ID NO: 161)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	VKG (SEQ ID NO: 304) (Chothia)	
	GFTFSSYAMN (SEQ ID NO: 152) (extended)	SGWGGS (SEQ ID NO: 179) (Kabat)	
A02_Rd4_6nM_C04	SYAMN (SEQ ID NO: 150) (Kabat);	AIMSSGGPLYADSV	YWPM AL (SEQ ID NO: 182)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	KG (SEQ ID NO: 180) (Chothia)	
	GFTFSSYAMN (SEQ ID NO: 152) (extended)	MSSGGP (SEQ ID NO: 181) (Kabat)	
A02_Rd4_0.6nM_C26	SYAMN (SEQ ID NO: 150) (Kabat);	AILMSGGSTYYADSV	YWPM SL (SEQ ID NO: 164)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	KG (SEQ ID NO: 183)	
		(Chothia)	
	GFTFSSYAMN (SEQ ID NO: 152) (extended)	LMSGGS (SEQ ID NO: 184) (Kabat)	

Heavy Chain			
mAb	CDRH1	CDRH2	CDRH3
A02_Rd4_0.6nM_C13	SYAMN (SEQ ID NO: 150) (Kabat);	AISDSGGYRYYADSV KG	YWPM SL (SEQ ID NO: 164)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	(SEQ ID NO: 185) (Chothia)	
	GFTFSSYAMN (SEQ ID NO: 152) (extended)	SDSGGY (SEQ ID NO: 186) (Kabat)	
A02_Rd4_0.6nM_C01 (P5AC1)	SYAMN (SEQ ID NO: 150) (Kabat);	AILSSGGSTYYADSVK G	YWPM DI (SEQ ID NO: 155)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	(SEQ ID NO: 187) (Chothia)	
	GFTFSSYAMN (SEQ ID NO: 152) (extended)	LSSGGS (SEQ ID NO: 188) (Kabat)	
A02_Rd4_6nM_C08	SYAMN (SEQ ID NO: 150) (Kabat);	AILDSGGSTYYADSV KG (SEQ ID NO: 160) (Chothia)	YWPM SP (SEQ ID NO: 189)
	GFTFSSY (SEQ ID NO: 151) (Chothia);		
	GFTFSSYAMN (SEQ ID NO: 152) (extended)	LD SGGS (SEQ ID NO: 172) (Kabat)	
C01_Rd4_6nM_C12 (PC1C12)	SYPMS (SEQ ID NO: 156) (Kabat);	AIGGSGGWSYYADS VKG	YWPM DS (SEQ ID NO: 161)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	(SEQ ID NO: 190) (Chothia)	
	GFTFSSYPMS (SEQ ID NO: 157) (extended)	GGSGGW (SEQ ID NO: 191) (Kabat)	
C01_Rd4_6nM_C09	SYPMS (SEQ ID NO: 156) (Kabat);	ATVGS GG SIGYADSV KG	YWPM DS (SEQ ID NO: 161)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	(SEQ ID NO: 192)	
		(Chothia)	
COMBO_Rd4_0.6nM_C22 (COM22)		GFTFSSYPMS (SEQ ID NO: 157) (extended)	YWPM DI (SEQ ID NO: 155)
		VGSGGS (SEQ ID NO: 193) (Kabat)	
COMBO_Rd4_0.6nM_C22 (COM22)	SYAMN (SEQ ID NO: 150) (Kabat);	AISDSGGSRWYADS VKG	YWPM DI (SEQ ID NO: 155)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	(SEQ ID NO: 169) (Chothia)	
	GFTFSSYAMN (SEQ ID NO: 152) (extended)	SDSGGS (SEQ ID NO: 154) (Kabat)	
COMBO_Rd4_0.6nM_C10	SYPMS (SEQ ID NO: 156) (Kabat);	AIGGSGGSIHYADSV KG (SEQ ID NO: 194) (Chothia)	YWPM DS (SEQ ID NO: 161)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	GGSGGS (SEQ ID NO: 159) (Kabat)	
COMBO_Rd4_0.6nM_C10	GFTFSSYPMS (SEQ ID NO: 157) (extended)		

Heavy Chain			
mAb	CDRH1	CDRH2	CDRH3
COMBO_Rd4_0.6nM_C04	SYPMS (SEQ ID NO: 156) (Kabat);	AHIGSGGSTYYADSV KG (SEQ ID NO: 195) (Chothia)	YWPMDS (SEQ ID NO: 161)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	IGSGGS (SEQ ID NO: 196) (Kabat)	
	GFTFSSYPMS (SEQ ID NO: 157) (extended)		
COMBO_Rd4_0.6nM_C25	SYPMS (SEQ ID NO: 156) (Kabat);	AIGGSGGSTYYADSV KG (SEQ ID NO: 162) (Chothia)	YWPMDP (SEQ ID NO: 197)
	GFTFSSY (SEQ ID NO: 151) (Chothia);		
	GFTFSSYPMS (SEQ ID NO: 157) (extended)	GGSGGS (SEQ ID NO: 159) (Kabat)	
COMBO_Rd4_6nM_C21	SYPMS (SEQ ID NO: 156) (Kabat);	AIGGSGGSLPYADSV KG	YWPMDS (SEQ ID NO: 161)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	(SEQ ID NO: 158) (Chothia)	
	GFTFSSYPMS (SEQ ID NO: 157) (extended)	GGSGGS (SEQ ID NO: 159) (Kabat)	
COMBO_Rd4_6nM_C11	SYPMS (SEQ ID NO: 156) (Kabat);	AIGGSGGSLGYADSV KG (SEQ ID NO: 198) (Chothia)	YWPMDS (SEQ ID NO: 161)
	GFTFSSY (SEQ ID NO: 151) (Chothia);		
	GFTFSSYPMS (SEQ ID NO: 157) (extended)	GGSGGS (SEQ ID NO: 159) (Kabat)	
COMBO_Rd4_6nM_C09	SYPMS (SEQ ID NO: 156) (Kabat);	AIFASGGSTYYADSV KG (SEQ ID NO: 177) (Chothia)	YWPMDS (SEQ ID NO: 161)
	GFTFSSY (SEQ ID NO: 151) (Chothia);		
	GFTFSSYPMS (SEQ ID NO: 157) (extended)	FASGGS (SEQ ID NO: 178) (Kabat)	
COMBO_Rd4_6nM_C08	SYPMS (SEQ ID NO: 156) (Kabat);	AIGGSGTWYYADS VKG (SEQ ID NO: 199) (Chothia)	YWPMDS (SEQ ID NO: 161)
	GFTFSSY (SEQ ID NO: 151) (Chothia);		
	GFTFSSYPMS (SEQ ID NO: 157) (extended)	GGSGTW (SEQ ID NO: 200) (Kabat)	
COMBO_Rd4_0.6nM_C23	SYPMS (SEQ ID NO: 156) (Kabat);	ALFGSGGSTYYADSV KG (SEQ ID NO: 201) (Chothia)	YWPMDS (SEQ ID NO: 161)
	GFTFSSY (SEQ ID NO: 151) (Chothia);		
	GFTFSSYPMS (SEQ ID NO: 157) (extended)	FGSGGS (SEQ ID NO: 202)	

Heavy Chain			
mAb	CDRH1	CDRH2	CDRH3
	157) (extended)	(Kabat)	
COMBO_Rd4_0.6nM_C12	SYPMS (SEQ ID NO: 156) (Kabat);	AALGSGGSTYYADSV	YWPMDS (SEQ ID NO: 161)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	KG (SEQ ID NO: 203) (Chothia)	
	GFTFSSYPMS (SEQ ID NO: 157) (extended)	LGSGGS (SEQ ID NO: 204) (Kabat)	
COMBO_Rd4_6nM_C07	SYPMS (SEQ ID NO: 156) (Kabat);	AIGGSGGSLPYADSV	YWPMAD (SEQ ID NO: 205)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	KG (SEQ ID NO: 158) (Chothia)	
	GFTFSSYPMS (SEQ ID NO: 157) (extended)	GGSGGS (SEQ ID NO: 159) (Kabat)	
COMBO_Rd4_6nM_C02	SYAMN (SEQ ID NO: 150) (Kabat);	AISDSGGFVYYADSV	YWPMDS (SEQ ID NO: 161)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	KG (SEQ ID NO: 206) (Chothia)	
	GFTFSSYAMN (SEQ ID NO: 152) (extended)	SDSGGF (SEQ ID NO: 207) (Kabat)	
COMBO_Rd4_6nM_C05	SYAMN (SEQ ID NO: 150) (Kabat);	AIGGSGGSTYYADSV	YWPMSL (SEQ ID NO: 164)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	KG (SEQ ID NO: 162) (Chothia)	
	GFTFSSYAMN (SEQ ID NO: 152) (extended)	GGSGGS (SEQ ID NO: 159) (Kabat)	
COMBO_Rd4_6nM_C22	SYAMN (SEQ ID NO: 150) (Kabat);	ACLDSGGSTYYADSV	YWPMDS (SEQ ID NO: 161)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	KG (SEQ ID NO: 208) (Chothia)	
	GFTFSSYAMN (SEQ ID NO: 152) (extended)	LDSGGS (SEQ ID NO: 172) (Kabat)	
COMBO_Rd4_6nM_C11	SYPMS (SEQ ID NO: 156) (Kabat);	AALGSGGSTYYADSV	YWPMSL (SEQ ID NO: 164)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	KG (SEQ ID NO: 203) (Chothia)	
	GFTFSSYPMS (SEQ ID NO: 157) (extended)	LGSGGS (SEQ ID NO: 204) (Kabat)	
Heavy chain consensus	SYX ₁ MX ₂ , wherein X ₁ is A or P; and X ₂ is T, N, or S (Kabat) (SEQ ID NO: 301)	AX ₁ X ₂ X ₃ X ₄ GX ₅ X ₆ X ₇ X ₈ YADX ₉ X ₁₀ KG, wherein X ₁ is I, V, T, H, L, A, or C; X ₂ is S, D, G, T, I, L, F, M, or V; X ₃ is G, Y, L, H, D, A, S, or M; X ₄ is S, Q, T, A, F, or W; X ₅ is G or T; X ₆ is N,	VSPIX ₁ X ₂ X ₃ MD Y, wherein X ₁ is A or Y; X ₂ is A or S; and X ₃ is G, Q, L, P, or E (SEQ ID NO: 307)
	GFTFX ₁ SY, wherein X ₁ is G or S (Chothia) (SEQ ID NO: 302)		

Heavy Chain			
mAb	CDRH1	CDRH2	CDRH3
	GFTFX ₁ 5YX ₂ MX ₃ , wherein X ₁ is G or S, X ₂ is A or P; and X ₃ is T, N, or S (SEQ ID NO: 303) (extended)	S, P, Y, W, or F; X ₇ is S, T, I, L, T, A, R, V, K, G, or C; X ₈ is F, Y, P, W, H, or G; X ₉ is V, R, or L; and X ₁₀ is G or T (Chothia) (SEQ ID NO: 305)	YWPMX ₁ X ₂ , wherein X ₁ is D, S, T, or A; and X ₂ is I, S, L, P, or D (SEQ ID NO: 308)
		X ₁ X ₂ X ₃ X ₄ X ₅ X ₆ , wherein X ₁ is S, V, I, D, G, T, L, F, or M; X ₂ is G, Y, L, H, D, A, S, or M; X ₃ is S, G, F, or W; X ₄ is G or S; X ₅ is G or T; and X ₆ is N, S, P, Y, or W (Kabat) (SEQ ID NO: 306)	
P4G4	SYAMS (SEQ ID NO: 381) (Kabat);	SASGGS (SEQ ID NO: 383) (Kabat)	LSWSGAFDN (SEQ ID NO: 385)
	GFTFSSY (SEQ ID NO: 151) (Chothia);	AISASGGSTYYADSV	
	GFTFSSYAMS (SEQ ID NO: 382) (extended)	KG (SEQ ID NO: 384) (Chothia)	
P1A11	SYAMS (SEQ ID NO: 386) (Kabat);	SGSGGS (SEQ ID NO: 389) (Kabat)	VGTSGAFGI (SEQ ID NO: 391)
	GFTFRSY (SEQ ID NO: 387)	AISGSGGSTFYADSV	
	GFTFRSYAMS (SEQ ID NO: 388)	KG (SEQ ID NO: 390) (Chothia)	
Light Chain			
mAb	CDRL1	CDRL2	CDRL3
P6E01	RASQSVSSSYLA (SEQ ID NO: 209)	GASSRAT (SEQ ID NO: 210)	QHYGSPPSFT (SEQ ID NO: 211)
For the following mAbs: P6E01/P6E01; and			
P6E01/H3.AQ.			
L1.LGF/L3.KW	RASQSLGSFYLA (SEQ ID NO: 212)	GASSRAT (SEQ ID NO: 210)	KHYGWPPSFT (SEQ ID NO: 213)
For the following mAbs:			
L1.LGF/L3.KW/P6E01;			
L1.LGF/L3.KW/H3.AL;			
L1.LGF/L3.KW/H3.AP; and			
L1.LGF/L3.KW/H3.AQ			
L1.LGF/L3.NY	RASQSLGSFYLA (SEQ ID NO: 212)	GASSRAT (SEQ ID NO: 210)	QHYNPPSFT (SEQ ID NO: 214)
For the following mAbs:			
L1.LGF/L3.NY/P6E01;			
L1.LGF/L3.NY/H3.AL;			
L1.LGF/L3.NY/H3.AP; and			
L1.LGF/L3.NY/H3AQ			
L1.GDF/L3.NY	RASQSVGDFYLA (SEQ ID NO: 215)	GASSRAT (SEQ ID NO: 210)	QHYNPPSFT (SEQ ID NO: 214)
For the following mAbs:			
L1.GDF/L3.NY/P6E01;			
L1.GDF/L3.NY/H3.AL;			
L1.GDF/L3.NY/H3.AP; and			
L1.GDF/L3.NY/H3.AQ			
L1.LGF/L3.PY	RASQSLGSFYLA (SEQ ID NO: 212)	GASSRAT (SEQ ID NO: 210)	QHYPYPPSFT (SEQ ID NO: 216)
For the following mAbs:			
L1.LGF/L3.PY/H3.AP; and			

Light Chain			
mAb	CDRL1	CDRL2	CDRL3
L1.LGF/L3.PY/H3.AQ			
L1.GDF /L3.KW	RASQSVGDFYLA (SEQ ID NO: 215)	GASSRAT (SEQ ID NO: 210)	KHYGWPPSFT (SEQ ID NO: 213)
For the following mAbs:			
L1.GDF /L3.KW/H3.AL;			
L1.GDF /L3.KW/H3.AP;			
and L1.GDF /L3.KW/H3.AQ			
L1.GDF /L3.PY/H3.AQ	RASQSVGDFYLA (SEQ ID NO: 215)	GASSRAT (SEQ ID NO: 210)	QHYPYPPSFT (SEQ ID NO: 216)
L3.KW/P6E01	RASQSVSSSYLA (SEQ ID NO: 209)	GASSRAT (SEQ ID NO: 210)	KHYGWPPSFT (SEQ ID NO: 213)
L3.PY	RASQSVSSSYLA (SEQ ID NO: 209)	GASSRAT (SEQ ID NO: 210)	QHYPYPPSFT (SEQ ID NO: 216)
For the following mAbs:			
L3.PY/P6E01;			
L3.PY/H2.QR;			
L3.PY/H2.DY;			
L3.PY/H2.YQ;			
L3.PY/H2.LT;			
L3.PY/H2.HA;			
L3.PY/H2.QL;			
L3.PY/H3.YA;			
L3.PY/H3.AE;			
L3.PY/H3.AQ;			
L3.PY/H3.TAQ			
L3.NY/P6E01	RASQSVSSSYLA (SEQ ID NO: 209)	GASSRAT (SEQ ID NO: 210)	QHYNPPSFT (SEQ ID NO: 214)
L3.PY/L1.PS	RASQSVSSSYPS (SEQ ID NO: 217)	GASSRAT (SEQ ID NO: 210)	QHYPYPPSFT (SEQ ID NO: 216)
For the following mAbs:			
L3.PY/L1.PS/P6E01; P6DY;			
L3.PY/L1.PS/H2.QR;			
L3.PY/L1.PS/H2.DY;			
L3.PY/L1.PS/H2.YQ;			
L3.PY/L1.PS/H2.LT;			
L3.PY/L1.PS/H2.HA;			
L3.PY/L1.PS/H2.QL;			
L3.PY/L1.PS/H3.YA;			
L3.PY/L1.PS/H3.AE;			
L3.PY/L1.PS/H3.AQ;			
L3.PY/L1.PS/H3.TAQ;			
L3.PY/L1.AH	RASQSVSAHYLA (SEQ ID NO: 218)	GASSRAT (SEQ ID NO: 210)	QHYPYPPSFT (SEQ ID NO: 216)
For the following mAbs:			
L3.PY/L1.AH/P6E01;			
L3.PY/L1.AH/H2.QR;			
L3.PY/L1.AH/H2.DY;			
L3.PY/L1.AH/H2.YQ;			
L3.PY/L1.AH/H2.LT;			
L3.PY/L1.AH/H2.HA;			
L3.PY/L1.AH/H2.QL;			
L3.PY/L1.AH/H3.YA;			

Light Chain			
mAb	CDRL1	CDRL2	CDRL3
L3.PY/L1.AH/H3.AE;			
L3.PY/L1.AH/H3.AQ;			
L3.PY/L1.AH/H3.TAQ			
L3.PY/L1.FF			
For the following mAbs:	RASQSVSSFFLA (SEQ ID NO: 219)	GASSRAT (SEQ ID NO: 210)	QHYPYPPSFT (SEQ ID NO: 216)
L3.PY/L1.FF/P6E01;			
L3.PY/L1.FF/H2.QR;			
L3.PY/L1.FF/H2.DY;			
L3.PY/L1.FF/H2.YQ;			
L3.PY/L1.FF/H2.LT;			
L3.PY/L1.FF/H2.HA;			
L3.PY/L1.FF/H2.QL;			
L3.PY/L1.FF/H3.YA;			
L3.PY/L1.FF/H3.AE;			
L3.PY/L1.FF/H3.AQ; and			
L3.PY/L1.FF/H3.TAQ			
L3.PY/L1.PH	RASQSVSPHYLA (SEQ ID NO: 219)	GASSRAT (SEQ ID NO: 210)	QHYPYPPSFT (SEQ ID NO: 216)
For the following mAbs:			
L3.PY/L1.PH/P6E01;			
L3.PY/L1.PH/H2.QR;			
L3.PY/L1.PH/H2.HA;			
L3.PY/L1.PH/H3.AE;			
L3.PY/L1.PH/H3.AQ; and			
L3.PY/L1.PH/H3.TAQ			
L3.PY/L3.KY	RASQSVSSSYLA (SEQ ID NO: 209)	GASSRAT (SEQ ID NO: 210)	KYYPYPPSFT (SEQ ID NO: 220)
For the following mAbs:			
L3.PY/L3.KY/P6E01;			
L3.PY/L3.KY/H2.QR;			
L3.PY/L3.KY/H2.DY;			
L3.PY/L3.KY/H2.YQ;			
L3.PY/L3.KY/H2.LT;			
L3.PY/L3.KY/H2.HA;			
L3.PY/L3.KY/H2.QL;			
L3.PY/L3.KY/H3.YA; and			
L3.PY/L3.KY/H3.TAQ			
L3.PY/L3.KF	RASQSVSSSYLA (SEQ ID NO: 209)	GASSRAT (SEQ ID NO: 210)	KFYPYPPSFT (SEQ ID NO: 220)
For the following mAbs:			
L3.PY/L3.KF/H2.DY;			
L3.PY/L3.KF/H2.YQ;			
L3.PY/L3.KF/H2.LT;			
L3.PY/L3.KF/H2.QL;			
L3.PY/L3.KF/H3.YA;			
L3.PY/L3.KF/H3.AE;			
L3.PY/L3.KF/H3.AQ; and			
L3.PY/L3.KF/H3.TAQ			
P5A2_VHVL (P5A)	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYGSWPLT (SEQ ID NO: 222)
A02_Rd4_0.6nM_C06	RASQSVSVIYLA (SEQ ID NO: 223)	DASIRAT (SEQ ID NO: 221)	QQYQRWPLT (SEQ ID NO: 224)

Light Chain			
mAb	CDRL1	CDRL2	CDRL3
A02_Rd4_0.6nM_C09; COMBO_Rd_0.6nM_C29; and COMBO_Rd4_0.6nM_C21	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYQSWPLT (SEQ ID NO: 225)
A02_Rd4_6nM_C16 (P5AC16)	RASQSVSDIYLA (SEQ ID NO: 226)	DASIRAT (SEQ ID NO: 221)	QQYQTWPLT (SEQ ID NO: 227)
A02_Rd4_6nM_C03	RASQSVSNIYLA (SEQ ID NO: 228)	DASIRAT (SEQ ID NO: 221)	QQYQGWPLT (SEQ ID NO: 229)
A02_Rd4_6nM_C01	RASQSVSAYYLA (SEQ ID NO: 230)	DASIRAT (SEQ ID NO: 221)	QQYERWPLT (SEQ ID NO: 231)
A02_Rd4_6nM_C26	RASQSVSSIYLA (SEQ ID NO: 232)	DASIRAT (SEQ ID NO: 221)	QQYQVWPLT (SEQ ID NO: 233)
A02_Rd4_6nM_C25	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYLDWPLT (SEQ ID NO: 234)
A02_Rd4_6nM_C22	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYQVWPLT (SEQ ID NO: 233)
A02_Rd4_6nM_C19	RASQSVSVIYLA (SEQ ID NO: 223)	DASIRAT (SEQ ID NO: 221)	QQYLAWPLT (SEQ ID NO: 236)
A02_Rd4_0.6nM_C03	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYFTWPLT (SEQ ID NO: 237)
A02_Rd4_6n_M_C07	RASQSVSPYYLA (SEQ ID NO: 238)	DASIRAT (SEQ ID NO: 221)	QQYERWPLT (SEQ ID NO: 231)
A02_Rd4_6nM_C23	RASQSVSVEYLA (SEQ ID NO: 239)	DASIRAT (SEQ ID NO: 221)	QQYARWPLT (SEQ ID NO: 240)
A02_Rd4_0.6nM_C18	RASQSVSEIYLA (SEQ ID NO: 241)	DASIRAT (SEQ ID NO: 221)	QQYFGWPLT (SEQ ID NO: 242)
A02_Rd4_6n_M_C10	RASQSVEMSYLA (SEQ ID NO: 243)	DASIRAT (SEQ ID NO: 221)	QQYAHWPLT (SEQ ID NO: 244)
A02_Rd4_6nM_C05	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYQRWPLT (SEQ ID NO: 224)
A02_Rd4_0.6nM_C10	RASQSVSAQYLA (SEQ ID NO: 245)	DASIRAT (SEQ ID NO: 221)	QQYQRWPLT (SEQ ID NO: 224)
A02_Rd4_6nM_C04	RASQSVSAIYLA (SEQ ID NO: 235)	DASIRAT (SEQ ID NO: 221)	QQYQVWPLT (SEQ ID NO: 233)
A02_Rd4_0.6nM_C26	GPSQSVSSSYLA (SEQ ID NO: 246)	DASIRAT (SEQ ID NO: 221)	QQYQSWPLT (SEQ ID NO: 225)
A02_Rd4_0.6nM_C13	RASQSVSSSYWA (SEQ ID NO: 247)	DASIRAT (SEQ ID NO: 221)	QQYESWPLT (SEQ ID NO: 248)
A02_Rd4_0.6nM_C01 (P5AC1)	RGGQSVSSSYLA (SEQ ID NO: 249)	DASIRAT (SEQ ID NO: 221)	QQYQSWPLT (SEQ ID NO: 225)
A02_Rd4_6n_M_C08	RASQSVSFIYLA (SEQ ID NO: 250)	DASIRAT (SEQ ID NO: 221)	QQYGSWPLT (SEQ ID NO: 222)
P5C1_VHVL (PC1)	RASQSVSSTYLA (SEQ ID NO: 251)	DASSRAP (SEQ ID NO: 252)	QQYSTSPLT (SEQ ID NO: 253)
C01_Rd4_6nM_C24	RASQSVSPEYLA (SEQ ID NO: 254)	DASSRAP (SEQ ID NO: 252)	QQYSVWPLT (SEQ ID NO: 255)
C01_Rd4_6nM_C26	RASQSVSAIYLA (SEQ ID NO: 235)	DASSRAP (SEQ ID NO: 252)	QQYSAWPLT (SEQ ID NO: 256)
C01_Rd4_6nM_C10	RASQSVSSVYLA (SEQ ID NO: 257)	DASSRAP (SEQ ID NO: 252)	QQYSTWPLT (SEQ ID NO: 258)
C01_Rd4_0.6nM_C27	RASQSVSSTYLA (SEQ ID NO: 251)	DASSRAP (SEQ ID NO: 252)	QQYSRWPLT (SEQ ID NO: 259)
C01_Rd4_6nM_C20	RASQSVSPIYLA (SEQ ID NO: 260)	DASSRAP (SEQ ID NO: 252)	QQYSAFPLT (SEQ ID NO: 261)
C01_Rd4_6nM_C12 (PC1C12)	WLSQSVSSTYLA (SEQ ID NO: 262)	DASSRAP (SEQ ID NO: 252)	QQYSEWPLT (SEQ ID NO: 263)
C01_Rd4_0.6nM_C16	RASQSVSSTYLA (SEQ ID NO: 251)	DASSRAP (SEQ ID NO: 252)	QQYSSWPLT (SEQ ID NO: 253)

Light Chain			
mAb	CDRL1	CDRL2	CDRL3
	251)		NO: 264)
C01_Rd4_0.6nM_C09	RASQSVSSIFLA (SEQ ID NO: 265)	DASSRAP (SEQ ID NO: 252)	QQYSAWPLT (SEQ ID NO: 256)
C01_Rd4_6nM_C09	ACSQSVSSTYLA (SEQ ID NO: 266)	DASSRAP (SEQ ID NO: 252)	QQYSAWPLT (SEQ ID NO: 256)
C01_Rd4_0.6nM_C03	RASCDVSSTYLA (SEQ ID NO: 267)	DASSRAP (SEQ ID NO: 252)	QQYMRSPLT (SEQ ID NO: 268)
C01_Rd4_0.6nM_C06	RASEAVPSTYLA (SEQ ID NO: 269)	DASSRAP (SEQ ID NO: 252)	QQYSAFPLT (SEQ ID NO: 261)
C01_Rd4_0.6nM_C04	CSSQSVSSTYLA (SEQ ID NO: 270)	DASSRAP (SEQ ID NO: 252)	QQYSAFPLT (SEQ ID NO: 261)
COMBO_Rd4_0.6nM_C22 (COM22)	RASVRVSSTYLA (SEQ ID NO: 271)	DASIRAT (SEQ ID NO: 221)	QQYMKWPLT (SEQ ID NO: 272)
COMBO_Rd4_6nM_C21	RASQSVSAAYLA (SEQ ID NO: 273)	DASIRAT (SEQ ID NO: 221)	QQYMCWPLT (SEQ ID NO: 274)
COMBO_Rd4_6nM_C10	RASQSVSSSYWG (SEQ ID NO: 275)	DASIRAT (SEQ ID NO: 221)	QQYQCWPLT (SEQ ID NO: 276)
COMBO_Rd4_0.6nM_C04	RASQSVSSTYLA (SEQ ID NO: 251)	DASIRAT (SEQ ID NO: 221)	QQYQSWPLT (SEQ ID NO: 225)
COMBO_Rd4_6nM_C25	RASQSVSSPYLA (SEQ ID NO: 277)	DASIRAT (SEQ ID NO: 221)	QQYQSWPLT (SEQ ID NO: 225)
COMBO_Rd4_6nM_C11	RASQSVSPIYLA (SEQ ID NO: 260)	DASIRAT (SEQ ID NO: 221)	QQYKAWPLT (SEQ ID NO: 278)
COMBO_Rd4_0.6nM_C20	RASQSVSYLYLA (SEQ ID NO: 279)	DASIRAT (SEQ ID NO: 221)	QQYMEWPLT (SEQ ID NO: 280)
COMBO_Rd4_6nM_C09	RASQSVSAQYLA (SEQ ID NO: 245)	DASIRAT (SEQ ID NO: 221)	QQYQAWPLT (SEQ ID NO: 281)
COMBO_Rd4_6nM_C08	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYQKWPLT (SEQ ID NO: 282)
COMBO_Rd4_0.6nM_C19	RASQSVSAVYLA (SEQ ID NO: 283)	DASIRAT (SEQ ID NO: 221)	QQYRAWPLT (SEQ ID NO: 284)
COMBO_Rd4_0.6nM_C02	RASIAVSSTYLA (SEQ ID NO: 285)	DASIRAT (SEQ ID NO: 221)	QQYMWPLT (SEQ ID NO: 286)
COMBO_Rd4_0.6nM_C23	RPRQSVSSSYLA (SEQ ID NO: 287)	DASIRAT (SEQ ID NO: 221)	QQYQDWPLT (SEQ ID NO: 288)
COMBO_Rd4_0.6nM_C09	RASQSVSSTYLA (SEQ ID NO: 251)	DASIRAT (SEQ ID NO: 221)	QQYQEWPLT (SEQ ID NO: 289)
COMBO_Rd4_6nM_C12	RASQSVSASYLA (SEQ ID NO: 290)	DASIRAT (SEQ ID NO: 221)	QQYMSWPLT (SEQ ID NO: 291)
COMBO_Rd4_0.6nM_C30	RASQSVSYMILA (SEQ ID NO: 292)	DASIRAT (SEQ ID NO: 221)	QQYKSWPLT (SEQ ID NO: 293)
COMBO_Rd4_0.6nM_C14	RASQSVSAIYLA (SEQ ID NO: 235)	DASIRAT (SEQ ID NO: 221)	QQYYGWPLT (SEQ ID NO: 294)
COMBO_Rd4_6nM_C07	RASQPISSSYLA (SEQ ID NO: 295)	DASIRAT (SEQ ID NO: 221)	QQYQGWPLT (SEQ ID NO: 229)
COMBO_Rd4_6nM_C02	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYEFWPLT (SEQ ID NO: 296)
COMBO_Rd4_0.6nM_C05	RASQSVSSTYLA (SEQ ID NO: 251)	DASIRAT (SEQ ID NO: 221)	QQYMSWPLT (SEQ ID NO: 291)
COMBO_Rd4_0.6nM_C17	RASQGISSTYLA (SEQ ID NO: 297)	DASIRAT (SEQ ID NO: 221)	QQYAYWPLT (SEQ ID NO: 298)
COMBO_Rd4_6nM_C22	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYQGWPLT (SEQ ID NO: 229)
COMBO_Rd4_0.6nM_C11	RASQSVSVRYLA (SEQ ID NO: 299)	DASIRAT (SEQ ID NO: 221)	QQYGSWPIT (SEQ ID NO: 300)
Light chain consensus	X ₁ X ₂ X ₃ X ₄ X ₅ X ₆ X ₇ X ₈ X ₉ X ₁₀ X ₁₁ X ₁₂ , wherein X ₁ is R, G, W, A, or C; X ₂	X ₁ ASX ₂ RAX ₃ , wherein X ₁ is G or D; X ₂ is S or I; and X ₃ is	X ₁ X ₂ YX ₃ X ₄ PPSF T, wherein X ₁ is Q or K;

Light Chain			
mAb	CDRL1	CDRL2	CDRL3
	is A, P, G, L, C, or S; X ₃ is S, G, or R; X ₄ is Q, C, E, V, or I; X ₅ is S, P, G, A, R, or D; X ₆ is V, G, I, or L; X ₇ is S, E, D, P, or G; X ₈ is S, P, F, A, M, E, V, N, D, or Y; X ₉ is I, T, V, E, F S, A, M, Q, Y, H, or R; X ₁₀ is Y or F; X ₁₁ is L, W, or P; and X ₁₂ is A, S, or G (SEQ ID NO: 309)	T or P (SEQ ID NO: 310)	X ₂ is H or Y; X ₃ is G, N, or P; and X ₄ is S, W, or Y (SEQ ID NO: 311) QQYX ₁ X ₂ X ₃ PX ₄ T, wherein X ₁ is G, Q, E, L, F, A, S, M, K, R, or Y; X ₂ is S, R, T, G, V, F, Y, D, A, H, V, E, K, or C; X ₃ is W, F, or S; and X ₄ is L or I (SEQ ID NO: 312)
P4G4	RASQSVSSSYLA (SEQ ID NO: 209)	GASSRAY (SEQ ID NO: 392)	QHYGSPPLFT (SEQ ID NO: 393)
P1A11	RASQNVSSSYLA (SEQ ID NO: 379)	GASYRAT (SEQ ID NO: 395)	QHYGSPPSFT (SEQ ID NO: 211)
P6AP	RASQLGSFYLA (SEQ ID NO: 377)	GASSRAT (SEQ ID NO: 210)	QHYNPPSFT (SEQ ID NO: 214)

[0100] The disclosure encompasses modifications to the CARs and polypeptides of the variants shown in Table 1, including functionally equivalent CARs having modifications which do not significantly affect their properties and variants which have enhanced or decreased activity and/or affinity. For example, the amino acid sequence may be mutated to obtain an antibody with the desired binding affinity to BCMA. Modification of polypeptides is routine practice in the art and need not be described in detail herein. Examples of modified polypeptides include polypeptides with conservative substitutions of amino acid residues, one or more deletions or additions of amino acids which do not significantly deleteriously change the functional activity, or which mature (enhance) the affinity of the polypeptide for its ligand, or use of chemical analogs.

[0101] Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an antibody with an N-terminal methionyl residue or the antibody fused to an epitope tag. Other insertional variants of the antibody molecule include the fusion to the N- or C-terminus of the antibody of an enzyme or a polypeptide which increases the half-life of the antibody in the blood circulation.

[0102] Substitution variants have at least one amino acid residue in the antibody molecule removed and a different residue inserted in its place. The sites of greatest interest for substitutional mutagenesis include the hypervariable regions, but FR alterations are also contemplated. Conservative substitutions are shown in Table 2.1 under the heading of "conservative substitutions." If such substitutions result in a change in biological activity, then more substantial changes, denominated "exemplary substitutions" in Table 2.1, or as further described below in reference to amino acid classes, may be introduced and the products screened.

Table 2.1: Amino Acid Substitutions

Original Residue (naturally occurring amino acid)	Conservative Substitutions	Exemplary Substitutions
Ala (A)	Val	Val; Leu; Ile
Arg (R)	Lys	Lys; Gln; Asn
Asn (N)	Gln	Gln; His; Asp, Lys; Arg
Asp (D)	Glu	Glu; Asn
Cys (C)	Ser	Ser; Ala
Gln (Q)	Asn	Asn; Glu
Glu (E)	Asp	Asp; Gln
Gly (G)	Ala	Ala
His (H)	Arg	Asn; Gln; Lys; Arg
Ile (I)	Leu	Leu; Val; Met; Ala; Phe; Norleucine
Leu (L)	Ile	Norleucine; Ile; Val; Met; Ala; Phe
Lys (K)	Arg	Arg; Gln; Asn
Met (M)	Leu	Leu; Phe; Ile
Phe (F)	Tyr	Leu; Val; Ile; Ala; Tyr
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr

Original Residue (naturally occurring amino acid)	Conservative Substitutions	Exemplary Substitutions
Thr (T)	Ser	Ser
Trp (W)	Tyr	Tyr; Phe
Tyr (Y)	Phe	Trp; Phe; Thr; Ser
Val (V)	Leu	Ile; Leu; Met; Phe; Ala; Norleucine

[0103] In some examples, the disclosure provides a CAR comprising an extracellular ligand-binding domain that binds to BCMA and competes for binding to BCMA with a CAR described herein, including P6E01/P6E01, P6E01/H3.AQ, L1.LGF/L3.KW/P6E01; L1.LGF/L3.NY/P6E01, L1.GDF/L3.NY/P6E01, L1.LGF/L3.KW/H3.AL, L1.LGF/L3.KW/H3.AP, L1.LGF/L3.KW/H3.AQ, L1.LGF/L3.PY/H3.AP, L1.LGF/L3.PY/H3.AQ, L1.LGF/L3.NY/H3.AL, L1.LGF/L3.NY/H3.AP, L1.LGF/L3.NY/H3.AQ, L1.GDF/L3.KW/H3.AL, L1.GDF/L3.KW/H3.AP, L1.GDF/L3.KW/H3.AQ, L1.GDF/L3.PY/H3.AQ, L1.GDF/L3.NY/H3.AL, L1.GDF/L3.NY/H3.AP, L1.GDF/L3.NY/H3.AQ, L3.KW/P6E01, L3.PY/P6E01, L3.NY/P6E01, L3.PY/L1.PS/P6E01, L3.PY/L1.AH/P6E01, L3.PY/L1.FF/P6E01, L3.PY/L1.PH/P6E01, L3.PY/L3.KY/P6E01, L3.PY/L3.KF/P6E01, L3.PY/H2.QR, L3.PY/H2.DY, L3.PY/H2.YQ, L3.PY/H2.LT, L3.PY/H2.HA, L3.PY/H2.QL, L3.PY/H3.YA, L3.PY/H3.AE, L3.PY/H3.AQ, L3.PY/H3.TAQ, L3.PY/P6E01, L3.PY/L1.PS/H2.QR, L3.PY/L1.PS/H2.DY, L3.PY/L1.PS/H2.YQ, L3.PY/L1.PS/H2.LT, L3.PY/L1.PS/H2.HA, L3.PY/L1.PS/H2.QL, L3.PY/L1.PS/H3.YA, L3.PY/L1.PS/H3.AE, L3.PY/L1.PS/H3.AQ, L3.PY/L1.PS/H3.TAQ, L3.PY/L1.AH/H2.QR, L3.PY/L1.AH/H2.DY, L3.PY/L1.AH/H2.YQ, L3.PY/L1.AH/H2.LT, L3.PY/L1.AH/H2.HA, L3.PY/L1.AH/H2.QL, L3.PY/L1.AH/H3.YA, L3.PY/L1.AH/H3.AE, L3.PY/L1.AH/H3.AQ, L3.PY/L1.AH/H3.TAQ, L3.PY/L1.FF/H2.QR, L3.PY/L1.FF/H2.DY, L3.PY/L1.FF/H2.YQ, L3.PY/L1.FF/H2.LT, L3.PY/L1.FF/H2.HA, L3.PY/L1.FF/H2.QL, L3.PY/L1.FF/H3.YA, L3.PY/L1.FF/H3.AE, L3.PY/L1.FF/H3.AQ, L3.PY/L1.FF/H3.TAQ, L3.PY/L1.PH/H2.QR, L3.PY/L1.PH/H2.HA, L3.PY/L1.PH/H3.AE, L3.PY/L1.PH/H3.AQ, L3.PY/L1.PH/H3.TAQ, L3.PY/L3.KY/H2.QR, L3.PY/L3.KY/H2.DY, L3.PY/L3.KY/H2.YQ, L3.PY/L3.KY/H2.LT, L3.PY/L3.KY/H2.HA, L3.PY/L3.KY/H2.QL, L3.PY/L3.KY/H3.YA, L3.PY/L3.KY/H3.TAQ, L3.PY/L3.KF/H2.DY, L3.PY/L3.KF/H2.YQ, L3.PY/L3.KF/H2.LT, L3.PY/L3.KF/H2.QL, L3.PY/L3.KF/H3.YA, L3.PY/L3.KF/H3.AE, L3.PY/L3.KF/H3.AQ, L3.PY/L3.KF/H3.TAQ, P5A2_VHVL, A02_Rd4_0.6nM_C06, A02_Rd4_0.6nM_C09, A02_Rd4_6nM_C16, A02_Rd4_6nM_C03, A02_Rd4_6nM_C01, A02_Rd4_6nM_C26, A02_Rd4_6nM_C25, A02_Rd4_6nM_C22, A02_Rd4_6nM_C19, A02_Rd4_0.6nM_C03, A02_Rd4_6nM_C07, A02_Rd4_6nM_C23, A02_Rd4_0.6nM_C18, A02_Rd4_6nM_C10, A02_Rd4_6nM_C05, A02_Rd4_0.6nM_C10, A02_Rd4_6nM_C04, A02_Rd4_0.6nM_C26, A02_Rd4_0.6nM_C13, A02_Rd4_0.6nM_C01, A02_Rd4_6nM_C08, P5C1_VHVL, C01_Rd4_6nM_C24, C01_Rd4_6nM_C26, C01_Rd4_6nM_C10, C01_Rd4_0.6nM_C27, C01_Rd4_6nM_C20, C01_Rd4_6nM_C12, C01_Rd4_0.6nM_C16, C01_Rd4_0.6nM_C09, C01_Rd4_6nM_C09, C01_Rd4_0.6nM_C03, C01_Rd4_0.6nM_C06, C01_Rd4_6nM_C04, COMBO_Rd4_0.6nM_C22, COMBO_Rd4_6nM_C21, COMBO_Rd4_6nM_C10, COMBO_Rd4_0.6nM_C04, COMBO_Rd4_6nM_C25, COMBO_Rd4_0.6nM_C21, COMBO_Rd4_6nM_C11, COMBO_Rd4_0.6nM_C20, COMBO_Rd4_6nM_C09, COMBO_Rd4_6nM_C08, COMBO_Rd4_0.6nM_C19, COMBO_Rd4_0.6nM_C02, COMBO_Rd4_0.6nM_C23, COMBO_Rd4_0.6nM_C29, COMBO_Rd4_0.6nM_C09, COMBO_Rd4_6nM_C12, COMBO_Rd4_0.6nM_C30, COMBO_Rd4_0.6nM_C14, COMBO_Rd4_6nM_C07, COMBO_Rd4_6nM_C02, COMBO_Rd4_0.6nM_C05, COMBO_Rd4_0.6nM_C17, COMBO_Rd4_6nM_C22, COMBO_Rd4_0.6nM_C11, or COMBO_Rd4_0.6nM_C29.

[0104] In some embodiments, the invention provides a CAR, which specifically binds to BCMA, wherein the CAR comprises a VH region comprising a sequence shown in SEQ ID NO: 33; and/or a VL region comprising a sequence shown in SEQ ID NO: 34. In some examples, the disclosure provides a CAR, which specifically binds to BCMA, wherein the CAR comprises a VH region comprising a sequence shown in SEQ ID NO: 33, 72, 39, 76, 83, 92, 25, or 8; and/or a VL region comprising a sequence shown in SEQ ID NO: 34, 73, 40, 77, 84, 93, 18, or 80. In some examples, the disclosure also provides CARs comprising CDR portions of antibodies to BCMA antibodies based on CDR contact regions. CDR contact regions are regions of an antibody that imbue specificity to the antibody for an antigen. In general, CDR contact regions include the residue positions in the CDRs and Vernier zones which are constrained in order to maintain proper loop structure for the antibody to bind a specific antigen. See, e.g., Makabe et al., J. Biol. Chem., 283:1156-1166, 2007. Determination of CDR contact regions is well within the skill of the art.

[0105] The binding affinity (K_D) of the BCMA specific CAR as described herein to BCMA (such as human BCMA (e.g., (SEQ ID NO: 354) can be about 0.002 to about 6500 nM. In some embodiments, the binding affinity is about any of 6500 nm, 6000 nm, 5986 nm, 5567 nm, 5500 nm, 4500 nm, 4000 nm, 3500 nm, 3000 nm, 2500 nm, 2134 nm, 2000 nm, 1500 nm, 1000 nm, 750 nm, 500 nm, 400 nm, 300 nm, 250 nm, 200 nM, 193 nM, 100 nM, 90 nM, 50 nM, 45 nM, 40 nM, 35 nM, 30 nM, 25 nM, 20 nM, 19 nm, 18 nm, 17 nm, 16 nm, 15 nM, 10 nM, 8 nM, 7.5 nM, 7 nM, 6.5 nM, 6 nM, 5.5 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, 0.5 nM, 0.3 nM, 0.1 nM, 0.01 nM, or 0.002 nM. In some embodiments, the binding affinity is less than about any of 6500 nm, 6000 nm, 5500 nm, 5000 nm, 4000 nm, 3000 nm, 2000 nm, 1000 nm, 900 nm, 800 nm, 250 nM, 200 nM, 100 nM, 50 nM, 30 nM, 20 nM, 10 nM, 7.5 nM, 7 nM, 6.5 nM, 6 nM, 5 nM, 4.5 nM, 4 nM, 3.5 nM, 3 nM, 2.5 nM, 2 nM, 1.5 nM, 1 nM, or 0.5 nM.

[0106] The intracellular signaling domain of a CAR according to the invention is responsible for intracellular signaling following the binding of extracellular ligand-binding domain to the target resulting in the activation of the immune cell and immune response. The intracellular signaling domain has the ability to activate of at least one of the normal effector functions of the immune cell in which the CAR is expressed. For example, the effector function of a T cell can be a cytolytic activity or helper activity including the secretion of cytokines.

[0107] In some embodiments, an intracellular signaling domain for use in a CAR can be the cytoplasmic sequences of, for example without limitation, the T cell receptor and co-receptors that act in concert to initiate signal transduction following antigen receptor engagement, as well as any derivative or variant of these sequences and any synthetic sequence that has the same functional capability. Intracellular signaling domains comprise two distinct classes of cytoplasmic signaling sequences: those that initiate antigen-dependent primary activation, and those that act in an antigen- independent manner to provide a secondary or co-stimulatory signal. Primary cytoplasmic signaling sequences can comprise signaling motifs which are known as immunoreceptor tyrosine-based activation motifs of ITAMs. ITAMs are well defined signaling motifs found in the intracytoplasmic tail of a variety of receptors that serve as binding sites for syk/zap70 class tyrosine kinases. Examples of ITAM used in the invention can include as non limiting examples those derived from TCR ζ , FcR γ , FcR β , FcR ϵ , CD3 γ , CD3 δ , CD3 ϵ , CD5, CD22, CD79a, CD79b and CD66d. In some embodiments, the intracellular signaling domain of the CAR can comprise the CD3 ζ signaling domain which has amino acid sequence with at least about 70%, preferably at least 80%, more preferably at least 90%, 95%, 97%, or 99% sequence identity with an amino acid sequence shown in SEQ. ID NO: 324. In some embodiments the intracellular signaling domain of the CAR of the invention comprises a domain of a co-stimulatory molecule.

[0108] In some embodiments, the intracellular signaling domain of a CAR of the invention comprises a part of co-stimulatory molecule selected from the group consisting of fragment of 41BB (GenBank: AAA53133.) and CD28 (NP_006130.1). In some embodiments, the intracellular signaling domain of the CAR of the invention comprises amino acid sequence which comprises at least 70%, preferably at least 80%, more preferably at least 90%, 95%, 97%, or 99% sequence identity with an amino acid sequence shown in SEQ. ID NO: 323 and SEQ. ID NO: 327.

[0109] CARs are expressed on the surface membrane of the cell. Thus, the CAR can comprise a transmembrane domain. Suitable transmembrane domains for a CAR disclosed herein have the ability to (a) be expressed at the surface of a cell, preferably an immune cell such as, for example without limitation, lymphocyte cells or Natural killer (NK) cells, and (b) interact with the ligand-binding domain and intracellular signaling domain for directing cellular response of immune cell against a predefined target cell. The transmembrane domain can be derived either from a natural or from a synthetic source. The transmembrane domain can be derived from any membrane-bound or transmembrane protein. As non-limiting examples, the transmembrane polypeptide can be a subunit of the T cell receptor such as α , β , γ or δ , polypeptide constituting CD3 complex, IL-2 receptor p55 (a chain), p75 (β chain) or γ chain, subunit chain of Fc receptors, in particular Fc γ receptor III or CD proteins. Alternatively, the transmembrane domain can be synthetic and can comprise predominantly hydrophobic residues such as leucine and valine. In some embodiments said transmembrane domain is derived from the human CD8 α chain (e.g., NP_001139345.1). The transmembrane domain can further comprise a stalk domain between the extracellular ligand-binding domain and said transmembrane domain. A stalk domain may comprise up to 300 amino acids, preferably 10 to 100 amino acids and most preferably 25 to 50 amino acids. Stalk region may be derived from all or part of naturally occurring molecules, such as from all or part of the extracellular region of CD8, CD4, or CD28, or from all or part of an antibody constant region. Alternatively the stalk domain may be a synthetic sequence that corresponds to a naturally occurring stalk sequence, or may be an entirely synthetic stalk sequence. In some embodiments said stalk domain is a part of human CD8 α chain (e.g., NP_001139345.1). In another particular embodiment, said transmembrane and hinge domains comprise a part of human CD8 α chain, preferably which comprises at least 70%, preferably at least 80%, more preferably at least 90%, 95% 97%, or 99% sequence identity with amino acid sequence selected from the group consisting of SEQ ID NO: 318. In some embodiments, CARs disclosed herein can comprise an extracellular ligand-binding domain that specifically binds BCMA, CD8 α human hinge and transmembrane domains, the CD3 ζ signaling domain, and 4-1BB signaling domain.

[0110] Table 3 provides exemplary sequences of domains which can be used in the CARs disclosed herein.

Table 3: Exemplary sequences of CAR Components

Domain	Amino Acid Sequence	SEQ ID NO:
CD8 α signal peptide	MALPVTALLLPLALLLHAARP	318
Fc γ RIIIa hinge	GLAVSTISSFFPPGYQ	319
CD8 α hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD	320
IgG1 hinge	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSEFLYSKLTVDKS RWQQGNVVFSCSVMHEALHNHYTQKSLSLSPGK	321
CD8 α transmembrane (TM) domain	IYIWAPLAGTCGVLLLSLVITLYC	322
41BB intracellular signaling domain (ISD)	KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL	323
CD3 ζ intracellular signaling domain (ISD)	RVKFSRSADAPAYQQGQNQLYNELNLRREEYDVLDKRRGRDPEMGG	324

Domain	Amino Acid Sequence	SEQ ID NO:
	KPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKHGDGLYQGLST ATKDTYDALHMQALPPR	
FcεRI α-TM-IC (FcεRI α chain transmembrane and intracellular domain)	FFIPLLVLFAVDTGFLISTQQQVTFLLKIKRTRKGFRLLNPHPKPNPKNN	325
FcεRIβ-ΔITAM (FcεRI β chain without ITAM)	MDTESNRRANLALPQEPSSVPAFEVLEISPQEVSSGRLLKSASSPPLHTWL TVLKKEQEFLGVTQILTAMICLCFGTVVCSVLDISHIEGDIFSSFKAGYPFW GAIFFSISGMLSIIERRRNATYLVRGSLGANTASSIAGGTGITILIINLKSLAY IHIHSCQKFFETKCFMASFSTEIVVMMLFLTILGLGSAVSLTICGAGEELKG NKVPE	326
41BB-IC (41BB co-stimulatory domain)	KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEEGGCEL	327
CD28-IC (CD28 co-stimulatory domain)	RSKRSRGGHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRS	328
FcεRIγ-SP (signal peptide)	MIPAVVLLLLLLVEQAAA	329
FcεRI γ-ΔITAM (FcεRI γ chain without ITAM)	LGEPQLCYILDAILFLYGIVLTLLYCRLKIQVRKAAITSYEKS	330
GSG-P2A (GSG-P2A ribosomal skip polypeptide)	GSGATNFSLLKQAGDVEENPGP	331
GSG-T2A (GSG-T2A ribosomal skip polypeptide)	GSGEGRGSLTLCGDVEENPGP	332

[0111] Downregulation or mutation of target antigens is commonly observed in cancer cells, creating antigen-loss escape variants. Thus, to offset tumor escape and render immune cell more specific to target, the BCMA specific CAR can comprise one or more additional extracellular ligand-binding domains, to simultaneously bind different elements in target thereby augmenting immune cell activation and function. In one embodiment, the extracellular ligand-binding domains can be placed in tandem on the same transmembrane polypeptide, and optionally can be separated by a linker. In some embodiments, said different extracellular ligand-binding domains can be placed on different transmembrane polypeptides composing the CAR. In some embodiments, the invention relates to a population of CARs, each CAR comprising a different extracellular ligand-binding domain. In a particular, the invention relates to a method of engineering immune cells comprising providing an immune cell and expressing at the surface of the cell a population of CARs, each CAR comprising different extracellular ligand-binding domains. In another particular embodiment, the invention relates to a method of engineering an immune cell comprising providing an immune cell and introducing into the cell polynucleotides encoding polypeptides composing a population of CAR each one comprising different extracellular ligand-binding domains. By population of CARs, it is meant at least two, three, four, five, six or more CARs each one comprising different extracellular ligand-binding domains. The different extracellular ligand-binding domains according to the invention can preferably simultaneously bind different elements in target thereby augmenting immune cell activation and function. The invention also relates to an isolated immune cell which comprises a population of CARs each one comprising different extracellular ligand-binding domains.

[0112] The disclosure provides polynucleotides encoding any of the CARs and polypeptides described herein. Polynucleotides can be made and expressed by procedures known in the art.

[0113] In another aspect, the invention provides compositions (such as a pharmaceutical compositions) comprising any of the cells of the invention. In some embodiments, the composition comprises a cell comprising a polynucleotide encoding any of the CARs described herein. In still other embodiments, the composition comprises either or both of the polynucleotides shown in SEQ ID NO: 367 and SEQ ID NO:368 below:

P5A heavy chain variable region

GAGGTGCAGCTGCTGGAATCTGGCGGAGGACTGGTGCAGCCTGGCGGCTCTCTGAG
ACTGTCTTGTGCCGCCAGCGGCTTCACCTTCAGCAGCTACGCCATGAACTGGGTGCG
CCAGGCCCTGGCAAAGGCCTGGAATGGGTGTCCGCCATCAGCGATAGCGGCGGCA
GCACCTACTACGCCGATAGCGTGAAGGGCCGGTTCACCATCAGCCGGGACAACAGCA
AGAACACCCTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGACACCGCCGTGTACT
ACTGTGCCANATACTGGCCCATGGACATCTGGGGCCAGGGAACCTTGGTACCGTCT

CCTCA (SEQ ID NO: 367)

P5A light chain variable region

GAGATCGTGCTGACACAGAGCCCTGGCACCCCTGAGCCTGTCTCCAGGCGAAAGAGC
CACCCCTGTCCTGCAAAGCCAGCCAGAGCGTGTCCAGCAGCTACCTGGCCTGGTATCA
GCAAAAGCCCGGCCAGGCTCCCCGGCTGCTGATGTACGATGCCAGCATCAGAGCCA
CCGGCATCCCCGACAGATTTTCCGGCTCTGGCAGCGGCACCGACTTCACCCTGACCA
TCAGCAGACTGGAACCCGAGGACTTCGCCGTGTACTACTGCCAGCAGTACGGCAGCT
GGCCCCTGACATTTGGCCAGGGCACAAAGGTGGAGATCAAA (SEQ ID NO: 368)

[0114] In other embodiments, the composition comprises either or both of the polynucleotides shown in SEQ ID NO: 369 and SEQ ID NO: 370 below:

P5AC1 heavy chain variable region

GAGGTGCAGCTGCTGGAATCTGGCGGAGGACTGGTGCAGCCTGGCGGCTCTCTGAG
ACTGTCTTGTGCCGCCAGCGGCTTCACCTTCAGCAGCTACGCCATGAACTGGGTGCG
CCAGGCCCCCTGGTAAAGGTTTGAATGGGTTTCTGCTATTCTGTCGTCTGGTGGTTCT
ACTTACTATGCCGATTCTGTAAAGGGTAGATTACCATTTCTAGAGACAACCTCTAAGAA
CACCTTGTAAGTGAATGAACCTCCTTGAGAGCTGAAGATACTGCTGTTTATTACTGTG
CTAGATACTGGCCAATGGATATTTGGGGTCAAGGTACTCTGGTCACCGTCTCCTCA
(SEQ ID NO: 369)

P5AC1 light chain variable region

GAGATCGTGCTGACACAGAGCCCTGGCACCCCTGAGCCTGTCTCCTGGTGAAAGAGCT
ACTTTGTCTTGTAGAGGGGGTCAATCCGTTTCCTCTTCTTATTTGGCTTGGTATCAACA
AAAACCAGGTCAAGCTCCAAGATTATTGATGTACGATGCTTCTATTAGAGCCACCGGT
ATTCCAGATAGATTTTCTGGTTCTGGTTCCGGTACTGATTTCACTTTGACTATCTCTAGA
TTGGAACCAGAAGATTTGCTGTTTACTACTGTCAACAATATCAGTCTTGGCCATTGAC
TTTTGGTCAAGGTACAAAGGTTGAAATCAAA (SEQ ID NO: 370)

[0115] In other embodiments, the composition comprises either or both of the polynucleotides shown in SEQ ID NO: 371 and SEQ ID NO: 372 below:

PC1 heavy chain variable region

GAGGTGCAGCTGCTGGAATCTGGCGGAGGACTGGTGCAGCCTGGCGGCTCTCTGAG
ACTGTCTTGTGCCGCCAGCGGCTTCACCTTCAGCAGCTACCCTATGAGCTGGGTGCG
CCAGGCCCCCTGGCAAAGGACTGGAATGGGTGTCCGCCATCGGAGGCTCTGGCGGCA
GCACCTACTACGCCGATAGCGTGAAGGGCCGGTTACCATCAGCCGGGACAACAGCA
AGAACACCCTGTACCTGCAAATGAACAGCCTGCGGGCCGAGGACACCGCCGTGTACT
ACTGTGCCAGATACTGGCCCATGGACAGCTGGGGCCAGGGAACCTTTGGTCACCGTCT
CCTCA (SEQ ID NO: 371)

PC1 light chain variable region

GAGATCGTGCTGACACAGAGCCCTGGCACCCCTGAGCCTGTCTCCAGGCGAAAGAGC
CACCCCTGTCCTGCAAAGCCAGCCAGAGCGTGTCCAGCACATACCTGGCCTGGTATCA
GCAAAAGCCCGGCCAGGCTCCCCGGCTGCTGATCTACGATGCCTCTTCTAGAGCCCC
TGGCATCCCCGACAGATTCAGCGGCTCTGGCAGCGGCACCGACTTCACCCTGACCAT

CAGCAGACTGGAACCCGAGGACTTCGCCGTGTACTACTGCCAGCAGTACAGCACCAAG
CCCCCTGACCTTTGGCCAGGGCACAAAGGTGGAGATCAAA (SEQ ID NO: 372).

[0116] In other embodiments, the composition comprises either or both of the polynucleotides shown in SEQ ID NO: 373 and SEQ ID NO: 374 below:

PC1C12 heavy chain variable region

GAGGTGCAGCTGCTGGAATCTGGCGGAGGACTGGTGCAGCCTGGCGGCTCTCTGAG
ACTGTCTTGTGCCGCCAGCGGCTTCACCTTCAGCAGCTACCCTATGAGCTGGGTGCG
CCAGGCCCCCTGGTAAAGGTTTGAATGGGTTTCTGCTATTGGTGGTTCAGGTGGTTG
GAGTTATTATGCCGATTCTGTAAAGGGTAGATTACCATTTCTAGAGACAACCTCTAAGA
ACACCTTGTAAGTGAATGAACCTCCTTGAGAGCTGAAGATACTGCTGTTTATTACTGT
GCTAGATACTGGCCAATGGATTCTTGGGGTCAAGGTACTCTGGTCACCGTCTCCTCA

(SEQ ID NO: 373)

PC1C12 *light chain variable region*

GAGATCGTGCTGACACAGAGCCCTGGCACCCCTGAGCCTGTCTCCTGGTGAAAGAGCT
ACTTTGTCTTGTGGTTGTCTCAATCTGTTTCCTCTACTTACTTGGCTTGGTATCAACAA
AAACCAGGTCAAGCTCCAAGATTATTGATCTACGATGCTTCTTCTAGAGCACCAGGTAT
TCCAGATAGATTTTCTGGTTCTGGTTCCGGTACTGATTTCACTTTGACTATCTCTAGATT
GGAACCAGAAGATTTGCTGTTTACTACTGCCAACAATACTCTGAGTGGCCATTGACT
TTTGGTCAAGGTACAAAGGTTGAAATCAAA (SEQ ID NO: 374).

[0117] In other embodiments, the composition comprises either or both of the polynucleotides shown in SEQ ID NO: 375 and SEQ ID NO: 376 below:

COM22 *heavy chain variable region*

GAGGTGCAGCTGCTGGAATCTGGCGGAGGACTGGTGCAGCCTGGCGGCTCTCTGAG
ACTGTCTTGTGCCGCCAGCGCTTCACCTTCAGCAGCTACGCCATGAACTGGGTGCG
CCAGGCCCCCTGGTAAAGGTTTGAATGGGTTTCTGCTATTTCTGATTCTGGTGGTTCT
AGGTGGTATGCCGATTCTGTTAAGGGTAGATTCACCATTCTAGAGACAACTCTAAGA
ACACCTTGACTTGCAAATGAACTCCTTGAGAGCTGAAGATACTGCTGTTTATTACTGT
ACGCGGTACTGGCCAATGGATATTTGGGGTCAAGGTACTCTGGTCACCGTCTCCTCA
(SEQ ID NO: 375)

COM22 *light chain variable region*

GAGATCGTGCTGACACAGAGCCCTGGCACCCCTGAGCCTGTCTCCTGGTGAAAGAGCT
ACTTTGTCTTGTGGTTGTCTCAATCTGTTTCCTCTACTTACTTGGCTTGGTATCAACAA
AAACCAGGTCAAGCTCCAAGATTATTGATCTACGATGCTTCTTCTAGAGCACCAGGTAT

TCCAGATAGATTTTCTGGTTCTGGTTCCGGTACTGATTTCACTTTGACTATCTCTAGATT
GGAACCAGAAGATTTGCTGTTTACTACTGCCAACAATACTCTGAGTGGCCATTGACT
TTTGGTCAAGGTACAAAGGTTGAAATCAAA (SEQ ID NO: 376).

[0118] Expression vectors, and administration of polynucleotide compositions are further described herein.

[0119] The disclosure provides a method of making any of the polynucleotides described herein.

[0120] Polynucleotides complementary to any such sequences are also encompassed by the invention. Polynucleotides may be single-stranded (coding or antisense) or doublestranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

[0121] Polynucleotides may comprise a native sequence (i.e., an endogenous sequence that encodes an antibody or a portion thereof) or may comprise a variant of such a sequence. Polynucleotide variants contain one or more substitutions, additions, deletions and/or insertions such that the immunoreactivity of the encoded polypeptide is not diminished, relative to a native immunoreactive molecule. The effect on the immunoreactivity of the encoded polypeptide may generally be assessed as described herein. Variants preferably exhibit at least about 70% identity, more preferably, at least about 80% identity, yet more preferably, at least about 90% identity, and most preferably, at least about 95% identity to a polynucleotide sequence that encodes a native antibody or a portion thereof.

[0122] Two polynucleotide or polypeptide sequences are said to be "identical" if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, or 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

[0123] Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O., 1978, A model of evolutionary change in proteins - Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J., 1990, Unified Approach to Alignment and Phylogenesis pp. 626-645 Methods in Enzymology vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M., 1989, CABIOS 5:151-153; Myers, E.W. and Muller W.,

1988, CABIOS 4:11-17; Robinson, E.D., 1971, Comb. Theor. 11:105; Santou, N., Nes, M., 1987, Mol. Biol. Evol. 4:406-425; Sneath, P.H.A. and Sokal, R.R., 1973, Numerical Taxonomy the Principles and Practice of Numerical Taxonomy, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J., 1983, Proc. Natl. Acad. Sci. USA 80:726-730.

[0124] Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (i.e., gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (i.e. the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

[0125] Variants may also, or alternatively, be substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are capable of hybridizing under moderately stringent conditions to a naturally occurring DNA sequence encoding a native antibody (or a complementary sequence).

[0126] Suitable "moderately stringent conditions" include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1 % SDS.

[0127] As used herein, "highly stringent conditions" or "high stringency conditions" are those that: (1) employ low ionic strength and high temperature for washing, for example 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50 mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; or (3) employ 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

[0128] It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

[0129] The polynucleotides of this invention can be obtained using chemical synthesis, recombinant methods, or PCR. Methods of chemical polynucleotide synthesis are well known in the art and need not be described in detail herein. One of skill in the art can use the sequences provided herein and a commercial DNA synthesizer to produce a desired DNA sequence.

[0130] For preparing polynucleotides using recombinant methods, a polynucleotide comprising a desired sequence can be inserted into a suitable vector, and the vector in turn can be introduced into a suitable host cell for replication and amplification, as further discussed herein. Polynucleotides may be inserted into host cells by any means known in the art. Cells are transformed by introducing an exogenous polynucleotide by direct uptake, endocytosis, transfection, F-mating or electroporation. Once introduced, the exogenous polynucleotide can be maintained within the cell as a non-integrated vector (such as a plasmid) or integrated into the host cell genome. The polynucleotide so amplified can be isolated from the host cell by methods well known within the art. See, e.g., Sambrook et al., 1989.

[0131] Alternatively, PCR allows reproduction of DNA sequences. PCR technology is well known in the art and is described in U.S. Patent Nos. 4,683,195, 4,800,159, 4,754,065 and 4,683,202, as well as PCR: The Polymerase Chain Reaction, Mullis et al. eds., Birkaswer Press, Boston, 1994.

[0132] RNA can be obtained by using the isolated DNA in an appropriate vector and inserting it into a suitable host cell. When the cell replicates and the DNA is transcribed into RNA, the RNA can then be isolated using methods well known to those of skill in the art, as set forth in Sambrook et al., 1989, supra, for example.

[0133] Suitable cloning vectors may be constructed according to standard techniques, or may be selected from a large number of cloning vectors available in the art. While the cloning vector selected may vary according to the host cell intended to be used, useful cloning vectors will generally have the ability to self-replicate, may possess a single target for a particular restriction endonuclease, and/or may carry genes for a marker that can be used in selecting clones containing the vector. Suitable examples include plasmids and bacterial viruses, e.g., pUC18, pUC19, Bluescript (e.g., pBS SK+) and its derivatives, mp18, mp19, pBR322, pMB9, ColE1, pCR1,

RP4, phage DNAs, and shuttle vectors such as pSA3 and pAT28. These and many other cloning vectors are available from commercial vendors such as BioRad, Strategene, and Invitrogen.

[0134] Expression vectors generally are replicable polynucleotide constructs that contain a polynucleotide according to the invention. It is implied that an expression vector must be replicable in the host cells either as episomes or as an integral part of the chromosomal DNA. Suitable expression vectors include but are not limited to plasmids, viral vectors, including adenoviruses, adeno-associated viruses, retroviruses, cosmids, and expression vector(s) disclosed in PCT Publication No. WO 87/04462. Vector components may generally include, but are not limited to, one or more of the following: a signal sequence; an origin of replication; one or more marker genes; suitable transcriptional controlling elements (such as promoters, enhancers and terminator). For expression (i.e., translation), one or more translational controlling elements are also usually required, such as ribosome binding sites, translation initiation sites, and stop codons.

[0135] The vectors containing the polynucleotides of interest can be introduced into the host cell by any of a number of appropriate means, including electroporation, transfection employing calcium chloride, rubidium chloride, calcium phosphate, DEAE-dextran, or other substances; microprojectile bombardment; lipofection; and infection (e.g., where the vector is an infectious agent such as vaccinia virus). The choice of introducing vectors or polynucleotides will often depend on features of the host cell.

[0136] A polynucleotide encoding a BCMA specific CAR disclosed herein may exist in an expression cassette or expression vector (e.g., a plasmid for introduction into a bacterial host cell, or a viral vector such as a baculovirus vector for transfection of an insect host cell, or a plasmid or viral vector such as a lentivirus for transfection of a mammalian host cell). In some embodiments, a polynucleotide or vector can include a nucleic acid sequence encoding ribosomal skip sequences such as, for example without limitation, a sequence encoding a 2A peptide. 2A peptides, which were identified in the Aphthovirus subgroup of picornaviruses, causes a ribosomal "skip" from one codon to the next without the formation of a peptide bond between the two amino acids encoded by the codons (see (Donnelly and Elliott 2001; Atkins, Wills et al. 2007; Doronina, Wu et al. 2008)). By "codon" is meant three nucleotides on an mRNA (or on the sense strand of a DNA molecule) that are translated by a ribosome into one amino acid residue. Thus, two polypeptides can be synthesized from a single, contiguous open reading frame within an mRNA when the polypeptides are separated by a 2A oligopeptide sequence that is in frame. Such ribosomal skip mechanisms are well known in the art and are known to be used by several vectors for the expression of several proteins encoded by a single messenger RNA.

[0137] To direct transmembrane polypeptides into the secretory pathway of a host cell, in some embodiments, a secretory signal sequence (also known as a leader sequence, prepro sequence or pre sequence) is provided in a polynucleotide sequence or vector sequence. The secretory signal sequence is operably linked to the transmembrane nucleic acid sequence, i.e., the two sequences are joined in the correct reading frame and positioned to direct the newly synthesized polypeptide into the secretory pathway of the host cell. Secretory signal sequences are commonly positioned 5' to the nucleic acid sequence encoding the polypeptide of interest, although certain secretory signal sequences may be positioned elsewhere in the nucleic acid sequence of interest (see, e.g., Welch et al., U.S. Patent No. 5,037,743; Holland et al., U.S. Patent No. 5,143,830). In some embodiments the signal peptide comprises the amino acid sequence shown in SEQ ID NO: 318 or 329. Those skilled in the art will recognize that, in view of the degeneracy of the genetic code, considerable sequence variation is possible among these polynucleotide molecules. In some embodiments, nucleic acid sequences of the invention are codon-optimized for expression in mammalian cells, preferably for expression in human cells. Codon-optimization refers to the exchange in a sequence of interest of codons that are generally rare in highly expressed genes of a given species by codons that are generally frequent in highly expressed genes of such species, such codons encoding the amino acids as the codons that are being exchanged.

[0138] In some embodiments, a polynucleotide according to the invention comprises the nucleic acid sequence selected from the group consisting of: SEQ. ID NO: 1397. The invention relates to polynucleotides comprising a nucleic acid sequence that has at least 70%, preferably at least 80%, more preferably at least 90%, 95%, 97%, or 99 % sequence identity with nucleic acid sequence selected from the group consisting of SEQ ID NO: 1397.

Methods of engineering an immune cell

[0139] *In vitro* methods of preparing immune cells for use in immunotherapy are provided herein. In some embodiments, the methods comprise introducing a CAR according to the invention into immune cells, and expanding the cells. In some embodiments, the invention relates to a method of engineering an immune cell comprising: providing a cell and expressing at the surface of the cell at least one CAR as described above. Methods for engineering immune cells are described in, for example, PCT Patent Application Publication Nos. WO/2014/039523, WO/2014/184741, WO/2014/191128, WO/2014/184744, and WO/2014/184143. In some embodiments, the method comprises: transfecting the cell with at least one polynucleotide encoding CAR as described above, and expressing the polynucleotides in the cell.

[0140] In some embodiments, the polynucleotides are present in lentiviral vectors for stable expression in the cells.

[0141] In some embodiments, the method can further comprise a step of genetically modifying a cell by inactivating at least one gene

expressing, for example without limitation, a component of the TCR, a target for an immunosuppressive agent, an HLA gene, and/or an immune checkpoint protein such as, for example, PDCD1 or CTLA-4. By inactivating a gene it is intended that the gene of interest is not expressed in a functional protein form. In some embodiments, the gene to be inactivated is selected from the group consisting of, for example without limitation, TCR α , TCR β , CD52, GR, PD-1, and CTLA-4. In some embodiments the method comprises inactivating one or more genes by introducing into the cells a rare-cutting endonuclease able to selectively inactivate a gene by selective DNA cleavage. In some embodiments the rare-cutting endonuclease can be, for example, a transcription activator-like effector nuclease (TALE-nuclease) or Cas9 endonuclease.

[0142] In some embodiments, an additional catalytic domain is used with a rare-cutting endonuclease to enhance its capacity to inactivate targeted genes. For example, an additional catalytic domain can be a DNA end-processing enzyme. Non-limiting examples of DNA end-processing enzymes include 5-3' exonucleases, 3-5' exonucleases, 5-3' alkaline exonucleases, 5' flap endonucleases, helicases, phosphatase, hydrolases and template-independent DNA polymerases. Non-limiting examples of such catalytic domain comprise of a protein domain or catalytically active derivative of the protein domain selected from the group consisting of hExol (EXO1_HUMAN), Yeast Exol (EXO1_YEAST), *E. coli* Exol, Human TREX2, Mouse TREX1, Human TREX1, Bovine TREX1, Rat TREX1, TdT (terminal deoxynucleotidyl transferase) Human DNA2, Yeast DNA2 (DNA2_YEAST). In some embodiments, an additional catalytic domain can have a 3'-5'-exonuclease activity, and In some embodiments, said additional catalytic domain is TREX, more preferably TREX2 catalytic domain (WO2012/058458). In some embodiments, said catalytic domain is encoded by a single chain TREX polypeptide. The additional catalytic domain may be fused to a nuclease fusion protein or chimeric protein. In some embodiments, the additional catalytic domain is fused using, for example, a peptide linker.

[0143] In some embodiments, the method further comprises a step of introducing into cells an exogenous nucleic acid comprising at least a sequence homologous to a portion of the target nucleic acid sequence, such that homologous recombination occurs between the target nucleic acid sequence and the exogenous nucleic acid. In some embodiments, said exogenous nucleic acid comprises first and second portions which are homologous to region 5' and 3' of the target nucleic acid sequence, respectively. The exogenous nucleic acid may also comprise a third portion positioned between the first and the second portion which comprises no homology with the regions 5' and 3' of the target nucleic acid sequence. Following cleavage of the target nucleic acid sequence, a homologous recombination event is stimulated between the target nucleic acid sequence and the exogenous nucleic acid. In some embodiments, homologous sequences of at least about 50 bp, greater than about 100 bp, or greater than about 200 bp can be used within the donor matrix. The exogenous nucleic acid can be, for example without limitation, from about 200 bp to about 6000 bp, more preferably from about 1000 bp to about 2000 bp. Shared nucleic acid homologies are located in regions flanking upstream and downstream the site of the break, and the nucleic acid sequence to be introduced is located between the two arms.

[0144] In some embodiments, a nucleic acid successively comprises a first region of homology to sequences upstream of said cleavage; a sequence to inactivate a targeted gene selected from the group consisting of TCR α , TCR β , CD52, glucocorticoid receptor (GR), deoxycytidine kinase (DCK), and an immune checkpoint protein such as for example programmed death-1 (PD-1); and a second region of homology to sequences downstream of the cleavage. The polynucleotide introduction step can be simultaneous, before or after the introduction or expression of the rare-cutting endonuclease. Depending on the location of the target nucleic acid sequence wherein break event has occurred, such exogenous nucleic acid can be used to knock-out a gene, e.g. when exogenous nucleic acid is located within the open reading frame of the gene, or to introduce new sequences or genes of interest. Sequence insertions by using such exogenous nucleic acid can be used to modify a targeted existing gene, by correction or replacement of the gene (allele swap as a non-limiting example), or to up- or down-regulate the expression of the targeted gene (promoter swap as non-limiting example), the targeted gene correction or replacement. In some embodiments, inactivation of a genes selected from the group consisting of TCR α , TCR β , CD52, GR, DCK, and immune checkpoint proteins, can be done at a precise genomic location targeted by a specific TALE-nuclease, wherein said specific TALE-nuclease catalyzes a cleavage and wherein the exogenous nucleic acid successively comprising at least a region of homology and a sequence to inactivate one targeted gene selected from the group consisting of TCR α , TCR β , CD52, GR, DCK, immune checkpoint proteins which is integrated by homologous recombination. In some embodiments, several genes can be, successively or at the same time, inactivated by using several TALE-nucleases respectively and specifically targeting one defined gene and several specific polynucleotides for specific gene inactivation.

[0145] In some embodiments, the method comprises inactivation of one or more additional genes selected from the group consisting of TCR α , TCR β , CD52, GR, DCK, and immune checkpoint proteins. In some embodiments, inactivation of a gene can be accomplished by introducing into the cells at least one rare-cutting endonuclease such that the rare-cutting endonuclease specifically catalyzes cleavage in a targeted sequence of the cell genome; and optionally, introducing into the cells an exogenous nucleic acid successively comprising a first region of homology to sequences upstream of the cleavage, a sequence to be inserted in the genome of the cell, and a second region of homology to sequences downstream of the cleavage; wherein the introduced exogenous nucleic acid inactivates a gene and integrates at least one exogenous polynucleotide sequence encoding at least one recombinant protein of interest. In some embodiments, the exogenous polynucleotide sequence is integrated within a gene encoding a protein selected from the group consisting of TCR α , TCR β , CD52, GR, DCK, and immune checkpoint protein.

[0146] In another aspect, a step of genetically modifying cells can comprise : modifying T cells by inactivating at least one gene expressing a target for an immunosuppressive agent, and; expanding the cells, optionally in presence of the immunosuppressive agent. An immunosuppressive agent is an agent that suppresses immune function by one of several mechanisms of action. An immunosuppressive agent can diminish the extent and/or voracity of an immune response. Non-limiting examples of

immunosuppressive agents include calcineurin inhibitors, targets of rapamycin, interleukin-2 α -chain blockers, inhibitors of inosine monophosphate dehydrogenase, inhibitors of dihydrofolic acid reductase, corticosteroids, and immunosuppressive antimetabolites. Some cytotoxic immunosuppressants act by inhibiting DNA synthesis. Others may act through activation of T cells or by inhibiting the activation of helper cells. The methods according to the invention allow conferring immunosuppressive resistance to T cells for immunotherapy by inactivating the target of the immunosuppressive agent in T cells. As non-limiting examples, targets for immunosuppressive agent can be a receptor for an immunosuppressive agent such as for example without limitation CD52, glucocorticoid receptor (GR), FKBP family gene members, and cyclophilin family gene members.

[0147] In some embodiments, the genetic modification of the method involves expression, in provided cells to engineer, of one rare-cutting endonuclease such that the rare-cutting endonuclease specifically catalyzes cleavage in one targeted gene, thereby inactivating the targeted gene. In some embodiments, a method of engineering cells comprises at least one of the following steps: providing a T cell, such as from a cell culture or from a blood sample; selecting a gene in the T cell expressing a target for an immunosuppressive agent; introducing into the T cell a rare-cutting endonuclease able to selectively inactivate by DNA cleavage, preferably by double-strand break the gene encoding a target for the immunosuppressive agent, and expanding the cells, optionally in presence of the immunosuppressive agent.

[0148] In some embodiments, the method comprises: providing a T cell, such as from a cell culture or from a blood sample; selecting a gene in the T cell wherein the gene expresses a target for an immunosuppressive agent; transfecting the T cell with nucleic acid encoding a rare-cutting endonuclease able to selectively inactivate by DNA cleavage, preferably by double-strand break the gene encoding a target for the immunosuppressive agent, and expressing the rare-cutting endonucleases into the T cells; and expanding the cells, optionally in presence of the immunosuppressive agent.

[0149] In some embodiments, the rare-cutting endonuclease specifically targets CD52 or GR. In some embodiments, the gene selected for inactivation encodes CD52, and the immunosuppressive treatment comprises a humanized antibody targeting CD52 antigen. In some embodiments, the gene selected for inactivation encodes GR, and the immunosuppressive treatment comprises a corticosteroid such as dexamethasone. In some embodiments, the gene selected for inactivation is a FKBP family gene member or a variant thereof and the immunosuppressive treatment comprises FK506, also known as Tacrolimus or fujimycin. In some embodiments, the FKBP family gene member is FKBP12 or a variant thereof. In some embodiments, gene selected for inactivation is a cyclophilin family gene member or a variant thereof and the immunosuppressive treatment comprises cyclosporine.

[0150] In some embodiments, the rare-cutting endonuclease can be, for example, a meganuclease, a zinc finger nuclease, or a TALE-nuclease (TALEN). In some embodiments, the rare-cutting endonuclease is a TALE-nuclease.

[0151] Also provided herein are methods of engineering T cells, suitable for immunotherapy, wherein the methods comprise: genetically modifying T cells by inactivating at least immune checkpoint protein. In some embodiments the immune checkpoint protein is, for example, PD-1 and/or CTLA-4. In some embodiments, methods of genetically modifying a cell comprises: modifying T cells by inactivating at least one immune checkpoint protein; and expanding the cells. Immune checkpoint proteins include, but are not limited to Programmed Death 1 (PD-1, also known as PDCD1 or CD279, accession number: NM_005018), Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4, also known as CD152, GenBank accession number AF414120.1), LAG3 (also known as CD223, accession number: NM_002286.5), Tim3 (also known as HAVCR2, GenBank accession number: JX049979.1), BTLA (also known as CD272, accession number: NM_181780.3), BY55 (also known as CD160, GenBank accession number: CR541888.1), TIGIT (also known as VSTM3, accession number: NM_173799), B7H5 (also known as C10orf54, homolog of mouse vista gene, accession number: NM_022153.1), LAIR1 (also known as CD305, GenBank accession number: CR542051.1), SIGLEC10 (GeneBank accession number: AY358337.1), 2B4 (also known as CD244, accession number: NM_001166664.1), which directly inhibit immune cells. For example, CTLA-4 is a cell-surface protein expressed on certain CD4 and CD8 T cells; when engaged by its ligands (B7-1 and B7-2) on antigen presenting cells, T cell activation and effector function are inhibited.

[0152] In some embodiments, said method to engineer cells comprises at least one of the following steps: providing a T cell, such as from a cell culture or from a blood sample; introducing into the T cell a rare-cutting endonuclease able to selectively inactivate by DNA cleavage, preferably by double-strand break one gene encoding a immune checkpoint protein; and expanding the cells. In some embodiments, the method comprises: providing a T cell, such as from a cell culture or from a blood sample; transfecting said T cell with nucleic acid encoding a rare-cutting endonuclease able to selectively inactivate by DNA cleavage, preferably by double-strand break a gene encoding a immune checkpoint protein; expressing the rare-cutting endonucleases into the T cells; expanding the cells. In some embodiments, the rare-cutting endonuclease specifically targets a gene selected from the group consisting of: PD-1, CTLA-4, LAG3, Tim3, BTLA, BY55, TIGIT, B7H5, LAIR1, SIGLEC10, 2B4, TCR α , and TCR β . In some embodiments, the rare-cutting endonuclease can be a meganuclease, a zinc finger nuclease or a TALE-nuclease. In some embodiments, the rare-cutting endonuclease is a TALE-nuclease.

[0153] In some embodiments, the present invention can be particularly suitable for allogeneic immunotherapy. In such embodiments, cells may be modified by a method comprising: inactivating at least one gene encoding a component of the T cell receptor (TCR) in T cells; and expanding the T cells. In some embodiments, the genetic modification of the method relies on the expression, in provided cells to engineer, of one rare-cutting endonuclease such that the rare-cutting endonuclease specifically catalyzes cleavage in one targeted gene thereby inactivating the targeted gene. In some embodiments, said method to engineer cells comprises at least one of

the following steps: providing a T cell, such as from a cell culture or from a blood sample; introducing into the T cell a rare-cutting endonuclease able to selectively inactivate by DNA cleavage, preferably by double-strand break at least one gene encoding a component of the T cell receptor (TCR), and expanding the cells.

[0154] In some embodiments, the method comprises: providing a T cell, such as from a cell culture or from a blood sample; transfecting said T cell with nucleic acid encoding a rare-cutting endonuclease able to selectively inactivate by DNA cleavage, preferably by double-strand break at least one gene encoding a component of the T cell receptor (TCR); expressing the rare-cutting endonucleases into the T cells; sorting the transformed T cells, which do not express TCR on their cell surface; and expanding the cells.

[0155] In some embodiments, the rare-cutting endonuclease can be a meganuclease, a zinc finger nucleasase or a TALE-nuclease. In some embodiments, the rare-cutting endonuclease is a TALE-nuclease. In some embodiments the TALE-nucleases recognize and cleave a sequence encoding TCR α or TCR β . In some embodiments a TALE-nuclease comprises a polypeptide sequence selected from the amino acid sequence shown in SEQ ID NO: 334, 335, 336, 337, 338, 339, 340, or 341

TALE-nuclease polypeptide sequences:

[0156]

Repeat TRAC T01-L

LTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLL
PVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQA
LETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIA
SHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALETVQALLPVLCQAHGLT
PEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALETVQALLPV
LCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALE
TVQALLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASN
IGGKQALETVQALLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPE
QVVAIASHDGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQALLPVLCQAHGLTPE
(SEQ ID NO: 334)

Repeat TRAC T01-R

LTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLL
PVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQA
LETVQALLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIA
SHDGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLT
PQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPV
LCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALE
TVQALLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASN
IGGKQALETVQALLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPQ
QVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQALLPVLCQAHGLTPE
(SEQ ID NO: 335)

Repeat TRBC T01-L

LTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLL
PVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQ
ALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAI
ASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHG
LTPEQVVAIASNIGGKQALETVQALLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLP
VLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQAL
ETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALETVQALLPVLCQAHGLTPQQVVAIASN
GGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPE
QVVAIASNIGGKQALETVQALLPVLCQAHGLTPQQVVAIASNNGGKQALETVQALLPVLCQAHGLTPE
(SEQ ID NO: 336)

Repeat TRBC T01-R

NPQRSTVWYLTQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGK
QALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVA
IASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHG
LTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLL
PVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQ
.....

ALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAI
 ASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGL
 TPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLP
 VLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGGRPAL
 E (SEQ ID NO: 337)

Repeat TRBC_T02-L

LTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLL
 PVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQA
 LETVQALLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIA
 SHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLT
 PQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALETVQALLPV
 LCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALE
 TVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASH
 DGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPE
 QVVAIASHDGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGGRPALE (SEQ ID NO:
 338)

Repeat TRBC_T02-R

LTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLL
 PVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQA
 LETVQALLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIA
 SNIGGKQALETVQALLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLT
 PEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPV
 LCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALE
 TVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASH
 DGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTP
 QQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGGRPALE
 (SEQ ID NO: 339)

Repeat CD52_T02-L

LTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLL
 PVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQA
 LETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPEQVVAIA
 SHDGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLT
 PEQVVAIASNIGGKQALETVQALLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPV
 LCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQALE
 TVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALETVQALLPVLCQAHGLTPEQVVAIASH
 DGGKQALETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPE
 QVVAIASNIGGKQALETVQALLPVLCQAHGLTPQQVVAIASNNGGGRPALE (SEQ ID NO:
 340)

Repeat CD52_T02-R

LTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLL
 PVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQA
 LETVQRLLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPQQVVAIA
 SNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGL
 TPEQVVAIASNIGGKQALETVQALLPVLCQAHGLTPEQVVAIASHDGGKQALETVQRLLPV
 LCQAHGLTPEQVVAIASHDGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALE
 TVQRLLPVLCQAHGLTPQQVVAIASNNGGKQALETVQRLLPVLCQAHGLTPQQVVAIASN
 GGGKQALETVQRLLPVLCQAHGLTPEQVVAIASNIGGKQALETVQALLPVLCQAHGLTPE
 QVVAIASHDGGKQALETVQRLLPVLCQAHGLTPQQVVAIASNNGGGRPALE
 (SEQ ID NO: 341)

[0157] In another aspect, one another step of genetically modifying cell can be a method of expanding TCR α deficient T cells comprising introducing into the T cell pT α (also known as preTCR α) or a functional variant thereof and expanding the cells, optionally through stimulation of the CD3 complex. In some embodiments, the method comprises: a) transfecting the cells with nucleic acid encoding at least a fragment of pT α to support CD3 surface expression; b) expressing said pT α into the cells; and c) expanding the

cells, optionally through stimulation of the CD3 complex.

[0158] Also provided are methods of preparing T cells for immunotherapy comprising steps of the method for expansion for T cell. In some embodiments, the pTα polynucleotide sequence can be introduced randomly or by homologous recombination. In some embodiments, the insertion can be associated with the inactivation of the TCRα gene. Different functional variants of pTα can be used. A "functional variant" of the peptide refers to a molecule substantially similar to either the entire peptide or a fragment thereof. A "fragment" of the pTα or functional variant thereof refers to any subset of the molecule, that is, a shorter peptide than the full-length pTα. In some embodiments, pTα or functional variants can be, for example, full-length pTα or a C-terminal truncated pTα version. C-terminal truncated pTα lacks in C-terminal end one or more residues. As non limiting examples, C-terminal truncated pTα version lacks 18, 48, 62, 78, 92, 110 or 114 residues from the C-terminus of the protein. Amino acid sequence variants of the peptide can be prepared by mutations in the DNA which encodes the peptide. Such functional variants include, for example, deletions from, or insertions or substitutions of, residues within the amino acid sequence. Any combination of deletion, insertion, and substitution may also be made to arrive at the final construct, provided that the final construct possesses the desired activity, in particular the restoration of a functional CD3 complex. In preferred embodiment, at least one mutation is introduced in the different pTα versions as described above to affect dimerization. As non limiting example, mutated residue can be at least W46R, D22A, K24A, R102A or R117A of the human pTα protein or aligned positions using CLUSTALW method on pTα family or homologue member. Preferably pTα or variant thereof as described above comprise the mutated residue W46R or the mutated residues D22A, K24A, R102A and R117A. In some embodiments, said pTα or variants are also fused to a signal-transducing domain such as CD28, OX40, ICOS, CD27, CD137 (4-1BB) and CD8 as non limiting examples. The extracellular domain of pTα or variants as described above can be fused to a fragment of the TCRα protein, particularly the transmembrane and intracellular domain of TCRα. pTα variants can also be fused to the intracellular domain of TCRα.

[0159] In some embodiments, pTα versions can be fused to an extracellular ligand-binding domain. In some embodiments, pTα or functional variant thereof is fused to a single chain antibody fragment (scFv) comprising the light and the heavy variable fragment of a target antigen specific monoclonal antibody joined by a flexible linker.

[0160] The term "TCRα deficient T cell" refers to an isolated T cell that lacks expression of a functional TCRα chain. This may be accomplished by different means, as non limiting examples, by engineering a T cell such that it does not express any functional TCRα on its cell surface or by engineering a T cell such that it produces very little functional TCRα chain on its surface or by engineering a T cell to express mutated or truncated form of TCRα chain. TCRα deficient cells can no longer be expanded through CD3 complex. Thus, to overcome this problem and to allow proliferation of TCRα deficient cells, pTα or functional variant thereof is introduced into the cells, thus restoring a functional CD3 complex. In some embodiments, the method further comprises introducing into said T cells rare-cutting endonucleases able to selectively inactivate by DNA cleavage one gene encoding one component of the T cell receptor (TCR). In some embodiments, the rare-cutting endonuclease is a TALE-nuclease.

[0161] In another aspect, engineered T cells obtained by the methods described herein can be contacted with bispecific antibodies. For example, the T cells can be contacted with bispecific antibodies ex vivo prior to administration to a patient, or in vivo following administration to a patient. Bispecific antibodies comprise two variable regions with distinct antigen properties that facilitate bringing the engineered cells into proximity to a target antigen. As a non-limiting example, a bispecific antibody can be directed against a tumor marker and lymphocyte antigen, such as for example without limitation CD3, and has the potential to redirect and activate any circulating T cells against tumors.

[0162] In some embodiments, polynucleotides encoding polypeptides according to the present invention can be mRNA which is introduced directly into the cells, for example by electroporation. In some embodiments, cytoPulse technology can be used to transiently permeabilize living cells for delivery of material into the cells. Parameters can be modified in order to determine conditions for high transfection efficiency with minimal mortality.

[0163] Also provided herein are methods of transfecting T cell. In some embodiments, the method comprises: contacting a T cell with RNA and applying to T cell an agile pulse sequence consisting of: (a) an electrical pulse with a voltage range from about 2250 to 3000 V per centimeter; (b) a pulse width of 0.1 ms; (c) a pulse interval of about 0.2 to 10 ms between the electrical pulses of step (a) and (b); (d) an electrical pulse with a voltage range from about 2250 to 3000 V with a pulse width of about 100 ms and a pulse interval of about 100 ms between the electrical pulse of step (b) and the first electrical pulse of step (c); and (e) four electrical pulses with a voltage of about 325 V with a pulse width of about 0.2 ms and a pulse interval of 2 ms between each of 4 electrical pulses. In some embodiments, a method of transfecting T cell comprising contacting said T cell with RNA and applying to T cell an agile pulse sequence comprising: (a) an electrical pulse with a voltage of about 2250, 2300, 2350, 2400, 2450, 2500, 2550, 2600, 2700, 2800, 2900 or 3000V per centimeter; (b) a pulse width of 0.1 ms; (c) and a pulse interval of about 0.2, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 ms between the electrical pulses of step (a) and (b); (d) one electrical pulse with a voltage range from about 2250, of 2250, 2300, 2350, 2400, 2450, 2500, 2550, 2600, 2700, 2800, 2900 or 3000V with a pulse width of 100 ms and a pulse interval of 100 ms between the electrical pulse of step (b) and the first electrical pulse of step (c); and (e) 4 electrical pulses with a voltage of about 325 V with a pulse width of about 0.2 ms and a pulse interval of about 2 ms between each of 4 electrical pulses. Any values included in the value range described above are disclosed in the present application. Electroporation medium can be any suitable medium known in the art. In some embodiments, the electroporation medium has conductivity in a range spanning about 0.01 to about 1.0 milliSiemens.

[0164] In some embodiments, as non limiting examples, an RNA encodes a rare-cutting endonuclease, one monomer of the rare-cutting endonuclease such as half-TALE-nuclease, a CAR, at least one component of the multi-chain chimeric antigen receptor, a pTα or functional variant thereof, an exogenous nucleic acid, and/or one additional catalytic domain.

Engineered immune cells

[0165] The disclosure also provides engineered immune cells comprising any of the CAR polynucleotides described herein. In some embodiments, a CAR can be introduced into an immune cell as a transgene via a plasmid vector. In some embodiments, the plasmid vector can also contain, for example, a selection marker which provides for identification and/or selection of cells which received the vector.

[0166] CAR polypeptides may be synthesized in situ in the cell after introduction of polynucleotides encoding the CAR polypeptides into the cell. Alternatively, CAR polypeptides may be produced outside of cells, and then introduced into cells. Methods for introducing a polynucleotide construct into cells are known in the art. In some embodiments, stable transformation methods can be used to integrate the polynucleotide construct into the genome of the cell. In other embodiments, transient transformation methods can be used to transiently express the polynucleotide construct, and the polynucleotide construct not integrated into the genome of the cell. In other embodiments, virus-mediated methods can be used. The polynucleotides may be introduced into a cell by any suitable means such as for example, recombinant viral vectors (e.g. retroviruses, adenoviruses), liposomes, and the like. Transient transformation methods include, for example without limitation, microinjection, electroporation or particle bombardment. Polynucleotides may be included in vectors, such as for example plasmid vectors or viral vectors.

[0167] Also provided herein are isolated cells and cell lines obtained by the above-described methods of engineering cells provided herein. In some embodiments, an isolated cell comprises at least one CAR as described above. In some embodiments, an isolated cell comprises a population of CARs, each CAR comprising different extracellular ligand-binding domains.

[0168] Also provided herein are isolated immune cells obtained according to any one of the methods described above. Any immune cell capable of expressing heterologous DNAs can be used for the purpose of expressing the CAR of interest. In some embodiments, the immune cell is a T cell. In some embodiments, an immune cell can be derived from, for example without limitation, a stem cell. The stem cells can be adult stem cells, non-human embryonic stem cells, more particularly non-human stem cells, cord blood stem cells, progenitor cells, bone marrow stem cells, induced pluripotent stem cells, totipotent stem cells or hematopoietic stem cells. Representative human cells are CD34+ cells. The isolated cell can also be a dendritic cell, killer dendritic cell, a mast cell, a NK-cell, a B-cell or a T cell selected from the group consisting of inflammatory T-lymphocytes, cytotoxic T-lymphocytes, regulatory T-lymphocytes or helper T-lymphocytes. In some embodiments, the cell can be derived from the group consisting of CD4+ T-lymphocytes and CD8+ T-lymphocytes.

[0169] Prior to expansion and genetic modification, a source of cells can be obtained from a subject through a variety of non-limiting methods. Cells can be obtained from a number of non-limiting sources, including peripheral blood mononuclear cells, bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion, spleen tissue, and tumors. In some embodiments, any number of T cell lines available and known to those skilled in the art, may be used. In some embodiments, cells can be derived from a healthy donor, from a patient diagnosed with cancer or from a patient diagnosed with an infection. In some embodiments, cells can be part of a mixed population of cells which present different phenotypic characteristics.

[0170] Also provided herein are cell lines obtained from a transformed T cell according to any of the above-described methods. Also provided herein are modified cells resistant to an immunosuppressive treatment. In some embodiments, an isolated cell according to the invention comprises a polynucleotide encoding a CAR of the invention.

[0171] The immune cells of the invention can be activated and expanded, either prior to or after genetic modification of the T cells, using methods as generally described, for example without limitation, in U.S. Patents 6,352,694; 6,534,055; 6,905,680; 6,692,964; 5,858,358; 6,887,466; 6,905,681; 7,144,575; 7,067,318; 7,172,869; 7,232,566; 7,175,843; 5,883,223; 6,905,874; 6,797,514; 6,867,041; and U.S. Patent Application Publication No. 20060121005. T cells can be expanded in vitro or in vivo. Generally, the T cells of the invention can be expanded, for example, by contact with an agent that stimulates a CD3 TCR complex and a co-stimulatory molecule on the surface of the T cells to create an activation signal for the T cell. For example, chemicals such as calcium ionophore A23187, phorbol 12-myristate 13-acetate (PMA), or mitogenic lectins like phytohemagglutinin (PHA) can be used to create an activation signal for the T cell.

[0172] In some embodiments, T cell populations may be stimulated in vitro by contact with, for example, an anti-CD3 antibody, or antigen-binding fragment thereof, or an anti-CD2 antibody immobilized on a surface, or by contact with a protein kinase C activator (e.g., bryostatin) in conjunction with a calcium ionophore. For co-stimulation of an accessory molecule on the surface of the T cells, a ligand that binds the accessory molecule is used. For example, a population of T cells can be contacted with an anti-CD3 antibody and an anti-CD28 antibody, under conditions appropriate for stimulating proliferation of the T cells. Conditions appropriate for T cell culture

include an appropriate media (e.g., Minimal Essential Media or RPMI Media 1640 or, X-vivo 5, (Lonza)) that may contain factors necessary for proliferation and viability, including serum (e.g., fetal bovine or human serum), interleukin-2 (IL-2), insulin, IFN- γ , IL-4, IL-7, GM-CSF, IL-10, IL-2, IL-15, TGF β , and TNF, or any other additives for the growth of cells known to the skilled artisan. Other additives for the growth of cells include, but are not limited to, surfactant, plasmanate, and reducing agents such as N-acetyl- cysteine and 2-mercaptoethanol. Media can include RPMI 1640, A1M-V, DMEM, MEM, α - MEM, F-12, X-Vivo 1, and X-Vivo 20, Optimizer, with added amino acids, sodium pyruvate, and vitamins, either serum-free or supplemented with an appropriate amount of serum (or plasma) or a defined set of hormones, and/or an amount of cytokine(s) sufficient for the growth and expansion of T cells. Antibiotics, e.g., penicillin and streptomycin, are included only in experimental cultures, not in cultures of cells that are to be infused into a subject. The target cells are maintained under conditions necessary to support growth, for example, an appropriate temperature (e.g., 37° C) and atmosphere (e.g., air plus 5% CO₂). T cells that have been exposed to varied stimulation times may exhibit different characteristics

[0173] In some embodiments, the cells of the invention can be expanded by co-culturing with tissue or cells. The cells can also be expanded in vivo, for example in the subject's blood after administering the cell into the subject.

[0174] In some embodiments, an isolated cell according to the present invention comprises one inactivated gene selected from the group consisting of CD52, GR, PD-1, CTLA-4, LAG3, Tim3, BTLA, BY55, TIGIT, B7H5, LAIR1, SIGLEC10, 2B4, HLA, TCR α and TCR β and/or expresses a CAR, a multi-chain CAR and/or a pTa transgene. In some embodiments, an isolated cell comprises polynucleotides encoding polypeptides comprising a multi-chain CAR. In some embodiments, the isolated cell according to the present invention comprises two inactivated genes selected from the group consisting of: CD52 and GR, CD52 and TCR α , CDR52 and TCR β , GR and TCR α , GR and TCR β , TCR α and TCR β , PD-1 and TCR α , PD-1 and TCR β , CTLA-4 and TCR α , CTLA-4 and TCR β , LAG3 and TCR α , LAG3 and TCR β , Tim3 and TCR α , Tim3 and TCR β , BTLA and TCR α , BTLA and TCR β , BY55 and TCR α , BY55 and TCR β , TIGIT and TCR α , TIGIT and TCR β , B7H5 and TCR α , B7H5 and TCR β , LAIR1 and TCR α , LAIR1 and TCR β , SIGLEC10 and TCR α , SIGLEC10 and TCR β , 2B4 and TCR α , 2B4 and TCR β and/or expresses a CAR, a multi-chain CAR and a pTa transgene.

[0175] In some embodiments, TCR is rendered not functional in the cells according to the invention by inactivating TCR α gene and/or TCR β gene(s). In some embodiments, a method to obtain modified cells derived from an individual is provided, wherein the cells can proliferate independently of the major histocompatibility complex (MHC) signaling pathway. Modified cells, which can proliferate independently of the MHC signaling pathway, susceptible to be obtained by this method are encompassed in the scope of the present invention. Modified cells disclosed herein can be used in for treating patients in need thereof against Host versus Graft (HvG) rejection and Graft versus Host Disease (GvHD). Therefore, disclosed herein is a method of treating patients in need thereof against Host versus Graft (HvG) rejection and Graft versus Host Disease (GvHD) comprising treating said patient by administering to said patient an effective amount of modified cells comprising inactivated TCR α and/or TCR β genes.

[0176] In some embodiments, the immune cells are engineered to be resistant to one or more chemotherapy drugs. The chemotherapy drug can be, for example, a purine nucleotide analogue (PNA), thus making the immune cell suitable for cancer treatment combining adoptive immunotherapy and chemotherapy. Exemplary PNAs include, for example, clofarabine, fludarabine, and cytarabine, alone or in combination. PNAs are metabolized by deoxycytidine kinase (dCK) into mono-, di-, and tri-phosphate PNA. Their tri-phosphate forms compete with ATP for DNA synthesis, act as pro-apoptotic agents, and are potent inhibitors of ribonucleotide reductase (RNR), which is involved in trinucleotide production. Provided herein are BCMA specific CAR-T cells comprising an inactivated dCK gene. In some embodiments, the dCK knockout cells are made by transfection of T cells using polynucleotides encoding specific TAL-nuclease directed against dCK genes by, for example, electroporation of mRNA. The dCK knockout BCMA specific CAR-T cells are resistant to PNAs, including for example clofarabine and/or fludarabine, and maintain T cell cytotoxic activity toward BCMA-expressing cells.

[0177] In some embodiments, isolated cells or cell lines of the invention can comprise a pTa or a functional variant thereof. In some embodiments, an isolated cell or cell line can be further genetically modified by inactivating the TCR α gene.

[0178] In some embodiments, the CAR-T cell comprises a polynucleotide encoding a suicide polypeptide, such as for example RQR8. See, e.g., WO2013153391A. In CAR-T cells comprising the polynucleotide, the suicide polypeptide is expressed at the surface of a CAR-T cell. In some embodiments, the suicide polypeptide comprises the amino acid sequence shown in SEQ ID NO: 342.

CPYSNPSLCSGGGGSELPTQGTFSNVSTNVSPAKPTTTACPYSNPSLCSGGGGSP
APRPPTPAPTASQPLSLRPEACRPAAGGAVHTRGLDFACDIYWAPLAGTCGVLLLS
LVITLYCNHRNRRRVCKCPRPVV (SEQ ID NO: 342)

The suicide polypeptide may also comprise a signal peptide at the amino terminus. In some embodiments, the suicide polypeptide comprises the amino acid sequence shown in SEQ ID NO: 400.

MGTSLLCWMALCLLGADHADACPYSNPSLCSGGGGSELPTQGTFSNVSTNVSPAKPTTT
ACPYSNPSLCSGGGGSPAPRPPTPAPTASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI
WAPLAGTCGVLLLSLVITLYCNHRNRRRVCKCPRPVV (SEQ ID NO: 400)

When the suicide polypeptide is expressed at the surface of a CAR-T cell, binding of rituximab to the R epitopes of the polypeptide causes lysis of the cell. More than one molecule of rituximab may bind per polypeptide expressed at the cell surface. Each R epitope of the polypeptide may bind a separate molecule of rituximab. Deletion of BCMA specific CAR-T cells may occur in vivo, for example by administering rituximab to a patient. The decision to delete the transferred cells may arise from undesirable effects being detected in

the patient which are attributable to the transferred cells, such as for example, when unacceptable levels of toxicity are detected.

[0179] In some embodiments, the CAR-T cell comprises a selected epitope within the scFv having a specificity to be recognized by a specific antibody. See, e.g., PCT application "mAb-DRIVEN CHIMERIC ANTIGEN RECEPTOR SYSTEMS FOR SORTING/DEPLETING ENGINEERED IMMUNE CELLS," WO 2016/120216 A1, filed on January 25, 2016. Such an epitope facilitates sorting and/or depleting the CAR-T cells. The epitope can be selected from any number of epitopes known in the art. In some embodiments, the epitope can be a target of a monoclonal antibody approved for medical use, such as, for example without limitation, the CD20 epitope recognized by rituximab. In some embodiments, the epitope comprises the amino acid sequence shown in SEQ ID NO: 397.

[0180] CPYSNPSLC (SEQ ID NO: 397)

In some embodiments, the epitope is located within the CAR. For example without limitation, the epitope can be located between the scFv and the hinge of a CAR. In some embodiments, two instances of the same epitope, separate by linkers, may be used in the CAR. For example, the polypeptide comprising the amino acid sequence shown in SEQ ID NO: 398 can be used within a CAR, located between the light chain variable region and the hinge.

[0181] GSGGGGSCPYSNPSLCGSGGGGSCPYSNPSLCGSGGGGS (SEQ ID NO: 398)

In some embodiments, the epitope-specific antibody may be conjugated with a cytotoxic drug. It is also possible to promote CDC cytotoxicity by using engineered antibodies on which are grafted component(s) of the complement system. In some embodiments, activation of the CAR-T cells can be modulated by depleting the cells using an antibody which recognizes the epitope.

Therapeutic applications

[0182] Isolated cells obtained by the methods described above, or cell lines derived from such isolated cells, can be used as a medicament. In some embodiments, such a medicament can be used for treating cancer. In some embodiments, the cancer is multiple myeloma malignant plasma cell neoplasm, Hodgkin's lymphoma, nodular lymphocyte predominant Hodgkin's lymphoma, Kahler's disease and Myelomatosis, plasma cell leukemia, plasmacytoma, B-cell prolymphocytic leukemia, hairy cell leukemia, B-cell non-Hodgkin's lymphoma (NHL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), follicular lymphoma, Burkitt's lymphoma, marginal zone lymphoma, mantle cell lymphoma, large cell lymphoma, precursor B-lymphoblastic lymphoma, myeloid leukemia, Waldenstrom's macroglobulinemia, diffuse large B cell lymphoma, follicular lymphoma, marginal zone lymphoma, mucosa-associated lymphatic tissue lymphoma, small cell lymphocytic lymphoma, mantle cell lymphoma, Burkitt lymphoma, primary mediastinal (thymic) large B-cell lymphoma, lymphoplasmacytic lymphoma, Waldenstrom macroglobulinemia, nodal marginal zone B cell lymphoma, splenic marginal zone lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, lymphomatoid granulomatosis, T cell/histiocyte-rich large B-cell lymphoma, primary central nervous system lymphoma, primary cutaneous diffuse large B-cell lymphoma (leg type), EBV positive diffuse large B-cell lymphoma of the elderly, diffuse large B-cell lymphoma associated with inflammation, intravascular large B-cell lymphoma, ALK-positive large B-cell lymphoma, plasmablastic lymphoma, large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease, B-cell lymphoma unclassified with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma, B-cell lymphoma unclassified with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma, or another B-cell related lymphomas.

[0183] An isolated cell according to the invention, or cell line derived from the isolated cells, can be used in the manufacture of a medicament for treatment of a cancer in a patient in need thereof.

[0184] Also provided herein are methods for treating patients. In some examples the method comprises providing an immune cell of the invention to a patient in need thereof. In some examples, the method comprises a step of administering transformed immune cells of the invention to a patient in need thereof.

[0185] In some examples, T cells of the invention can undergo robust in vivo T cell expansion and can persist for an extended amount of time.

[0186] Methods of treatment of the present disclosure can be ameliorating, curative or prophylactic. The method may be either part of an autologous immunotherapy or part of an allogenic immunotherapy treatment. The immune cells of the invention are particularly suitable for allogeneic immunotherapy. T cells from donors can be transformed into non-alloreactive cells using standard protocols and reproduced as needed, thereby producing CAR-T cells which may be administered to one or several patients. Such CAR-T cell therapy can be made available as an "off the shelf" therapeutic product.

[0187] Cells that can be used with the disclosed methods are described in the previous section. Treatment can be used to treat patients diagnosed with, for example, cancer. Cancers that may be treated include, for example without limitation, cancers that involve B lymphocytes, including any of the above-listed cancers. Types of cancers to be treated with the CARs and CAR-T cells of the invention include, but are not limited to certain leukemia or lymphoid malignancies. Adult tumors/cancers and pediatric tumors/cancers are also included. In some examples, the treatment can be in combination with one or more therapies against cancer selected from the

group of antibodies therapy, chemotherapy, cytokines therapy, dendritic cell therapy, gene therapy, hormone therapy, laser light therapy and radiation therapy.

[0188] In some examples, treatment can be administrated into patients undergoing an immunosuppressive treatment. Indeed, the invention preferably relies on cells or population of cells, which have been made resistant to at least one immunosuppressive agent due to the inactivation of a gene encoding a receptor for such immunosuppressive agent. In this aspect, the immunosuppressive treatment should help the selection and expansion of the T cells according to the invention within the patient. The administration of the cells or population of cells according to the invention may be carried out in any convenient manner, including by aerosol inhalation, injection, ingestion, transfusion, implantation or transplantation. The compositions described herein may be administered to a patient subcutaneously, intradermally, intratumorally, intranodally, intramedullary, intramuscularly, by intravenous or intralymphatic injection, or intraperitoneally. In one example, the cell compositions of the invention are preferably administered by intravenous injection.

[0189] In some examples, the administration of the cells or population of cells can comprise administration of, for example, about 10^4 to about 10^9 cells per kg body weight including all integer values of cell numbers within those ranges. In some examples, the administration of the cells or population of cells can comprise administration of about 10^5 to 10^6 cells per kg body weight including all integer values of cell numbers within those ranges. The cells or population of cells can be administrated in one or more doses. In some examples, said effective amount of cells can be administrated as a single dose. In some examples, said effective amount of cells can be administrated as more than one dose over a period time. Timing of administration is within the judgment of managing physician and depends on the clinical condition of the patient. The cells or population of cells may be obtained from any source, such as a blood bank or a donor. While individual needs vary, determination of optimal ranges of effective amounts of a given cell type for a particular disease or conditions within the skill of the art. An effective amount means an amount which provides a therapeutic or prophylactic benefit. The dosage administrated will be dependent upon the age, health and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment and the nature of the effect desired. In some examples, an effective amount of cells or composition comprising those cells are administrated parenterally. In some examples, administration can be an intravenous administration. In some examples, administration can be directly done by injection within a tumor.

[0190] In some examples, cells are administered to a patient in conjunction with (e.g., before, simultaneously or following) any number of relevant treatment modalities, including but not limited to treatment with agents such as monoclonal antibody therapy, CCR2 antagonist (e.g., INC-8761), antiviral therapy, cidofovir and interleukin-2, Cytarabine (also known as ARA-C) or natalizimab treatment for MS patients or efalizumab treatment for psoriasis patients or other treatments for PML patients. In some examples, BCMA specific CAR-T cells are administered to a patient in conjunction with one or more of the following: an anti-PD-1 antibody (e.g., nivolumab, pembrolizumab, or PF-06801591), an anti-PD-L1 antibody (e.g., avelumab, atezolizumab, or durvalumab), an anti-OX40 antibody (e.g., PF-04518600), an anti-4-1 BB antibody (e.g., PF-05082566), an anti-MCSF antibody (e.g., PD-0360324), an anti-GITR antibody, and/or an anti-TIGIT antibody. In some examples, a BCMA specific CAR comprising the amino acid sequence shown in SEQ ID NO: 396 is administered to a patient in conjunction with anti-PD-L1 antibody avelumab. In further examples, the T cells of the invention may be used in combination with chemotherapy, radiation, immunosuppressive agents, such as cyclosporin, azathioprine, methotrexate, mycophenolate, and FK506, antibodies, or other immunoablative agents such as CAMPATH, anti-CD3 antibodies or other antibody therapies, cytoxin, fludarabine, cyclosporin, FK506, rapamycin, mycophenolic acid, steroids, FR901228, cytokines, and/or irradiation. These drugs inhibit either the calcium dependent phosphatase calcineurin (cyclosporine and FK506) or inhibit the p70S6 kinase that is important for growth factor induced signaling (rapamycin) (Henderson, Naya et al. 1991; Liu, Albers et al. 1992; Bierer, Hollander et al. 1993). In a further example, the cell compositions of the invention are administered to a patient in conjunction with (e.g., before, simultaneously or following) bone marrow transplantation, T cell ablative therapy using either chemotherapy agents such as, fludarabine, external-beam radiation therapy (XRT), cyclophosphamide, or antibodies such as OKT3 or CAMPATH. In some examples, the cell compositions of the invention are administered following B-cell ablative therapy such as agents that react with CD20, e.g., Rituxan. For example, subjects may undergo standard treatment with high dose chemotherapy followed by peripheral blood stem cell transplantation. In certain examples, following the transplant, subjects receive an infusion of the expanded immune cells of the invention. In some examples, expanded cells are administered before or following surgery.

Kits

[0191] The invention also provides kits for use in the instant methods. Kits of the invention include one or more containers comprising a polynucleotide encoding a BCMA specific CAR, or an engineered immune cell comprising a polynucleotide encoding a BCMA specific CAR of the invention, and instructions for use in accordance with any of the methods of the invention described herein. Generally, these instructions comprise a description of administration of the engineered immune cell for the above described therapeutic treatments.

[0192] The instructions relating to the use of the engineered immune cells as described herein generally include information as to dosage, dosing schedule, and route of administration for the intended treatment. The containers may be unit doses, bulk packages (e.g., multi-dose packages) or sub-unit doses. Instructions supplied in the kits of the invention are typically written instructions on a label or package insert (e.g., a paper sheet included in the kit), but machine-readable instructions (e.g., instructions carried on a magnetic or optical storage disk) are also acceptable.

[0193] The kits of this invention are in suitable packaging. Suitable packaging includes, but is not limited to, vials, bottles, jars, flexible packaging (e.g., sealed Mylar or plastic bags), and the like. Also contemplated are packages for use in combination with a specific device, such as an inhaler, nasal administration device (e.g., an atomizer) or an infusion device such as a minipump. A kit may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The container may also have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is a BCMA antibody. The container may further comprise a second pharmaceutically active agent.

[0194] Kits may optionally provide additional components such as buffers and interpretive information. Normally, the kit comprises a container and a label or package insert(s) on or associated with the container.

[0195] The following examples are offered for illustrative purposes only. Indeed, various modifications in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description.

[0196] Representative materials of the present invention were deposited in the American Type Culture Collection (ATCC) on February 9, 2016. The biological deposit having ATCC Accession No. PTA-122834 is a vector comprising a polynucleotide encoding a BCMA specific CAR. The deposit was made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and Regulations thereunder (Budapest Treaty). This assures maintenance of a viable culture of the deposit for 30 years from the date of deposit. The deposit will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement between Pfizer, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the culture of the deposit to the public upon issuance of the pertinent U.S. patent or upon laying open to the public of any U.S. or foreign patent application, whichever comes first, and assures availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to 35 U.S.C. Section 122 and the Commissioner's rules pursuant thereto (including 37 C.F.R. Section 1.14 with particular reference to 886 OG 638).

[0197] The assignee of the present application has agreed that if a culture of the materials on deposit should die or be lost or destroyed when cultivated under suitable conditions, the materials will be promptly replaced on notification with another of the same. Availability of the deposited material is not to be construed as a license to practice the invention in contravention of the rights granted under the authority of any government in accordance with its patent laws.

Examples

Example 1: Determination of kinetics and affinity of BCMA/human IgG interactions at 25°C and/or 37°C

[0198] This example determines the kinetics and affinity of various anti-BCMA antibodies at 25°C and 37°C.

[0199] All experiments were performed on a Bio-Rad Proteon XPR36 surface Plasmon resonance biosensor (Bio-Rad, Hercules, CA). An array of anti-BCMA antibodies was prepared using an amine-coupling method on a Bio-Rad GLC Sensor Chip similar to that described in Abdiche, et al., Anal. Biochem. 411, 139-151 (2011). The analysis temperature for the immobilization was 25°C and the running buffer was HBS-T+ (10 mM HEPES, 150 mM NaCl, 0.05% Tween-20, pH 7.4). Channels were activated in the analyte (horizontal) direction by injecting a mixture of 1 mM ECD and 0.25 mM NHS for 3 minutes at a flow rate of 30 µL/min. IgGs were immobilized on the activated spots by injecting them in the ligand (vertical) direction at 20 µg/mL in 10 mM Acetate pH 4.5 buffer for 1.5 minutes at 30 µg/mL. The activated surfaces were blocked by injecting 1M ethanolamine, pH 8.5 in the analyte direction for 3 minutes at 30 µL/min.

[0200] The analysis temperature for the BCMA binding analysis was 37°C or 25°C in a running buffer of HBS-T+, supplemented with 1 mg/mL BSA. A kinetic titration method was employed for the interaction analysis as described in Abdiche, et al. Human BCMA (huBCMA) or cynomolgus monkey BCMA (cyBCMA) analyte was injected in the analyte direction using a series of injections from low to high concentration. The concentrations used were 0.08 nM, 0.4 nM, 2 nM, 10 nM and 50 nM (a 5-membered series, with a 5-fold dilution factor and top concentration of 50 nM). The association time for a given analyte dilution was two minutes. Immediately after the 50 nM BCMA injection, dissociation was monitored for 2 hours. Prior to the BCMA analyte injections, buffer was injected 5 times using the same association and dissociation times at the BCMA analyte cycles to prepare a buffer blank sensorgram for double-referencing purposes (double referencing as described in Myszk, J. Mol. Recognit. 12, 279-284 (1999)).

[0201] The sensorgrams were double-referenced and fit to a *1:1 Langmuir with mass transport* kinetic titration model in BIAevaluation Software version 4.1.1 (GE Lifesciences, Piscataway, NJ). The kinetics and affinity parameters for various anti-BCMA antibodies of the disclosure are shown in Tables 4A-4C. The antibodies shown in Tables 4A-4C share the same VH and VL regions as the CARs shown in Table 1 having the same name.

Table 4A

Sample	k _a (1/Ms)	k _d (1/s)	t _{1/2} (min)	K _D (pM)
A02_Rd4_6nM_C01	1.2E+06	2.8E-05	411	24
A02_Rd4_6nM_C16	1.1E+06	6.2E-05	187	59
Combo_Rd4_0.6nM_C29	6.6E+06	1.4E-04	83	21
L3PY/H3TAQ	2.6E+06	1.4E-04	84	53

Table 4B

Antibody	k _a (1/Ms) huBCMA @ 25°C	k _d (1/s) huBCMA @25°C	T _{1/2} (min) to huBCMA @25°C	KD (nM) to huBCMA @ 25°C
P6E01/P6E01	1.04E+06	4.15E-03	2.8	4.0
P6E01/H3.AQ	8.35E+05	3.45E-04	33.53	0.41
L1.LGF/L3.KW/P6E01	8.31E+05	7.55E-03	1.53	9.08
L1.LGF/L3.NY/P6E01	1.33E+06	4.40E-03	2.63	3.32
L1.GDF/L3.NY/P6E01	1.60E+06	5.92E-03	1.95	3.70
L1.LGF/L3.KW/H3.AL	4.28E+05	1.23E-03	9.40	2.87
L1.LGF/L3.KW/H3.AP	9.28E+05	2.27E-03	5.10	2.44
L1.LGF/L3.KW/H3.AQ	5.24E+05	9.56E-04	12.09	1.82
L1.LGF/L3.PY/H3.AP	4.57E+05	9.69E-04	11.92	2.12
L1.LGF/L3.PY/H3.AQ	9.31E+05	8.86E-04	13.04	0.95
L1.LGF/L3.NY/H3.AL	7.63E+05	9.70E-04	11.91	1.27
L1.LGF/L3.NY/H3.AP	9.36E+05	5.33E-04	21.67	0.57
L1.LGF/L3.NY/H3.AQ	6.66E+05	2.99E-04	38.61	0.45
L1.GDF/L3.KW/H3.AL	4.45E+05	3.90E-03	2.96	8.76
L1.GDF/L3.KW/H3.AP	1.17E+06	4.61E-03	2.51	3.93
L1.GDF/L3.KW/H3.AQ	7.97E+05	3.48E-03	3.32	4.37
L1.GDF/L3.PY/H3.AQ	1.42E+06	1.35E-02	0.86	9.49
L1.GDF/L3.NY/H3.AL	9.07E+05	4.03E-03	2.87	4.44
L1.GDF/L3.NY/H3.AP	1.41E+06	1.41E-03	8.21	1.00
L1.GDF/L3.NY/H3.AQ	9.84E+05	7.22E-04	16.00	0.73
L3.KW/P6E01	7.40E+05	3.15 E-04	36.66	0.43
L3.PY/P6E01	7.12E+05	2.28E-04	50.74	0.32
L3.NY/P6E01	8.76E+05	3.84E-04	30.08	0.44
Antibody	k _a (1/Ms) huBCMA @ 37°C	k _d (1/s) huBCMA @37°C	T _{1/2} (min) to huBCMA @37°C	KD (nM) to huBCMA @ 37°C
L3.PY/L1.PS/P6E01	2.49E+06	1.13E-03	10.21	0.45
L3.PY/L1.AH/P6E01	2.55E+06	1.26E-03	9.19	0.49
L3.PY/L1.FF/P6E01	2.39E+06	1.41E-03	8.18	0.59
L3.PY/L1.PH/P6E01	2.81E+06	9.13E-04	12.65	0.32
L3.PY/L3.KY/P6E01	3.18E+06	1.09E-03	10.65	0.34
L3.PY/L3.KF/P6E01	2.88E+06	2.08E-03	5.56	0.72
L3.PY/H2.QR	2.56E+06	1.19E-03	9.75	0.46
L3.PY/H2.DY	2.60E+06	1.38E-03	8.37	0.53
L3.PY/H2.YQ	2.58E+06	1.56E-03	7.41	0.60
L3.PY/H2.LT	2.40E+06	1.29E-03	8.95	0.54
L3.PY/H2.HA	2.43E+06	1.47E-03	7.89	0.60
L3.PY/H2.QL	2.64E+06	2.18E-03	5.31	0.82
L3.PY/H3.YA	3.15E+06	1.18E-03	9.82	0.37
L3.PY/H3.AE	3.29E+06	1.39E-03	8.32	0.42
L3.PY/H3.AQ	3.08E+06	1.73E-03	6.69	0.56
L3.PY/H3.TAQ	3.08E+06	1.14E-03	10.13	0.37
L3.PY/P6E01	2.65E+06	1.96E-03	5.91	0.74

Antibody	ka (1/Ms) huBCMA @ 37°C	kd (1/s) huBCMA @37°C	T½ (min) to huBCMA @37°C	KD (nM) to huBCMA @ 37°C
L3.PY/L1.PS/H2.QR	3.97E+06	1.03E-01	0.11	25.85
L3.PY/L1.PS/H2.DY	3.22E+06	3.61E-03	3.20	1.12
L3.PY/L1.PS/H2.YQ	3.35E+06	4.30E-03	2.69	1.28
L3.PY/L1.PS/H2.LT	3.40E+06	4.65E-03	2.49	1.37
L3.PY/L1.PS/H2.HA	3.30E+06	1.06E-02	1.09	3.21
L3.PY/L1.PS/H2.QL	1.52E+07	3.14E-01	0.04	20.64
L3.PY/L1.PS/H3.YA	3.07E+06	9.05E-03	1.28	2.95
L3.PY/L1.PS/H3.AE	3.14E+06	1.46E-03	7.93	0.46
L3.PY/L1.PS/H3.AQ	3.26E+06	1.79E-03	6.46	0.55
L3.PY/L1.PS/H3.TAQ	3.25E+06	2.46E-03	4.70	0.76
L3.PY/L1.AH/H2.QR	3.13E+06	1.81E-03	6.39	0.58
L3.PY/L1.AH/H2.DY	3.05E+06	1.52E-03	7.62	0.50
L3.PY/L1.AH/H2.YQ	2.42E+06	1.93E-03	6.00	0.80
L3.PY/L1.AH/H2.LT	3.16E+06	1.23E-03	9.38	0.39
L3.PY/L1.AH/H2.HA	3.33E+06	1.81E-03	6.37	0.54
L3.PY/L1.AH/H2.QL	3.04E+06	1.60E-03	7.22	0.53
L3.PY/L1.AH/H3.YA	3.00E+06	1.50E-03	7.73	0.50
L3.PY/L1.AH/H3.AE	3.32E+06	1.73E-03	6.70	0.52
L3.PY/L1.AH/H3.AQ	3.03E+06	1.97E-03	5.85	0.65
L3.PY/L1.AH/H3.TAQ	3.27E+06	1.19E-03	9.68	0.37
L3.PY/L1.FF/H2.QR	3.47E+06	1.77E-03	6.54	0.51
L3.PY/L1.FF/H2.DY	4.14E+06	2.71E-03	4.27	0.65
L3.PY/L1.FF/H2.YQ	3.32E+06	1.52E-03	7.61	0.46
L3.PY/L1.FF/H2.LT	3.30E+06	1.67E-03	6.92	0.51
L3.PY/L1.FF/H2.HA	3.49E+06	2.19E-03	5.29	0.63
L3.PY/L1.FF/H2.QL	3.48E+06	1.40E-03	8.28	0.40
L3.PY/L1.FF/H3.YA	3.50E+06	1.80E-03	6.41	0.51
L3.PY/L1.FF/H3.AE	3.82E+06	2.63E-03	4.39	0.69
L3.PY/L1.FF/H3.AQ	3.32E+06	1.54E-03	7.51	0.46
L3.PY/L1.FF/H3.TAQ	3.52E+06	1.89E-03	6.12	0.54
L3.PY/L1.PH/H2.QR	3.69E+06	2.36E-03	4.89	0.64
L3.PY/L1.PH/H2.HA	2.37E+06	1.16E-03	9.99	0.49
L3.PY/L1.PH/H3.AE	3.68E+06	1.34E-03	8.61	0.36
L3.PY/L1.PH/H3.AQ	3.08E+06	1.59E-03	7.27	0.52
L3.PY/L1.PH/H3.TAQ	3.58E+06	2.13E-03	5.43	0.59
L3.PY/L3.KY/H2.QR	2.95E+06	9.90E-04	11.67	0.34
L3.PY/L3.KY/H2.DY	3.19E+06	6.42E-04	18.00	0.20
L3.PY/L3.KY/H2.YQ	2.14E+06	1.65E-03	7.02	0.77
L3.PY/L3.KY/H2.LT	2.92E+06	9.06E-04	12.75	0.31
L3.PY/L3.KY/H2.HA	3.29E+06	1.63E-03	7.10	0.49
L3.PY/L3.KY/H2.QL	3.65E+06	2.08E-03	5.56	0.57
L3.PY/L3.KY/H3.YA	3.30E+06	9.12E-04	12.67	0.28
L3.PY/L3.KY/H3.TAQ	2.79E+06	6.49E-04	17.79	0.23
L3.PY/L3.KF/H2.DY	2.74E+06	1.82E-03	6.35	0.67
L3.PY/L3.KF/H2.YQ	1.96E+06	2.23E-03	5.18	1.14
L3.PY/L3.KF/H2.LT	2.75E+06	1.91E-03	6.05	0.69
L3.PY/L3.KF/H2.QL	2.07E+06	1.25E-03	9.26	0.60
L3.PY/L3.KF/H3.YA	3.12E+06	1.47E-03	7.85	0.47
L3.PY/L3.KF/H3.AE	3.07E+06	1.55E-03	7.44	0.51

Antibody	ka (1/Ms) huBCMA @ 37°C	kd (1/s) huBCMA @37°C	T½ (min) to huBCMA @37°C	KD (nM) to huBCMA @ 37°C
L3.PY/L3.KF/H3.AQ	3.48E+06	2.27E-03	5.09	0.65
L3.PY/L3.KF/H3.TAQ	2.82E+06	1.62E-03	7.12	0.58
Antibody	ka (1/Ms) cyBCMA @ 25°C	kd (1/s) cyBCMA @25°C	T½ (min) to cyBCMA @25°C	KD (nM) to cyBCMA @ 25°C
P6E01/P6E01		7.02E-02	0.16	115.4
P6E01/H3.AQ	1.08E+06	7.40E-03	1.6	6.9
L1.LGF/L3.KW/P6E01	4.55E+05	1.95E-02	0.6	42.8
L1.LGF/L3.NY/P6E01	9.20E+05	1.05E-02	1.1	11.4
L1.GDF/L3.NY/P6E01	1.20E+06	7.67E-03	1.5	6.4
L1.LGF/L3.KW/H3.AL	2.90E+05	1.21E-02	1.0	41.8
L1.LGF/L3.KW/H3.AP	5.54E+05	1.54E-02	0.7	27.8
L1.LGF/L3.KW/H3.AQ	5.27E+05	3.55E-03	3.3	6.7
L1.LGF/L3.PY/H3.AP	3.64E+05	1.30E-02	0.9	35.8
L1.LGF/L3.PY/H3.AQ	1.00E+06	4.77E-03	2.4	4.8
L1.LGF/L3.NY/H3.AL	6.35E+05	1.48E-02	0.8	23.2
L1.LGF/L3.NY/H3.AP	8.30E+05	5.57E-03	2.1	6.7
L1.LGF/L3.NY/H3.AQ	7.51E+05	1.48E-03	7.8	2.0
L1.GDF/L3. KW/H3.AL	3.18E+05	1.80E-02	0.6	56.7
L1.GDF/L3.KW/H3.AP	8.14E+05	2.03E-02	0.6	24.9
L1.GDF/L3.KW/H3.AQ	8.02E+05	5.65E-03	2.0	7.0
L1.GDF/L3.PY/H3.AQ	1.55E+06	1.66E-02	0.7	10.7
L1.GDF/L3.NY/H3.AL	9.00E+05	2.19E-02	0.5	24.3
L1.GDF/L3.NY/H3.AP	1.36E+06	7.02E-03	1.6	5.2
L1.GDF/L3.NY/H3.AQ	1.18E+06	1.36E-03	8.5	1.2
L3.KW/P6E01	7.63E+05	2.57E-03	4.5	3.4
L3.PY/P6E01	8.55E+05	2.93E-03	3.9	3.4
L3.NY/P6E01	1.01E+06	2.87E-03	4.0	2.8
Antibody	ka (1/Ms) cyBCMA @ 37°C	kd (1/s) cyBCMA @37°C	T½ (min) to cyBCMA @37°C	KD (nM) to cyBCMA @ 37°C
L3.PY/L1.PS/P6E01	2.17E+06	6.06E-03	1.91	2.79
L3.PY/L1.AH/P6E01	2.16E+06	5.72E-03	2.02	2.65
L3.PY/L1.FF/P6E01	2.45E+06	5.91E-03	1.96	2.41
L3.PY/L1.PH/P6E01	2.17E+06	7.89E-03	1.46	3.63
L3.PY/L3.KY/P6E01	2.27E+06	5.02E-03	2.30	2.21
L3.PY/L3.KF/P6E01	2.39E+06	8.30E-03	1.39	3.48
L3.PY/H2.QR	2.18E+06	6.58E-03	1.76	3.02
L3.PY/H2.DY	2.24E+06	6.18E-03	1.87	2.76
L3.PY/H2.YQ	2.46E+06	6.21E-03	1.86	2.53
L3.PY/H2.LT	2.09E+06	7.57E-03	1.53	3.63
L3.PY/H2.HA	1.99E+06	7.55E-03	1.53	3.79
L3.PY/H2.QL	2.05E+06	1.26E-02	0.91	6.16
L3.PY/H3.YA	2.87E+06	5.40E-03	2.14	1.88
L3.PY/H3.AE	2.82E+06	5.04E-03	2.29	1.79
L3.PY/H3.AQ	2.77E+06	5.39E-03	2.14	1.94
L3.PY/H3.TAQ	2.57E+06	4.37E-03	2.64	1.70
L3.PY/P6E01	2.20E+06	1.31E-02	0.88	5.96

Antibody	ka (1/Ms) cyBCMA @ 37°C	kd (1/s) cyBCMA @37°C	T½ (min) to cyBCMA @37°C	KD (nM) to cyBCMA @ 37°C
L3.PY/L1.PS/H2.QR	5.25E+05	6.70E-04	17.23	1.28
L3.PY/L1.PS/H2.DY	1.90E+06	3.78E-03	3.06	1.99
L3.PY/L1.PS/H2.YQ	2.00E+06	3.74E-03	3.09	1.87
L3.PY/L1.PS/H2.LT	2.17E+06	4.11E-03	2.81	1.89
L3.PY/L1.PS/H2.HA	1.45E+06	2.69E-03	4.30	1.86
L3.PY/L1.PS/H2.QL	6.57E+05	6.36E-04	18.17	0.97
L3.PY/L1.PS/H3.YA	1.77E+06	9.98E-03	1.16	5.65
L3.PY/L1.PS/H3.AE	2.46E+06	4.13E-03	2.80	1.68
L3.PY/L1.PS/H3.AQ	2.52E+06	4.33E-03	2.67	1.72
L3.PY/L1.PS/H3.TAQ	2.58E+06	5.52E-03	2.09	2.14
L3.PY/L1.AH/H2.QR	2.20E+06	4.91E-03	2.35	2.23
L3.PY/L1.AH/H2.DY	2.32E+06	4.51E-03	2.56	1.95
L3.PY/L1.AH/H2.YQ	1.58E+06	4.31E-03	2.68	2.74
L3.PY/L1.AH/H2.LT	2.19E+06	2.96E-03	3.91	1.35
L3.PY/L1.AH/H2.HA	2.58E+06	4.39E-03	2.63	1.70
L3.PY/L1.AH/H2.QL	2.62E+06	9.55E-03	1.21	3.65
L3.PY/L1.AH/H3.YA	2.37E+06	5.26E-03	2.20	2.22
L3.PY/L1.AH/H3.AE	2.25E+06	3.56E-03	3.25	1.58
L3.PY/L1.AH/H3.AQ	2.24E+06	3.99E-03	2.90	1.78
L3.PY/L1.AH/H3.TAQ	2.28E+06	3.02E-03	3.83	1.32
L3.PY/L1.FF/H2.QR	2.55E+06	4.21E-03	2.75	1.65
L3.PY/L1.FF/H2.DY	2.66E+06	5.00E-03	2.31	1.88
L3.PY/L1.FF/H2.YQ	2.19E+06	3.26E-03	3.55	1.49
L3.PY/L1.FF/H2.LT	2.19E+06	3.41E-03	3.38	1.56
L3.PY/L1.FF/H2.HA	2.33E+06	4.17E-03	2.77	1.79
L3.PY/L1.FF/H2.QL	2.36E+06	4.49E-03	2.57	1.91
L3.PY/L1.FF/H3.YA	2.46E+06	4.16E-03	2.77	1.69
L3.PY/L1.FF/H3.AE	2.85E+06	5.01E-03	2.31	1.76
L3.PY/L1.FF/H3.AQ	2.18E+06	3.29E-03	3.51	1.51
L3.PY/L1.FF/H3.TAQ	2.32E+06	3.76E-03	3.07	1.62
L3.PY/L1.PH/H2.QR	2.42E+06	4.36E-03	2.65	1.80
L3.PY/L1.PH/H2.HA	1.61E+06	5.53E-03	2.09	3.44
L3.PY/L1.PH/H3.AE	2.61E+06	2.02E-03	5.72	0.77
L3.PY/L1.PH/H3.AQ	2.28E+06	3.41E-03	3.39	1.50
L3.PY/L1.PH/H3.TAQ	2.51E+06	3.20E-03	3.61	1.28
L3.PY/L3.KY/H2.QR	2.05E+06	7.74E-03	1.49	3.78
L3.PY/L3.KY/H2.DY	1.96E+06	2.43E-03	4.75	1.24
L3.PY/L3.KY/H2.YQ	1.27E+06	2.58E-03	4.47	2.04
L3.PY/L3.KY/H2.LT	1.82E+06	2.32E-03	4.98	1.27
L3.PY/L3.KY/H2.HA	2.28E+06	3.18E-03	3.63	1.40
L3.PY/L3.KY/H2.QL	2.75E+06	4.09E-03	2.83	1.49
L3.PY/L3.KY/H3.YA	1.84E+06	4.28E-03	2.70	2.33
L3.PY/L3.KY/H3.TAQ	1.81E+06	1.92E-03	6.03	1.06
L3.PY/L3.KF/H2.DY	2.08E+06	3.68E-03	3.14	1.77
L3.PY/L3.KF/H2.YQ	1.41E+06	5.01E-03	2.30	3.55
L3.PY/L3.KF/H2.LT	1.91E+06	4.13E-03	2.80	2.16
L3.PY/L3.KF/H2.QL	1.42E+06	3.10E-03	3.73	2.18
L3.PY/L3.KF/H3.YA	2.10E+06	7.96E-03	1.45	3.78
L3.PY/L3.KF/H3.AE	1.85E+06	5.64E-03	2.05	3.05

Antibody	ka (1/Ms) cyBCMA @ 37°C	kd (1/s) cyBCMA @37°C	T½ (min) to cyBCMA @37°C	KD (nM) to cyBCMA @ 37°C
L3.PY/L3.KF/H3.AQ	2.55E+06	2.38E-03	4.85	0.93
L3.PY/L3.KF/H3.TAQ	2.01E+06	1.91E-03	6.05	0.95

Table 4C

Antibody	Human BCMA			Cyno BCMA		
	ka (1/Ms)	kd (1/s)	KD (pM)	ka (1/Ms)	kd (1/s)	KD (pM)
P5A2_VHVL (P5A)	6.96E+06	3.87E-02	5567	1.61E+06	1.64E-02	10230
A02_Rd4_0.6nM_C06	3.49E+06	7.37E-05	21	1.81E+06	1.05E-04	58
A02_Rd4_0.6nM_C09	5.50E+06	9.75E-05	18	2.13E+06	1.74E-04	82
A02_Rd4_6nM_C16 (PSAC16)	1.56E+06	1.41E-04	90	1.34E+06	1.58E-04	118
A02_Rd4_6nM_C03	1.69E+06	1.26E-04	75	1.17E+06	1.85E-04	158
A02_Rd4_6nM_C01	3.11E+06	9.20E-05	30	1.45E+06	5.83E-04	401
A02_Rd4_6nM_C26	4.26E+06	1.39E-04	33	2.21E+06	4.48E-04	203
A02_Rd4_6nM_C25	2.75E+06	1.80E-04	65	1.50E+06	3.30E-04	220
A02_Rd4_6nM_C22	3.38E+06	1.82E-04	54	1.84E+06	3.24E-04	176
A02_Rd4_6nM_C19	3.00E+06	1.48E-04	49	2.54E+06	6.61E-04	260
A02_Rd4_0.6nM_C03	4.27E+06	1.82E-04	43	2.12E+06	4.26E-04	201
A02_Rd4_6nM_C07	1.48E+06	1.89E-04	128	6.91E+05	7.86E-04	1138
A02_Rd4_6nM_C23	1.22E+07	2.55E-04	21	2.63E+06	4.14E-04	157
A02_Rd4_0.6nM_C18	4.73E+06	2.29E-04	48	3.24E+06	6.39E-04	197
A02_Rd4_6nM_C10	4.51E+06	3.15E-04	70	1.90E+06	8.98E-04	472
A02_Rd4_6nM_C05	3.10E+06	3.08E-04	99	1.36E+06	1.29E-03	950
A02_Rd4_0.6nM_C10	2.30E+06	2.96E-04	129	8.83E+05	1.63E-03	1842
A02_Rd4_6nM_C04	4.47E+06	6.03E-04	135	2.18E+06	8.31E-04	381
A02_Rd4_0.6nM_C26	7.26E+06	4.43E-04	61	2.71E+06	2.56E-03	941
A02_Rd4_0.6nM_C13	8.53E+06	5.66E-04	66	2.29E+06	1.28E-03	560
A02_Rd4_0.6nM_C01 (P5AC1)	4.74E+06	9.15E-04	193	2.39E+06	1.57E-03	655
A02_Rd4_6nM_C08	3.92E+06	7.38E-04	188	2.23E+06	1.13E-02	5072
P5C1_VHVL (PC1)	1.16E+07	6.92E-02	5986	3.53E+06	5.38E-02	15231
C01_Rd4_6nM_C24	7.47E+06	3.48E-03	467	3.17E+06	8.91E-04	281
C01_Rd4_6nM_C26	1.50E+07	1.36E-03	90	4.75E+06	1.99E-03	419
C01_Rd4_6nM_C02	1.61E+07	1.44E-03	89	5.12E+06	2.18E-03	426
C01_Rd4_6nM_C10	1.31E+07	2.12E-03	162	4.44E+06	2.19E-03	493
C01_Rd4_0.6nM_C27	1.23E+07	3.74E-03	303	3.34E+06	2.85E-03	852
C01_Rd4_6nM_C20	6.02E+06	2.76E-03	459	3.60E+06	6.25E-03	1737
C01_Rd4_6nM_C12	1.21E+07	6.49E-03	535	4.51E+06	3.70E-03	820
C01_Rd4_0.6nM_C16	1.55E+07	6.30E-03	407	4.95E+06	4.64E-03	939
Antibody	Human BCMA			Cyno BCMA		
	ka (1/Ms)	kd (1/s)	KD (pM)	ka (1/Ms)	kd (1/s)	KD (pM)
C01_Rd4_0.6nM_C09	1.51E+07	8.25E-03	545	5.28E+06	9.36E-03	1773
C01_Rd4_6nM_C09	1.58E+07	1.28E-02	811	3.73E+06	8.68E-03	2328
C01_Rd4_0.6nM_C03	1.55E+07	1.50E-02	964	4.72E+06	1.19E-02	2528
C01_Rd4_0.6nM_C06	1.82E+07	1.54E-02	847	6.22E+06	1.21E-02	1948
C01_Rd4_6nM_C04	2.33E+07	4.97E-02	2134	6.34E+06	3.27E-02	5156
COMBO_Rd4_0.6nM_C22	1.97E+06	7.15E-05	36	1.34E+06	6.66E-05	50
COMBO_Rd4_6nM_C21	1.17E+07	7.34E-05	6	3.17E+06	2.48E-04	78
COMBO_Rd4_6nM_C10	5.47E+06	9.72E-05	18	1.52E+06	1.60E-04	105
COMBO_Rd4_0.6nM_C04	1.07E+07	1.58E-04	15	3.52E+06	1.37E-04	39
COMBO_Rd4_6nM_C25	7.98E+06	1.13E-04	14	2.85E+06	2.26E-04	79
COMBO_Rd4_0.6nM_C21	1.34E+07	1.15E-04	9	3.63E+06	3.04E-04	84

Antibody	Human BCMA			Cyno BCMA		
	ka (1/Ms)	kd (1/s)	KD (pM)	ka (1/Ms)	kd (1/s)	KD (pM)
COMBO_Rd4_6nM_C11	6.74E+06	1.24E-04	18	2.64E+06	4.12E-04	156
COMBO_Rd4_0.6nM_C20	7.65E+06	1.46E-04	19	3.09E+06	2.84E-04	92
COMBO_Rd4_6nM_C09	8.85E+06	1.43E-04	16	2.37E+06	3.18E-04	134
COMBO_Rd4_6nM_C08	8.99E+06	1.69E-04	19	3.06E+06	4.28E-04	140
COMBO_Rd4_0.6nM_C19	7.86E+06	1.55E-04	20	2.92E+06	9.79E-04	336
COMBO_Rd4_0.6nM_C02	8.57E+06	1.85E-04	22	3.01E+06	4.94E-04	164
COMBO_Rd4_0.6nM_C23	7.39E+06	2.10E-04	28	2.81E+06	5.31E-04	189
COMBO_Rd4_0.6nM_C29	1.47E+07	2.77E-04	19	4.00E+06	3.36E-04	84
COMBO_Rd4_0.6nM_C09	1.04E+07	3.19E-04	31	3.77E+06	3.46E-04	92
COMBO_Rd4_6nM_C12 (PC1C12)	1.38E+07	2.70E-04	20	3.29E+06	4.86E-04	148
COMBO_Rd4_0.6nM_C30	4.35E+06	2.82E-04	65	1.68E+06	8.08E-04	481
COMBO_Rd4_0.6nM_C14	8.66E+06	3.28E-04	38	3.48E+06	6.45E-04	185
COMBO_Rd4_6nM_C07	1.05E+07	3.71E-04	35	3.94E+06	9.34E-04	237
COMBO_Rd4_6nM_C02	1.05E+06	4.43E-04	422	7.95E+05	1.36E-03	1714
COMBO_Rd4_0.6nM_C05	4.32E+06	4.97E-04	115	1.94E+06	1.72E-03	886
COMBO_Rd4_0.6nM_C17	8.68E+06	8.01E-04	92	3.06E+06	1.01E-03	330
COMBO_Rd4_6nM_C22 (COM22)	3.03E+06	7.75E-04	256	1.70E+06	1.65E-03	972
COMBO_Rd4_0.6nM_C11	5.11E+06	1.06E-03	207	2.20E+06	4.23E-03	1924

Example 2: BCMA Specific CAR-T Cells

[0202] This example demonstrates functional activity of BCMA specific CAR-T cells against BCMA positive (BCMA+) tumor cells.

[0203] Among all the BCMA specific CAR molecules generated, eight were selected for further activity tests based on affinity to BCMA, cross-reactivity to human BCMA and cyno BCMA, and epitope. The CAR molecules tested included: P5A, P5AC1, P5AC16, PC1, PC1 C12, COM22, P6DY, and P6AP. Three different architectures were designed: version 1 (v1) comprises an FcγRIIIα hinge, version 2 (v2) comprises a CD8α hinge, and version 3 (v3) comprises and IgG1 hinge. The chimeric antigen receptors (CARs) shown in Table 5 were prepared and used and assessed for their degranulation activity towards BCMA+ cells. Degranulation activity was determined upon transient expression of each CAR in human T cells.

Table 5: Exemplary BCMA specific CARs

CAR	CAR Amino Acid Sequence	Components
P5A-V1	MALPVTALLLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLEWVSAISDSGGSTYYADSVK GRFTISRDNKNTLYLQMNSLRAEDTAVYYCARYWPMDIWGQ GTLVTVSSGGGSGGGGSGGGGSEIVLTQSPGTLSPGERATL SCRASQSVSSSYLAWYQQKPGQAPRLLMYDASIRATGIPDRFS GSGSGTDFTLTISRLEPEDFAVYYCQYGSWPLTFGQGTKVEIK GLAVSTISSFFPPGYQIYWAPLAGTCGVLLSLVITLYCKRGRKKL LYIFKQPFMRPVQTTQEEDGCSCRFPEEEGGCELRVKFSRSAD APAYQQGQNQLYNELNLRREEYDVLDKRRGRDPEMGGKPR RKNPQEGLYNELQDKMAEAYSEIGMKGERRRGKGHGGLYQ GLSTATKDTYDALHMQALPPR (SEQ ID NO: 343)	CD8α signal peptide;
		P5A2_VHVL VH (Table 1 SEQ ID NO: 33);
		GS linker;
		P5A2_VHVLVL (SEQ ID NO: 34);
		FcγRIIIα hinge;
		CD8α TM domain;
		41BB ISD;
		CD3ζ ISD
P5A-V2	MALPVTALLLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLEWVSAISDSGGSTYYADSVK GRFTISRDNKNTLYLQMNSLRAEDTAVYYCARYWPMDIWGQ GTLVTVSSGGGSGGGGSGGGGSEIVLTQSPGTLSPGERATL SCRASQSVSSSYLAWYQQKPGQAPRLLMYDASIRATGIPDRFS	CD8α signal peptide;
		P5A2_VHVL VH;
		GS linker;
		P5A2_VHVL VL;

CAR	CAR Amino Acid Sequence	Components
	GSGSGTDFTLTISRLEPEDFAVYYCQQYGSWPLTFGQGTKVEIK TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFAC DIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQT TQEEDGCSCRFEEEEGGCELRVKFSRSADAPAYQQGQNQLY NELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQ KDKMAEAYSEIGMKGERRRGKGHGDLGYQGLSTATKDTYDALH MQALPPR(SEQ ID NO: 344)	CD8α hinge;
		CD8α TM domain;
		41BB ISD;
		CD3ζ ISD
P5A-V3	MALPVTALLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLEWVS AISDSGGSTYYADSVK GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARYWPMDIWGQ GTLVTVSSGGGSGGGGSGGGGSEIVLTQSPGTL SLSPGERATL SCRASQSVSSSYLAWYQQKPGQAPRLLMYDASIRATGIPDRFS GSGSGTDFTLTISRLEPEDFAVYYCQQYGSWPLTFGQGTKVEIK EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSV MHEAL HNHYTQKSLSLSPGKIYIWAPLAGTCGVLLLSLVITLYCKRGRKKL LYIFKQPFMRPVQTTQEEDGCSCRFEEEEGGCELRVKFSRSAD APAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPR RKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHGDLGYQ GLSTATKDTYDALHMQALPPR(SEQ ID NO: 345)	CD8α signal peptide;
		P5A2_VHVL VH ;
		GS linker;
		P5A2_VHVL VL;
		IgG1 hinge;
		CD8α TM domain;
		41BB ISD;
		CD3ζ ISD
P5AC1-V1	MALPVTALLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLEWVSAILsSGGSTYYADSVK GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARYWPMDIWGQ GTLVTVSSGGGSGGGGSGGGGSEIVLTQSPGTL SLSPGERATL SCRGGQSVSSSYLAWYQQKPGQAPRLLMYDASIRATGIPDRFS GSGSGTDFTLTISRLEPEDFAVYYCQQYQSWPLTFGQGTKVEIK	CD8α signal peptide;
		A02_Rd4_0.6nM_C01 VH (SEQ ID NO: 72);
		GS linker;
		A02_Rd4_0.6nM_C01
	GLAVSTISSFFPPGYQIYIWAPLAGTCGVLLLSLVITLYCKRGRKKL LYIFKQPFMRPVQTTQEEDGCSCRFEEEEGGCELRVKFSRSAD APAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPR RKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHGDLGYQ GLSTATKDTYDALHMQALPPR (SEQ ID NO: 346)	VL (SEQ ID NO: 73);
		FcγRIIIa hinge;
		CD8α TM domain;
		41BB ISD;
		CD3ζ ISD
P5AC1-V2	MALPVTALLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLEWVSAILsSGGSTYYADSVK GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARYWPMDIWGQ GTLVTVSSGGGSGGGGSGGGGSEIVLTQSPGTL SLSPGERATL SCRGGQSVSSSYLAWYQQKPGQAPRLLMYDASIRATGIPDRFS GSGSGTDFTLTISRLEPEDFAVYYCQQYQSWPLTFGQGTKVEIK TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFAC DIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQT TQEEDGCSCRFEEEEGGCELRVKFSRSADAPAYQQGQNQLY NELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQ KDKMAEAYSEIGMKGERRRGKGHGDLGYQGLSTATKDTYDALH MQALPPR (SEQ ID NO: 347)	CD8α signal peptide;
		A02_Rd4_0.6nM_C01 VH;
		GS linker;
		A02_Rd4_0.6nM_C01 VL;
		CD8α hinge;
		CD8α TM domain;
		41BB ISD;

CAR	CAR Amino Acid Sequence	Components
	MQALPPR (SEQ ID NO: 347)	CD3ζ ISD
P5AC1-V2.1	MALPVTALLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLEWVSAILSSGGSTYYADSVK GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARYWPMDIWGQ GTLVTVSSGGGGSGGGSGGGGSEIVLTQSPGTLSPGERATL SCRGGQSVSSSYLAWYQQKPGQAPRLLMYDASIRATGIPDRFS GSGSGTDFTLTISRLEPEDFAVYYCQYQSWPLTFGQGTKVEIK GSGGGGSCPYSNP SLCSGGGGSCPYSNP SLCSGGGGSTTTPAP RPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWA PLAGTCGVLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEED GCSCRFEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMA	CD8α signal peptide;
		A02_Rd4_0.6nM_C01 VH;
		GS linker;
		A02_Rd4_0.6nM_C01 VL; rituximab epitope;
		CD8α hinge;
		CD8α TM domain;
		41BB ISD;
	EAYSEIGMKGERRRGKGH DGLYQGLSTATKDTYDALHMQALP PR (SEQ ID NO: 396)	CD3ζ ISD
P5AC1-V3	MALPVTALLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLEWVSAILSSGGSTYYADSVK GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARYWPMDIWGQ GTLVTVSSGGGGSGGGSGGGGSEIVLTQSPGTLSPGERATL SCRGGQSVSSSYLAWYQQKPGQAPRLLMYDASIRATGIPDRFS GSGSGTDFTLTISRLEPEDFAVYYCQYQSWPLTFGQGTKVEIK EPKSPDKTHTCPPCAPPVAGPSVFLFPPKPKDTLMIARTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGKIYIWAPLAGTCGVLLSLVITLYCKRGRKKL LYIFKQPFMRPVQTTQEEDGCSCRFEEEEGGCELRVKFSRSAD APAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPR RKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGH DGLYQ GLSTATKDTYDALHMQALPPR (SEQ ID NO: 348)	CD8α signal peptide;
		A02_Rd4_0.6nM_C01 VH;
		GS linker;
		A02_Rd4_0.6nM_C01 VL;
		IgG1 hinge;
		CD8α TM domain;
		41BB ISD;
		CD3ζ ISD
P5AC16-V1	MALPVTALLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLEWVS AISdFGGSTYYADSVK GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARYWPMDIWGQ GTLVTVSSGGGGSGGGSGGGGSEIVLTQSPGTLSPGERATL SCRASQSVSDIYLAWYQQKPGQAPRLLMYDASIRATGIPDRFS GSGSGTDFTLTISRLEPEDFAVYYCQYQTWPLTFGQGTKVEIK GLAVSTISSFFPPGYQIYWAPLAGTCGVLLSLVITLYCKRGRKKL LYIFKQPFMRPVQTTQEEDGCSCRFEEEEGGCELRVKFSRSAD APAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPR RKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGH DGLYQ	CD8α signal peptide;
		A02_Rd4_6nM_C16 VH (SEQ ID NO: 39);
		GS linker;
		A02_Rd4_6nM_C16 VL (SEQ ID NO: 40);
		FcγRIIIα hinge;
		CD8α TM domain;
		41BB ISD;
	GLSTATKDTYDALHMQALPPR (SEQ ID NO: 349)	CD3ζ ISD;
P5AC16-V2	MALPVTALLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLEWVS AISdFGGSTYYADSVK GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARYWPMDIWGQ GTLVTVSSGGGGSGGGSGGGGSEIVLTQSPGTLSPGERATL	CD8α signal peptide;
		A02_Rd4_6nM_C16 VH;
		GS linker;

CAR	CAR Amino Acid Sequence	Components
	SCRASQSVSDIYLAWYQQKPGQAPRLLMYDASIRATGIPDRFS GSGSGTDFTLTISRLEPEDFAVYYCQQYQTWPLTFGQGTKVEIK TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFAC DIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQT TQEEDGCSCRFEEEEGGCELRVKFSRSADAPAYQQGQNQLY NELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQ KDKMAEAYSEIGMKGERRRGKGHGGLYQGLSTATKDTYDALH MQALPPR (SEQ ID NO: 350)	A02_Rd4_6nM_C16 VL;
		CD8α hinge;
		CD8α TM domain;
		41BB ISD;
		CD3ζ ISD
P5AC16-V3	MALPVTALLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLEWVSAISdFGGSTYYADSVK GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARYWPMDIWGQ GTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSLSPGERATL SCRASQSVSDIYLAWYQQKPGQAPRLLMYDASIRATGIPDRFS GSGSGTDFTLTISRLEPEDFAVYYCQQYQTWPLTFGQGTKVEIK EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGKIYIWAPLAGTCGVLLLSLVITLYCKRGRKKL LYIFKQPFMRPVQTTQEEDGCSCRFEEEEGGCELRVKFSRSAD APAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPR	CD8α signal peptide;
		A02_Rd4_6nM_C16 VH;
		GS linker;
		A02_Rd4_6nM_C16 VL;
		IgG1 hinge;
		CD8α TM domain;
		41BB ISD;
		CD3ζ ISD
	RKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHGGLYQ GLSTATKDTYDALHMQALPPR (SEQ ID NO: 351)	
PC1-V1	MALPVTALLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLEWVSAIGSGGGSTYYADSVK GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARYWPMDSWG QGTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSLSPGERA TLSCRASQSVSSTYLAWYQQKPGQAPRLLIYDASSRAPGIPDRF SGSGSGTDFTLTISRLEPEDFAVYYCQQYSTSPLTFGQGTKVEIK GLAVSTISSFFPPGYQIYWAPLAGTCGVLLLSLVITLYCKRGRKKL LYIFKQPFMRPVQTTQEEDGCSCRFEEEEGGCELRVKFSRSAD APAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPR RKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHGGLYQ GLSTATKDTYDALHMQALPPR (SEQ ID NO: 352)	CD8α signal peptide;
		P5C1_VHVL VH (SEQ ID NO: 76);
		GS linker;
		P5C1_VHVL VL (SEQ ID NO: 77);
		FcγRIIIα hinge;
		CD8α TM domain;
		41BB ISD;
		CD3ζ ISD
PC1-V2	MALPVTALLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLEWVSAIGSGGGSTYYADSVK GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARYWPMDSWG QGTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSLSPGERA TLSCRASQSVSSTYLAWYQQKPGQAPRLLIYDASSRAPGIPDRF SGSGSGTDFTLTISRLEPEDFAVYYCQQYSTSPLTFGQGTKVEIK TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFAC DIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQT TQEEDGCSCRFEEEEGGCELRVKFSRSADAPAYQQGQNQLY NELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQ KDKMAEAYSEIGMKGERRRGKGHGGLYQGLSTATKDTYDALH	CD8α signal peptide;
		P5C1_VHVL VH;
		GS linker;
		P5C1_VHVL VL;
		CD8α hinge;
		CD8α TM domain;
		41BB ISD;

CAR	CAR Amino Acid Sequence	Components
	MQALPPR (SEQ ID NO: 353)	CD3ζ ISD
PC1-V3	MALPVTALLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLEWVSAIGSGGGSTYYADSVK	CD8α signal peptide;
		P5C1_VHVL VH;
	GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARYWPMDSWG QGT LVTVSSGGGGSGGGSGGGGSEIVLTQSPGTL SLSPGERA TLSCRASQSVSSTYLAWYQQKPGQAPRLLIYDASSRAPGIPDRF SGSGSGTDFTLTISRLEPEDFAVYYCQYSTSPLTFGQG TKVEIK EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEAL HNHYTQKSLSLSPGKIYIWAPLAGTCGVLLSLVITLYCKRGRKKL LYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL RVKFSRSAD APAYQQGQNQLYNELNLGRREEYDVLDKRRGRDP EMGGKPR RKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQ GLSTATKDTYDALHMQALPPR (SEQ ID NO: 354)	GS linker;
		P5C1_VHVL VL;
		IgG1 hinge;
		CD8α TM domain;
		41BB ISD;
		CD3ζ ISD
PC1C12-V1	MALPVTALLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLEWVSAIGSGGWSYYADSVK GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARYWPMDSWG QGT LVTVSSGGGGSGGGSGGGGSEIVLTQSPGTL SLSPGERA TLSCWLSQSVSSTYLAWYQQKPGQAPRLLIYDASSRAPGIPDRF SGSGSGTDFTLTISRLEPEDFAVYYCQYSEWPLTFGQGT KVEIK GLAVSTISSFFPPGYQIYWAPLAGTCGVLLSLVITLYCKRGRKKL LYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL RVKFSRSAD APAYQQGQNQLYNELNLGRREEYDVLDKRRGRDP EMGGKPR RKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQ GLSTATKDTYDALHMQALPPR (SEQ ID NO: 355)	CD8α signal peptide;
		C01_Rd4_6nM_C12 VH (SEQ ID NO: 83);
		GS linker;
		C01_Rd4_6nM_C12 VL (SEQ ID NO: 84);
		FcγRIIIα hinge;
		CD8α TM domain;
		41BB ISD;
		CD3ζ ISD
PC1C12-V2	MALPVTALLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLEWVSAIGSGGWSYYADSVK GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARYWPMDSWG	CD8α signal peptide;
		C01_Rd4_6nM_C12
	QGT LVTVSSGGGGSGGGSGGGGSEIVLTQSPGTL SLSPGERA TLSCWLSQSVSSTYLAWYQQKPGQAPRLLIYDASSRAPGIPDRF SGSGSGTDFTLTISRLEPEDFAVYYCQYSEWPLTFGQGT KVEIK TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFAC DIYIWAPLAGTCGVLLSLVITLYCKRGRKKLLYIFKQPFMRPVQT TQEEDGCSCRFPEEEEGGCEL RVKFSRSADAPAYQQGQNQLY NELNLGRREEYDVLDKRRGRDP EMGGKPRRKNPQEGLYNELQ KDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALH MQALPPR (SEQ ID NO: 356)	VH;
		GS linker;
		C01_Rd4_6nM_C12 VL;
		CD8α hinge;
		CD8α TM domain;
		41BB ISD;
		CD3ζ ISD
PC1C12-V3	MALPVTALLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLEWVSAIGSGGWSYYADSVK GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARYWPMDSWG QGT LVTVSSGGGGSGGGSGGGGSEIVLTQSPGTL SLSPGERA	CD8α signal peptide;
		C01_Rd4_6nM_C12 VH;

CAR	CAR Amino Acid Sequence	Components
	TLSCWLSQSVSSTYLAWYQQKPGQAPRLLIYDASSRAPGIPDRF SGSGSGTDFTLTISRLEPEDFAVYYCQQYSEWPLTFGQGTKVEIK EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTTPVLDSGSEFLYSKLTVDKSRWQQGNVFCFSVMHEAL HNHYTQKSLSLSPGKIYIWAPLAGTCGVLLLSLVITLYCKRGRKKL LYIFKQPFMRPVQTTQEEDGCSCRFEEEEGGCELRVKFSRSAD APAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPR RKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQ GLSTATKDTYDALHMQALPPR (SEQ ID NO: 357)	GS linker;
		C01_Rd4_6nM_C12 VL;
		IgG1 hinge;
		CD8α TM domain;
		41BB ISD;
		CD3ζ ISD
COM22-V1	MALPVTALLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLEWVSAISdSGGSRWYADSV KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTRYWPMDIWG QGTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSPGERA	CD8α signal peptide;
		COMBO_Rd4_0.6nM_C 22 VH (SEQ ID NO: 92);
	TLSCRASVRVSSTYLAWYQQKPGQAPRLLMYDASIRATGIPDRF SGSGSGTDFTLTISRLEPEDFAVYYCQQYMKWPLTFGQGTKVEI KGLAVSTISSFFPPGYQIYWAPLAGTCGVLLLSLVITLYCKRGRK KLLYIFKQPFMRPVQTTQEEDGCSCRFEEEEGGCELRVKFSRS ADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGK PRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLY QGLSTATKDTYDALHMQALPPR (SEQ ID NO: 358)	GS linker;
		COMBO_Rd4_0.6nM_C 22 VL (SEQ ID NO: 93);
		FcγRIIIa hinge;
		CD8α TM domain;
		41BB ISD;
		CD3ζ ISD
COM22-V2	MALPVTALLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLEWVSAISdSGGSRWYADSV KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTRYWPMDIWG QGTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSPGERA TLSCRASVRVSSTYLAWYQQKPGQAPRLLMYDASIRATGIPDRF SGSGSGTDFTLTISRLEPEDFAVYYCQQYMKWPLTFGQGTKVEI KTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFA CDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPV QTTQEEDGCSCRFEEEEGGCELRVKFSRSADAPAYQQGQNQ LYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNE LQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDA LHMQALPPR (SEQ ID NO: 359)	CD8α signal peptide;
		COMBO_Rd4_0.6nM_C 22 VH;
		GS linker;
		COMBO_Rd4_0.6nM_C 22 VL;
		CD8α hinge;
		CD8α TM domain;
		41BB ISD;
		CD3ζ ISD
COM22-V3	MALPVTALLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLEWVSAISdSGGSRWYADSV KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTRYWPMDIWG QGTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSPGERA TLSCRASVRVSSTYLAWYQQKPGQAPRLLMYDASIRATGIPDRF SGSGSGTDFTLTISRLEPEDFAVYYCQQYMKWPLTFGQGTKVEI KEPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR	CD8α signal peptide;
		COMBO_Rd4_0.6nM_C 22 VH;
		GS linker;
		COMBO_Rd4_0.6nM_C 22 VL;
		IgG1 hinge;
	VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSGSEFLYSKLTVDKSRWQQGNVFCFSVMHEAL	CD8α TM domain;

CAR	CAR Amino Acid Sequence	Components
	ALHNHYTQKSLSLSPGKIYIWAPLAGTCGVLLLSLVITLYCKRGRK KLLYIFKQPFMRPVQTTQEEDGCSCRFEEEEGGCELRVKFSRS ADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGK PRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLY QGLSTATKDTYDALHMQALPPR (SEQ ID NO: 360)	41BB ISD;
		CD3ζ ISD
P6DY-V1	MALPVTALLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLEWVSAIDYSGGNTFYADSVK GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARVSPIASGMDY WGQGT LTVSSGGGGSGGGGSGGGGSEIVLTQSPGTL SLSPG ERATLSCRASQSVSSSYPSWYQQKPGQAPRLLIYGASSRATGIP DRFSGSGSGTDFTLTISRLEPEDFAVYYCQHYPYPPSFTFGQGTK VEIKGLAVSTISSFFPGYQIYWAPLAGTCGVLLLSLVITLYCKRG RKLLYIFKQPFMRPVQTTQEEDGCSCRFEEEEGGCELRVKFS RSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHD GLYQGLSTATKDTYDALHMQ (SEQ ID NO: 361)	CD8α signal peptide;
		L3.PY/H2.DY VH (SEQ ID NO: 25);
		GS linker;
		L3.PY /L1.PS/P6E01
		VL (SEQ ID NO: 18);
		FcγRIIIα hinge;
		CD8α TM domain;
		41BB ISD;
		CD3ζ ISD
P6DY-V2	MALPVTALLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLEWVSAIDYSGGNTFYADSVK GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARVSPIASGMDY WGQGT LTVSSGGGGSGGGGSGGGGSEIVLTQSPGTL SLSPG ERATLSCRASQSVSSSYPSWYQQKPGQAPRLLIYGASSRATGIP DRFSGSGSGTDFTLTISRLEPEDFAVYYCQHYPYPPSFTFGQGTK VEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLD FACDIYWAPLAGTCGVLLLSLVITLYCKRGRKLLYIFKQPFMRP VQTTQEEDGCSCRFEEEEGGCELRVKFSRSADAPAYQQGQN	CD8α signal peptide;
		L3.PY/H2.DYVH;
		GS linker;
		L3.PY/L1.PS/P6E01
		VL;
		CD8α hinge;
		CD8α TM domain;
	QLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYN ELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYD ALHMQALPPR (SEQ ID NO: 362)	41BB ISD;
		CD3ζ ISD
P6DY-V3	MALPVTALLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLEWVSAIDYSGGNTFYADSVK GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARVSPIASGMDY WGQGT LTVSSGGGGSGGGGSGGGGSEIVLTQSPGTL SLSPG ERATLSCRASQSVSSSYPSWYQQKPGQAPRLLIYGASSRATGIP DRFSGSGSGTDFTLTISRLEPEDFAVYYCQHYPYPPSFTFGQGTK VEIKEPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIA RTP EVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP REPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMH EALHNHYTQKSLSLSPGKIYIWAPLAGTCGVLLLSLVITLYCKRGR KLLYIFKQPFMRPVQTTQEEDGCSCRFEEEEGGCELRVKFSR SADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGG KPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGL YQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 363)	CD8α signal peptide;
		L3.PY/H2.DYVH;
		GS linker;
		L3.PY/L1.PS/P6E01 VL;
		IgG1 hinge;
		CD8α TM domain;
		41BB ISD;
		CD3ζ ISD
P6AP-V1	MALPVTALLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA	CD8α signal peptide;

CAR	CAR Amino Acid Sequence	Components
	ASGFTFGSYAMTWVRQAPGKGLEWVSAISGSGGNTFYADSVK GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARVSPIAAPMDY WGQGTLTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSPG ERATLSCRASQLGSFYLA WYQQKPGQAPRLLIYGASSRATGIPD RFSGSGSGTDFTLTISRLEPEDFAVYYCQHYNPPSFTEGQGTKV EIKGLAVSTISSFFPPGYQIYWAPLAGTCGVLLLSLVITLYCKRGR KKLLYIFKQPFMRPVQTTQEEDGCSCRFEEEEGGCEL RVKFSR SADAPAYQQGQNQLYNELNLGRREEYDVL DKRRGRDPEMGG KPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGL	P6AP-V1 VH (SEQ ID NO: 8);
		GS linker;
		P6AP-V1 VL (SEQ ID NO: 80)
		FcγRIIIα hinge;
		CD8α TM domain;
	YQGLSTATKDTYDALHMQA (SEQ ID NO: 364)	41BB ISD;
		CD3ζ ISD
P6AP-V2	MALPVTALLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLEWVSAISGSGGNTFYADSVK GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARVSPIAAPMDY WGQGTLTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSPG ERATLSCRASQLGSFYLA WYQQKPGQAPRLLIYGASSRATGIPD RFSGSGSGTDFTLTISRLEPEDFAVYYCQHYNPPSFTEGQGTKV EIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDF ACDIYWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPV QTTQEEDGCSCRFEEEEGGCEL RVKFSRSADAPAYQQGQNQ LYNELNLGRREEYDVL DKRRGRDPEMGGKPRRKNPQEGLYNE LQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDA LHMQALPPR (SEQ ID NO: 365)	CD8α signal peptide;
		L1.LGF/L3.KW/H3.AP VH;
		GS linker;
		P6AP-V1 VL;
		CD8α hinge;
		CD8α TM domain;
		41BB ISD;
		CD3ζ ISD
P6AP-V3	MALPVTALLPLALLHAARPEVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLEWVSAISGSGGNTFYADSVK GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARVSPIAAPMDY WGQGTLTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSPG ERATLSCRASQLGSFYLA WYQQKPGQAPRLLIYGASSRATGIPD RFSGSGSGTDFTLTISRLEPEDFAVYYCQHYNPPSFTEGQGTKV EIKEPKSPDKTHTCPPCAPPVAGPSVFLFPPKPKDTLMIARTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR EPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHE ALHNHYTQKSLSLSPGKIYWAPLAGTCGVLLLSLVITLYCKRGRK KLLYIFKQPFMRPVQTTQEEDGCSCRFEEEEGGCEL RVKFSRS ADAPAYQQGQNQLYNELNLGRREEYDVL DKRRGRDPEMGGK	CD8α signal peptide;
		L1.LGF/L3.KW/H3.AP VH;
		GS linker;
		P6AP-V1 VL;
		IgG1 hinge;
		CD8α TM domain;
		41BB ISD;
		CD3ζ ISD
	PRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLY QGLSTATKDTYDALHMQALPPR (SEQ ID NO: 366)	

[0204] For the activity assays, T cells from thirteen healthy donors (Donors 1-13) were obtained. Briefly, the T cells were purified from buffy-coat samples and activated using CD3/CD28 beads. Cells were transiently transfected with mRNAs encoding the different CAR molecules at D11/12 after activation. CAR activity was assessed by measuring their degranulation capacity, the inteferon-γ (IFNγ) release, and the cytotoxic activity when co-cultured with (a) cells expressing BCMA (MM1S, KMS12BM, and L363), or (b) cells that do not express the BCMA protein (K562). Also included for each assay were mock transfected T cells (T cells in in buffer) to determine baseline activity of T cells that do not express a CAR.

[0205] CAR detection was done using a fusion protein in which the extracellular domain of the human BCMA protein was fused to a

mouse IgG1 derived Fc fragment. Binding of the CAR at the cell surface with the BCMA portion of the fusion protein was detected with anti-Fc PE-conjugated antibody and analyzed by flow cytometry.

Materials and Methods

Primary T cell cultures

[0206] T cells were purified from Buffy coat samples provided by EFS (Etablissement Français du Sang, Paris, France) using Ficoll gradient density medium (Ficoll Paque PLUS / GE Healthcare Life Sciences). The PBMC layer was recovered and T cells were purified using a commercially available T cell enrichment kit (Stem Cell Technologies). Purified T cells were activated in X-Vivo™-15 medium (Lonza) supplemented with 20ng/mL Human IL-2 (Miltenyi Biotec), 5% Human Serum (Sera Laboratories), and Dynabeads Human T activator CD3/CD28 at a bead:cell ratio 1:1 (Life Technologies). After activation cells were grown and maintained in X-Vivo™-15 medium (Lonza) supplemented with 20ng/mL Human IL-2 (Miltenyi Biotec) and 5% Human Serum (Sera Laboratories)

CAR mRNA transfection

[0207] Transfections were done at Day 4/5 or Day 11/12 after T cell purification and activation. 5 millions of cells were transfected with 15µg of mRNA encoding the different CAR constructs. CAR mRNAs were produced using the mMMESSAGE mMACHINE T7 Kit (Life Technologies) and purified using RNeasy Mini Spin Columns (Qiagen). Transfections were done using PulseAgile™ Cytopulse technology, by applying two 0.1 mS pulses at 3000V/cm followed by four 0.2 mS pulses at 325V/cm in 0.4cm gap cuvettes in a final volume of 200µl of "Cytoporation buffer T" (BTX Harvard Apparatus). Cells were immediately diluted in X-Vivo™-15 media (Lonza) and incubated at 37°C with 5% CO₂. IL-2 (from Miltenyi Biotec) was added 2h after electroporation at 20ng/mL.

Degranulation assay (CD107a mobilization)

[0208] T cells were incubated in 96-well plates (50,000 cells/well), together with an equal amount of cells expressing or not the BCMA protein. Co-cultures were maintained in a final volume of 100µl of X-Vivo™-15 medium (Lonza) for 6 hours at 37°C with 5% CO₂. CD107a staining was done during cell stimulation, by the addition of a fluorescent anti-CD107a antibody (APC conjugated, from Miltenyi Biotec) at the beginning of the co-culture, together with 1µg/ml of anti-CD49d (BD Pharmingen), 1µg/ml of anti-CD28 (Miltenyi Biotec), and 1x Monensin solution (eBioscience). After the 6h incubation period, cells were stained with a fixable viability dye (eFluor 780, from eBioscience) and fluorochrome-conjugated anti-CD8 (PE conjugated Miltenyi Biotec) and analyzed by flow cytometry. The degranulation activity was determined as the % of CD8+/CD107a+ cells, and by determining the mean fluorescence intensity signal (MFI) for CD107a staining among CD8+ cells. Degranulation assays were carried out 24h after mRNA transfection. Results are summarized in the Tables 6A-9H and 9A-9C below. In the tables, the second column (labeled "CAR-T cell") indicates the BCMA specific CAR being expressed in the transfected T cells.

[0209] CD107a expression on cells is a marker of antigen specific activation. The percent and MFI of CD107a on CD8 T cells expressing BCMA specific CARs increase when incubated with BCMA high (H929), medium (MM1S) and low (KMS12BM, L363) expressing cells but not BCMA negative cells (K562 and Daudi) (Tables 6A-9H and 9A-9C). CD107a expression levels did not increase on mock transfected T cells contacted with BCMA. Thus, the BCMA specific CAR-T cells are activated in the presence of BCMA-expressing cells but not in the presence of cells that do not express BCMA.

[0210] These results demonstrate that T cells expressing BCMA specific CARs are activated when incubated with BCMA expressing cells, and that the activation is antigen-specific.

IFNγ release assay

[0211] T cells were incubated in 96-well plates (50,000 cells/well), together with (a) cells expressing BCMA (MM1S, KMS12BM, and L363) or (b) cells that do not express the BCMA protein (K562). Co-cultures were maintained in a final volume of 100µl of X-Vivo™-15 medium (Lonza) for 24 hours at 37°C with 5% CO₂. After this incubation period the plates were centrifuged at 1500 rpm for 5 minutes and the supernatants were recovered in a new plate. IFNγ detection in the cell culture supernatants was done by ELISA assay (Human IFNγ Quantikine ELISA Kit, from R&D Systems). The IFNγ release assays were carried by starting the cell co-cultures 24h after mRNA transfection. Results are summarized in the Tables 8A-8D and 10 below.

[0212] As shown in Tables 8A-8D and 10, CD8 T cells expressing BCMA specific CARs produce IFNγ when incubated with either

medium BCMA-expressing cells (MM1S) or low BCMA-expressing cells (KMS12BM, L363). In contrast, CD8 T cells expressing BCMA specific CARs produce negligible IFN γ when incubated with BCMA negative cells (K562).

[0213] These results demonstrate that T cells expressing BCMA specific CARs are activated when incubated with BCMA expressing cells, and that the activation is antigen-specific.

- Cytotoxicity assay

[0214] T cells were incubated in 96-well plates (100,000 cells/well), together with 10,000 target cells (expressing BCMA) and 10,000 control (BCMA neg) cells in the same well. Target and control cells were labelled with fluorescent intracellular dyes (CFSE or Cell Trace Violet, from Life Technologies) before co-culturing them with CAR+ T cells. The co-cultures were incubated for 4 hours at 37°C with 5% CO $_2$. After this incubation period, cells were labelled with a fixable viability dye (eFluor 780, from eBioscience) and analyzed by flow cytometry. Viability of each cellular population (target cells or BCMA neg control cells) was determined and the % of specific cell lysis was calculated. Cytotoxicity assays were carried out 48h after mRNA transfection. Results are summarized in the Tables 7A-7H below. In the tables, the cytotoxicity data are shown as percent viable cells, then calculated as a ratio of live BCMA positive cells/live BCMA negative cells. Cell lysis is calculated as 100 - mock transfected T cells.

[0215] As shown in Tables 7A-7H, T cells expressing BCMA specific CARs exhibit killing activity when incubated with either medium BCMA-expressing cells (MM1S) or low BCMA-expressing cells (L363). In contrast, CD8 T cells expressing BCMA specific CARs do not exhibit killing activity when incubated with BCMA negative cells (K562).

[0216] In summary, T cells expressing the selected BCMA specific CARs shown in Table 5 are selectively activated upon contact with BCMA-expressing cells. While all versions of the BCMA specific CARs exhibited BCMA-specific activation, BCMA specific CARs comprising a CD8 α hinge (v2) exhibited increased activation levels compared to BCMA specific CARs comprising a Fc γ RIII α (v1) hinge or IgG1 (v3) hinge.

Table 6A: Degranulation Assay Results, Donor 1

			T cells	MFI CD107a+	% CD107a+ (in CD8+)
	mock transfected T cells		T cells	410	2.45
			PMA/Iono	4038	76.1
			MM1S	547	6.78
			K562	610	7.55
	P6DY	v1	T cells	588	5.19
			PMA/Iono	3758	75.1
			MM1S	850	14.9
			K562	829	9.76
		v2	T cells	756	6.86
			PMA/Iono	4103	75.5
			MM1S	3872	75.4
			K562	1130	20.7
Donor 1		v3	T cells	707	7.71
			PMA/Iono	4336	78.7
			MM1S	3665	72.6
			K562	612	7.7
	P6AP	v1	T cells	604	4.61
			PMA/Iono	3526	72.8
			MM1S	1847	46.4
			K562	503	4.28
		v2	T cells	1380	27.8
			PMA/Iono	2504	58
			MM1S	5299	83.9
			K562	949	14.6
		v3	T cells	856	12.6
			PMA/Iono	2500	58.9
			MM1S	3638	73

				MFI CD107a+	% CD107a+ (in CD8+)
			K562	718	9.15

Table 6B: Degranulation Assay Results, Donor 2

				MFI CD107a+	% CD107a+ (in CD8+)
	mock transfected T cells		T cells	270	1.66
			PMA/Iono	3872	88.3
			MM1S	499	11
			K562	492	8.78
	P5A	v1	T cells	423	7.2
			PMA/Iono	6034	96.3
			MM1S	2670	77.6
			K562	648	16.6
		v2	T cells	428	7.14
			PMA/Iono	4420	90.7
			MM1S	5019	91.8
			K562	620	13.8
		v3	T cells	451	8.87
			PMA/Iono	4835	93.2
			MM1S	4191	88.5
			K562	607	14.1
Donor 2	P5A_C1	v1	T cells	315	4.12
			PMA/Iono	3567	85.8
			MM1S	2193	68.6
			K562	537	10.1
		v2	T cells	413	7.46
			PMA/Iono	4423	91.1
			MM1S	4575	90.6
			K562	660	17.2
		v3	T cells	429	7.82
			PMA/Iono	4442	93.5
			MM1S	3710	84.4
			K562	597	13.9
	P5A_C16	v1	T cells	424	7.95
			PMA/Iono	4325	91.1
			MM1S	1858	61.6
			K562	636	14.9
		v2	T cells	401	5.69
			PMA/Iono	3007	80
			MM1S	4228	87.9
			K562	696	17.6
		v3	T cells	372	5.25
			PMA/Iono	3611	86.6
			MM1S	3372	83.6
			K562	476	7.72

Table 6C: Degranulation Assay Results, Donor 3

				MFI CD107a+	% CD107a+ (in CD8+)
	mock transfected T cells		T cells	338	3.61
			PMA/Iono	7111	98.1
			MM1S	464	9.44
			K562	533	9.73
			T cells	454	6.67

				MFI CD107a+	% CD107a+ (in CD8+)
	PC1	v1	PMA/Iono	5226	96.5
			MM1S	2178	75.6
			K562	753	22.3
		v2	T cells	507	13
			PMA/Iono	4743	95.2
			MM1S	759	25.5
			K562	649	15.5
		v3	T cells	463	6.84
Donor 3			PMA/Iono	7092	98.1
			MM1S	2857	87.2
			K562	665	15
	PC1C12	v1	T cells	373	3.35
			PMA/Iono	6214	97.2
			MM1S	1960	68.2
			K562	513	7.61
		v2	T cells	579	11.5
			PMA/Iono	6341	97.5
			MM1S	4478	95.1
			K562	680	15
		v3	T cells	533	10.1
			PMA/Iono	5785	97.4
			MM1S	3739	91
			K562	648	13.2
	COM22	v1	T cells	354	2.74
			PMA/Iono	5894	96.7
			MM1S	2219	76.1
			K562	445	5.62
		v2	T cells	401	6.52
			PMA/Iono	5802	94.6
			MM1S	2372	79.2
			K562	534	8.9
		v3	T cells	501	10.4
			PMA/Iono	6387	97.6
			MM1S	2780	85.9
			K562	648	13.8

Table 6D: Degranulation Assay Results, Donor 4

			MFI CD107a+	% CD107a+ (in CD8+)
	mock transfected T cells	T cells	248	2.64
		PMA/Iono	5750	94.9
		MM1S	363	8.89
		K562	368	6.86
	P5A	T cells	335	3.82
		PMA/Iono	6025	93
		MM1S	3150	86.7
		K562	418	9.91
	P5AC1	T cells	505	22.1
		PMA/Iono	6950	98.3
		MM1S	2975	84.7
Donor 4 (v3 only)		K562	575	23.3
		T cells	368	6.2

			MFI CD107a+	% CD107a+ (in CD8+)
	P5AC16	PMA/Iono	5775	97.7
		MM1S	3675	86.8
		K562	420	9.73
	PC1	T cells	403	9.05
		PMA/Iono	6975	97.8
		MM1S	4625	93
		K562	543	15.8
	PC1C12	T cells	485	12.9
		PMA/Iono	6400	96.5
		MM1S	3575	90.4
		K562	585	18.9
	COM22	T cells	535	20.5
		PMA/Iono	7250	98.3
		MM1S	3725	91.4
		K562	533	16.9
	P6DY	T cells	313	3.08
		PMA/Iono	5125	94.3
		MM1S	2435	79.9
		K562	438	10.4
	P6AP	T cells	430	10.4
		PMA/Iono	6100	94.2
		MM1S	3800	91.7
		K562	478	14.6

Table 6E: Degranulation Assay Results, Donor 5

			% CD107a+ (in CD8+)	MFI CD107a+
	CAR-BCMA-P5A	L363	47	917
		MM1S	65.3	1713
		K562	3.65	247
		T cells	1.71	199
		PMA/iono	98.6	4797
	CAR-BCMA-P5AC1	L363	50.6	1117
		MM1S	65.5	1753
		K562	5.29	265
		T cells	1.93	213
		PMA/iono	99.1	5755
Donor 5 (v3 only)	CAR-BCMA-P5AC16	L363	57.2	1392
		MM1S	73.9	2520
		K562	4.13	273
		T cells	2.57	232
		PMA/iono	98.1	5120
	CAR-BCMA-PC1	L363	71.9	2167
		MM1S	82.9	2987
		K562	4.5	316
		T cells	2.47	273
		PMA/iono	98.5	5556
	CAR-BCMA-PC1C12	L363	57.8	1492
		MM1S	71.5	2094
		K562	3.72	313
		T cells	2.53	272
		PMA/iono	98.2	4480

			% CD107a+ (in CD8+)	MFI CD107a+
	CAR-BCMA-COM22	L363	61.3	1574
		MM1S	78.1	2602
		K562	5.84	296
		T cells	5.26	284
		PMA/iono	98.3	4434
	CAR-BCMA-P6DY	L363	43.4	859
		MM1S	63.6	1624
		K562	3.99	256
		T cells	1.95	228
		PMA/iono	98.1	4075
	CAR-BCMA-P6AP	L363	63.4	1745
		MM1S	77.8	2461
		K562	4.81	310
		T cells	4.74	300
		PMA/iono	98.9	32
	mock transfected T cells	L363	2.54	200
		MM1S	5.19	233
		K562	4.02	201
		T cells	1.95	192
		PMA/iono	97.7	3216

Table 6F: Degranulation Assay Results, Donor 6

			MFI CD107a+	% CD107a+ (in CD8+)
Donor 6	BCMA_BC30_v3 (18)	Tcells alone	121	1.04
		T cells PMA IONO	5253	87.4
		T cells K562	230	3.21
		T cells MM1S	1321	50.4
		T cells L363	986	41.8
	CAR_BCMA_P5AC1_v2	Tcells alone	150	1.07
		T cells PMA IONO	4701	83.2
		T cells K562	256	5.5
		T cells MM1S	2193	63.8
		T cells L363	1400	50.9
	CAR_BCMA_P5AC1_v3	Tcells alone	166	0.96
		T cells PMA IONO	4518	80.2
		T cells K562	301	6.87
		T cells MM1S	1101	40.7
		T cells L363	728	29.8
	CAR_BCMA_PC1_v3	Tcells alone	217	1.63
		T cells PMA IONO	4711	82.4
		T cells K562	329	6.36
		T cells MM1S	2083	60.3
		T cells L363	1500	52.1
	CAR_BCMA_PC1C12_v2	Tcells alone	209	2.01
		T cells PMA IONO	5401	87.8
		T cells K562	332	7.7
		T cells MM1S	2588	68.4
		T cells L363	1976	59.5
	CAR_BCMA_PC1C12_v3	Tcells alone	162	1.72
		T cells PMA IONO	5299	85.3
		T cells K562	266	6.25

			MFI CD107a+	% CD107a+ (in CD8+)
		T cells MM1S	669	28.8
		T cells L363	414	18.6
	CAR_BCMA_COM22_v3	Tcells alone	193	3.23
		T cells PMA IONO	4750	82.7
		T cells K562	288	5.13
		T cells MM1S	814	35.7
		T cells L363	606	26.8
		Tcells alone	359	9.69
	CAR_BCMA_P6AP_v2	T cells PMA IONO	5521	87.4
		T cells K562	327	7.69
		T cells MM1S	2289	63.8
		T cells L363	1876	56.9
		Tcells alone	284	4.87
	CAR_BCMA_P6AP_v3	T cells PMA IONO	4480	82.7
		T cells K562	331	5.9
		T cells MM1S	1409	46.9
		T cells L363	926	35.3
		Tcells alone	184	0.92
	mock transfected T cells	T cells PMA IONO	3955	78.6
		T cells K562	278	3.58
		T cells MM1S	393	4.7
		T cells L363	190	1.12

Table 6G: Degranulation Assay Results, Donor 7

			MFI CD107a+	% CD107a+ (in CD8+)
	mock transfected T cells	Tcells alone	68.3	1.55
		T cells PMA IONO	3097	94.6
		T cells MM1S	118	7.15
		T cells L363	90.3	2.63
		T cells K562	144	3.4
		T cells Daudi	117	1.93
	BCMA_BC30_v3 (18)	Tcells alone	69.7	2.69
		T cells PMA IONO	2864	94.9
		T cells MM1S	1630	68.9
		T cells L363	529	43.8
		T cells K562	125	3.85
		T cells Daudi	426	38.5
Donor	P5AC1_v2	Tcells alone	111	3.67
7		T cells PMA IONO	2859	95.6
		T cells MM1S	2305	71.5
		T cells L363	877	53.1
		T cells K562	166	8.54
		T cells Daudi	770	51.5
	P5AC1_v3	Tcells alone	70.8	1.04
		T cells PMA IONO	2740	94.6
		T cells MM1S	526	43.3
		T cells L363	209	20.4
		T cells K562	118	8.32
		T cells Daudi	450	35.9
		Tcells alone	61	1.37

			MFI CD107a+	% CD107a+ (in CD8+)
	PC1_v3	T cells PMA IONO	2786	94.6
		T cells MM1S	1027	56.3
		T cells L363	314	29.9
		T cells K562	140	12.1
		T cells Daudi	536	39.6
	PC1C12_v2	Tcells alone	98	5.95
		T cells PMA IONO	3493	95.3
		T cells MM1S	1917	73.7
		T cells L363	939	56.2
		T cells K562	192	11.5
		T cells Daudi	1485	64.6
	PC1C12_v3	Tcells alone	84.2	2.28
		T cells PMA IONO	3017	95.2
		T cells MM1S	342	28.2
		T cells L363	145	8.72
		T cells K562	186	7.53
		T cells Daudi	223	11.8
	COM22_v3	Tcells alone	93.6	5.32
		T cells PMA IONO	2989	96.3
		T cells MM1S	540	40
		T cells L363	154	12.5
		T cells K562	138	8.29
		T cells Daudi	93.5	3.99
	P6AP_v2	Tcells alone	164	13.7
		T cells PMA IONO	3303	95.9
		T cells MM1S	2755	76
		T cells L363	859	50.3
		T cells K562	287	15.8
		T cells Daudi	1263	58.2
	P6AP_v3	Tcells alone	114	10.5
		T cells PMA IONO	3084	94.5
		T cells MM1S	849	51.6
		T cells L363	380	30.9
		T cells K562	211	8.46
		T cells Daudi	678	42.7

Table 6H: Degranulation Assay Results, Donor 8

			MFI CD107a+	% CD107a+ (in CD8+)
Donor 8	mock transfected T cells	Tcells alone	154	0.67
		T cells PMA IONO	3777	66.2
		T cells MM1S	229	2.16
		T cells L363	166	1.51
		T cells K562	220	2.08
	BCMA_BC30_v3 (18)	Tcells alone	210	1.05
		T cells PMA IONO	4302	70.6
		T cells MM1S	1661	42
		T cells L363	1049	26.5
		T cells K562	262	3.46
	P5AC1_v2	Tcells alone	207	0.86
		T cells PMA IONO	4298	71.5
		T cells MM1S	1648	40.8

			MFI CD107a+	% CD107a+ (in CD8+)
		T cells L363	1099	26.5
		T cells K562	232	1.72
	P5AC1_v3	Tcells alone	187	0.84
		T cells PMA IONO	3989	68.8
		T cells MM1S	766	21.2
		T cells L363	521	14.2
		T cells K562	258	2.05
	PC1_v3	Tcells alone	242	1.23
		T cells PMA IONO	4256	70.6
		T cells MM1S	1046	23.1
		T cells L363	1183	27.4
		T cells K562	283	2.97
	PC1C12_v2	Tcells alone	257	1.87
		T cells PMA IONO	3487	60.2
		Tcells MM1S	2463	51.2
		T cells L363	1657	35.4
		T cells K562	314	4.05
	PC1C12_v3	Tcells alone	166	0.86
		T cells PMA IONO	4238	69.1
		T cells MM1S	641	17.3
		T cells L363	507	14.2
		T cells K562	296	3.52
	COM22_v3	Tcells alone	283	2.55
		T cells PMA IONO	4800	75.9
		T cells MM1S	1035	27.9
		T cells L363	704	22.7
		T cells K562	334	4.82
	P6AP_v2	Tcells alone	545	8.33
		T cells PMA IONO	4362	68.6
		T cells MM1S	2273	46.7
		T cells L363	1671	34.7
		T cells K562	629	9.71
	P6AP_v3	Tcells alone	360	3.87
		T cells PMA IONO	3584	61.5
		T cells MM1S	1553	34.5
		T cells L363	1045	23
		T cells K562	595	7.4

Table 7A: Cytotoxicity Data, Donor 6

Donor 6	CAR	Viability (mean)			
		L363	K562	MM1S	K562
	BC30_v3	22.93	89.90	16.30	88.43
	P5AC1_v2	27.27	90.07	21.47	90.17
	P5AC1_v3	36.03	89.30	19.80	88.50
	PC1_v3	19.03	88.23	13.57	87.50
	PC1C12_v2	19.60	86.13	14.67	84.67
	PC1C12_v3	55.50	89.33	41.33	88.67
	COM22_v3	42.00	90.33	25.67	88.30
	P6AP_v2	29.40	80.27	21.07	82.10
	P6AP_v3	48.53	85.20	25.57	81.30
	mock transfected T cells	90.90	88.20	91.77	86.30

Table 7B: Cytotoxicity Data, Donor 6

Donor 6	CAR	BCMA+/BCMA-		Ratio to Mock transfected T cells		Cell lysis	
		L363	MM1S	L363	MM1S	L363	MM1S
	BC30_v3	25.51	18.43	0.24752108	0.17333946	75.2	82.7
	P5AC1_v2	30.27	23.81	0.29374647	0.22389502	70.6	77.6
	P5AC1_v3	40.35	22.37	0.39152336	0.21040098	60.8	79.0
	PC1_v3	21.57	15.50	0.2093085	0.14581122	79.1	85.4
	PC1C12_v2	22.76	17.32	0.22079514	0.1629089	77.9	83.7
	PC1C12_v3	62.13	46.62	0.60281513	0.4383953	39.7	56.2
	COM22_v3	46.49	29.07	0.45113441	0.27335977	54.9	72.7
	P6AP_v2	36.63	25.66	0.35539949	0.24131177	64.5	75.9
	P6AP_v3	56.96	31.45	0.55272006	0.29573955	44.7	70.4
	mock transfected T cells	103.06	106.33	1	1	0.0	0.0

Table 7C: Cytotoxicity Data, Donor 7

	CAR	Viability (mean)			
		L363	K562	MM1S	K562
Donor 7	mock transfected T cells	92.53	92.80	90.70	92.33
	BC30_v3	46.00	90.40	34.00	89.83
	P5AC1_v2	50.50	90.73	35.17	89.40
	P5AC1_v3	60.20	89.97	43.03	89.53
	PC1_v3	49.43	89.67	37.33	88.97
	PC1C12_v2	40.23	88.50	22.53	87.53
	PC1C12_v3	81.03	91.30	71.70	89.83
	COM22_v3	67.87	90.00	52.97	89.20
	P6AP_v2	57.33	89.93	32.87	87.10
	P6AP_v3	66.37	91.60	46.35	94.00

Table 7D: Cytotoxicity Data, Donor 7

	CAR	BCMA+/BCMA-		Ratio to Mock transfected T cells		Cell lysis	
		L363	MM1S	L363	MM1S	L363	MM1S
Donor 7	mock transfected T cells	99.71	98.23	1	1	0.0	0.0
	BC30_v3	50.88	37.85	0.51031598	0.38529434	49.0	61.5
	P5AC1_v2	55.66	39.34	0.55818001	0.40044688	44.2	60.0
	P5AC1_v3	66.91	48.06	0.67106507	0.48929577	32.9	51.1
	PC1_v3	55.13	41.96	0.55288988	0.4271896	44.7	57.3
	PC1C12_v2	45.46	25.74	0.45592406	0.26206149	54.4	73.8
	PC1C12_v3	88.76	79.81	0.89010798	0.81251777	11.0	18.7
	COM22_v3	75.41	59.38	0.7562472	0.60448985	24.4	39.6
	P6AP_v2	63.75	37.73	0.63934647	0.38413929	36.1	61.6
	P6AP_v3	72.45	49.31	0.7266149	0.50196463	27.3	49.8

Table 7E: Cytotoxicity Data, Donor 8

	CAR	Viability (mean)			
		L363	K562	MM1S	K562
Donor 8	mock transfected T cells	93.97	91.13	95.97	88.07
	BC30_v3	67.97	86.80	46.40	78.87
	P5AC1_v2	69.80	85.37	47.13	79.17
	P5AC1_v3	77.90	88.77	62.70	84.40
	PC1_v3	61.67	86.60	41.67	78.97
	PC1C12_v2	62.43	85.27	35.27	78.20
	PC1C12_v3	85.17	85.27	78.87	77.77
	COM22_v3	76.70	87.87	56.40	84.50
	P6AP_v2	77.23	84.90	61.47	83.47

	P6AP_v3	83.23	85.67	72.57	84.63
	cell lines	95.20	94.97	96.97	94.20

Table 7F: Cytotoxicity Data, Donor 8

Donor 8	CAR	BCMA+/BCMA-		Ratio to Mock transfected T cells		Cell lysis	
		L363	MM1S	L363	MM1S	L363	MM1S
	mock transfected T cells	1.03	0.95	1	1	0.0	0.0
	BC30_v3	0.78	0.59	0.75941589	0.61953757	24.1	38.0
	P5AC1_v2	0.82	0.60	0.79299515	0.62694429	20.7	37.3
	P5AC1_v3	0.88	0.74	0.85112036	0.78229085	14.9	21.8
	PC1_v3	0.71	0.53	0.69061501	0.5556331	30.9	44.4
	PC1C12_v2	0.73	0.45	0.7101346	0.47489852	29.0	52.5
	PC1C12_v3	1.00	1.01	0.96871004	1.06793091	3.1	-6.8
	COM22_v3	0.87	0.67	0.84659295	0.70285469	15.3	29.7
	P6AP_v2	0.91	0.74	0.88226799	0.77547847	11.8	22.5
	P6AP_v3	0.97	0.86	0.94229927	0.9028984	5.8	9.7
	cell lines	1.00	1.03	0.97223038	1.08396365	2.8	-8.4

Table 7G: Cytotoxicity Data, Donor 9

Donor 9	CAR	Viability (mean)			
		L363	K562	MM1S	K562
	mock transfected T cells	86.3	87.8	69.6	86.5
	BC30_v3	27.1	86.6	16.0	86.6
	P5AC1_v2	31.9	87.9	21.0	87.2
	P5AC1_v3	46.9	85.1	36.3	84.0
	PC1_v3	27.8	85.3	25.4	85.0
	PC1C12_v2	29.3	88.7	15.0	86.0
	COM22_v3	49.0	88.8	35.7	87.5
	P6AP_v2	41.4	85.7	22.8	84.0
	P6AP_v3	56.4	84.3	44.9	84.4
	Cell lines	92.3	91.7	83.5	91.8

Table 7H: Cytotoxicity Data, Donor 9

Donor 9	CAR	BCMA+/BCMA-		Ratio to Mock transfected T cells		Cell lysis	
		L363	MM1S	L363	MM1S	L363	MM1S
	mock transfected T cells	0.98216319	0.80469954	1	1	0	0
	BC30_v3	0.31331794	0.18444359	0.31900802	0.22920802	68.10	77.08
	P5AC1_v2	0.3631539	0.24111578	0.36974905	0.29963455	63.03	70.04
	P5AC1_v3	0.55133229	0.43231441	0.56134489	0.53723706	43.87	46.28
	PC1_v3	0.32551778	0.29831439	0.33142942	0.37071525	66.86	62.93
	PC1C12_v2	0.3298272	0.17473847	0.3358171	0.21714748	66.42	78.29
	COM22_v3	0.55159475	0.40746382	0.56161212	0.50635523	43.84	49.36
	P6AP_v2	0.48289269	0.27092424	0.49166238	0.33667751	50.83	66.33
	P6AP_v3	0.66903915	0.53199052	0.68118939	0.66110454	31.88	33.89
	Cell lines	1.00690909	0.90889292	1.02519531	1.1294811	-2.52	-12.95

Table 8A: IFNγ Production (pg/mL), Donor 6

Donor 6		
CAR		pg/ml
mock transfected T cells	Tcells alone	155.1
BCMA_BC30_v3 (18)		654.71
P5AC1_v2		174.035
P5AC1_v3		61.215
PC1_v3		255.045
PC1C12_v2		481.595
P6AP_v3		168.88

PC1C12_v3	T cell s PM A IO NO	463.08
COM22_v3		2996.305
P6AP_v2		1294.055
P6AP_v3		500.435
mock transfected T		81654.2

cells		
BCMA_BC30_v3 (18)		49368.7
P5AC1_v2		49102.7
P5AC1_v3		66837.7
PC1_v3		70798.2
PC1C12_v2		56402.2
PC1C12_v3		121954.7
COM22_v3		125878.7
P6AP_v2		73577.2
P6AP_v3		51242.7
mock transfected T cells	T cells K562	-83.215
BCMA_BC30_v3 (18)		265.565
P5AC1_v2		-10.05
P5AC1_v3		36.475
PC1_v3		-74.04
PC1C12_v2		344.72
PC1C12_v3		583.99
COM22_v3		610.97
P6AP_v2		40.66
P6AP_v3		36.775
mock transfected T cells	T cells MM1S	660.33
BCMA_BC30_v3 (18)		8004.42
P5AC1_v2		5667.72
P5AC1_v3		2619.735
PC1_v3		6152.67
PC1C12_v2		8526.27
PC1C12_v3		1405.945
COM22_v3		3330.27
P6AP_v2		5436.27
P6AP_v3		3881.115
mock transfected T cells	T cells L363	1287.38
BCMA_BC30_v3 (18)		6363.72
P5AC1_v2		3116.725
P5AC1_v3		2720.52
PC1_v3		6661.97
PC1C12_v2		9478.72
PC1C12_v3		1707.885

COM22_v3		2397.83
P6AP_v2		5911.97
P6AP_v3		3470.38

Table 8B: IFN γ Production (pg/mL), Donor 7

Donor 7		
CAR		pg/ml
mock transfected T cells	Tcells alone	-3.1
BCMA_BC30_v3 (18)		64.1
P5AC1_v2		-18.0
P5AC1_v3		-73.0
PC1_v3		6.1
PC1C12_v2		156.5
PC1C12_v3		100.1
COM22_v3		182.9
P6AP_v2		564.7
P6AP_v3		107.0
mock transfected T cells	ONO	44970.8
BCMA_BC30_v3 (18)		32725.3
P5AC1_v2		27476.6

P5AC1_v3	T cells PMA I	13100.5
PC1_v3		40824.4
PC1C12_v2		39884.0
PC1C12_v3		30245.2
COM22_v3		62690.4
P6AP_v2		69923.2
P6AP_v3		88578.4
mock transfected T cells	T cells MM1S	29.9
BCMA_BC30_v3 (18)		4662.6
P5AC1_v2		3420.3
P5AC1_v3		1173.7
PC1_v3		2478.5
PC1C12_v2		5314.6
PC1C12_v3		809.9
COM22_v3		1344.6
P6AP_v2		3020.3

P6AP_v3		2166.7
mock transfected T cells	T cells L363	15.6
BCMA_BC30_v3 (18)		2360.2
P5AC1_v2		2576.3
P5AC1_v3		582.7
PC1_v3		1723.3
PC1C12_v2		2962.9
PC1C12_v3		136.6
COM22_v3		467.4
P6AP_v2		2081.4
P6AP_v3		1119.0
mock transfected T cells	T cells K562	-80.5
BCMA_BC30_v3 (18)		-127.2
P5AC1_v2		-124.4
P5AC1_v3		-47.9
PC1_v3		-93.6
PC1C12_v2		21.8
PC1C12_v3		-55.4
COM22_v3		-36.1
P6AP_v2		83.8
P6AP_v3		83.8
mock transfected T cells	T cells Daudi	335.1
BCMA_BC30_v3 (18)		7794.8
P5AC1_v2		8093.7
P5AC1_v3		3870.6
PC1_v3		6068.9
PC1C12_v2		10190.2
PC1C12_v3		1638.8
COM22_v3		4287.6
P6AP_v2		6971.6
P6AP_v3		5280.0

Table 8C: IFN-γ Production (pg/mL), Donor 8

Donor 8		
CAR		pg/ml
mock transfected T cells	Tcells alone	-697.44

BCMA_BC30_v3 (18)		-660.92
P5AC1_v2		-603.38
P5AC1_v3		-543.44
PC1_v3		-552.22
PC1C12_v2		-399.26
PC1C12_v3		-652.73
COM22_v3		-530.09
P6AP_v2		17.24
P6AP_v3		-289.82
mock transfected T cells		37206.73

BCMA_BC30_v3 (18)	T cells PMA IONO	53311.73
P5AC1_v2		57732.14
P5AC1_v3		52577.56
PC1_v3		48925.48
PC1C12_v2		38310.06
PC1C12_v3		71881.73
COM22_v3		61941.73
P6AP_v2		82339.64
P6AP_v3		63337.14
mock transfected T cells		-684.65
BCMA_BC30_v3 (18)	T cells MM1S	2976.34
P5AC1_v2		2727.71
P5AC1_v3		769.05
PC1_v3		2682.98
PC1C12_v2		5019.05
PC1C12_v3		-198.04
COM22_v3		1155.19
P6AP_v2		2945.65
P6AP_v3		671.21
mock transfected T cells	T cells L363	-664.74
BCMA_BC30_v3 (18)		2934.77
P5AC1_v2		2342.50
P5AC1_v3		579.85
PC1_v3		2232.65
PC1C12_v2		3676.59
PC1C12_v3		-303.86
COM22_v3		695.72

P6AP_v2	T cells K562	1612.74
P6AP_v3		311.07
mock transfected T cells		-672.42
BCMA_BC30_v3 (18)		-583.71
P5AC1_v2		-631.02
P5AC1_v3		-650.83
PC1_v3		-615.50
PC1C12_v2		-501.18
PC1C12_v3		-615.17
COM22_v3		-596.02
P6AP_v2		-393.94
P6AP_v3		-476.71

Table 8D: IFN-γ Production (pg/mL), Donor 9

Donor 9		
CAR		pg/ml
mock transfected T cells	T cells alone	93.2
BCMA_BC30_v3 (18)		1225.2
P5AC1_v2		1344.5
P5AC1_v3		632.3
PC1_v3		2745.7
PC1C12_v2		48.1
COM22_v3		2656.5
P6AP_v2		566.5
P6AP_v3		-335.8
mock transfected T cells	T cells PMA IONO	12505.8
BCMA_BC30_v3 (18)		12312.2
P5AC1_v2		10607.5
P5AC1_v3		12014.7
PC1_v3		12829.9
PC1C12_v2		13829.5
COM22_v3		13489.5
P6AP_v2		13182.1
P6AP_v3		13506.3
mock transfected T cells	T cells MM1S	1006.4
BCMA_BC30_v3 (18)		2376.8
P5AC1_v2		-359.5
P5AC1_v3		97.8

PC1_v3	290.1
--------	-------

PC1C12_v2		752.7
COM22_v3		-601.0
P6AP_v2		-304.1
P6AP_v3		-394.9
mock transfected T cells		-228.2
BCMA_BC30_v3 (18)	T cells L363	3000.2
P5AC1_v2		2314.0
P5AC1_v3		1646.4
PC1_v3		-15.4
PC1C12_v2		2796.5
COM22_v3		320.6
P6AP_v2		-163.0
P6AP_v3		-233.9
mock transfected T cells		-227.9
BCMA_BC30_v3 (18)		2027.5
P5AC1_v2	T cells K562	3928.4
P5AC1_v3		300.2
PC1_v3		74.9
PC1C12_v2		1835.7
COM22_v3		45.0
P6AP_v2		51.4
P6AP_v3		158.3

Table 9A: Degranulation Assay Results, Donor 10

Donor 10		MFI CD107a+	% CD107a+ (in CD8+)
LT alone	mock transfected T cells	82.2	1.95
	26859 P5AC1-V2	83.8	1.47
	26868 PC1C12-V2	94.2	3.21
	26871 COM22-V2	107	5.96
PMA Iono	mock transfected T cells	5933	99
	26859 P5AC1-V2	5863	99
	26868 PC1C12-V2	6366	99.4
	26871 COM22-V2	6149	99
MM1S	mock transfected T cells	211	16.5
	26859 P5AC1-V2	1377	74.4
	26868 PC1C12-V2	1760	79.1
	26871 COM22-V2	1470	76.5
H929	mock transfected T cells	141	6.09
	26859 P5AC1-V2	1026	65.4
	26868 PC1C12-V2	1262	71.1
	26871 COM22-V2	784	59.2
L363	mock transfected T cells	153	6.48
	26859 P5AC1-V2	793	60.1
	26868 PC1C12-V2	1054	67.3
	26871 COM22-V2	827	61.7
MM1S GFP LUC	mock transfected T cells	187	9.88
	26859 P5AC1-V2	1228	70.5
	26868 PC1C12-V2	1476	74.9
	26871 COM22-V2	1095	68.5
H929 GFP LUC	mock transfected T cells	153	9.48
	26859 P5AC1-V2	1648	77.8
	26868 PC1C12-V2	1960	84
	26871 COM22-V2	1029	69.4
L363 GFP LUC	mock transfected T cells	104	3.06
	26859 P5AC1-V2	753	60.7
	26868 PC1C12-V2	873	64.6

Donor 10		MFI CD107a+	% CD107a+ (in CD8+)
KMS12BM GFP LUC	26871 COM22-V2	766	61.1
	mock transfected T cells	91.3	2.67
	26859 P5AC1-V2	945	67.2
	26868 PC1C12-V2	1192	71.2
	26871 COM22-V2	961	67.2
K562	mock transfected T cells	127	6.06
	26859 P5AC1-V2	136	9.1
	26868 PC1C12-V2	119	9.49
	26871 COM22-V2	135	9.55

Table 9B: Degranulation Assay Results, Donor 11

Donor 11		MFI CD107a+	% CD107a+ (in CD8+)
LT alone	mock transfected T cells	69.9	0.57
	26859 P5AC1-V2	68.3	0.62
	26868 PC1C12-V2	67.2	0.88
	26871 COM22-V2	80.9	3.95
PMA Iono	mock transfected T cells	5511	91.7
	26859 P5AC1-V2	5360	97.4
	26868 PC1C12-V2	4741	96.1
	26871 COM22-V2	5066	95.7
KMS12BM GFP LUC	mock transfected T cells	77.8	1.81
	26859 P5AC1-V2	1304	68.3
	26868 PC1C12-V2	650	45.5
	26871 COM22-V2	986	62.5
H929 GFP LUC	mock transfected T cells	73	1.04
	26859 P5AC1-V2	738	49.6
	26868 PC1C12-V2	428	30.9
	26871 COM22-V2	468	35.5
MM1S	mock transfected T cells	121	2.67
	26859 P5AC1-V2	854	52
	26868 PC1C12-V2	399	26.4
	26871 COM22-V2	486	33.4
K562	mock transfected T cells	125	3.08
	26859 P5AC1-V2	140	3.35
	26868 PC1C12-V2	123	1.84
	26871 COM22-V2	161	4.11

Table 9C: Degranulation Assay Results, Donor 12

Donor 11		MFI CD107a+	% CD107a+ (in CD8+)
LT alone	mock transfected T cells	69.9	0.57
	26859 P5AC1-V2	68.3	0.62
	26868 PC1C12-V2	67.2	0.88
	26871 COM22-V2	80.9	3.95
PMA Iono	mock transfected T cells	5511	91.7
	26859 P5AC1-V2	5360	97.4
	26868 PC1C12-V2	4741	96.1
	26871 COM22-V2	5066	95.7
KMS12BM GFP LUC	mock transfected T cells	77.8	1.81
	26859 P5AC1-V2	1304	68.3
	26868 PC1C12-V2	650	45.5
	26871 COM22-V2	986	62.5
	mock transfected T cells	73	1.04

Donor 11		MFI CD107a+	% CD107a+ (in CD8+)
H929 GFP LUC	26859 P5AC1-V2	738	49.6
	26868 PC1C12-V2	428	30.9
	26871 COM22-V2	468	35.5
MM1S	mock transfected T cells	121	2.67
	26859 P5AC1-V2	854	52
	26868 PC1C12-V2	399	26.4
	26871 COM22-V2	486	33.4
K562	mock transfected T cells	125	3.08
	26859 P5AC1-V2	140	3.35
	26868 PC1C12-V2	123	1.84
	26871 COM22-V2	161	4.11

Table 10: IFN gamma release assay results, Donor 10

Donor 10		
mock transfected T cells	T cells alone	871.8 pg/mL
pCLS26859 CAR_BCMA_P5AC1_v2		1466.2 pg/mL
pCLS26868 CAR_BCMA_PC1C12_v2		1172.2 pg/mL
pCLS26871 CAR_BCMA_COM22_v2		1873.1 pg/mL
mock transfected T cells	MM1S LucGFP	1436.5 pg/mL
pCLS26859 CAR_BCMA_P5AC1_v2		12208.4 pg/mL
pCLS26868 CAR_BCMA_PC1C12_v2		13695.3 pg/mL
pCLS26871 CAR_BCMA_COM22_v2		10784.1 pg/mL
mock transfected T cells	MM1S	5329.0 pg/mL
pCLS26859 CAR_BCMA_P5AC1_v2		6060.3 pg/mL
pCLS26868 CAR_BCMA_PC1C12_v2		6776.1 pg/mL
pCLS26871 CAR_BCMA_COM22_v2		7827.0 pg/mL
mock transfected T cells	H929 LucGFP	754.2 pg/mL
pCLS26859 CAR_BCMA_P5AC1_v2		16589.9 pg/mL
pCLS26868 CAR_BCMA_PC1C12_v2		15989.7 pg/mL
pCLS26871 CAR_BCMA_COM22_v2		14410.4 pg/mL
mock transfected T cells	H929	809.8 pg/mL
pCLS26859 CAR_BCMA_P5AC1_v2		18072.7 pg/mL
pCLS26868 CAR_BCMA_PC1C12_v2		17948.1 pg/mL
pCLS26871 CAR_BCMA_COM22_v2		14437.3 pg/mL
mock transfected T cells	L363 LucGFP	1184.5 pg/mL
pCLS26859 CAR_BCMA_P5AC1_v2		11556.9 pg/mL
pCLS26868 CAR_BCMA_PC1C12_v2		13254.5 pg/mL
pCLS26871 CAR_BCMA_COM22_v2		11384.1 pg/mL
mock transfected T cells	L363	1777.3 pg/mL
pCLS26859 CAR_BCMA_P5AC1_v2		15685.1 pg/mL
pCLS26868 CAR_BCMA_PC1C12_v2		14929.1 pg/mL
pCLS26871 CAR_BCMA_COM22_v2		14995.7 pg/mL
mock transfected T cells	L363 LucGFP	1184.5 pg/mL
pCLS26859 CAR_BCMA_P5AC1_v2		11556.9 pg/mL
pCLS26868 CAR_BCMA_PC1C12_v2		13254.5 pg/mL
pCLS26871 CAR_BCMA_COM22_v2		11384.1 pg/mL
mock transfected T cells	KMS12BM LucGFP	1283.2 pg/mL
pCLS26859 CAR_BCMA_P5AC1_v2		9073.3 pg/mL
pCLS26868 CAR_BCMA_PC1C12_v2		10060.6 pg/mL
pCLS26871 CAR_BCMA_COM22_v2		10687.2 pg/mL
mock transfected T cells		691.6 pg/mL

Donor 10		
pCLS26859 CAR_BCMA_P5AC1_v2	K562	684.1 pg/mL
pCLS26868 CAR_BCMA_PC1C12_v2		904.2 pg/mL
pCLS26871 CAR_BCMA_COM22_v2		969.0 pg/mL

Example 3: BCMA specific CAR-T cells induce tumor regression in MM1.S tumor model

[0217] This example illustrates treatment of tumors with BCMA specific CAR-T cells using the MM1.S tumor model.

[0218] *In vivo* efficacy study of BCMA specific CAR-T cells was performed with MM1.S, expressing luciferase and GFP, orthotopic model. Five million MM1.S Luc2AGFP cells were injected intravenously through the tail vein into 6-8 weeks old female Nod/Scid/IL2Rg^{-/-}(NSG) animals. Intraperitoneal injection of D-luciferin (Regis Technologies, Morton Grove, IL) (200uL per animal at 15mg/mL), followed by anesthesia with isoflurane and subsequent whole body bioluminescence imaging (BLI) enable monitoring of tumor burden. Bioluminescent signals emitted by the interaction between luciferase expressed by the tumor cells and luciferin were captured by imaging using an IVIS Spectrum CT (Perkin Elmer, MA) and quantified as total flux (photons/sec) using Living Image 4.4 (Caliper Life Sciences, Alameda, CA).

[0219] Three different BCMA specific CAR-T cells were used in this study: T cells expressing the BCMA specific CAR constructs P5AC1-V2, PC1C12-V2, or COM22-V2 (see, Table 5 above). Non-transduced control T cells were used as the negative control. All T cells were engineered to be TCRα deficient.

[0220] When the total flux reached an average of 45E6 for all animals (day 20 post tumor implant), the animals were randomized into four groups. A single dose of human either BCMA specific CAR-T cells or non-transduced control T cells was administered through bolus tail vein injection. Animals were terminated when they exhibit hindlimb paralysis or a 20% loss of body weight, an endpoint for MM1.S orthotopic models.

[0221] Results of this study are summarized in Figure 1. In Figure 1, total flux [p/s] represents tumor progression. Treatment with BCMA specific CAR-T cells (triangles, diamonds, squares) resulted in lower total flux as compared to the negative control (circles). Thus, treatment with BCMA specific CAR-T cells inhibited tumor progression as compared to the negative control.

[0222] These results demonstrate BCMA specific CAR-T cells are effective to induce tumor regression.

Example 4: Treatment of Multiple Myeloma with BCMA specific CAR-T Cells

[0223] This example illustrates treatment of multiple myeloma with BCMA specific CAR-T cells using the Molp8 orthotopic model.

[0224] *In vivo* efficacy study of BCMA specific CAR-T cells was performed with Molp8, expressing luciferase and GFP, orthotopic model. Two million Molp8 Luc2AGFP cells were injected intravenously through the tail vein into 6-8 weeks old female NSG animals. Intraperitoneal injection of D-luciferin (Regis Technologies, Morton Grove, IL) (200uL per animal at 15mg/mL), followed by anesthesia with isoflurane and subsequent whole body bioluminescence imaging (BLI) enable monitoring of tumor burden. Bioluminescent signals emitted by the interaction between luciferase expressed by the tumor cells and luciferin were captured by imaging using an IVIS Spectrum CT (Perkin Elmer, MA) and quantified as total flux (photons/sec) using Living Image 4.4 (Caliper Life Sciences, Alameda, CA).

[0225] When the total flux reached an average of 30E6 for all animals (day 8 post tumor implant), the animals were randomized into three groups. Each group was administered one of the following cells: 1) non-transduced T cells TCR KO ("TCR KO") used as a control, 2) BCMA specific CAR-T cells expressing P5AC1-V2.1 ("P5AC1 V2 R2 TCR KO"), or 3) BCMA specific CAR-T cells expressing P5AC1-V2 and the RQR8 suicide polypeptide ("P5AC1 V2 RQR8 TCR KO"). All of cells 1-3 are TCRα deficient. The BCMA specific CAR-T cells were prepared as described in example above. BCMA specific CAR constructs P5AC1-V2.1 and P5AC1-V2 are shown in Table 5 above. A single dose of 3 million control (TCR KO) or BCMA specific CAR-T (P5AC1 V2 R2 TCR KO or P5AC1 V2 RQR8 TCR KO) cells were administered through bolus tail vein injection. Animals were terminated when they lose more than 15% of total body weight, an endpoint for Molp8 orthotopic models.

[0226] Results from the study are summarized in Figure 2. A single dose of 3 million P5AC1 R2 TCRKO BCMA specific CAR-T cells (squares) or P5AC1 RQR8 TCRKO CAR-T cells (triangles) BCMA specific CAR-T cells resulted in lower total flux from days 10-35 post tumor implant as compared to the negative control (circles) (Figure 2). Thus, treatment with BCMA specific CAR-T cells inhibited tumor progression as compared to the negative control.

[0227] These results demonstrate BCMA specific CAR-T cells are effective to inhibit tumor progression.

Example 5: Treatment of multiple myeloma with BCMA specific CAR-T cells

[0228] This example illustrates the therapeutic activity of BCMA specific CAR-T cells in orthotopic mouse models of multiple myeloma.

[0229] Two humanized mouse models were used to evaluate the efficacy of BCMA specific CAR-T cells against human myeloma cell lines expressing BCMA. Six (6) to eight (8) week old female Nod/Scid IL2rg^{-/-} (NSG) mice were purchased from the Jackson Laboratories. All animals were housed in a pathogen free vivarium facility at Rinat and experiments were conducted according to the protocols in accordance with the Institutional Animal Care and Use Committee (IACUC) guidelines.

[0230] The MM1.S and Molp-8 cell lines were purchased from the American Type Culture Collection (ATCC.org) and the Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSMZ.de). Cell lines were engineered to express a Luc-GFP fusion protein using lentiviral particles (amsbio). Cells were cultured in RPMI 1640 medium with L-glutamine supplemented with either 10% fetal calf serum for MM1.S or with 20% FCS for Molp-8 cells at 37°C in 5% carbon dioxide (CO₂). Cells growing in an exponential growth phase were harvested and used for tumor inoculation.

[0231] Therapeutic BCMA specific CAR-T cells were produced as described. Healthy human donor cells, peripheral blood mononuclear cells (PBMC) or purified pan-T cells, are activated and transduced with lentiviral particles encoding a BCMA specific CAR and RQR8 driven by EF-1a promoter. Three different BCMA specific CARs were used in this study: P5AC1-V2, PC1C12-V2 and COM22-V2 (see, Table 5 above). T cells were gene edited for deletion of the TCR α gene. Cells were cultured for 14 to 17 days and then cryopreserved in 90% FCS/10% DMSO. For T cell injection, T cells were rapidly thawed in a 37°C waterbath and washed twice with RPMI 1640 medium containing 25mM Hepes. Cells were injected in 0.2 ml RPMI 1640 with 25 mM Hepes into the tail vein of tumor-bearing animals.

[0232] NSG mice were irradiated with 1 Gy total body irradiation (RAD Source Technologies) one day prior to tumor cell inoculation. 5x10⁶ MM1.S/Luc2-EGFP cells or 2x10⁶ Molp-8/Luc2-EGFP cells were injected into the tail vein in 0.1 ml of phosphate-buffered saline (PBS). Tumor burden was measured twice weekly using bioluminescence imaging. Mice were injected with 3 ug D-Luciferin dissolved in 0.2 ml PBS and anesthetized using isofluorane. 7 minutes after injection animals were imaged using a Perkin Elmer IVIS Spectrum camera system. The total body luminescence with the exception of the mouse tail was measured and tumor burden is reported as total flux (photons per second). Tumors were allowed to establish until exponential growth occurred. Animals were randomized into treatment groups based on total flux and treated with BCMA specific CAR-T cells or untransduced control T cells from the same donor. The effect of CAR-T treatment was assessed twice weekly using bioluminescence imaging and body weight measurements. The study endpoint was reached when the first animal exhibited end-stage disease as indicated by body weight loss (>20% of initial body weight), hindleg paralysis, or other signs of animal distress. Statistical analysis was performed using GraphPad Prism 6. Repeated measures one-way ANOVA with Tukey's correction was used to compare anti-tumor efficacy between all groups. P<0.05 was considered significant.

[0233] Results are summarized in Table 11 (MM1.S) and Table 12 (Molp-8) below (log₁₀ values of total flux in photons per second +/- SEM). A suboptimal CAR-T cell dose was used to compare BCMA specific CAR-T cells having different scFvs. The BCMA specific CAR-T cell groups are P5AC1-V2, PC1C12-V2 and COM22-V2 (see, Table 5 above). In the MM1.S model, 3.5x10⁶ CAR-expressing T cells were injected on day 17 after tumor implantation. In the Molp8 model, 4x10⁶ CAR-expressing T cells were injected on day 7 after tumor implantation. Transduction efficiencies ranged from 19% to 29% for BCMA specific CAR-T cells dosed in MM1.S mouse model and 31% to 36% for BCMA specific CAR-T cells dosed in Molp8 mouse model. An equivalent total dose of untransduced T cells was used for the control group. The control T cell-treated group exhibited progressive tumor growth until the study endpoint was reached at day 35 for MM1.S and day 23 for Molp8. Statistical analysis of the tumor burden using the RM-ANOVA test with Dunnett's correction showed that in all three BCMA specific CAR-T treated groups, tumor burden was significantly lower compared to the tumor burden in the control group (p<0.01) (Tables 11 and 12). For example, in the MM1.S tumor model, mean total flux in animals treated with P5AC1-V2 BCMA specific CAR-T cells was 6.44 log₁₀ photons/s at day 25, compared to 9.22 log₁₀ photons/s in animals given control T cells (Table 11). At day 35 post tumor implantation, mean total flux in animals treated with P5AC1-V2 BCMA specific CAR-T cells was 6.82 log₁₀ photons/s, compared to 10.18 log₁₀ photons/s in animals given control T cells (Table 11). In the Molp8 tumor model, mean total flux in animals treated with P5AC1-V2 BCMA specific CAR-T cells was 7.88 log₁₀ photons/s at day 14, compared to 9.39 log₁₀ photons/s in animals given control T cells (Table 12). At day 23 post tumor implantation, mean total flux in animals treated with P5AC1-V2 BCMA specific CAR-T cells was 9.29 log₁₀ photons/s, compared 10.37 log₁₀ photons/s in animals given control T cells (Table 12).

[0234] These results demonstrate that treatments with BCMA specific CAR-T cells are effective to induce tumor regression.

Table 11: Tumor bioluminescence measurements of orthotopic MM1.S tumor model

Group 1: Control T cells			
Days after tumor implantation	Mean total flux (log10 photons/s)	SEM	N
17	7.84	0.04	10
21	8.16	0.19	10
25	9.22	0.02	10
28	9.53	0.02	10
32	9.96	0.05	10
35	10.18	0.07	10
Group 2: P5AC1-V2 BCMA specific CAR-T cells			
Days after tumor implantation	Mean total flux (log10)	SEM	N
17	7.84	0.03	10
21	8.14	0.11	10
25	6.44	0.16	10
28	6.51	0.09	10
32	6.72	0.10	10
35	6.82	0.09	10
Group 3: PC1C12-V2 BCMA specific CAR-T cells			
Days after tumor implantation	Mean total flux (log 10)	SEM	N
17	7.86	0.04	10
21	8.56	0.15	10
25	6.85	0.26	10
28	6.41	0.30	10
32	6.64	0.29	10
35	6.62	0.30	10
Group 4: COM22-V2 BCMA specific CAR-T cells			
Days after tumor implantation	Mean total flux (log 10)	SEM	N
17	7.84	0.04	10
21	8.49	0.10	10
25	6.55	0.08	10
28	6.40	0.09	10
32	6.98	0.14	10
35	6.87	0.22	10

Table 12: Tumor bioluminescence measurements of orthotopic Molp-8 tumor model

Group 1: T cell only control			
Days after tumor implantation	Mean total flux (log10)	SEM	N
0	5.80	0.02	10
7	7.48	0.04	10
10	8.24	0.06	10
14	9.39	0.04	10
17	9.88	0.03	10
21	10.12	0.04	10
23	10.37	0.03	10
Group 2: P5AC1-V2 BCMA specific CAR-T cells			
Days after tumor implantation	Mean total flux (log10)	SEM	N
0	5.80	0.02	10
7	7.48	0.04	10
10	8.41	0.05	10
14	7.88	0.18	10
17	7.39	0.21	10
21	7.98	0.12	10

Group 2: P5AC1-V2 BCMA specific CAR-T cells			
Days after tumor implantation	Mean total flux (log10)	SEM	N
23	8.29	0.11	10
Group 3: PC1C12-V2 BCMA specific CAR-T cells			
Days after tumor implantation	Mean total flux (log10)	SEM	N
0	5.80	0.02	10
7	7.51	0.04	10
10	8.31	0.07	10
14	7.07	0.21	10
17	6.51	0.15	10
21	7.37	0.13	10
23	7.75	0.13	10
Group 4: COM22-V2 BCMA specific CAR-T cells			
Days after tumor implantation	Mean total flux (log10)	SEM	N
0	5.80	0.02	10
7	7.49	0.04	10
10	8.39	0.07	10
14	7.78	0.16	10
17	7.51	0.21	10
21	7.89	0.17	10
23	8.32	0.14	10

Example 6: Treatment of multiple myeloma with TCRα/dCK knockout BCMA specific CAR-T cells

[0235] This example illustrates the therapeutic activity of BCMA specific CAR-T cells in orthotopic mouse models of multiple myeloma.

[0236] A humanized mouse model was used to evaluate the efficacy of BCMA CAR-T cells against human myeloma cell lines expressing BCMA. 6 to 8 week old female Nod/Scid IL2rg^{-/-} (NSG) mice were purchased from the Jackson Laboratories. All animals were housed in a pathogen free vivarium facility at Rinat and experiments were conducted according to the protocols in accordance with the Institutional Animal Care and Use Committee (IACUC) guidelines.

[0237] The MM1.S cell lines was purchased from the American Type Culture Collection (ATCC.org). The Cell line was engineered to express a Luc-GFP fusion protein using lentiviral particles (amsbio)and gene edited using TALEN nucleases to disable the deoxycytidine (dCK) gene. Cells were cultured in RPMI 1640 medium with L-glutamine supplemented with 10% fetal calf serum at 37°C in 5% carbon dioxide (CO₂). Cells growing in an exponential growth phase were harvested and used for tumor inoculation.

[0238] Therapeutic CAR-T cells were produced as described. Healthy human donor cells, peripheral blood mononuclear cells (PBMC) or purified pan-T cells, are activated and transduced with lentiviral particles encoding for BCMA scFV, CD8 hinge, CD8 transmembrane, 41BB and CD3ζ with RQR8 genes under the control of the EF-1a promoter. The BCMA specific CAR-T cells were gene edited to delete the TCRα and/or the dCK gene using a combination of TCRα and dCK TALEN, or TCRα TALEN alone. Transduction efficiency for all T cells was 70%. TCRα knockout T cells were purified using magnetic selection kits for CD3-positive cells (Miltenyi); dCK knockout T cells were purified by expansion in the presence of 0.5 μM clofarabine. Cells were cultured for 14 to 17 days and then cryopreserved in 90% FCS/10% DMSO. For T cell injection, T cells were rapidly thawed in a 37°C water bath and washed twice with RPMI 1640 medium containing 25mM Hepes. For treatment, T cells were injected in 0.2 ml RPMI 1640 with 25 mM Hepes into the tail vein of tumor-bearing animals.

[0239] For the mouse tumor model, animals were injected with MM1.S/dCK KO tumor cells. Mice were then treated with 2.5x10⁶ BCMA specific CAR-T cells on day 18 post tumor cell implantation. An equivalent dose of untransduced T cells that received TCRα and dCK TALEN was used as control. Animals were treated with clofarabine or vehicle for five days after T cell injection.

[0240] Results: the control T cell-treated group exhibited progressive tumor growth until the study endpoint was reached at day 35 (Table 13, Group 1). Compared against control, groups treated with TCRα knockout BCMA specific CAR-T cells and vehicle exhibited a significant decrease in tumor burden (p<0.05) that was diminished upon coadministration of clofarabine (p<0.05) (Table 13, Groups 2 and 3). Tumor burden was significantly reduced in animals treated with TCRα/dCK double knockout CAR-T cells, irrespective of whether the animals received vehicle or clofarabine (p<0.05) (Table 13, Groups 4 and 5). Reduction of tumor burden in the groups

receiving TCRα/dCK double knockout T cells did not differ from the group receiving TCRα single knockout T cells and vehicle (p>0.1) (Table 13, Groups 2, 4, and 5).

[0241] These results demonstrate that treatments with TCRα/dCK double knockout BCMA CAR-T cells are effective to induce tumor regression in the presence of nucleoside analog therapies such as fludarabine and clofarabine.

Table 13: Tumor bioluminescence measurements of nucleoside analog therapy-resistant orthotopic MM1.S tumor model.

Group 1: TCRα/dCK KO control T cells + clofarabine			
Days after T cell administration	Mean total flux (log10 photons/s)	SEM	N
0	7.87	0.04	10
4	8.94	0.08	10
8	9.22	0.05	10
11	9.52	0.04	10
15	10.00	0.04	10
18	10.38	0.04	10
Group 2: TCRα KO BCMA specific CAR-T cells + vehicle			
Days after T cell administration	Mean total flux (log10)	SEM	N
0	7.86	0.04	10
4	9.28	0.07	10
8	8.58	0.12	10
11	8.04	0.14	10
15	8.14	0.15	10
18	8.24	0.15	10
Group 3: TCRα KO BCMA specific CAR-T cells + clofarabine			
Days after T cell administration	Mean total flux (log 10)	SEM	N
0	7.87	0.04	10
4	9.33	0.07	10
8	9.17	0.07	10
11	8.95	0.14	10
15	9.36	0.08	10
18	9.50	0.07	10
Group 4: TCRα/dCK KO BCMA specific CAR-T cells + vehicle			
Days after T cell administration	Mean total flux (log10)	SEM	N
0	7.86	0.04	10
4	9.19	0.08	10
8	9.08	0.12	10
11	8.59	0.18	10
15	8.60	0.21	10
18	8.69	0.18	10
Group 5: TCRα/dCK KO BCMA specific CAR-T cells + clofarabine			
Days after T cell administration	Mean total flux (log10)	SEM	N
0	7.87	0.04	10
4	9.26	0.09	10
8	9.07	0.10	10
11	8.51	0.14	10
15	8.42	0.21	10
18	8.49	0.18	10

[0242] Although the disclosed teachings have been described with reference to various applications, methods, kits, and compositions, it will be appreciated that various changes and modifications can be made without departing from the teachings herein. The foregoing examples are provided to better illustrate the disclosed teachings. While the present teachings have been described in terms of these exemplary embodiments, the skilled artisan will readily understand that numerous variations and modifications of these exemplary embodiments are possible without undue experimentation.

[0243] The foregoing description and Examples detail certain specific embodiments of the invention and describes the best mode contemplated by the inventors.

SEQUENCE LISTING

[0244]

<110> PFIZER INC.
Kuo, Tracy
Boldajipour, Bijan Andre
Chaparro-Riggers, Javier
Duchateau, Philippe
Galetto, Roman
Juillerat, Alexandre
Pertel, Thomas Charles
Rajpal, Arvind
Sasu, Barbra J.
Sommer, Cesar Adolfo
Valton, Julien
Van Blarcom, Thomas John

<120> CHIMERIC ANTIGEN RECEPTORS TARGETING B-CELL MATURATION ANTIGEN

<130> PC72207A

<150> 62/146,825
<151> 2015-04-13

<150> 62/286,473
<151> 2016-01-25

<150> 62/301,177
<151> 2016-02-29

<160> 401

<170> PatentIn version 3.5

<210> 1
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 1
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
 20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
 50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Gly Ser Pro Pro
 85 90 95

Ser Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 2

<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 2
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Asn Thr Phe Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Val Ser Pro Ile Ala Ser Gly Met Asp Tyr Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
 115

<210> 3
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 3
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Asn Thr Phe Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Val Ser Pro Ile Ala Ala Gln Met Asp Tyr Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
 115

<210> 4
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 4
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Leu Gly Ser Phe
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Lys His Tyr Gly Trp Pro Pro
85 90 95

Ser Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 5
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 5
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Leu Gly Ser Phe
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Asn Tyr Pro Pro
85 90 95

Ser Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 6
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 6
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

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

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Asn Tyr Pro Pro
85 90 95

Ser Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 7
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 7
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Asn Thr Phe Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ala Arg Val Ser Pro Ile Ala Ala Leu Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 8
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 8
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Asn Thr Phe Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val Ser Pro Ile Ala Ala Pro Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 9
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 9
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly

Glu Ile Val Leu Thr Ser Cys Arg Ala Ser Gln Ser Leu Gly Ser Phe
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Leu Gly Ser Phe
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Pro Tyr Pro Pro
85 90 95
Ser Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 10
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 10
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Leu Gly Ser Phe
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Asn Tyr Pro Pro
85 90 95
Ser Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 11
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 11
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Gly Asp Phe
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Lys His Tyr Gly Trp Pro Pro
85 90 95

Ser Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 12
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 12
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

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

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Pro Tyr Pro Pro
85 90 95

Ser Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 13
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 13
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

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

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Asn Tyr Pro Pro
85 90 95

Ser Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 14
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 14
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

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

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Asn Tyr Pro Pro
85 90 95

Ser Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 15
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 15
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Lys His Tyr Gly Trp Pro Pro
85 90 95

Ser Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 16
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 16
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Pro Tyr Pro Pro
85 90 95

Ser Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 17
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 17
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
 20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Asn Tyr Pro Pro
 85 90 95

Ser Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 18
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 18
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
 20 25 30

Tyr Pro Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Pro Tyr Pro Pro
 85 90 95

Ser Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 19
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 19
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ala His
 20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu

- 35 - - 40 - 45 -
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Pro Tyr Pro Pro
85 90 95
Ser Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 20
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 20
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Phe
20 25 30
Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Pro Tyr Pro Pro
85 90 95
Ser Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 21
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 21
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Pro His
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Pro Tyr Pro Pro
85 90 95
Ser Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 22

<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 22
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Lys Tyr Tyr Pro Tyr Pro Pro
85 90 95

Ser Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

100 105

<210> 23
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 23
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Lys Phe Tyr Pro Tyr Pro Pro
85 90 95

Ser Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

100 105

<210> 24
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 24
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Thr Tyr Val Arg Gln Ala Pro Gly Tyr Gly Leu Gly Thr Val

Ala Met Thr Trp Val Arg Gln Ala Phe Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Asn Thr Phe Tyr Ala Asp Gln Arg
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val Ser Pro Ile Ala Ser Gly Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 25
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 25
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Asp Tyr Ser Gly Gly Asn Thr Phe Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val Ser Pro Ile Ala Ser Gly Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 26
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 26
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Tyr Gln Gly Gly Asn Thr Phe Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val Ser Pro Ile Ala Ser Gly Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 27
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 27
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Leu Thr Gly Gly Asn Thr Phe Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val Ser Pro Ile Ala Ser Gly Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 28
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 28
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser His Ala Gly Gly Asn Thr Phe Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val Ser Pro Ile Ala Ser Gly Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 29
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 29
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Asn Thr Phe Tyr Ala Asp Gln Leu
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Val Ser Pro Ile Ala Ser Gly Met Asp Tyr Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
 115

<210> 30
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 30
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Asn Thr Phe Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Val Ser Pro Ile Tyr Ala Gly Met Asp Tyr Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
 115

<210> 31
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 31
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Asn Thr Phe Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val Ser Pro Ile Ala Ala Glu Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 32
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 32

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Asn Thr Phe Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Val Ser Pro Ile Ala Ala Gln Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 33
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 33

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Asp Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Asp Ile Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 34
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 34
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 35
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 35
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Asp Ser Gly Gly Ser Ala Trp Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Ser Leu Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 36
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 36
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Val Leu
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Arg Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 37
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 37
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Asp Ser Gly Gly Ser Met Trp Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Ser Leu Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 38
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 38
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu

65707580

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Ser Trp Pro
859095

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100105

<210> 39

<211> 115

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 39

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
151015

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
202530

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
354045

Ser Ala Ile Ser Asp Phe Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
505560

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65707580

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
859095

Ala Arg Tyr Trp Pro Met Asp Ile Trp Gly Gln Gly Thr Leu Val Thr
100105110

Val Ser Ser
115

<210> 40

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 40

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
151015

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Asp Leu
202530

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
354045

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
505560

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65707580

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Thr Trp Pro
859095

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100105

<210> 41

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 41

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Asn Leu
 20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
 50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
 65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Gly Trp Pro
 85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 42

<211> 115

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 42

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

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

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ala Ile Thr Ala Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Tyr Trp Pro Met Ser Leu Trp Gly Gln Gly Thr Leu Val Thr
 100 105 110

Val Ser Ser
 115

<210> 43

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 43

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ala Tyr
 20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
 50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Glu Arg Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 44
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 44
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Asp Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Ser Leu Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 45
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 45
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Leu
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Val Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 46
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 46
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Asp Ser Gly Gly Ser Arg Trp Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Thr Pro Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 47
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 47
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Leu Asp Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 48
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 48
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Val Leu Asp Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Thr Pro Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 49
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 49
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Val Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 50
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 50
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Asp Ser Gly Gly Ser Arg Trp Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Ser Asp Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 51
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 51
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Val Leu
 20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
 50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Leu Ala Trp Pro
 85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 52
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 52
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ala Ile Ser Asp Ser Gly Gly Ser Lys Trp Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Tyr Trp Pro Met Ser Leu Trp Gly Gln Gly Thr Leu Val Thr
 100 105 110

Val Ser Ser
 115

<210> 53
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 53
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
 20 25 30

20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Phe Thr Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 54
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 54
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Gly Gly Ser Gly Gly Ser Leu Pro Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Asp Ser Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 55
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 55
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Pro Tyr
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Glu Arg Trp Pro
85 90 95

- - - - -

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 56
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 56
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Asp Ser Gly Gly Ser Gly Trp Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Ser Leu Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 57
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 57
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Val Glu
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ala Arg Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 58
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 58
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Val Leu Asp Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Ser Leu Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 59
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 59
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Glu Leu
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Phe Gly Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 60
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 60
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Asp Ser Gly Gly Ser Cys Trp Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Thr Pro Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 61
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 61
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Glu Met Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ala His Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 62
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 62
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Phe Ala Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Thr Pro Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 63
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 63
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Arg Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 64
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 64
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Trp Gly Gly Ser Leu Pro Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Asp Ser Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 65
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 65
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ala Gln
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Arg Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 66
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 66
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Met Ser Ser Gly Gly Pro Leu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Ala Leu Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 67
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 67
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ala Leu
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Val Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 68
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 68
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Leu Met Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Ser Leu Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 69
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 69
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Gly Pro Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Ser Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 70
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 70
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Asp Ser Gly Gly Tyr Arg Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Ser Leu Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 71
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 71
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Trp Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Glu Ser Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 72
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 72
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Leu Ser Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Asp Ile Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser

115

<210> 73
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 73
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Gly Gly Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Ser Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 74
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 74
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Leu Asp Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Ser Pro Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 75
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 75
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Phe Leu
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 76
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 76
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Pro Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Gly Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Asp Ser Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 77
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 77
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Thr
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Asp Ala Ser Ser Arg Ala Pro Gly Ile Pro Asp Arg Phe Ser

115 Tyr Asp Ala Ser Ser Arg Ala Phe Gly 115 Phe Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Thr Ser Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 78
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 78
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Pro Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Gly Gly Ser Gly Gly Ser Leu Pro Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Asp Ser Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 79
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 79
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Pro Glu
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Asp Ala Ser Ser Arg Ala Pro Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Val Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 80
<211> 108
<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 80

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Leu Gly Ser Phe Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Asn Tyr Pro Pro Ser
85 90 95

Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 81

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 81

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Thr
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Asp Ala Ser Ser Arg Ala Pro Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Arg Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 82

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 82

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Pro Leu
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Asp Ala Ser Ser Arg Ala Pro Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Ala Phe Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 83
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 83
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Pro Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Gly Gly Ser Gly Gly Trp Ser Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Asp Ser Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 84
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 84
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Trp Leu Ser Gln Ser Val Ser Ser Thr
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Asp Ala Ser Ser Arg Ala Pro Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Glu Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 85
<211> 108
<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 85

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Thr
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Asp Ala Ser Ser Arg Ala Pro Gly Ile Pro Asp Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Ser Trp Pro
85 90 95
Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 86

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 86

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Leu
20 25 30
Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Asp Ala Ser Ser Arg Ala Pro Gly Ile Pro Asp Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Ala Trp Pro
85 90 95
Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 87

<211> 115

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 87

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Pro Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Thr Val Gly Ser Gly Gly Ser Ile Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Asp Ser Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 88
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 88
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Ala Cys Ser Gln Ser Val Ser Ser Thr
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Asp Ala Ser Ser Arg Ala Pro Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Ala Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 89
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 89
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Cys Asp Val Ser Ser Thr
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Asp Ala Ser Ser Arg Ala Pro Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Met Arg Ser Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 90
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 90
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Ala Val Pro Ser Thr
 20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Ile Tyr Asp Ala Ser Ser Arg Ala Pro Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Ala Phe Pro
 85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 91
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 91
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Cys Ser Ser Gln Ser Val Ser Ser Thr
 20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Ile Tyr Asp Ala Ser Ser Arg Ala Pro Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Ala Phe Pro
 85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 92
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 92
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ala Ile Ser Asp Ser Gly Gly Ser Arg Trp Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Tyr Trp Pro Met Asp Ile Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 93
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 93
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Val Arg Val Ser Ser Thr
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Met Lys Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 94
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 94
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ala Ala
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Met Cys Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 95
<211> 115
<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 95
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Pro Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Gly Gly Ser Gly Gly Ser Ile His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Asp Ser Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 96

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 96
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Trp Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Cys Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 97

<211> 115

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 97
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Pro Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Pro Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala His Ile Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Asp Ser Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 98
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 98
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Thr
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Ser Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 99
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 99
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Pro Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Gly Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Asp Pro Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

100100100

Val Ser Ser
115

<210> 100

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 100

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
151015

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Pro
202530

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
354045

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
505560

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65707580

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Ser Trp Pro
859095

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100105

<210> 101

<211> 115

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 101

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
151015

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
202530

Pro Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
354045

Ser Ala Ile Gly Gly Ser Gly Gly Ser Leu Gly Tyr Ala Asp Ser Val
505560

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65707580

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
859095

Ala Arg Tyr Trp Pro Met Asp Ser Trp Gly Gln Gly Thr Leu Val Thr
100105110

Val Ser Ser
115

<210> 102

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Sequence Listing

<400> 102

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Pro Leu
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Lys Ala Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 103

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 103

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Tyr Leu
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Met Glu Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 104

<211> 115

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 104

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Pro Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Phe Ala Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Arg Tyr Trp Pro Met Asp Ser Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser

115

<210> 105
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 105
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ala Gln
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Ala Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 106
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 106
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Pro Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Gly Gly Ser Gly Thr Trp Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Asp Ser Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 107
<211> 108
<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 107

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Lys Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 108

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 108

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ala Val
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Arg Ala Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 109

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 109

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Ile Ala Val Ser Ser Thr
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Met Val Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 110
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 110
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Pro Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Leu Phe Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Asp Ser Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 111
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 111
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Pro Arg Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Asp Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 112
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 112
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Pro Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Gly Gly Ser Gly Gly Ser Leu Pro Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Asp Ile Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 113
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 113
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Thr
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Glu Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 114
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 114
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Pro Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ala Leu Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Asp Ser Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser

<210> 115
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 115
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ala Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Met Ser Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 116
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 116
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Tyr Met
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Lys Ser Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 117
<211> 108

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 117
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ala Leu
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Gly Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 118
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 118
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Pro Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Gly Gly Ser Gly Gly Ser Leu Pro Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Ala Asp Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 119
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 119
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Pro Ile Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu

354045

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
505560

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65707580

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Gly Trp Pro
859095

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100105

<210> 120

<211> 115

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 120

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
151015

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
202530

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
354045

Ser Ala Ile Ser Asp Ser Gly Gly Phe Val Tyr Tyr Ala Asp Ser Val
505560

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65707580

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
859095

Ala Arg Tyr Trp Pro Met Asp Ser Trp Gly Gln Gly Thr Leu Val Thr
100105110

Val Ser Ser
115

<210> 121

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 121

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
151015

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
202530

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
354045

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
505560

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65707580

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Glu Phe Trp Pro
859095

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100105

<210> 122
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 122
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Gly Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Ser Leu Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 123
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 123
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Thr
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Met Ser Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 124
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 124
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Gly Ile Ser Ser Thr
10 20 30 40 50 60 70 80 90 100 110 120

20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ala Tyr Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 125
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 125

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Cys Leu Asp Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Asp Ser Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 126
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 126

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Gly Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 127
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 127
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1 5 10 15

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

Pro Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ala Leu Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Ser Leu Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 128
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 128
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Val Arg
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Trp Pro
85 90 95

Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 129
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 129
Ser Tyr Ala Met Thr

Ser Tyr Ala Met Thr
1 5

<210> 130
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 130
Gly Phe Thr Phe Gly Ser Tyr
1 5

<210> 131
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 131
Gly Phe Thr Phe Gly Ser Tyr Ala Met Thr
1 5 10

<210> 132
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 132
Ala Ile Ser Gly Ser Gly Gly Asn Thr Phe Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 133
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 133
Ser Gly Ser Gly Gly Asn
1 5

<210> 134
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 134
Val Ser Pro Ile Ala Ser Gly Met Asp Tyr
1 5 10

<210> 135
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 135

Val Ser Pro Ile Ala Ala Gln Met Asp Tyr
1 5 10

<210> 136
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 136
Val Ser Pro Ile Ala Ala Leu Met Asp Tyr
1 5 10

<210> 137
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 137
Val Ser Pro Ile Ala Ala Pro Met Asp Tyr
1 5 10

<210> 138
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 138
Ala Ile Ser Gly Ser Gly Gly Asn Thr Phe Tyr Ala Asp Gln Arg Lys
1 5 10 15

Gly
<210> 139
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 139
Ala Ile Asp Tyr Ser Gly Gly Asn Thr Phe Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly
<210> 140
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 140
Asp Tyr Ser Ser Gly Asn
1 5

<210> 141
<211> 17
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 141
Ala Ile Ser Tyr Gln Gly Gly Asn Thr Phe Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 142
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 142
Ser Tyr Gln Gly Gly Asn
1 5

<210> 143
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 143
Ala Ile Ser Leu Thr Gly Gly Asn Thr Phe Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 144
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 144
Ser Leu Thr Gly Gly Asn
1 5

<210> 145
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 145
Ala Ile Ser His Ala Gly Gly Asn Thr Phe Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 146
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 146
Ser His Ala Gly Gly Asn
1 5

<210> 147

<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 147
Ala Ile Ser Gly Ser Gly Gly Asn Thr Phe Tyr Ala Asp Gln Leu Lys
1 5 10 15

Gly

<210> 148
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 148
Val Ser Pro Ile Tyr Ala Gly Met Asp Tyr
1 5 10

<210> 149
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 149
Val Ser Pro Ile Ala Ala Glu Met Asp Tyr
1 5 10

<210> 150
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 150
Ser Tyr Ala Met Asn
1 5

<210> 151
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 151
Gly Phe Thr Phe Ser Ser Tyr
1 5

<210> 152
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 152
Gly Phe Thr Phe Ser Ser Tyr Ala Met Asn
1 5 10

<210> 153
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 153
Ala Ile Ser Asp Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 154
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 154
Ser Asp Ser Gly Gly Ser
1 5

<210> 155
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 155
Tyr Trp Pro Met Asp Ile
1 5

<210> 156
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 156
Ser Tyr Pro Met Ser
1 5

<210> 157
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 157
Gly Phe Thr Phe Ser Ser Tyr Pro Met Ser

1 5 10

<210> 158
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 158
Ala Ile Gly Gly Ser Gly Gly Ser Leu Pro Tyr Ala Asp Ser Val Lys

1 5 10 15

Gly

<210> 159
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 159
Gly Gly Ser Gly Gly Ser
1 5

<210> 160
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 160
Ala Ile Leu Asp Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 161
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 161
Tyr Trp Pro Met Asp Ser
1 5

<210> 162
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 162
Ala Ile Gly Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 163
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 163
Ala Ile Ser Asp Ser Gly Gly Ser Ala Trp Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 164
<211> 6
<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 164

Tyr Trp Pro Met Ser Leu
1 5

<210> 165

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 165

Ala Ile Ser Asp Phe Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 166

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 166

Ser Asp Phe Gly Gly Ser
1 5

<210> 167

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 167

Ala Ile Thr Ala Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 168

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 168

Thr Ala Ser Gly Gly Ser Leu Thr Ser
1 5

<210> 169

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 169

Ala Ile Ser Asp Ser Gly Gly Ser Arg Trp Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

Gly

<210> 170

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 170

Tyr	Trp	Pro	Met	Thr	Pro
1				5	

<210> 171

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 171

Ala	Val	Leu	Asp	Ser	Gly	Gly	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 172

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 172

Leu	Asp	Ser	Gly	Gly	Ser
1					5

<210> 173

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 173

Tyr	Trp	Pro	Met	Ser	Asp
1				5	

<210> 174

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 174

Ala	Ile	Ser	Asp	Ser	Gly	Gly	Ser	Lys	Trp	Tyr	Ala	Asp	Ser	Val	Lys
1				5					10					15	

Gly

<210> 175

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 175
Ala Ile Ser Asp Ser Gly Gly Ser Gly Trp Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 176
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 176
Ala Ile Ser Asp Ser Gly Gly Ser Cys Trp Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 177
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 177
Ala Ile Phe Ala Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 178
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 178
Phe Ala Ser Gly Gly Ser
1 5

<210> 179
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 179
Ser Gly Trp Gly Gly Ser
1 5

<210> 180
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 180
Ala Ile Met Ser Ser Gly Gly Pro Leu Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 181

<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 181
Met Ser Ser Gly Gly Pro
1 5

<210> 182
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 182
Tyr Trp Pro Met Ala Leu
1 5

<210> 183
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 183
Ala Ile Leu Met Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 184
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 184
Leu Met Ser Gly Gly Ser
1 5

<210> 185
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 185
Ala Ile Ser Asp Ser Gly Gly Tyr Arg Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 186
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 186
Ser Asp Ser Gly Gly Tyr

1 5

<210> 187
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 187
Ala Ile Leu Ser Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 188
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 188
Leu Ser Ser Gly Gly Ser
1 5

<210> 189
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 189
Ala Tyr Trp Pro Met Ser Pro
1 5

<210> 190
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 190
Ala Ile Gly Gly Ser Gly Gly Trp Ser Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 191
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 191
Gly Gly Ser Gly Gly Trp
1 5

<210> 192
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 192
Ala Thr Val Gly Ser Gly Gly Ser Ile Gly Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 193
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 193
Val Gly Ser Gly Gly Ser
1 5

<210> 194
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 194
Ala Ile Gly Gly Ser Gly Gly Ser Ile His Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 195
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 195
Ala His Ile Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 196
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 196
Ile Gly Ser Gly Gly Ser
1 5

<210> 197
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 197
Tyr Trp Pro Met Asp Pro
1 5

<210> 198
<211> 17

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 198
Ala Ile Gly Gly Ser Gly Gly Ser Leu Gly Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 199
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 199
Ala Ile Gly Gly Ser Gly Thr Trp Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 200
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 200
Gly Gly Ser Gly Thr Trp
1 5

<210> 201
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 201
Ala Leu Phe Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 202
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 202
Phe Gly Ser Gly Gly Ser
1 5

<210> 203
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Constrict

<400> 203

Ala Ala Leu Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 204
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 204
Leu Gly Ser Gly Gly Ser
1 5

<210> 205
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 205
Tyr Trp Pro Met Ala Asp
1 5

<210> 206
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 206
Ala Ile Ser Asp Ser Gly Gly Phe Val Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 207
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 207
Ser Asp Ser Gly Gly Phe
1 5

<210> 208
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 208
Ala Cys Leu Asp Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 209
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 209
Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala
1 5 10

<210> 210
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 210
Gly Ala Ser Ser Arg Ala Thr
1 5

<210> 211
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 211
Gln His Tyr Gly Ser Pro Pro Ser Phe Thr
1 5 10

<210> 212
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 212
Arg Ala Ser Gln Ser Leu Gly Ser Phe Tyr Leu Ala
1 5 10

<210> 213
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 213
Lys His Tyr Gly Trp Pro Pro Ser Phe Thr
1 5 10

<210> 214
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 214
Gln His Tyr Asn Tyr Pro Pro Ser Phe Thr
1 5 10

<210> 215
<211> 12
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 215
Arg Ala Ser Gln Ser Val Gly Asp Phe Tyr Leu Ala
1 5 10

<210> 216

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 216
Gln His Tyr Pro Tyr Pro Pro Ser Phe Thr
1 5 10

<210> 217

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 217
Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Pro Ser
1 5 10

<210> 218

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 218
Arg Ala Ser Gln Ser Val Ser Ala His Tyr Leu Ala
1 5 10

<210> 219

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 219
Arg Ala Ser Gln Ser Val Ser Ser Phe Phe Leu Ala
1 5 10

<210> 220

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 220
Lys Tyr Tyr Pro Tyr Pro Pro Ser Phe Thr
1 5 10

<210> 221

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 221
Asp Ala Ser Ile Arg Ala Thr
1 5

<210> 222
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 222
Gln Gln Tyr Gly Ser Trp Pro Leu Thr
1 5

<210> 223
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 223
Arg Ala Ser Gln Ser Val Ser Val Leu Tyr Leu Ala
1 5 10

<210> 224
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 224
Gln Gln Tyr Gln Arg Trp Pro Leu Thr
1 5

<210> 225
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 225
Gln Gln Tyr Gln Ser Trp Pro Leu Thr
1 5

<210> 226
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 226
Arg Ala Ser Gln Ser Val Ser Asp Leu Tyr Leu Ala
1 5 10

<210> 227
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 227
Gln Gln Tyr Gln Met Met Asp Tyr Met

Gln Gln Tyr Gln Thr Trp Pro Leu Thr
1 5

<210> 228
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 228
Arg Ala Ser Gln Ser Val Ser Asn Leu Tyr Leu Ala
1 5 10

<210> 229
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 229
Gln Gln Tyr Gln Gly Trp Pro Leu Thr
1 5

<210> 230
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 230
Arg Ala Ser Gln Ser Val Ser Ala Tyr Tyr Leu Ala
1 5 10

<210> 231
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 231
Gln Gln Tyr Glu Arg Trp Pro Leu Thr
1 5

<210> 232
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 232
Arg Ala Ser Gln Ser Val Ser Ser Leu Tyr Leu Ala
1 5 10

<210> 233
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 233
Gln Gln Tyr Gln Val Trp Pro Leu Thr
1 5

<210> 234
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 234
Gln Gln Tyr Leu Asp Trp Pro Leu Thr
1 5

<210> 235
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 235
Arg Ala Ser Gln Ser Val Ser Ala Leu Tyr Leu Ala
1 5 10

<210> 236
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> SEQ ID NO.: 237

<400> 236
Gln Gln Tyr Leu Ala Trp Pro Leu Thr
1 5

<210> 237
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 237
Gln Gln Tyr Phe Thr Trp Pro Leu Thr
1 5

<210> 238
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 238
Arg Ala Ser Gln Ser Val Ser Pro Tyr Tyr Leu Ala
1 5 10

<210> 239
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 239
Arg Ala Ser Gln Ser Val Ser Val Glu Tyr Leu Ala
1 5 10

<210> 240

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

<220>
<223> Synthetic Construct

<400> 240
Gln Gln Tyr Ala Arg Trp Pro Leu Thr
1 5

<210> 241
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 241
Arg Ala Ser Gln Ser Val Ser Glu Leu Tyr Leu Ala
1 5 10

<210> 242
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 242
Gln Gln Tyr Phe Gly Trp Pro Leu Thr
1 5

<210> 243
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 243
Arg Ala Ser Gln Ser Val Glu Met Ser Tyr Leu Ala
1 5 10

<210> 244
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 244
Gln Gln Tyr Ala His Trp Pro Leu Thr
1 5

<210> 245
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 245
Arg Ala Ser Gln Ser Val Ser Ala Gln Tyr Leu Ala
1 5 10

<210> 246
<211> 12

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 246
Gly Pro Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala
1 5 10

<210> 247
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 247
Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Trp Ala
1 5 10

<210> 248
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 248
Gln Gln Tyr Glu Ser Trp Pro Leu Thr
1 5

<210> 249
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 249
Arg Gly Gly Gln Ser Val Ser Ser Ser Tyr Leu Ala
1 5 10

<210> 250
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 250
Arg Ala Ser Gln Ser Val Ser Phe Leu Tyr Leu Ala
1 5 10

<210> 251
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 251
Arg Ala Ser Gln Ser Val Ser Ser Thr Tyr Leu Ala
1 5 10

<210> 252
<211> 7
<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 252

Asp Ala Ser Ser Arg Ala Pro
1 5

<210> 253

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 253

Gln Gln Tyr Ser Thr Ser Pro Leu Thr
1 5

<210> 254

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 254

Arg Ala Ser Gln Ser Val Ser Pro Glu Tyr Leu Ala
1 5 10

<210> 255

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 255

Gln Gln Tyr Ser Val Trp Pro Leu Thr
1 5

<210> 256

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 256

Gln Gln Tyr Ser Ala Trp Pro Leu Thr
1 5

<210> 257

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 257

Arg Ala Ser Gln Ser Val Ser Ser Val Tyr Leu Ala
1 5 10

<210> 258

<211> 9

<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 258
Gln Gln Tyr Ser Thr Trp Pro Leu Thr
1 5

<210> 259
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 259
Gln Gln Tyr Ser Arg Trp Pro Leu Thr
1 5

<210> 260
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 260
Arg Ala Ser Gln Ser Val Ser Pro Leu Tyr Leu Ala
1 5 10

<210> 261
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 261
Gln Gln Tyr Ser Ala Phe Pro Leu Thr
1 5

<210> 262
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 262
Trp Leu Ser Gln Ser Val Ser Ser Thr Tyr Leu Ala
1 5 10

<210> 263
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 263
Gln Gln Tyr Ser Glu Trp Pro Leu Thr
1 5

<210> 264
<211> 9
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 264

Gln Gln Tyr Ser Ser Trp Pro Leu Thr
1 5

<210> 265

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 265

Arg Ala Ser Gln Ser Val Ser Ser Leu Phe Leu Ala
1 5 10

<210> 266

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 266

Ala Cys Ser Gln Ser Val Ser Ser Thr Tyr Leu Ala
1 5 10

<210> 267

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 267

Arg Ala Ser Cys Asp Val Ser Ser Thr Tyr Leu Ala
1 5 10

<210> 268

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 268

Gln Gln Tyr Met Arg Ser Pro Leu Thr
1 5

<210> 269

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 269

Arg Ala Ser Glu Ala Val Pro Ser Thr Tyr Leu Ala
1 5 10

<210> 270

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 270
Cys Ser Ser Gln Ser Val Ser Ser Thr Tyr Leu Ala
1 5 10

<210> 271
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 271
Arg Ala Ser Val Arg Val Ser Ser Thr Tyr Leu Ala
1 5 10

<210> 272
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 272
Gln Gln Tyr Met Lys Trp Pro Leu Thr
1 5

<210> 273
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 273
Arg Ala Ser Gln Ser Val Ser Ala Ala Tyr Leu Ala
1 5 10

<210> 274
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 274
Gln Gln Tyr Met Cys Trp Pro Leu Thr
1 5

<210> 275
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 275
Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Trp Gly
1 5 10

<210> 276
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 276
Gln Gln Tyr Gln Cys Trp Pro Leu Thr

Gln Gln Tyr Gln Gln Trp Pro Leu Thr
1 5

<210> 277
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 277
Arg Ala Ser Gln Ser Val Ser Ser Pro Tyr Leu Ala
1 5 10

<210> 278
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 278
Gln Gln Tyr Lys Ala Trp Pro Leu Thr
1 5

<210> 279
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 279
Arg Ala Ser Gln Ser Val Ser Tyr Leu Tyr Leu Ala
1 5 10

<210> 280
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 280
Gln Gln Tyr Met Glu Trp Pro Leu Thr
1 5

<210> 281
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 281
Gln Gln Tyr Gln Ala Trp Pro Leu Thr
1 5

<210> 282
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 282
Gln Gln Tyr Gln Lys Trp Pro Leu Thr
1 5

<210> 283
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 283
Arg Ala Ser Gln Ser Val Ser Ala Val Tyr Leu Ala
1 5 10

<210> 284
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 284
Gln Gln Tyr Arg Ala Trp Pro Leu Thr
1 5

<210> 285
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 285
Arg Ala Ser Ile Ala Val Ser Ser Thr Tyr Leu Ala
1 5 10

<210> 286
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 286
Gln Gln Tyr Met Val Trp Pro Leu Thr
1 5

<210> 287
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 287
Arg Pro Arg Gln Ser Val Ser Ser Ser Tyr Leu Ala
1 5 10

<210> 288
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 288
Gln Gln Tyr Gln Asp Trp Pro Leu Thr
1 5

<210> 289

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

<220>
<223> Synthetic Construct

<400> 289
Gln Gln Tyr Gln Glu Trp Pro Leu Thr
1 5

<210> 290
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 290
Arg Ala Ser Gln Ser Val Ser Ala Ser Tyr Leu Ala
1 5 10

<210> 291
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 291
Gln Gln Tyr Met Ser Trp Pro Leu Thr
1 5

<210> 292
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 292
Arg Ala Ser Gln Ser Val Ser Tyr Met Tyr Leu Ala
1 5 10

<210> 293
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 293
Gln Gln Tyr Lys Ser Trp Pro Leu Thr
1 5

<210> 294
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 294
Gln Gln Tyr Tyr Gly Trp Pro Leu Thr
1 5

<210> 295
<211> 12

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 295
Arg Ala Ser Gln Pro Ile Ser Ser Ser Tyr Leu Ala
1 5 10

<210> 296
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 296
Gln Gln Tyr Glu Phe Trp Pro Leu Thr
1 5

<210> 297
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 297
Arg Ala Ser Gln Gly Ile Ser Ser Thr Tyr Leu Ala
1 5 10

<210> 298
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 298
Gln Gln Tyr Ala Tyr Trp Pro Leu Thr
1 5

<210> 299
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 299
Arg Ala Ser Gln Ser Val Ser Val Arg Tyr Leu Ala
1 5 10

<210> 300
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 300
Gln Gln Tyr Gly Ser Trp Pro Ile Thr
1 5

<210> 301
<211> 5
<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<220>

<221> VARIANT

<222> (3)..(3)

<223> wherein X is A or P

<220>

<221> VARIANT

<222> (5)..(5)

<223> wherein X is T, N, or S

<400> 301

Ser	Tyr	Xaa	Met	Xaa
1				5

<210> 302

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<220>

<221> VARIANT

<222> (5)..(5)

<223> wherein X is G or S

<400> 302

Gly	Phe	Thr	Phe	Xaa	Ser	Tyr
1				5		

<210> 303

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<220>

<221> VARIANT

<222> (5)..(5)

<223> wherein X is G or S

<220>

<221> VARIANT

<222> (8)..(8)

<223> wherein X is A or P

<220>

<221> VARIANT

<222> (10)..(10)

<223> wherein X is T, N, or S

<400> 303

Gly	Phe	Thr	Phe	Xaa	Ser	Tyr	Xaa	Met	Xaa
1				5					10

<210> 304

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 304
Ala Ile Ser Gly Trp Gly Gly Ser Leu Pro Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 305
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<220>
<221> VARIANT
<222> (2)..(2)
<223> wherein X is I, V, T, H, L, A, or C

<220>
<221> VARIANT
<222> (3)..(3)
<223> wherein X is S, D, G, T, I, L, F, M, or V

<220>
<221> VARIANT
<222> (4)..(4)
<223> wherein X is G, Y, L, H, D, A, S, or M

<220>
<221> VARIANT
<222> (5)..(5)
<223> wherein X is S, Q, T, A, F, or W

<220>
<221> VARIANT
<222> (7)..(7)
<223> wherein X is G or T

<220>
<221> VARIANT
<222> (8)..(8)
<223> wherein ;X is N, S, P, Y, W, or F

<220>
<221> VARIANT
<222> (9)..(9)
<223> wherein ;X is S, T, I, L, T, A, R, V, K, G, or C

<220>
<221> VARIANT
<222> (10)..(10)
<223> wherein X is F, Y, P, W, H, or G

<220>
<221> VARIANT
<222> (14)..(14)
<223> wherein X is V, R, or L

<220>
<221> VARIANT
<222> (15)..(15)
<223> wherein X is G or T

<400> 305
Ala Xaa Xaa Xaa Xaa Gly Xaa Xaa Xaa Xaa Tyr Ala Asp Xaa Xaa Lys
1 5 10 15

Gly

<210> 306
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<220>
<221> VARIANT
<222> (1)..(1)
<223> wherein X is S, V, I, D, G, T, L, F, or M

<220>
<221> VARIANT
<222> (2)..(2)
<223> wherein X is G, Y, L, H, D, A, S, or M

<220>
<221> VARIANT
<222> (3)..(3)
<223> wherein X is S, G, F, or W

<220>
<221> VARIANT
<222> (4)..(4)
<223> wherein X is G or S

<220>
<221> VARIANT
<222> (5)..(5)
<223> wherein X is G or T

<220>
<221> VARIANT
<222> (6)..(6)
<223> wherein X is N, S, P, Y, or W

<400> 306
Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 307
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<220>
<221> VARIANT
<222> (5)..(5)
<223> wherein X is A or Y

<220>
<221> VARIANT
<222> (6)..(6)
<223> wherein X is A or S

<220>
<221> VARIANT
<222> (7)..(7)
<223> wherein X is G, Q, L, P, or E

<400> 307
Val Ser Pro Ile Xaa Xaa Xaa Met Asp Tyr
1 5 10

<210> 308
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<220>
<221> VARIANT
<222> (5)..(5)
<223> wherein X is D, S, T, or A

<220>
<221> VARIANT
<222> (6)..(6)
<223> wherein X is I, S, L, P, or D

<400> 308
Tyr Trp Pro Met Xaa Xaa
1 5

<210> 309
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<220>
<221> VARIANT
<222> (1)..(1)
<223> wherein X is R, G, W, A, or C

<220>
<221> VARIANT
<222> (2)..(2)
<223> wherein X is A, P, G, L, C, or S

<220>
<221> VARIANT
<222> (3)..(3)
<223> wherein X is S, G, or R

<220>
<221> VARIANT
<222> (4)..(4)
<223> wherein X is Q, C, E, V, or I

<220>
<221> VARIANT
<222> (5)..(5)
<223> wherein X is S, P, G, A, R, or D

<220>
<221> VARIANT
<222> (6)..(6)
<223> wherein X is V, G, I, or L

<220>
<221> VARIANT
<222> (7)..(7)
<223> wherein X is S, E, D, P, or G

<220>
<221> VARIANT
<222> (8)..(8)

<223> wherein X is S, P, F, A, M, E, V, N, D, or Y

<220>
<221> VARIANT
<222> (9)..(9)
<223> wherein X is T, I, V, E, S, F, A, M, Q, Y, H, or R

<220>
<221> VARIANT
<222> (10)..(10)
<223> wherein X is Y or F

<220>
<221> VARIANT
<222> (11)..(11)
<223> wherein X is L, W, or P

<220>
<221> VARIANT
<222> (12)..(12)
<223> wherein X is A, S, or G

<400> 309
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 310
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<220>
<221> VARIANT
<222> (1)..(1)
<223> wherein X is G or D

<220>
<221> VARIANT
<222> (4)..(4)
<223> wherein X is S or I

<220>
<221> VARIANT
<222> (7)..(7)
<223> wherein X is T or P

<400> 310
Xaa Ala Ser Xaa Arg Ala Xaa
1 5

<210> 311
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<220>
<221> VARIANT
<222> (1)..(1)
<223> wherein X is Q or K

<220>
<221> VARIANT
<222> (2)..(2)

<223> wherein X is H or Y

<220>
<221> VARIANT
<222> (4)..(4)
<223> wherein X is G, N, or P

<220>
<221> VARIANT
<222> (5)..(5)
<223> wherein X is S, W, or Y

<400> 311
Xaa Xaa Tyr Xaa Xaa Pro Pro Ser Phe Thr
1 5 10

<210> 312
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<220>
<221> VARIANT
<222> (4)..(4)
<223> wherein X is G, Q, E, L, F, A, S, M, K, R, or Y

<220>
<221> VARIANT
<222> (5)..(5)
<223> wherein X is S, R, T, G, V, F, Y, D, A, H, V, E, K, or C

<220>
<221> VARIANT
<222> (6)..(6)
<223> wherein X is W, F, or S

<220>
<221> VARIANT
<222> (8)..(8)
<223> wherein X is L or I

<400> 312
Gln Gln Tyr Xaa Xaa Xaa Pro Xaa Thr
1 5

<210> 313
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<220>
<221> VARIANT
<222> (30)..(30)
<223> wherein X is G or S

<220>
<221> VARIANT
<222> (33)..(33)
<223> wherein X is A or P

<220>
<221> VARIANT
<222> (35)..(35)

<223> wherein X is T, N, or S

<220>

<221> VARIANT

<222> (51)..(51)

<223> wherein X is I, V, T, H, L, A, or C

<220>

<221> VARIANT

<222> (52)..(52)

<223> wherein X is S, D, G, T, I, L, F, M, or V

<220>

<221> VARIANT

<222> (53)..(53)

<223> wherein X is G, Y, L, H, D, A, S, or M

<220>

<221> VARIANT

<222> (54)..(54)

<223> wherein X is S, Q, T, A, F, or W

<220>

<221> VARIANT

<222> (56)..(56)

<223> wherein X is G or T

<220>

<221> VARIANT

<222> (57)..(57)

<223> wherein X is N, S, P, Y, W, or F

<220>

<221> VARIANT

<222> (58)..(58)

<223> wherein X is S, T, I, L, T, A, R, V, K, G, or C

<220>

<221> VARIANT

<222> (59)..(59)

<223> wherein X is F, Y, P, W, H, or G

<220>

<221> VARIANT

<222> (63)..(63)

<223> wherein X is V, R, or L

<220>

<221> VARIANT

<222> (64)..(64)

<223> wherein X is G or T

<220>

<221> VARIANT

<222> (103)..(103)

<223> wherein X is A or Y

<220>

<221> VARIANT

<222> (104)..(104)

<223> wherein X is A or S

<220>

<221> VARIANT

<222> (105)..(105)

<223> wherein X is G, Q, L, P, or E

<400> 313
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Xaa Ser Tyr
20 25 30

Xaa Met Xaa Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Xaa Xaa Xaa Xaa Gly Xaa Xaa Xaa Xaa Tyr Ala Asp Xaa Xaa
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val Ser Pro Ile Xaa Xaa Xaa Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 314
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<220>
<221> VARIANT
<222> (30)..(30)
<223> wherein X is G or S

<220>
<221> VARIANT
<222> (33)..(33)
<223> wherein X is A or P

<220>
<221> VARIANT
<222> (35)..(35)
<223> wherein X is T, N, or S

<220>
<221> VARIANT
<222> (51)..(51)
<223> wherein X is I, V, T, H, L, A, or C

<220>
<221> VARIANT
<222> (52)..(52)
<223> wherein X is S, D, G, T, I, L, F, M, or V

<220>
<221> VARIANT
<222> (53)..(53)
<223> wherein X is G, Y, L, H, D, A, S, or M

<220>
<221> VARIANT
<222> (54)..(54)
<223> wherein X is S, Q, T, A, F, or W

<220>
<221> VARIANT

<222> (56)..(56)
<223> wherein X is G or T

<220>
<221> VARIANT
<222> (57)..(57)
<223> wherein X is N, S, P, Y, W, or F

<220>
<221> VARIANT
<222> (58)..(58)
<223> wherein X is S, T, I, L, T, A, R, V, K, G, or C

<220>
<221> VARIANT
<222> (59)..(59)
<223> wherein X is F, Y, P, W, H, or G

<220>
<221> VARIANT
<222> (63)..(63)
<223> wherein X is V, R, or L

<220>
<221> VARIANT
<222> (64)..(64)
<223> wherein X13 is G or T

<220>
<221> VARIANT
<222> (103)..(103)
<223> wherein X is D, S, T, or A

<220>
<221> VARIANT
<222> (104)..(104)
<223> wherein X is I, S, L, P, or D

<400> 314
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Xaa Ser Tyr
20 25 30

Xaa Met Xaa Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Xaa Xaa Xaa Xaa Gly Xaa Xaa Xaa Xaa Tyr Ala Asp Xaa Xaa
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Trp Pro Met Xaa Xaa Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 315
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<220>
<221> VARIANT
<222> (24)..(24)
<223> wherein X is R, G, W, A, or C

<220>
<221> VARIANT
<222> (25)..(25)
<223> wherein X is A, P, G, L, C, or S

<220>
<221> VARIANT
<222> (26)..(26)
<223> wherein X is S, G, or R

<220>
<221> VARIANT
<222> (27)..(27)
<223> wherein X is Q, C, E, V, or I

<220>
<221> VARIANT
<222> (28)..(28)
<223> wherein X is S, L, P, G, A, R, or D

<220>
<221> VARIANT
<222> (29)..(29)
<223> wherein X is V, G, I, or L

<220>
<221> VARIANT
<222> (30)..(30)
<223> wherein X is S, E, D, P, or G

<220>
<221> VARIANT
<222> (31)..(31)
<223> wherein X is S, P, F, A, M, E, V, N, D, or Y

<220>
<221> VARIANT
<222> (32)..(32)
<223> wherein X is I, T, V, E, S, A, M, Q, Y, H, R, or F

<220>
<221> VARIANT
<222> (33)..(33)
<223> wherein X is Y or F

<220>
<221> VARIANT
<222> (34)..(34)
<223> wherein X is L, W, or P

<220>
<221> VARIANT
<222> (35)..(35)
<223> wherein X is A, S, or G

<220>
<221> VARIANT
<222> (51)..(51)
<223> wherein X is G or D

<220>
<221> VARIANT

<222> (54)..(54)
<223> wherein X is S or I

<220>
<221> VARIANT
<222> (57)..(57)
<223> wherein X is T or P

<220>
<221> VARIANT
<222> (90)..(90)
<223> wherein X is Q or K

<220>
<221> VARIANT
<222> (91)..(91)
<223> wherein X is H or Y

<220>
<221> VARIANT
<222> (93)..(93)
<223> wherein X is G, N, or P

<220>
<221> VARIANT
<222> (94)..(94)
<223> wherein X is S, W, or Y

<400> 315
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
20 25 30

Xaa Xaa Xaa Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Xaa Ala Ser Xaa Arg Ala Xaa Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Xaa Xaa Tyr Xaa Xaa Pro Pro
85 90 95

Ser Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 316
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<220>
<221> VARIANT
<222> (24)..(24)
<223> wherein X is R, G, W, A, or C

<220>
<221> VARIANT
<222> (25)..(25)
<223> wherein X is A, P, G, L, C, or S

<220>
<221> VARIANT

<222> (26)..(26)
<223> wherein X is S, G, or R

<220>
<221> VARIANT
<222> (27)..(27)
<223> wherein X is Q, C, E, V, or I

<220>
<221> VARIANT
<222> (28)..(28)
<223> wherein X is S, L, P, G, A, R, or D

<220>
<221> VARIANT
<222> (29)..(29)
<223> wherein X is V, G, or I

<220>
<221> VARIANT
<222> (30)..(30)
<223> wherein X is S, E, D, or P

<220>
<221> VARIANT
<222> (31)..(31)
<223> wherein X is S, P, F, A, M, E, V, N, D, or Y

<220>
<221> VARIANT
<222> (32)..(32)
<223> wherein X is I, T, V, E, S, A, M, Q, Y, H, or R

<220>
<221> VARIANT
<222> (33)..(33)
<223> wherein X is Y or F

<220>
<221> VARIANT
<222> (34)..(34)
<223> wherein X is L, W, or P

<220>
<221> VARIANT
<222> (35)..(35)
<223> wherein X is A, S, or G

<220>
<221> VARIANT
<222> (51)..(51)
<223> wherein X is G or D

<220>
<221> VARIANT
<222> (54)..(54)
<223> wherein X is S or I

<220>
<221> VARIANT
<222> (57)..(57)
<223> wherein X is T or P

<220>
<221> VARIANT
<222> (93)..(93)
<223> wherein X is G, Q, E, L, F, A, S, M, R, K, or Y

<220>
<221> VARIANT
<222> (94)..(94)
<223> wherein X is S, R, T, G, R, V, D, A, H, E, K, C, F, or Y

<220>
<221> VARIANT
<222> (95)..(95)
<223> wherein X is W, S, or F

<220>
<221> VARIANT
<222> (97)..(97)
<223> wherein X is L or I

<400> 316
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
20 25 30

Xaa Xaa Xaa Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Xaa Ala Ser Xaa Arg Ala Xaa Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Xaa Xaa Xaa Pro
85 90 95

Xaa Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 317
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 317
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ala Leu
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Asp Ala Ser Ser Arg Ala Pro Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Ala Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 318
<211> 21
<212> PRT
<213> Homo sapiens

<400> 318
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu
1 5 10 15

- - - -

His Ala Ala Arg Pro
20

<210> 319
<211> 16
<212> PRT
<213> Homo sapiens

<400> 319
Gly Leu Ala Val Ser Thr Ile Ser Ser Phe Phe Pro Pro Gly Tyr Gln
1 5 10 15

<210> 320
<211> 45
<212> PRT
<213> Homo sapiens

<400> 320
Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
1 5 10 15

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
20 25 30

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
35 40 45

<210> 321
<211> 231
<212> PRT
<213> Homo sapiens

<400> 321
Glu Pro Lys Ser Pro Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
20 25 30

Asp Thr Leu Met Ile Ala Arg Thr Pro Glu Val Thr Cys Val Val Val
35 40 45

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
50 55 60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
65 70 75 80

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
85 90 95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
100 105 110

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
115 120 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
130 135 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145 150 155 160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
165 170 175

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
180 185 190

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
195 200 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
210 215 220

Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 322
<211> 24
<212> PRT
<213> Homo sapiens

<400> 322
Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu

1 5 10 15

Ser Leu Val Ile Thr Leu Tyr Cys
20

<210> 323
<211> 42
<212> PRT
<213> Homo sapiens

<400> 323
Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
1 5 10 15

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
20 25 30

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
35 40

<210> 324
<211> 112
<212> PRT
<213> Homo sapiens

<400> 324
Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly
1 5 10 15

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
20 25 30

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
35 40 45

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
50 55 60

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
65 70 75 80

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
85 90 95

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
100 105 110

<210> 325
<211> 52
<212> PRT
<213> Homo sapiens

<400> 325
Phe Phe Ile Pro Leu Leu Val Val Ile Leu Phe Ala Val Asp Thr Gly
1 5 10 15

Leu Phe Ile Ser Thr Gln Gln Gln Val Thr Phe Leu Leu Lys Ile Lys
20 25 30

Arg Thr Arg Lys Gly Phe Arg Leu Leu Asn Pro His Pro Lys Pro Asn
35 40 45

Pro Lys Asn Asn
50

<210> 326
<211> 215
<212> PRT
<213> Homo sapiens

<400> 326
Met Asp Thr Glu Ser Asn Arg Arg Ala Asn Leu Ala Leu Pro Gln Glu
1 5 10 15

Pro Ser Ser Val Pro Ala Phe Glu Val Leu Glu Ile Ser Pro Gln Glu
20 25 30

Val Ser Ser Gly Arg Leu Leu Lys Ser Ala Ser Ser Pro Pro Leu His
35 40 45

Thr Trp Leu Thr Val Leu Lys Lys Glu Gln Glu Phe Leu Gly Val Thr
50 55 60

Gln Ile Leu Thr Ala Met Ile Cys Leu Cys Phe Gly Thr Val Val Cys
65 70 75 80

Ser Val Leu Asp Ile Ser His Ile Glu Gly Asp Ile Phe Ser Ser Phe
85 90 95

Lys Ala Gly Tyr Pro Phe Trp Gly Ala Ile Phe Phe Ser Ile Ser Gly
100 105 110

Met Leu Ser Ile Ile Ser Glu Arg Arg Asn Ala Thr Tyr Leu Val Arg
115 120 125

Gly Ser Leu Gly Ala Asn Thr Ala Ser Ser Ile Ala Gly Gly Thr Gly
130 135 140

Ile Thr Ile Leu Ile Ile Asn Leu Lys Lys Ser Leu Ala Tyr Ile His
145 150 155 160

Ile His Ser Cys Gln Lys Phe Phe Glu Thr Lys Cys Phe Met Ala Ser
165 170 175

Phe Ser Thr Glu Ile Val Val Met Met Leu Phe Leu Thr Ile Leu Gly
180 185 190

Leu Gly Ser Ala Val Ser Leu Thr Ile Cys Gly Ala Gly Glu Glu Leu
195 200 205

Lys Gly Asn Lys Val Pro Glu
210 215

<210> 327
<211> 42
<212> PRT
<213> Homo sapiens

<400> 327
Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
1 5 10 15

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
20 25 30

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
35 40

<210> 328
<211> 41
<212> PRT
<213> Homo sapiens

<400> 328
Arg Ser Lys Arg Ser Arg Gly Gly His Ser Asp Tyr Met Asn Met Thr
1 5 10 15

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
20 25 30

Pro Arg Asp Phe Ala Ala Tyr Arg Ser
35 40

<210> 329
<211> 18
<212> PRT
<213> Homo sapiens

<400> 329
Met Ile Pro Ala Val Val Leu Leu Leu Leu Leu Leu Val Glu Gln Ala
1 5 10 15

Ala Ala

<210> 330
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 330
Leu Gly Glu Pro Gln Leu Cys Tyr Ile Leu Asp Ala Ile Leu Phe Leu
1 5 10 15

Tyr Gly Ile Val Leu Thr Leu Leu Tyr Cys Arg Leu Lys Ile Gln Val
20 25 30

Arg Lys Ala Ala Ile Thr Ser Tyr Glu Lys Ser
35 40

<210> 331
<211> 22
<212> PRT
<213> Homo sapiens

<400> 331
Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val
1 5 10 15

Glu Glu Asn Pro Gly Pro
20

<210> 332
<211> 21
<212> PRT
<213> Homo sapiens

<400> 332
Gly Ser Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp Val Glu
1 5 10 15

Glu Asn Pro Gly Pro
20

<210> 333
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 333
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 334
<211> 530
<212> PRT
<213> Homo Sapiens

<400> 334
Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Lys
1 5 10 15

Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala
 20 25 30
 His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Asn Gly
 35 40 45
 Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys
 50 55 60
 Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn
 65 70 75 80
 Gly Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val
 85 90 95
 Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala
 100 105 110
 Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu
 115 120 125
 Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala
 130 135 140
 Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg
 145 150 155 160
 Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val
 165 170 175
 Val Ala Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val
 180 185 190
 Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu
 195 200 205
 Gln Val Val Ala Ile Ala Ser Asn Ile Gly Gly Lys Gln Ala Leu Glu
 210 215 220
 Thr Val Gln Ala Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr
 225 230 235 240
 Pro Glu Gln Val Val Ala Ile Ala Ser His Asp Gly Gly Lys Gln Ala
 245 250 255
 Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly
 260 265 270
 Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser Asn Ile Gly Gly Lys
 275 280 285
 Gln Ala Leu Glu Thr Val Gln Ala Leu Leu Pro Val Leu Cys Gln Ala
 290 295 300
 His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Asn Gly
 305 310 315 320
 Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys
 325 330 335
 Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser Asn
 340 345 350
 Ile Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Ala Leu Leu Pro Val
 355 360 365
 Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala
 370 375 380
 Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu
 385 390 395 400
 Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala
 405 410 415
 Ile Ala Ser Asn Ile Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Ala
 420 425 430
 Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val

Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val
435 440 445

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

Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu
465 470 475 480

Gln Val Val Ala Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu
485 490 495

Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr
500 505 510

Pro Gln Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Arg Pro Ala
515 520 525

Leu Glu
530

<210> 335
<211> 530
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 335
Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His Asp Gly Gly Lys
1 5 10 15

Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala
20 25 30

His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Gly Gly
35 40 45

Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys
50 55 60

Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His
65 70 75 80

Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val
85 90 95

Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala
100 105 110

Ser Asn Ile Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Ala Leu Leu
115 120 125

Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala
130 135 140

Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg
145 150 155 160

Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val
165 170 175

Val Ala Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val
180 185 190

Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln
195 200 205

Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu
210 215 220

Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr
225 230 235 240

Pro Gln Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala
245 250 255

Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly
260 265 270 275

260 265 270

Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys
275 280 285

Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala
290 295 300

His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Gly Gly
305 310 315 320

Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys
325 330 335

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

Ile Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Ala Leu Leu Pro Val
355 360 365

Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala
370 375 380

Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu
385 390 395 400

Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala
405 410 415

Ile Ala Ser Asn Ile Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Ala
420 425 430

Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val
435 440 445

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

Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln
465 470 475 480

Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu
485 490 495

Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr
500 505 510

Pro Gln Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Arg Pro Ala
515 520 525

Leu Glu
530

<210> 336
<211> 530
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 336

Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys
1 5 10 15

Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala
20 25 30

His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Gly Gly
35 40 45

Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys
50 55 60

Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn
65 70 75 80

-- -- -- -- --

```

Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val
      85                      90                      95

Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala
      100                    105                    110

Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu
      115                    120                    125

Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala
      130                    135                    140

Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg
      145                    150                    155                    160

Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val
      165                    170                    175

Val Ala Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val
      180                    185                    190

Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln
      195                    200                    205

Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu
      210                    215                    220

Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr
      225                    230                    235                    240

Pro Glu Gln Val Val Ala Ile Ala Ser Asn Ile Gly Gly Lys Gln Ala
      245                    250                    255

Leu Glu Thr Val Gln Ala Leu Leu Pro Val Leu Cys Gln Ala His Gly
      260                    265                    270

Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys
      275                    280                    285

Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala
      290                    295                    300

His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His Asp Gly
      305                    310                    315                    320

Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys
      325                    330                    335

Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His
      340                    345                    350

Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val
      355                    360                    365

Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala
      370                    375                    380

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

Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala
      405                    410                    415

Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg
      420                    425                    430

Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val
      435                    440                    445

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

Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu
      465                    470                    475                    480

Gln Val Val Ala Ile Ala Ser Asn Ile Gly Gly Lys Gln Ala Leu Glu
      485                    490                    495

Thr Val Gln Ala Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr

```

500 505 510
 Pro Gln Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Arg Pro Ala
 515 520 525

 Leu Glu
 530

 <210> 337
 <211> 539
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Synthetic Construct

 <400> 337
 Asn Pro Gln Arg Ser Thr Val Trp Tyr Leu Thr Pro Gln Gln Val Val
 1 5 10 15

 Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln
 20 25 30

 Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln
 35 40 45

 Val Val Ala Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr
 50 55 60

 Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro
 65 70 75 80

 Gln Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu
 85 90 95

 Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu
 100 105 110

 Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln
 115 120 125

 Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His
 130 135 140

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

 Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln
 165 170 175

 Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His Asp

 180 185 190

 Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu
 195 200 205

 Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser
 210 215 220

 Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro
 225 230 235 240

 Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile
 245 250 255

 Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu
 260 265 270

 Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val
 275 280 285

 Ala Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val Gln
 290 295 300

 Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln
 305 310 315 320

Val Val Ala Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr
325 330 335

Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro
340 345 350

Gln Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu
355 360 365

Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu
370 375 380

Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln
385 390 395 400

Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His
405 410 415

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

Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln
435 440 445

Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Gly
450 455 460

Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu
465 470 475 480

Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser
485 490 495

Asn Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro
500 505 510

Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile
515 520 525

Ala Ser Asn Gly Gly Gly Arg Pro Ala Leu Glu
530 535

<210> 338

<211> 530

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 338

Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His Asp Gly Gly Lys
1 5 10 15

Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala
20 25 30

His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His Asp Gly
35 40 45

Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys
50 55 60

Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His
65 70 75 80

Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val
85 90 95

Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala
100 105 110

Ser Asn Ile Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Ala Leu Leu
115 120 125

Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala
130 135 140

```

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

Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val
                165                170                175

Val Ala Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val
                180                185                190

Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu
                195                200                205

Gln Val Val Ala Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu
210                215                220

Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr
225                230                235                240

Pro Gln Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala
                245                250                255

Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly
260                265                270

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

Gln Ala Leu Glu Thr Val Gln Ala Leu Leu Pro Val Leu Cys Gln Ala
290                295                300

His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Asn Gly
305                310                315                320

Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys
325                330                335

Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn
340                345                350

Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val
355                360                365

Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala
370                375                380

Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu
385                390                395                400

Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala
405                410                415

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

Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val
435                440                445

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

Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu
465                470                475                480

Gln Val Val Ala Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu
485                490                495

Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr
500                505                510

Pro Gln Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Arg Pro Ala
515                520                525

Leu Glu
530

<210> 339
<211> 530
<212> PRT

```

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 339

Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Asn Gly Gly Lys
1 5 10 15

Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala
20 25 30

His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Asn Gly
35 40 45

Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys
50 55 60

Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn
65 70 75 80

Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val
85 90 95

Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala
100 105 110

Ser Asn Ile Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Ala Leu Leu
115 120 125

Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala
130 135 140

Ile Ala Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg
145 150 155 160

Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val
165 170 175

Val Ala Ile Ala Ser Asn Ile Gly Gly Lys Gln Ala Leu Glu Thr Val
180 185 190

Gln Ala Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln
195 200 205

Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu
210 215 220

Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr
225 230 235 240

Pro Glu Gln Val Val Ala Ile Ala Ser His Asp Gly Gly Lys Gln Ala
245 250 255

Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly
260 265 270

Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Lys
275 280 285

Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala
290 295 300

His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His Asp Gly
305 310 315 320

Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys
325 330 335

Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn
340 345 350

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

Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala
370 375 380

Gln Ala Ser Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val

Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu
385 390 395 400

Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala
405 410 415

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

Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val
435 440 445

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

Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln
465 470 475 480

Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu
485 490 495

Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr
500 505 510

Pro Gln Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Arg Pro Ala
515 520 525

Leu Glu
530

<210> 340
<211> 530
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 340
Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Lys
1 5 10 15
Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala
20 25 30
His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His Asp Gly
35 40 45
Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys
50 55 60
Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His
65 70 75 80
Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val
85 90 95
Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala
100 105 110
Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu
115 120 125
Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala
130 135 140
Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg
145 150 155 160
Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val
165 170 175
Val Ala Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val
180 185 190
Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln
195 200 205
Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln
210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310 315 320 325 330 335 340

Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu
210 215 220

Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr
225 230 235 240

Pro Glu Gln Val Val Ala Ile Ala Ser Asn Ile Gly Gly Lys Gln Ala
245 250 255

Leu Glu Thr Val Gln Ala Leu Leu Pro Val Leu Cys Gln Ala His Gly
260 265 270

Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His Asp Gly Gly Lys
275 280 285

Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala
290 295 300

His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Gly Gly
305 310 315 320

Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys
325 330 335

Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His
340 345 350

Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val
355 360 365

Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala
370 375 380

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

Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala
405 410 415

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

Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val
435 440 445

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

Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu
465 470 475 480

Gln Val Val Ala Ile Ala Ser Asn Ile Gly Gly Lys Gln Ala Leu Glu
485 490 495

Thr Val Gln Ala Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr
500 505 510

Pro Gln Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Arg Pro Ala
515 520 525

Leu Glu
530

<210> 341
<211> 530
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 341
Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Lys
1 5 10 15

Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala
20 25 30

His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn Asn Gly
35 40 45

Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys
 50 55 60
 Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His
 65 70 75 80
 Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val
 85 90 95
 Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala
 100 105 110
 Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu
 115 120 125
 Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val Val Ala
 130 135 140
 Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg
 145 150 155 160
 Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val
 165 170 175
 Val Ala Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val
 180 185 190
 Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln
 195 200 205
 Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu
 210 215 220
 Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr
 225 230 235 240
 Pro Glu Gln Val Val Ala Ile Ala Ser Asn Ile Gly Gly Lys Gln Ala
 245 250 255
 Leu Glu Thr Val Gln Ala Leu Leu Pro Val Leu Cys Gln Ala His Gly
 260 265 270
 Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His Asp Gly Gly Lys
 275 280 285
 Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala
 290 295 300
 His Gly Leu Thr Pro Glu Gln Val Val Ala Ile Ala Ser His Asp Gly
 305 310 315 320
 Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val Leu Cys
 325 330 335
 Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala Ser Asn
 340 345 350
 Gly Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu Pro Val
 355 360 365
 Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala Ile Ala
 370 375 380
 Ser Asn Asn Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg Leu Leu
 385 390 395 400
 Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Gln Gln Val Val Ala
 405 410 415
 Ile Ala Ser Asn Gly Gly Gly Lys Gln Ala Leu Glu Thr Val Gln Arg
 420 425 430
 Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu Gln Val
 435 440 445
 Val Ala Ile Ala Ser Asn Ile Gly Gly Lys Gln Ala Leu Glu Thr Val
 450 455 460
 Gln Ala Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr Pro Glu
 465 470 475 480

485 490 495

Gln Val Val Ala Ile Ala Ser His Asp Gly Gly Lys Gln Ala Leu Glu

485 490 495

Thr Val Gln Arg Leu Leu Pro Val Leu Cys Gln Ala His Gly Leu Thr

500 505 510

Pro Gln Gln Val Val Ala Ile Ala Ser Asn Gly Gly Gly Arg Pro Ala

515 520 525

Leu Glu

530

<210> 342

<211> 136

<212> PRT

<213> Homo sapiens

<400> 342

Cys Pro Tyr Ser Asn Pro Ser Leu Cys Ser Gly Gly Gly Gly Ser Glu

1 5 10 15

Leu Pro Thr Gln Gly Thr Phe Ser Asn Val Ser Thr Asn Val Ser Pro

20 25 30

Ala Lys Pro Thr Thr Thr Ala Cys Pro Tyr Ser Asn Pro Ser Leu Cys

35 40 45

Ser Gly Gly Gly Gly Ser Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro

50 55 60

Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro

65 70 75 80

Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp

85 90 95

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu

100 105 110

Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg Asn Arg Arg Arg Val

115 120 125

Cys Lys Cys Pro Arg Pro Val Val

130 135

<210> 343

<211> 453

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 343

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu

1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu

20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe

35 40 45

Thr Phe Ser Ser Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys

50 55 60

Gly Leu Glu Trp Val Ser Ala Ile Ser Asp Ser Gly Gly Ser Thr Tyr

65 70 75 80

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

85 90 95

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr

100 105 110

Ala Val Tyr Tyr Cys Ala Arg Tyr Trp Pro Met Asp Ile Trp Gly Gln

115 120 125

--- --

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly
145 150 155 160

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
165 170 175

Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
180 185 190

Gly Gln Ala Pro Arg Leu Leu Met Tyr Asp Ala Ser Ile Arg Ala Thr
195 200 205

Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
210 215 220

Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
225 230 235 240

Gln Gln Tyr Gly Ser Trp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
245 250 255

Glu Ile Lys Gly Leu Ala Val Ser Thr Ile Ser Ser Phe Phe Pro Pro
260 265 270

Gly Tyr Gln Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
275 280 285

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys
290 295 300

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
305 310 315 320

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
325 330 335

Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
340 345 350

Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
355 360 365

Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
370 375 380

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
385 390 395 400

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
405 410 415

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
420 425 430

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
435 440 445

Ala Leu Pro Pro Arg
450

<210> 344
<211> 482
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 344
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
 35 40 45
 Thr Phe Ser Ser Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
 50 55 60
 Gly Leu Glu Trp Val Ser Ala Ile Ser Asp Ser Gly Gly Ser Thr Tyr
 65 70 75 80
 Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
 85 90 95
 Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
 100 105 110
 Ala Val Tyr Tyr Cys Ala Arg Tyr Trp Pro Met Asp Ile Trp Gly Gln
 115 120 125
 Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
 130 135 140
 Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly
 145 150 155 160
 Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
 165 170 175
 Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
 180 185 190
 Gly Gln Ala Pro Arg Leu Leu Met Tyr Asp Ala Ser Ile Arg Ala Thr
 195 200 205
 Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
 210 215 220
 Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
 225 230 235 240
 Gln Gln Tyr Gly Ser Trp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
 245 250 255
 Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
 260 265 270
 Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
 275 280 285
 Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
 290 295 300
 Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
 305 310 315 320
 Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu
 325 330 335
 Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
 340 345 350
 Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys
 355 360 365
 Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln
 370 375 380
 Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
 385 390 395 400
 Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
 405 410 415
 Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
 420 425 430
 Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
 435 440 445
 Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
 450 455 460

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
465 470 475 480

Pro Arg

<210> 345
<211> 668
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 345
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15
His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
20 25 30
Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45
Thr Phe Ser Ser Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
50 55 60
Gly Leu Glu Trp Val Ser Ala Ile Ser Asp Ser Gly Gly Ser Thr Tyr
65 70 75 80
Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
85 90 95
Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110
Ala Val Tyr Tyr Cys Ala Arg Tyr Trp Pro Met Asp Ile Trp Gly Gln
115 120 125
Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
130 135 140
Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly
145 150 155 160
Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
165 170 175
Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
180 185 190
Gly Gln Ala Pro Arg Leu Leu Met Tyr Asp Ala Ser Ile Arg Ala Thr
195 200 205
Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
210 215 220
Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
225 230 235 240
Gln Gln Tyr Gly Ser Trp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
245 250 255
Glu Ile Lys Glu Pro Lys Ser Pro Asp Lys Thr His Thr Cys Pro Pro
260 265 270
Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro
275 280 285
Lys Pro Lys Asp Thr Leu Met Ile Ala Arg Thr Pro Glu Val Thr Cys
290 295 300
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
305 310 315 320
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
325 330 335
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
340 345 350

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
355 360 365

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
370 375 380

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
385 390 395 400

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
405 410 415

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
420 425 430

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
435 440 445

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
450 455 460

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
465 470 475 480

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ile Tyr Ile Trp Ala Pro
485 490 495

Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu
500 505 510

Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
515 520 525

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
530 535 540

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
545 550 555 560

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu
565 570 575

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
580 585 590

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
595 600 605

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
610 615 620

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
625 630 635 640

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
645 650 655

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
660 665

<210> 346
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 346
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Met Phe Ser Ser Met Ala Met Ser Met Val Ser Glu Ala Pro Gly Thr

```

Tnr Phe Ser Ser Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
 50          55          60

Gly Leu Glu Trp Val Ser Ala Ile Leu Ser Ser Gly Gly Ser Thr Tyr
65          70          75          80

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

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
      100          105          110

Ala Val Tyr Tyr Cys Ala Arg Tyr Trp Pro Met Asp Ile Trp Gly Gln
      115          120          125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
      130          135          140

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly
      145          150          155          160

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Gly
      165          170          175

Gly Gln Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
      180          185          190

Gly Gln Ala Pro Arg Leu Leu Met Tyr Asp Ala Ser Ile Arg Ala Thr
      195          200          205

Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
      210          215          220

Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
      225          230          235          240

Gln Gln Tyr Gln Ser Trp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
      245          250          255

Glu Ile Lys Gly Leu Ala Val Ser Thr Ile Ser Ser Phe Phe Pro Pro
      260          265          270

Gly Tyr Gln Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
      275          280          285

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys
      290          295          300

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
      305          310          315          320

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
      325          330          335

Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
      340          345          350

Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
      355          360          365

Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
      370          375          380

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
      385          390          395          400

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
      405          410          415

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
      420          425          430

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
      435          440          445

Ala Leu Pro Pro Arg
      450

```

<210> 347

<211> 482

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 347

```

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1      5      10      15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
      20      25      30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
      35      40      45

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

Gly Leu Glu Trp Val Ser Ala Ile Leu Ser Ser Gly Gly Ser Thr Tyr
65      70      75      80

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

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
      100     105     110

Ala Val Tyr Tyr Cys Ala Arg Tyr Trp Pro Met Asp Ile Trp Gly Gln
      115     120     125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
      130     135     140

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly
      145     150     155     160

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Gly
      165     170     175

Gly Gln Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
      180     185     190

Gly Gln Ala Pro Arg Leu Leu Met Tyr Asp Ala Ser Ile Arg Ala Thr
      195     200     205

Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
      210     215     220

Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
      225     230     235     240

Gln Gln Tyr Gln Ser Trp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
      245     250     255

Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
      260     265     270

Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
      275     280     285

Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
      290     295     300

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
      305     310     315     320

Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu
      325     330     335

Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
      340     345     350

Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Gly Gly Cys
      355     360     365

Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln
      370     375     380

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu

```

385 390 395 400

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
 405 410 415

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
 420 425 430

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
 435 440 445

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
 450 455 460

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
465 470 475 480

Pro Arg

<210> 348
<211> 668
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 348
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
 20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
 35 40 45

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

Gly Leu Glu Trp Val Ser Ala Ile Leu Ser Ser Gly Gly Ser Thr Tyr
65 70 75 80

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

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
 100 105 110

Ala Val Tyr Tyr Cys Ala Arg Tyr Trp Pro Met Asp Ile Trp Gly Gln
 115 120 125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly
145 150 155 160

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Gly
 165 170 175

Gly Gln Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
 180 185 190

Gly Gln Ala Pro Arg Leu Leu Met Tyr Asp Ala Ser Ile Arg Ala Thr
195 200 205

Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
210 215 220

Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
225 230 235 240

Gln Gln Tyr Gln Ser Trp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
 245 250 255

Glu Ile Lys Glu Pro Lys Ser Pro Asp Lys Thr His Thr Cys Pro Pro
260 265 270

Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro
 275 280 285
 Lys Pro Lys Asp Thr Leu Met Ile Ala Arg Thr Pro Glu Val Thr Cys
 290 295 300
 Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 305 310 315 320
 Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 325 330 335
 Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 340 345 350
 His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 355 360 365
 Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 370 375 380
 Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
 385 390 395 400
 Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 405 410 415
 Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 420 425 430
 Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 435 440 445
 Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 450 455 460
 Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 465 470 475 480
 Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ile Tyr Ile Trp Ala Pro
 485 490 495
 Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu
 500 505 510
 Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
 515 520 525
 Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
 530 535 540
 Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
 545 550 555 560
 Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu
 565 570 575
 Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
 580 585 590
 Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
 595 600 605
 Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
 610 615 620
 Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
 625 630 635 640
 Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
 645 650 655
 Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
 660 665

<210> 349

<211> 453

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 349

```

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1      5      10      15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
      20      25      30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
      35      40      45

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

Gly Leu Glu Trp Val Ser Ala Ile Ser Asp Phe Gly Gly Ser Thr Tyr
65      70      75      80

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

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100     105     110

Ala Val Tyr Tyr Cys Ala Arg Tyr Trp Pro Met Asp Ile Trp Gly Gln
115     120     125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
130     135     140

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly
145     150     155     160

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
165     170     175

Ser Gln Ser Val Ser Asp Leu Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
180     185     190

Gly Gln Ala Pro Arg Leu Leu Met Tyr Asp Ala Ser Ile Arg Ala Thr
195     200     205

Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
210     215     220

Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
225     230     235     240

Gln Gln Tyr Gln Thr Trp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
245     250     255

Glu Ile Lys Gly Leu Ala Val Ser Thr Ile Ser Ser Phe Phe Pro Pro
260     265     270

Gly Tyr Gln Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
275     280     285

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys
290     295     300

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
305     310     315     320

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
325     330     335

Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
340     345     350

Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
355     360     365

Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
370     375     380

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr

```

385 390 395 400

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
 405 410 415

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
 420 425 430

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
 435 440 445

Ala Leu Pro Pro Arg
 450

<210> 350
<211> 482
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 350
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
 20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
 35 40 45

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

Gly Leu Glu Trp Val Ser Ala Ile Ser Asp Phe Gly Gly Ser Thr Tyr
65 70 75 80

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

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Tyr Trp Pro Met Asp Ile Trp Gly Gln
115 120 125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly
145 150 155 160

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
165 170 175

Ser Gln Ser Val Ser Asp Leu Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
180 185 190

Gly Gln Ala Pro Arg Leu Leu Met Tyr Asp Ala Ser Ile Arg Ala Thr
195 200 205

Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
210 215 220

Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
225 230 235 240

Gln Gln Tyr Gln Thr Trp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
245 250 255

Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
260 265 270

Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
275 280 285

.. .. .

Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
290 295 300

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
305 310 315 320

Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu
325 330 335

Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
340 345 350

Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys
355 360 365

Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln
370 375 380

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
385 390 395 400

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
405 410 415

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
420 425 430

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
435 440 445

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
450 455 460

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
465 470 475 480

Pro Arg

<210> 351
<211> 668
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 351
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

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

Gly Leu Glu Trp Val Ser Ala Ile Ser Asp Phe Gly Gly Ser Thr Tyr
65 70 75 80

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

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Tyr Trp Pro Met Asp Ile Trp Gly Gln
115 120 125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly
145 150 155 160

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
 165 170 175
 Ser Gln Ser Val Ser Asp Leu Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
 180 185 190
 Gly Gln Ala Pro Arg Leu Leu Met Tyr Asp Ala Ser Ile Arg Ala Thr
 195 200 205
 Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
 210 215 220
 Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
 225 230 235 240
 Gln Gln Tyr Gln Thr Trp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
 245 250 255
 Glu Ile Lys Glu Pro Lys Ser Pro Asp Lys Thr His Thr Cys Pro Pro
 260 265 270
 Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro
 275 280 285
 Lys Pro Lys Asp Thr Leu Met Ile Ala Arg Thr Pro Glu Val Thr Cys
 290 295 300
 Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 305 310 315 320
 Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 325 330 335
 Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 340 345 350
 His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 355 360 365
 Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 370 375 380
 Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
 385 390 395 400
 Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 405 410 415
 Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 420 425 430
 Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 435 440 445
 Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 450 455 460
 Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 465 470 475 480
 Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ile Tyr Ile Trp Ala Pro
 485 490 495
 Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu
 500 505 510
 Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
 515 520 525
 Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
 530 535 540
 Arg Phe Pro Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
 545 550 555 560
 Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu
 565 570 575
 Tyr Asn Glu Leu Asn Leu Glu Arg Arg Glu Glu Tyr Asn Val Leu Asn

```

Tyr Asn Glu Asn Asn Leu Gly Arg Arg Glu Glu Gly Gly Lys Pro Arg Arg Lys
580                               585                               590

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
595                               600                               605

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
610                               615                               620

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
625                               630                               635                               640

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
645                               650                               655

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
660                               665

<210> 352
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 352
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1      5      10      15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
20     25     30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35     40     45

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

Gly Leu Glu Trp Val Ser Ala Ile Gly Gly Ser Gly Gly Ser Thr Tyr
65     70     75     80

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

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100    105    110

Ala Val Tyr Tyr Cys Ala Arg Tyr Trp Pro Met Asp Ser Trp Gly Gln
115    120    125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
130    135    140

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly
145                                150                                155                                160

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
165                                170                                175

Ser Gln Ser Val Ser Ser Thr Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
180                                185                                190

Gly Gln Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser Ser Arg Ala Pro
195                                200                                205

Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
210                                215                                220

Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
225                                230                                235                                240

Gln Gln Tyr Ser Thr Ser Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
245                                250                                255

Glu Ile Lys Gly Leu Ala Val Ser Thr Ile Ser Ser Phe Phe Pro Pro
260                                265                                270

```

Gly Tyr Gln Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
275 280 285

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys
290 295 300

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
305 310 315 320

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
325 330 335

Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
340 345 350

Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
355 360 365

Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
370 375 380

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
385 390 395 400

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
405 410 415

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
420 425 430

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
435 440 445

Ala Leu Pro Pro Arg
450

<210> 353
<211> 482
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 353
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

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

Gly Leu Glu Trp Val Ser Ala Ile Gly Gly Ser Gly Gly Ser Thr Tyr
65 70 75 80

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

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Tyr Trp Pro Met Asp Ser Trp Gly Gln
115 120 125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly
145 150 155 160

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
165 170 175

Ser Gln Ser Val Ser Ser Thr Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
180 185 190

Gly Gln Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser Ser Arg Ala Pro
195 200 205

Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
210 215 220

Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
225 230 235 240

Gln Gln Tyr Ser Thr Ser Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
245 250 255

Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
260 265 270

Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
275 280 285

Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
290 295 300

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
305 310 315 320

Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu
325 330 335

Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
340 345 350

Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys
355 360 365

Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln
370 375 380

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
385 390 395 400

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
405 410 415

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
420 425 430

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
435 440 445

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
450 455 460

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
465 470 475 480

Pro Arg

<210> 354

<211> 668

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 354

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Met Phe Ser Ser Thr Pro Met Ser Thr Val Asp Gln Ala Pro Gln Tyr

```

Ile Phe Ser Ser Tyr Pro Met Ser Trp Val Arg Gln Ala Pro Gly Lys
50          55          60

Gly Leu Glu Trp Val Ser Ala Ile Gly Gly Ser Gly Gly Ser Thr Tyr
65          70          75          80

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

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100         105         110

Ala Val Tyr Tyr Cys Ala Arg Tyr Trp Pro Met Asp Ser Trp Gly Gln
115         120         125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
130         135         140

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly
145         150         155         160

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
165         170         175

Ser Gln Ser Val Ser Ser Thr Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
180         185         190

Gly Gln Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser Ser Arg Ala Pro
195         200         205

Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
210         215         220

Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
225         230         235         240

Gln Gln Tyr Ser Thr Ser Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
245         250         255

Glu Ile Lys Glu Pro Lys Ser Pro Asp Lys Thr His Thr Cys Pro Pro
260         265         270

Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro
275         280         285

Lys Pro Lys Asp Thr Leu Met Ile Ala Arg Thr Pro Glu Val Thr Cys
290         295         300

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
305         310         315         320

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
325         330         335

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
340         345         350

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
355         360         365

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
370         375         380

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
385         390         395         400

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
405         410         415

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
420         425         430

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
435         440         445

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
450         455         460

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
465         470         475         480

```

400 410 420 430

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ile Tyr Ile Trp Ala Pro
485 490 495

Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu
500 505 510

Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
515 520 525

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
530 535 540

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
545 550 555 560

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu
565 570 575

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
580 585 590

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
595 600 605

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
610 615 620

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
625 630 635 640

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
645 650 655

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
660 665

<210> 355
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 355

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

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

Gly Leu Glu Trp Val Ser Ala Ile Gly Gly Ser Gly Gly Trp Ser Tyr
65 70 75 80

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

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Tyr Trp Pro Met Asp Ser Trp Gly Gln
115 120 125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly
145 150 155 160

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Trp Leu
165 170 175

Ser Gln Ser Val Ser Ser Thr Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
180 185 190

Gly Gln Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser Ser Arg Ala Pro
195 200 205

Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
210 215 220

Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
225 230 235 240

Gln Gln Tyr Ser Glu Trp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
245 250 255

Glu Ile Lys Gly Leu Ala Val Ser Thr Ile Ser Ser Phe Phe Pro Pro
260 265 270

Gly Tyr Gln Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
275 280 285

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys
290 295 300

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
305 310 315 320

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
325 330 335

Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
340 345 350

Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
355 360 365

Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
370 375 380

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
385 390 395 400

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
405 410 415

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
420 425 430

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
435 440 445

Ala Leu Pro Pro Arg
450

<210> 356
<211> 482
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 356
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

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

Gly Leu Glu Trp Val Ser Ala Ile Gly Gly Ser Gly Gly Trp Ser Tyr
65 70 75 80

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

85 90 95

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Tyr Trp Pro Met Asp Ser Trp Gly Gln
115 120 125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly
145 150 155 160

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Trp Leu
165 170 175

Ser Gln Ser Val Ser Ser Thr Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
180 185 190

Gly Gln Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser Ser Arg Ala Pro
195 200 205

Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
210 215 220

Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
225 230 235 240

Gln Gln Tyr Ser Glu Trp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
245 250 255

Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
260 265 270

Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
275 280 285

Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
290 295 300

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
305 310 315 320

Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu
325 330 335

Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
340 345 350

Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys
355 360 365

Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln
370 375 380

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
385 390 395 400

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
405 410 415

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
420 425 430

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
435 440 445

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
450 455 460

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
465 470 475 480

Pro Arg

<210> 357

<211> 668

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 357

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

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

Gly Leu Glu Trp Val Ser Ala Ile Gly Gly Ser Gly Gly Trp Ser Tyr
65 70 75 80

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

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Tyr Trp Pro Met Asp Ser Trp Gly Gln
115 120 125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly
145 150 155 160

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Trp Leu
165 170 175

Ser Gln Ser Val Ser Ser Thr Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
180 185 190

Gly Gln Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser Ser Arg Ala Pro
195 200 205

Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
210 215 220

Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
225 230 235 240

Gln Gln Tyr Ser Glu Trp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
245 250 255

Glu Ile Lys Glu Pro Lys Ser Pro Asp Lys Thr His Thr Cys Pro Pro
260 265 270

Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro
275 280 285

Lys Pro Lys Asp Thr Leu Met Ile Ala Arg Thr Pro Glu Val Thr Cys
290 295 300

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
305 310 315 320

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
325 330 335

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
340 345 350

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
355 360 365

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
370 375 380

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
385 390 395 400

- - - - -

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
405 410 415

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
420 425 430

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
435 440 445

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
450 455 460

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
465 470 475 480

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ile Tyr Ile Trp Ala Pro
485 490 495

Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu
500 505 510

Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
515 520 525

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
530 535 540

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
545 550 555 560

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu
565 570 575

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
580 585 590

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
595 600 605

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
610 615 620

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
625 630 635 640

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
645 650 655

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
660 665

<210> 358
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 358
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

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

Gly Leu Glu Trp Val Ser Ala Ile Ser Asp Ser Gly Gly Ser Arg Trp
65 70 75 80

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

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Thr Arg Tyr Trp Pro Met Asp Ile Trp Gly Gln
115 120 125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly
145 150 155 160

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
165 170 175

Ser Val Arg Val Ser Ser Thr Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
180 185 190

Gly Gln Ala Pro Arg Leu Leu Met Tyr Asp Ala Ser Ile Arg Ala Thr
195 200 205

Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
210 215 220

Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
225 230 235 240

Gln Gln Tyr Met Lys Trp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
245 250 255

Glu Ile Lys Gly Leu Ala Val Ser Thr Ile Ser Ser Phe Phe Pro Pro
260 265 270

Gly Tyr Gln Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
275 280 285

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys
290 295 300

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
305 310 315 320

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
325 330 335

Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
340 345 350

Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
355 360 365

Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
370 375 380

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
385 390 395 400

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
405 410 415

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
420 425 430

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
435 440 445

Ala Leu Pro Pro Arg
450

<210> 359
<211> 482
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 359
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Glv Glv Glv Leu

```

-----
          20          25          30
Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
   35          40          45

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

Gly Leu Glu Trp Val Ser Ala Ile Ser Asp Ser Gly Gly Ser Arg Trp
   65          70          75          80

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

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
  100          105          110

Ala Val Tyr Tyr Cys Thr Arg Tyr Trp Pro Met Asp Ile Trp Gly Gln
  115          120          125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
  130          135          140

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly
  145          150          155          160

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
  165          170          175

Ser Val Arg Val Ser Ser Thr Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
  180          185          190

Gly Gln Ala Pro Arg Leu Leu Met Tyr Asp Ala Ser Ile Arg Ala Thr
  195          200          205

Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
  210          215          220

Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
  225          230          235          240

Gln Gln Tyr Met Lys Trp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
  245          250          255

Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
  260          265          270

Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
  275          280          285

Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
  290          295          300

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
  305          310          315          320

Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu
  325          330          335

Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
  340          345          350

Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys
  355          360          365

Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln
  370          375          380

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
  385          390          395          400

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
  405          410          415

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
  420          425          430

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
  435          440          445

```

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
450 455 460

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
465 470 475 480

Pro Arg

<210> 360
<211> 668
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 360
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

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

Gly Leu Glu Trp Val Ser Ala Ile Ser Asp Ser Gly Gly Ser Arg Trp
65 70 75 80

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

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Thr Arg Tyr Trp Pro Met Asp Ile Trp Gly Gln
115 120 125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly
145 150 155 160

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
165 170 175

Ser Val Arg Val Ser Ser Thr Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
180 185 190

Gly Gln Ala Pro Arg Leu Leu Met Tyr Asp Ala Ser Ile Arg Ala Thr
195 200 205

Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
210 215 220

Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
225 230 235 240

Gln Gln Tyr Met Lys Trp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
245 250 255

Glu Ile Lys Glu Pro Lys Ser Pro Asp Lys Thr His Thr Cys Pro Pro
260 265 270

Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro
275 280 285

Lys Pro Lys Asp Thr Leu Met Ile Ala Arg Thr Pro Glu Val Thr Cys
290 295 300

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
305 310 315 320

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
325 330 335

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
340 345 350

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
355 360 365

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
370 375 380

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
385 390 395 400

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
405 410 415

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
420 425 430

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
435 440 445

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
450 455 460

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
465 470 475 480

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ile Tyr Ile Trp Ala Pro
485 490 495

Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu
500 505 510

Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
515 520 525

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
530 535 540

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
545 550 555 560

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu
565 570 575

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
580 585 590

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
595 600 605

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
610 615 620

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
625 630 635 640

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
645 650 655

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
660 665

<210> 361
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 361
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
 35 40 45
 Thr Phe Gly Ser Tyr Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys
 50 55 60
 Gly Leu Glu Trp Val Ser Ala Ile Asp Tyr Ser Gly Gly Asn Thr Phe
 65 70 75 80
 Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
 85 90 95
 Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
 100 105 110
 Ala Val Tyr Tyr Cys Ala Arg Val Ser Pro Ile Ala Ser Gly Met Asp
 115 120 125
 Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
 130 135 140
 Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr
 145 150 155 160
 Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu
 165 170 175
 Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Pro Ser Trp Tyr
 180 185 190
 Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser
 195 200 205
 Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
 210 215 220
 Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala
 225 230 235 240
 Val Tyr Tyr Cys Gln His Tyr Pro Tyr Pro Pro Ser Phe Thr Phe Gly
 245 250 255
 Gln Gly Thr Lys Val Glu Ile Lys Gly Leu Ala Val Ser Thr Ile Ser
 260 265 270
 Ser Phe Phe Pro Pro Gly Tyr Gln Ile Tyr Ile Trp Ala Pro Leu Ala
 275 280 285
 Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
 290 295 300
 Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
 305 310 315 320
 Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
 325 330 335
 Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
 340 345 350
 Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn
 355 360 365
 Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
 370 375 380
 Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
 385 390 395 400
 Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
 405 410 415
 Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
 420 425 430
 Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
 435 440 445

Ala Leu His Met Gln
450

<210> 362

<211> 487

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 362

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

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

Gly Leu Glu Trp Val Ser Ala Ile Asp Tyr Ser Gly Gly Asn Thr Phe
65 70 75 80

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

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Val Ser Pro Ile Ala Ser Gly Met Asp
115 120 125

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
130 135 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr
145 150 155 160

Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu
165 170 175

Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Pro Ser Trp Tyr
180 185 190

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

Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
210 215 220

Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala
225 230 235 240

Val Tyr Tyr Cys Gln His Tyr Pro Tyr Pro Pro Ser Phe Thr Phe Gly
245 250 255

Gln Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro
260 265 270

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
275 280 285

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
290 295 300

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
305 310 315 320

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
325 330 335

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
340 345 350

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
355 360 365

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
370 375 380

Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
385 390 395 400

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
405 410 415

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
420 425 430

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
435 440 445

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
450 455 460

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

Met Gln Ala Leu Pro Pro Arg
485

<210> 363

<211> 673

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 363

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

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

Gly Leu Glu Trp Val Ser Ala Ile Asp Tyr Ser Gly Gly Asn Thr Phe
65 70 75 80

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

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Val Ser Pro Ile Ala Ser Gly Met Asp
115 120 125

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
130 135 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr
145 150 155 160

Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu
165 170 175

Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Pro Ser Trp Tyr
180 185 190

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

Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
210 215 220

```

Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala
225                230                235                240

Val Tyr Tyr Cys Gln His Tyr Pro Tyr Pro Pro Ser Phe Thr Phe Gly
                245                250                255

Gln Gly Thr Lys Val Glu Ile Lys Glu Pro Lys Ser Pro Asp Lys Thr
                260                265                270

His Thr Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val
                275                280                285

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ala Arg Thr
290                295                300

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
305                310                315                320

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
                325                330                335

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
                340                345                350

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
355                360                365

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
370                375                380

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
385                390                395                400

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
                405                410                415

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
420                425                430

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
435                440                445

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
450                455                460

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
465                470                475                480

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ile
485                490                495

Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser
500                505                510

Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr
515                520                525

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
530                535                540

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
545                550                555                560

Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln
565                570                575

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
580                585                590

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
595                600                605

Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
610                615                620

Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu
625                630                635                640

```

Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr
645 650 655

Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro
660 665 670

Arg

<210> 364

<211> 453

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 364

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

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

Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Asn Thr Phe
65 70 75 80

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

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Val Ser Pro Ile Ala Ala Pro Met Asp
115 120 125

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
130 135 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr
145 150 155 160

Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu
165 170 175

Ser Cys Arg Ala Ser Gln Leu Gly Ser Phe Tyr Leu Ala Trp Tyr Gln
180 185 190

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

Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
210 215 220

Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val
225 230 235 240

Tyr Tyr Cys Gln His Tyr Asn Tyr Pro Pro Ser Phe Thr Phe Gly Gln
245 250 255

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

Phe Phe Pro Pro Gly Tyr Gln Ile Tyr Ile Trp Ala Pro Leu Ala Gly
275 280 285

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys
290 295 300

Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg
305 310 315 320

Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro
325 330 335

Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser
340 345 350

Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu
355 360 365

Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg
370 375 380

Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln
385 390 395 400

Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
405 410 415

Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp
420 425 430

Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
435 440 445

Leu His Met Gln Ala
450

<210> 365
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 365
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

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

Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Asn Thr Phe
65 70 75 80

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

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Val Ser Pro Ile Ala Ala Pro Met Asp
115 120 125

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
130 135 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr
145 150 155 160

Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu
165 170 175

Ser Cys Arg Ala Ser Gln Leu Gly Ser Phe Tyr Leu Ala Trp Tyr Gln
180 185 190

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

Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
210 215 220

Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val
 225 230 235 240
 Tyr Tyr Cys Gln His Tyr Asn Tyr Pro Pro Ser Phe Thr Phe Gly Gln
 245 250 255
 Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
 260 265 270
 Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
 275 280 285
 Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
 290 295 300
 Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
 305 310 315 320
 Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
 325 330 335
 Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
 340 345 350
 Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
 355 360 365
 Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
 370 375 380
 Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
 385 390 395 400
 Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
 405 410 415
 Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
 420 425 430
 Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
 435 440 445
 Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
 450 455 460
 Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
 465 470 475 480
 Gln Ala Leu Pro Pro Arg
 485
 <210> 366
 <211> 672
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Synthetic Construct
 <400> 366
 Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
 1 5 10 15
 His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
 20 25 30
 Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
 35 40 45
 Thr Phe Gly Ser Tyr Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys
 50 55 60
 Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Asn Thr Phe
 65 70 75 80
 Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
 85 90 95

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
 100 105 110
 Ala Val Tyr Tyr Cys Ala Arg Val Ser Pro Ile Ala Ala Pro Met Asp
 115 120 125
 Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
 130 135 140
 Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr
 145 150 155 160
 Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu
 165 170 175
 Ser Cys Arg Ala Ser Gln Leu Gly Ser Phe Tyr Leu Ala Trp Tyr Gln
 180 185 190
 Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser
 195 200 205
 Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
 210 215 220
 Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val
 225 230 235 240
 Tyr Tyr Cys Gln His Tyr Asn Tyr Pro Pro Ser Phe Thr Phe Gly Gln
 245 250 255
 Gly Thr Lys Val Glu Ile Lys Glu Pro Lys Ser Pro Asp Lys Thr His
 260 265 270
 Thr Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
 275 280 285
 Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ala Arg Thr Pro
 290 295 300
 Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
 305 310 315 320
 Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
 325 330 335
 Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
 340 345 350
 Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
 355 360 365
 Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
 370 375 380
 Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
 385 390 395 400
 Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
 405 410 415
 Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
 420 425 430
 Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
 435 440 445
 Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
 450 455 460
 Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
 465 470 475 480
 Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Ile Tyr
 485 490 495
 Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu
 500 505 510

Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile
515 520 525

Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp
530 535 540

Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
545 550 555 560

Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly
565 570 575

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
580 585 590

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
595 600 605

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
610 615 620

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
625 630 635 640

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
645 650 655

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
660 665 670

<210> 367
<211> 345
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<220>
<221> misc_feature
<222> (293)..(293)
<223> n is a, c, g, or t

<400> 367
gaggtgcagc tgctggaatc tggcggagga ctggtgcagc ctggcggctc tctgagactg 60
tcttgtgccg ccagcggctt caccttcagc agctacgcca tgaactgggt gcgccaggcc 120
cctggcaaag gcctggaatg ggtgtccgcc atcagcgata gcggcggcag cacctactac 180
gccgatagcg tgaagggccg gttcaccatc agccgggaca acagcaagaa caccctgtac 240
ctgcagatga acagcctgcg ggccgaggac accgccgtgt actactgtgc canatactgg 300
cccatggaca tctggggcca ggaaccttg gtcaccgtct cctca 345

<210> 368
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 368
gagatcgtgc tgacacagag ccctggcacc ctgagcctgt ctccaggcga aagagccacc 60
ctgtcctgca aagccagcca gagcgtgtcc agcagctacc tggcctggta tcagcaaaag 120
cccggccagg ctccccggt gctgatgtac gatgccagca tcagagccac cggcatcccc 180
gacagatttt ccggtcttgg cagcggcacc gacttcaccc tgaccatcag cagactggaa 240
cccgaggact tcgccgtgta ctactgccag cagtacggca gctggcccct gacatttggc 300
cagggcacaa aggtggagat caaa 324

<210> 369
<211> 345
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 369
gaggtgcagc tgctggaatc tggcggagga ctggtgcagc ctggcggctc tctgagactg 60
tcttgtgccg ccagcggctt caccttcagc agctacgcc tgaactgggt gcgccaggcc 120
cctggtaaag gtttggaatg ggtttctgct attctgtcgt ctggtggttc tacttactat 180
gccgattctg ttaagggtag attcaccatt tctagagaca actotaagaa caccttgtag 240
ttgcaaata actccttgag agctgaagat actgctgttt attactgtgc tagatactgg 300
ccaatggata tttgggggtca aggtactctg gtcaccgtct cctca 345

<210> 370
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 370
gagatcgtgc tgacacagag ccctggcacc ctgagcctgt ctccctggtga aagagctact 60
ttgtcttgta gaggggggtca atccgtttcc tcttcttatt tggcttggtga tcaacaaaaa 120
ccaggtaag ctccaagatt attgatgtac gatgcttcta ttagagccac cggatttcca 180
gatagatttt ctggttctgg ttccggtact gatttcactt tgactatctc tagattggaa 240
ccagaagatt tcgctgttta ctactgtcaa caatatcagt ctgggccatt gacttttggg 300
caaggtacaa aggttgaaat caaa 324

<210> 371
<211> 345
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 371
gaggtgcagc tgctggaatc tggcggagga ctggtgcagc ctggcggctc tctgagactg 60
tcttgtgccg ccagcggctt caccttcagc agctacccta tgagctgggt gcgccaggcc 120
cctggcaaa gactggaatg ggtgtccgcc atcggaggct ctggcggcag cacctactac 180
gccgatagcg tgaagggccg gttcaccatc agccgggaca acagcaagaa caccctgtac 240
ctgcaaatga acagcctgcg ggcggaggac accgccgtgt actactgtgc cagatactgg 300
cccatggaca gctggggcca gggaaactttg gtcaccgtct cctca 345

<210> 372
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 372
gagatcgtgc tgacacagag ccctggcacc ctgagcctgt ctccaggcga aagagccacc 60
ctgtcctgca aagccagcca gagcgtgtcc agcacatacc tggcctggta tcagcaaaag 120
cccggccagg ctccccggt gctgatctac gatgcctctt ctagagcccc tggcatcccc 180
gacagattca gcggctctgg cagcggcacc gacttcaccc tgaccatcag cagactggaa 240
cccgaggact tcgccgtgta ctactgccag cagtacagca ccagccccct gacctttggc 300
cagggcacaa aggtggagat caaa 324

<210> 373
<211> 345
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 373
gaggtgcagc tgctggaatc tggcggagga ctggtgcagc ctggcggctc tctgagactg 60
tcttgtgccg ccagcggcctt caccttcagc agctacccta tgagctgggt gcgccaggcc 120
cctggtaaag gtttggaatg ggtttctgct attggtggtt caggtggttg gagttattat 180
gccgattctg ttaagggtag attcaccatt tctagagaca actctaagaa caccttgtag 240
ttgcaaatga actccttgag agctgaagat actgctgttt attactgtgc tagatactgg 300
ccaatggatt cttgggggtca aggtactctg gtcaccgtct cctca 345

<210> 374
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 374
gagatcgtgc tgacacagag ccctggcacc ctgagcctgt ctccctggtga aagagctact 60
ttgtcttggt ggttgtctca atctgtttcc tctacttact tggcttggtg tcaacaaaaa 120
ccaggtcaag ctccaagatt attgatctac gatgcttctt ctagagcacc aggtattcca 180
gatagatttt ctggttctgg ttccggtact gatttcactt tgactatctc tagattggaa 240
ccagaagatt tcgctgttta ctactgcaa caatactctg agtggccatt gacttttggt 300
caaggtacaa aggttgaaat caaa 324

<210> 375
<211> 345
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 375
gaggtgcagc tgctggaatc tggcggagga ctggtgcagc ctggcggctc tctgagactg 60
tcttgtgccg ccagcggcctt caccttcagc agctacgcca tgaactgggt gcgccaggcc 120
cctggtaaag gtttggaatg ggtttctgct atttctgatt ctggtggttc taggtggtat 180
gccgattctg ttaagggtag attcaccatt tctagagaca actctaagaa caccttgtag 240
ttgcaaatga actccttgag agctgaagat actgctgttt attactgtac gcggtactgg 300
ccaatggata tttgggggtca aggtactctg gtcaccgtct cctca 345

<210> 376
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 376
gagatcgtgc tgacacagag ccctggcacc ctgagcctgt ctccctggtga aagagctact 60
ttgtcttggt ggttgtctca atctgtttcc tctacttact tggcttggtg tcaacaaaaa 120
ccaggtcaag ctccaagatt attgatctac gatgcttctt ctagagcacc aggtattcca 180
gatagatttt ctggttctgg ttccggtact gatttcactt tgactatctc tagattggaa 240
ccagaagatt tcgctgttta ctactgcaa caatactctg agtggccatt gacttttggt 300
caaggtacaa aggttgaaat caaa 324

<210> 377
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 377
Arg Ala Ser Gln Leu Gly Ser Phe Tyr Leu Ala
1 5 10

<210> 378
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 378
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Ser Ala Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Leu Ser Trp Ser Gly Ala Phe Asp Asn Trp Gly Gln Gly Thr
100 105 110
Leu Val Thr Val Ser Ser
115

<210> 379
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 379
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Ser Ser Ser
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Gly Ala Ser Tyr Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Gly Ser Pro Pro
85 90 95
Ser Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 380
<211> 118
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 380
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

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

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Phe Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Val Gly Thr Ser Gly Ala Phe Gly Ile Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 381
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 381
Ser Tyr Ala Met Ser

1 5

<210> 382
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 382
Gly Phe Thr Phe Ser Ser Tyr Ala Met Ser
1 5 10

<210> 383
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 383
Ser Ala Ser Gly Gly Ser
1 5

<210> 384
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 384
Ala Ile Ser Ala Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 385
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 385
Leu Ser Trp Ser Gly Ala Phe Asp Asn
1 5

<210> 386
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 386
Ser Tyr Ala Met Ser
1 5

<210> 387
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 387
Gly Phe Thr Phe Arg Ser Tyr
1 5

<210> 388
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 388
Gly Phe Thr Phe Arg Ser Tyr Ala Met Ser
1 5 10

<210> 389
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 389
Ser Gly Ser Gly Gly Ser
1 5

<210> 390
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 390
Ala Ile Ser Gly Ser Gly Gly Ser Thr Phe Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 391
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 391
Val Gly Thr Ser Gly Ala Phe Gly Ile
1 5

<210> 392
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 392
Gly Ala Ser Ser Arg Ala Tyr
1 5

<210> 393
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 393
Gln His Tyr Gly Ser Pro Pro Leu Phe Thr
1 5 10

<210> 394
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 394
Arg Ala Ser Gln Asn Val Ser Ser Ser Tyr Leu Ala
1 5 10

<210> 395
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 395
Gly Ala Ser Tyr Arg Ala Thr
1 5

<210> 396
<211> 519
<212> PRT
<213> Artificial Sequence

<220>
<223> P5AC1-A2 BCMA CAR construct with R2 epitope

<400> 396
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

```

1           2           3           4           5
His Ala Ala Arg Pro Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu
20           25           30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35           40           45

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

Gly Leu Glu Trp Val Ser Ala Ile Leu Ser Ser Gly Gly Ser Thr Tyr
65           70           75           80

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

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100          105          110

Ala Val Tyr Tyr Cys Ala Arg Tyr Trp Pro Met Asp Ile Trp Gly Gln
115          120          125

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
130          135          140

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly
145          150          155          160

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Gly
165          170          175

Gly Gln Ser Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
180          185          190

Gly Gln Ala Pro Arg Leu Leu Met Tyr Asp Ala Ser Ile Arg Ala Thr
195          200          205

Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
210          215          220

Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
225          230          235          240

Gln Gln Tyr Gln Ser Trp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
245          250          255

Glu Ile Lys Gly Ser Gly Gly Gly Gly Ser Cys Pro Tyr Ser Asn Pro
260          265          270

Ser Leu Cys Ser Gly Gly Gly Gly Ser Cys Pro Tyr Ser Asn Pro Ser
275          280          285

Leu Cys Ser Gly Gly Gly Gly Ser Thr Thr Thr Pro Ala Pro Arg Pro
290          295          300

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
305          310          315          320

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
325          330          335

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
340          345          350

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
355          360          365

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
370          375          380

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
385          390          395          400

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
405          410          415

Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
420          425          430

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg

```

435 440 445

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
450 455 460

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
465 470 475 480

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
485 490 495

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
500 505 510

Met Gln Ala Leu Pro Pro Arg
515

<210> 397
<211> 9
<212> PRT
<213> Homo sapiens

<400> 397
Cys Pro Tyr Ser Asn Pro Ser Leu Cys
1 5

<210> 398
<211> 37
<212> PRT
<213> Artificial Sequence

<220>
<223> R2 epitope

<400> 398
Gly Ser Gly Gly Gly Ser Cys Pro Tyr Ser Asn Pro Ser Leu Cys
1 5 10 15

Ser Gly Gly Gly Gly Ser Cys Pro Tyr Ser Asn Pro Ser Leu Cys Ser
20 25 30

Gly Gly Gly Gly Ser
35

<210> 399
<211> 1497
<212> DNA
<213> Artificial Sequence

<220>
<223> nucleic acid sequence encoding P5AC1-V2.1

<400> 399
atggcactgc ctgtgaccgc cctgctgctg ccactggccc tgcctgctgca cgcgcgccgg 60
ccagagggtgc agctgctgga gagcggagga ggactggtgc agccaggagg aagcctgaga 120
ctgtcctgcg ccgcctcttg cttcaccttc agctcctacg ccatgaactg ggtgaggcag 180
gcaccaggca agggactgga gtgggtgtct gccatcctgt cttagcggcg cagcacctac 240
tatgccgatt ccgtgaaggg ccgcttcaca atcagccggg acaactccaa gaataccctg 300
tacctgcaga tgaacagcct gagagccgag gatacagccg tgtactattg cgcaggtat 360
tggcccatgg acatctgggg ccagggcaca ctggtgaccg tgtcctcttg aggaggagga 420
tccggcggag gaggtctctg cggcggcggc agcgagatcg tgctgacaca gagcccaggc 480
accctgagcc tgtccccttg agagagagcc accctgtctt gtaggggcgg ccagagcgtg 540
agctcctctt acctggcctg gtatcagcag aagccaggcc aggcgccag actgctgatg 600
tacgaagcct ccacagggc aacaggcatc ccgatacggt tctctggaag cggatccgga 660
accgacttta cactgaccat ctccaggctg gagcctgagg atttcgcctg gtactattgc 720
cagcagtacc agtcttgcc actgacattt ggccagggca ccaaggtgga gatcaaggga 780
tccggaggag gaggatcttg cccttattcc aaccatctc tgtgcaccac aaccctgca 840
ccaaggccac ctacaccagc acctaccatc gcctctcagc cactgagcct gagaccgag 900
gcctgtaggc ctgcagcagg aggagcagtg cacacacggg gactggactt tgctgcgat 960

atctacatct gggcacctct ggcaggaaca tgtggcgtgc tgctgctgag cctgggtcatc 1020
accctgtact gcaagagagg caggaagaag ctgctgtata tcttcaagca gccctttatg 1080
cgccctgtgc agacaacca ggaggaggat ggctgctcct gtaggttccc agaagaggag 1140
gagggaggat gtgagctgcg cgtgaagttt tctcggagcg ccgacgcacc tgcataccag 1200
cagggacaga atcagctgta taacgagctg aatctgggcc ggagagagga gtatgacgtg 1260
ctggataaga ggaggggaag ggacccagag atgggaggca agccacggag aaagaacccc 1320
caggagggcc tgtacaatga gctgcagaag gataagatgg ccgaggccta tagcgagatc 1380
ggcatgaagg gagagaggcg ccggggcaag ggacacgacg gactgtacca gggactgtcc 1440
acagccacca aggacaccta tgatgccctg cacatgcagg ccotgccacc aaggtga 1497

<210> 400
<211> 157
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic construct RQR8 with signal sequence

<400> 400
Met Gly Thr Ser Leu Leu Cys Trp Met Ala Leu Cys Leu Leu Gly Ala
1 5 10 15

Asp His Ala Asp Ala Cys Pro Tyr Ser Asn Pro Ser Leu Cys Ser Gly
20 25 30

Gly Gly Gly Ser Glu Leu Pro Thr Gln Gly Thr Phe Ser Asn Val Ser
35 40 45

Thr Asn Val Ser Pro Ala Lys Pro Thr Thr Thr Ala Cys Pro Tyr Ser
50 55 60

Asn Pro Ser Leu Cys Ser Gly Gly Gly Gly Ser Pro Ala Pro Arg Pro
65 70 75 80

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
85 90 95

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
100 105 110

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
115 120 125

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn His Arg
130 135 140

Asn Arg Arg Arg Val Cys Lys Cys Pro Arg Pro Val Val
145 150 155

<210> 401
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 401
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Tyr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Gly Ser Pro Pro
85 90 95

Leu Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- [WO2013154760A \[0006\]](#)
- [US4616567A \[0058\]](#)
- [WO9958572A \[0059\]](#)
- [US5545807A \[0060\]](#)
- [US5545806A \[0060\]](#)
- [US5569825A \[0060\]](#)
- [US5625126A \[0060\]](#)
- [US5633425A \[0060\]](#)
- [US5681016A \[0060\]](#)
- [US5750373A \[0060\]](#)
- [US4683195A \[0131\]](#)
- [US4800159A \[0131\]](#)
- [US4754065A \[0131\]](#)
- [US4683202A \[0131\]](#)
- [WO8704462A \[0134\]](#)
- [US6037743A \[0137\]](#)
- [US5143830A \[0137\]](#)
- [WO2014039523A \[0139\]](#)
- [WO2014184741PCT \[0139\]](#)
- [WO2014191128PCT \[0139\]](#)
- [WO2014184744PCT \[0139\]](#)
- [WO2014184143PCT \[0139\]](#)
- [WO2012058458A \[0142\]](#)
- [US6352694B \[0171\]](#)
- [US6534055B \[0171\]](#)
- [US6905680B \[0171\]](#)
- [US6692964B \[0171\]](#)
- [US6658366A \[0171\]](#)
- [US6887466B \[0171\]](#)
- [US6905681B \[0171\]](#)
- [US7144575B \[0171\]](#)
- [US7067316B \[0171\]](#)
- [US7172869B \[0171\]](#)
- [US7232566B \[0171\]](#)
- [US7175843B \[0171\]](#)
- [US5883223A \[0171\]](#)
- [US6905874B \[0171\]](#)
- [US6797514B \[0171\]](#)
- [US6867041B \[0171\]](#)
- [US20060121095 \[0171\]](#)
- [WO2013153391A \[0178\]](#)
- [WO2016120216A1 \[0179\]](#)
- [WO62146825A \[0244\]](#)
- [WO62286473A \[0244\]](#)

- WO62301177A [0244]

Non-patent literature cited in the description

- **LONIAL et al.**Clinical Cancer Res., 2011, vol. 77, 61264-1277 [0002]
- **RAJKUMAR**Nature Rev. Clinical Oncol, 2011, vol. 5, 8479-491 [0002]
- **BRENNER et al.**Current Opinion in Immunology, 2010, vol. 22, 2251-257 [0003]
- **ROSENBERG et al.**Nature Reviews Cance, 2008, vol. 8, 4299-308 [0003]
- **ESHHAR et al.**Proc. Natl. Acad. Sci. USA, 1993, vol. 90, 2720-724 [0003]
- **SADELAIN et al.**Curr. Opin. Immunol, 2009, vol. 21, 2215-223 [0003]
- **SAMBROOK et al.**Molecular Cloning: A Laboratory ManualCold Spring Harbor Press19890000 [0047]
- Oligonucleotide Synthesis19840000 [0047]
- Methods in Molecular BiologyHumana Press [0047]
- Cell Biology: A Laboratory NotebookAcademic Press19980000 [0047]
- Animal Cell Culture19870000 [0047]
- **J.P. MATHERP.E. ROBERTS**Introduction to Cell and Tissue CulturePlenum Press19980000 [0047]
- Cell and Tissue Culture: Laboratory ProceduresJ. Wiley and Sons19930000 [0047]
- Methods in EnzymologyHandbook of Experimental ImmunologyAcademic Press, Inc. [0047]
- Gene Transfer Vectors for Mammalian Cells19870000 [0047]
- Current Protocols in Molecular Biology19870000 [0047]
- PCR: The Polymerase Chain Reaction19940000 [0047]
- Current Protocols in Immunology19910000 [0047]
- Short Protocols in Molecular BiologyWiley and Sons19990000 [0047]
- **C.A. JANEWAYP. TRAVERS**Immunobiology, 1997, [0047]
- **P. FINCH**Antibodies, 1997, [0047]
- Antibodies: a practical approachIRL Press19880000 [0047]
- Monoclonal antibodies: a practical approachOxford University Press20000000 [0047]
- **E. HARLOWD. LANE**Using antibodies: a laboratory manualCold Spring Harbor Laboratory Press19990000 [0047]
- The AntibodiesHarwood Academic Publishers19950000 [0047]
- **WARD et al.**Nature, 1989, vol. 341, 544-546 [0054]
- Sequences of Proteins of Immunological Interest**KABAT et al.**National Institutes of Health19910000 [0056]
- **AL-LAZIKANI et al.**J. Molec. Biol., 1997, vol. 273, 927-948 [0056]
- **KABAT et al.**Sequences of Proteins of Immunological InterestPublic Health Service, NIH19920000 [0057]
- **CHOTHIA et al.**Nature, 1989, vol. 342, 877-883 [0057]
- **MACCALLUM et al.**J. Mol. Biol., 1996, vol. 262, 732-745 [0057]
- **MAKABE et al.**Journal of Biological Chemistry, 2008, vol. 283, 1156-1166 [0057]
- **KOHLERMILSTEIN**Nature, 1975, vol. 256, 495- [0058]
- **MCCAFFERTY et al.**Nature, 1990, vol. 348, 552-554 [0058]
- **VAUGHAN et al.**Nature Biotechnology, 1996, vol. 14, 309-314 [0060]
- **SHEETS et al.**Proc. Natl. Acad. Sci., 1998, vol. 95, 6157-6162 [0060]
- **HOOGENBOOMWINTER**J. Mol. Biol., 1991, vol. 227, 381- [0060]
- **MARKS et al.**J. Mol. Biol., 1991, vol. 222, 581- [0060]
- **COLE et al.**Monoclonal Antibodies and Cancer TherapyAlan R. Liss1985000077- [0060]
- **BOERNER et al.**J. Immunol., 1991, vol. 147, 186-95 [0060]
- **JAYASENA, S.D.**Clin. Chem., 1999, vol. 45, 1628-50 [0066]
- **FELLOUSE, F.A. et al.**J. Mol. Biol., 2007, vol. 373, 4924-40 [0066]
- **KABAT. KABAT et al.**Sequences of Proteins of Immunological InterestPublic Health Service, National Institutes of Health19910000 [0072]
- **RAVETCHKINET**Ann. Rev. Immunol., 1991, vol. 9, 457-92 [0073]
- **CAPEL et al.**Immunomethods, 1994, vol. 4, 25-34 [0073]
- **DE HAAS et al.**J. Lab. Clin. Med., 1995, vol. 126, 330-41 [0073]
- **GUYER et al.**J. Immunol., 1976, vol. 117, 587- [0073]
- **KIM et al.**J. Immunol., 1994, vol. 24, 249- [0073]
- Remington's Pharmaceutical SciencesMack Publishing Co.19900000 [0083]
- Remington, The Science and Practice of PharmacyMack Publishing20050000 [0083]
- **BIRD et al.**Science, 1988, vol. 242, 423-426 [0095]
- **MAKABE et al.**J. Biol. Chem., 2007, vol. 283, 1156-1166 [0104]
- A model of evolutionary change in proteins - Matrices for detecting distant relationships**DAYHOFF, M.O.**Atlas of Protein Sequence and Structure, National Biomedical Research Foundation19780000vol. 5, 345-358 [0123]

- Unified Approach to Alignment and Phylogenesis **HEIN J.** Methods in Enzymology Academic Press, Inc. 1990 0000 vol. 183, 626-645 [\[0123\]](#)
- **HIGGINS, D.G. SHARP, P.M.** CABIOS, 1989, vol. 5, 151-153 [\[0123\]](#)
- **MYERS, E.W. MULLER W.** CABIOS, 1988, vol. 4, 11-17 [\[0123\]](#)
- **ROBINSON, E.D.** Comb. Theor., 1971, vol. 11, 105- [\[0123\]](#)
- **SANTOU, N. NES, M.** Mol. Biol. Evol., 1987, vol. 4, 406-425 [\[0123\]](#)
- **SNEATH, P.H.A. SOKAL, R.R.** Numerical Taxonomy the Principles and Practice of Numerical Taxonomy Freeman Press 1973 0000 [\[0123\]](#)
- **WILBUR, W.J. LIPMAN, D.J.** Proc. Natl. Acad. Sci. USA, 1983, vol. 80, 726-730 [\[0123\]](#)
- PCR: The Polymerase Chain Reaction Birkauser Press 1994 0000 [\[0131\]](#)
- American Type Culture Collection (ATCC) on, 2016, [\[0196\]](#)
- **ABDICHE et al.** Anal. Biochem., 2011, vol. 411, 139-151 [\[0199\]](#)
- **MYSZKA J.** Mol. Recognit., 1999, vol. 12, 279-284 [\[0200\]](#)

PATENTKRAV

1. B-celle-modningsantigen (BCMA)-specifikt kimærisk antigenreceptor (CAR) omfattende et ekstracellulært ligandbindingsdomæne, et første transmembrandomæne og et intracellulært signaleringsdomæne, hvor det ekstracellulære domæne omfatter et enkelt kæde-
5 Fv-fragment (scFv) omfattende:

(a) et variabelt tungkæde (VH)-område, der omfatter et VH-komplementaritetsbestemmende område 1 (VH-CDR1), et VH-komplementaritetsbestemmende område 2 (VH-CDR2) og et VH-komplementaritetsbestemmende område 3 (VH-CDR3), hvor VH-CDR1 omfatter aminosyresekvensen ifølge SEQ ID NO: 150, 151 eller 152; VH-CDR2
10 omfatter aminosyresekvensen ifølge SEQ ID NO: 153 eller 154; og VH-CDR3 omfatter aminosyresekvensen ifølge SEQ ID NO: 155; og

et variabelt letkæde (VL)-område, der omfatter et VL-komplementaritetsbestemmende område 1 (VL-CDR1), et VL-komplementaritetsbestemmende område 2 (VL-CDR2) og et VL-komplementaritetsbestemmende område 3 (VL-CDR3), hvor VL-CDR1 omfatter
15 aminosyresekvensen ifølge SEQ ID NO: 209; VL-CDR2 omfatter aminosyresekvensen ifølge SEQ ID NO: 221; og VL-CDR3 omfatter aminosyresekvensen ifølge SEQ ID NO: 222;

(b) et VH-område, der omfatter et VH-CDR1, et VH-CDR2 og et VH-CDR3, hvor VH-CDR1 omfatter aminosyresekvensen ifølge SEQ ID NO: 150, 151 eller 152; VH-CDR2 omfatter aminosyresekvensen ifølge SEQ ID NO: 187 eller 188; og VH-CDR3 omfatter
20 aminosyresekvensen ifølge SEQ ID NO: 155; og

et VL-område, der omfatter et VL-CDR1, et VL-CDR2 og et VL-CDR3, hvor VL-CDR1 omfatter aminosyresekvensen ifølge SEQ ID NO: 249; VL-CDR2 omfatter aminosyresekvensen ifølge SEQ ID NO: 221; og VL-CDR3 omfatter aminosyresekvensen ifølge SEQ ID NO: 225;

(c) et VH-område, der omfatter et VH-CDR1, et VH-CDR2 og et VH-CDR3, hvor VH-CDR1 omfatter aminosyresekvensen ifølge SEQ ID NO: 150, 151 eller 152; VH-CDR2 omfatter aminosyresekvensen ifølge SEQ ID NO: 165 eller 166; og VH-CDR3 omfatter
25 aminosyresekvensen ifølge SEQ ID NO: 155; og

et VL-område, der omfatter et VL-CDR1, et VL-CDR2 og et VL-CDR3, hvor VL-CDR1 omfatter aminosyresekvensen ifølge SEQ ID NO: 226; VL-CDR2 omfatter aminosyresekvensen ifølge SEQ ID NO: 221; og VL-CDR3 omfatter aminosyresekvensen ifølge SEQ ID NO: 227;
30

(d) et VH-område, der omfatter et VH-CDR1, et VH-CDR2 og et VH-CDR3, hvor VH-CDR1 omfatter aminosyresekvensen ifølge SEQ ID NO: 151, 156 eller 157; VH-CDR2 omfatter aminosyresekvensen ifølge SEQ ID NO: 159 eller 162; og VH-CDR3 omfatter aminosyresekvensen ifølge SEQ ID NO: 161; og

et VL-område, der omfatter et VL-CDR1, et VL-CDR2 og et VL-CDR3, hvor VL-CDR1 omfatter aminosyresekvensen ifølge SEQ ID NO: 251; VL-CDR2 omfatter aminosyresekvensen ifølge SEQ ID NO: 252; og VL-CDR3 omfatter aminosyresekvensen ifølge SEQ ID NO: 253;

(e) et VH-område, der omfatter et VH-CDR1, et VH-CDR2 og et VH-CDR3, hvor VH-CDR1 omfatter aminosyresekvensen ifølge SEQ ID NO: 151, 156 eller 157; VH-CDR2 omfatter aminosyresekvensen ifølge SEQ ID NO: 190 eller 191; og VH-CDR3 omfatter aminosyresekvensen ifølge SEQ ID NO: 161; og

et VL-område, der omfatter et VL-CDR1, et VL-CDR2 og et VL-CDR3, hvor VL-CDR1 omfatter aminosyresekvensen ifølge SEQ ID NO: 262; VL-CDR2 omfatter aminosyresekvensen ifølge SEQ ID NO: 252; og VL-CDR3 omfatter aminosyresekvensen ifølge SEQ ID NO: 263;

(f) et VH-område, der omfatter et VH-CDR1, et VH-CDR2 og et VH-CDR3, hvor VH-CDR1 omfatter aminosyresekvensen ifølge SEQ ID NO: 150, 151 eller 152; VH-CDR2 omfatter aminosyresekvensen ifølge SEQ ID NO: 154 eller 169; og VH-CDR3 omfatter aminosyresekvensen ifølge SEQ ID NO: 155; og

et VL-område, der omfatter et VL-CDR1, et VL-CDR2 og et VL-CDR3, hvor VL-CDR1 omfatter aminosyresekvensen ifølge SEQ ID NO: 271; VL-CDR2 omfatter aminosyresekvensen ifølge SEQ ID NO: 221; og VL-CDR3 omfatter aminosyresekvensen ifølge SEQ ID NO: 272;

(g) et VH-område, der omfatter et VH-CDR1, et VH-CDR2 og et VH-CDR3, hvor VH-CDR1 omfatter aminosyresekvensen ifølge SEQ ID NO: 129, 130 eller 131; VH-CDR2 omfatter aminosyresekvensen ifølge SEQ ID NO: 139 eller 140; og VH-CDR3 omfatter aminosyresekvensen ifølge SEQ ID NO: 134; og

et VL-område, der omfatter et VL-CDR1, et VL-CDR2 og et VL-CDR3, hvor VL-CDR1 omfatter aminosyresekvensen ifølge SEQ ID NO: 217; VL-CDR2 omfatter aminosyresekvensen ifølge SEQ ID NO: 210; og VL-CDR3 omfatter aminosyresekvensen ifølge SEQ ID NO: 216; eller

(h) et VH-område, der omfatter et VH-CDR1, et VH-CDR2 og et VH-CDR3, hvor VH-CDR1 omfatter aminosyresekvensen ifølge SEQ ID NO: 151, 156 eller 157; VH-CDR2 omfatter aminosyresekvensen ifølge SEQ ID NO: 158 eller 159; og VH-CDR3 omfatter aminosyresekvensen ifølge SEQ ID NO: 155; og

et VL-område, der omfatter et VL-CDR1, et VL-CDR2 og et VL-CDR3, hvor VL-CDR1 omfatter aminosyresekvensen ifølge SEQ ID NO: 209; VL-CDR2 omfatter aminosyresekvensen ifølge SEQ ID NO: 221; og VL-CDR3 omfatter aminosyresekvensen ifølge SEQ ID NO: 225.

2. BCMA-specifik CAR ifølge krav 1, hvor VH-området omfatter et VH-CDR1 omfattende

aminosyresekvensen vist i SEQ ID NO: 150, 151 eller 152; et VH-CDR2 omfattende aminosyresekvensen vist i SEQ ID NO: 153 eller 154; og et VH-CDR3 omfattende aminosyresekvensen vist i SEQ ID NO: 155; og et variabelt letkædeområde (VL) omfattende følgende CDR'er: et VL-CDR1 omfattende aminosyresekvensen vist i SEQ ID NO: 209; et VL-
5 CDR2 omfattende aminosyresekvensen vist i SEQ ID NO: 221 og et VL-CDR3 omfattende aminosyresekvensen vist i SEQ ID NO: 222.

3. BCMA-specifik CAR ifølge krav 1, hvor VH-området omfatter et VH-CDR1 omfattende aminosyresekvensen vist i SEQ ID NO: 151, 156 eller 157; et VH-CDR2 omfattende
10 aminosyresekvensen vist i SEQ ID NO: 158 eller 159 og et VH-CDR3 omfattende aminosyresekvensen vist i SEQ ID NO: 155; og et variabelt letkædeområde (VL) omfattende følgende CDR'er: et VL-CDR1 omfattende aminosyresekvensen vist i SEQ ID NO: 209; et VL-CDR2 omfattende aminosyresekvensen vist i SEQ ID NO: 221; og et VL-CDR3 omfattende aminosyresekvensen vist i SEQ ID NO: 225.

15 4. BCMA-specifik CAR ifølge krav 1, hvor VH-området omfatter aminosyresekvensen vist i SEQ ID NO: 112 og VL-området omfatter aminosyresekvensen vist i SEQ ID NO: 38.

5. BCMA-specifik CAR ifølge krav 1, hvor VH-området omfatter aminosyresekvensen vist
20 i SEQ ID NO: 33 og VL-området omfatter aminosyresekvensen vist i SEQ ID NO: 34.

6. BCMA-specifik CAR ifølge et hvilket som helst af kravene 1 til 5, hvor:

(a) det intracellulære signaleringsdomæne omfatter et CD3 ζ -signaleringsdomæne og/eller et 4-1BB-domæne; og/eller

25 (b) det første transmembrandomæne omfatter et CD8 α -kædetransmembrandomæne; og/eller

(c) det eller de ekstracellulære ligand-bindingsdomæne(r), det første transmembrandomæne og det eller de intracellulære signaleringsdomæne(r) er på et enkelt polypeptid.

30 7. BCMA-specifik CAR ifølge et hvilket som helst af kravene 1 til 6, der endvidere omfatter:

(a) et andet intracellulært signaleringsdomæne; hvor eventuelt det andet intracellulære signaleringsdomæne omfatter et 4-1BB-domæne; og/eller

(b) et stilkdomæne mellem det ekstracellulære ligandbindingsdomæne og det første transmembrandomæne; hvor eventuelt stilkdomænet er udvalgt fra gruppen bestående af: et humant CD8 α -hængsel, et IgG1-hængsel og et Fc γ RIII α -hængsel; og/eller

(c) en CD20-epitop; eventuelt CD20-epitopen omfatter aminosyresekvensen vist i SEQ ID NO: 397 eller SEQ ID NO: 398; og eventuelt den BCMA-specifikke CAR omfatter aminosyresekvensen vist i SEQ ID NO: 396; og/eller

(d) et andet ekstracellulært ligandbindingsdomæne, der ikke er specifikt for BCMA.

8. Polynukleotid, der omfatter en nukleinsyresekvens, der koder for den BCMA-specifikke CAR ifølge et hvilket som helst af kravene 1 til 7.

9. Ekspressionsvektor, der omfatter polynukleotidet ifølge krav 8.

10. Manipuleret immun celle, der på dens celleoverflademembran udtrykker en BCMA-specifik CAR ifølge et hvilket som helst af kravene 1 til 7.

11. Manipuleret immun celle ifølge krav 10,

(a) der endvidere omfatter en anden CAR, der ikke er specifik for BCMA; og/eller

(b) der endvidere omfatter et polynukleotid, der koder for et selvmordspolypeptid; og/eller

(c) der endvidere omfatter en disruption af ét eller flere endogene gener, hvor det endogene gen koder for TCR α , TCR β , CD52, glucocorticoidreceptor (GR), deoxycytidinkinase (dCK) eller et immunt kontrolpunktsprotein, såsom for eksempel programmeret død-1 (PD-1); og/eller

(d) hvor den immune celle er opnået fra en rask donor.

12. Manipuleret immun celle ifølge et hvilket som helst af kravene 10 til 11 til anvendelse som et lægemiddel.

13. Manipuleret immun celle til anvendelse ifølge krav 12, hvor lægemidlet er til anvendelse i behandling af en B-celle-relateret cancer udvalgt fra gruppen bestående af multipelt myelom, ondartet plasmacelleneoplasma, Hodgkins lymfom, nodulært lymfocytdomineret Hodgkins lymfom, Kahlers sygdom og myelomatose, plasmacelleleukæmi, plasmacytom, prolymfocytisk B-celleleukæmi, hårcelleleukæmi, ikke-Hodgkins B-cellelymfom (NHL), akut myeloid leukæmi

(AML), kronisk lymfocytisk leukæmi (CLL), akut lymfocytisk leukæmi (ALL), kronisk myeloid leukæmi (CML), follikulært lymfom, marginalzonelymfom, mantlecellelymfom, storcellet lymfom, precursor B-lymfoblastisk lymfom, myeloid leukæmi, diffust storcellet B-cellelymfom, mucosa-associeret lymfevævslymfom, småcellet lymfocytisk lymfom, Burkitt lymfom, primært storcellet mediastinalt (thymus-) B-cellelymfom, lymfoplasmacytisk lymfom, Waldenströms makroglobulinæmi, nodalt marginalzone B-cellelymfom, marginalzone miltlymfom, intravaskulært storcellet B-cellelymfom, primært effusionslymfom, lymfomatoid granulomatose, T-celle/histiocytrigt storcellet B-cellelymfom, primært lymfom i centralnervesystem, primært kutant diffust storcellet B-cellelymfom (underekstremitetstype), EBV-positivt diffust storcellet B-cellelymfom hos ældre, diffust storcellet B-cellelymfom forbundet med inflammation, ALK-positivt storcellet B-cellelymfom, plasmablastisk lymfom, storcellet B-cellelymfom, der opstår i HHV8-associeret multicentrisk Castlemans sygdom, B-cellelymfom ikke-klassificeret med karakteristika mellem diffust storcellet B-cellelymfom og Burkitt lymfom, B-cellelymfom ikke-klassificeret med karakteristika mellem diffust storcellet B-cellelymfom og klassisk Hodgkin lymfom og et andet B-cellerelateret lymfom.

14. Farmaceutisk sammensætning, der omfatter den manipulerede immune celle ifølge et hvilket som helst af kravene 10 til 11.

15. Manipuleret immun celle ifølge krav 10 til 11 eller farmaceutisk sammensætning ifølge krav 14 til anvendelse i hæmning af tumorvækst eller -progression hos et individ, der har ondartede celler, som udtrykker BCMA, hæmning af metastase for ondartede celler, der udtrykker BCMA, hos et individ, eller induktion af tumorregression hos et individ, der har ondartede celler, som udtrykker BCMA; eventuelt hvor anvendelsen endvidere omfatter administration af en nukleosidanalogterapi, fludarabin, eller clofarabin til individet.

16. Fremgangsmåde *in vitro* til manipulering af en immun celle, der udtrykker en BCMA-specifik CAR, hvilken fremgangsmåde omfatter:

- a. tilvejebringelse af en immun celle;
- b. indføring i cellen af mindst ét polynukleotid, der koder for den BCMA-specifikke CAR ifølge et hvilket som helst af kravene 1 til 7; og
- c. eventuelt indføring i cellen af mindst ét polynukleotid, der koder for en CAR, der ikke er specifik for BCMA.

17. BCMA-specifik CAR ifølge krav 1, hvor den BCMA-specifikke CAR omfatter aminosyresekvensen vist i SEQ ID NO: 344.

18. BCMA-specifik CAR ifølge krav 17, der endvidere omfatter en CD20-epitop.

5

19. BCMA-specifik CAR ifølge krav 18, hvor CD20-epitopen omfatter aminosyresekvensen vist i SEQ ID NO: 397 eller SEQ ID NO: 398.

DRAWINGS

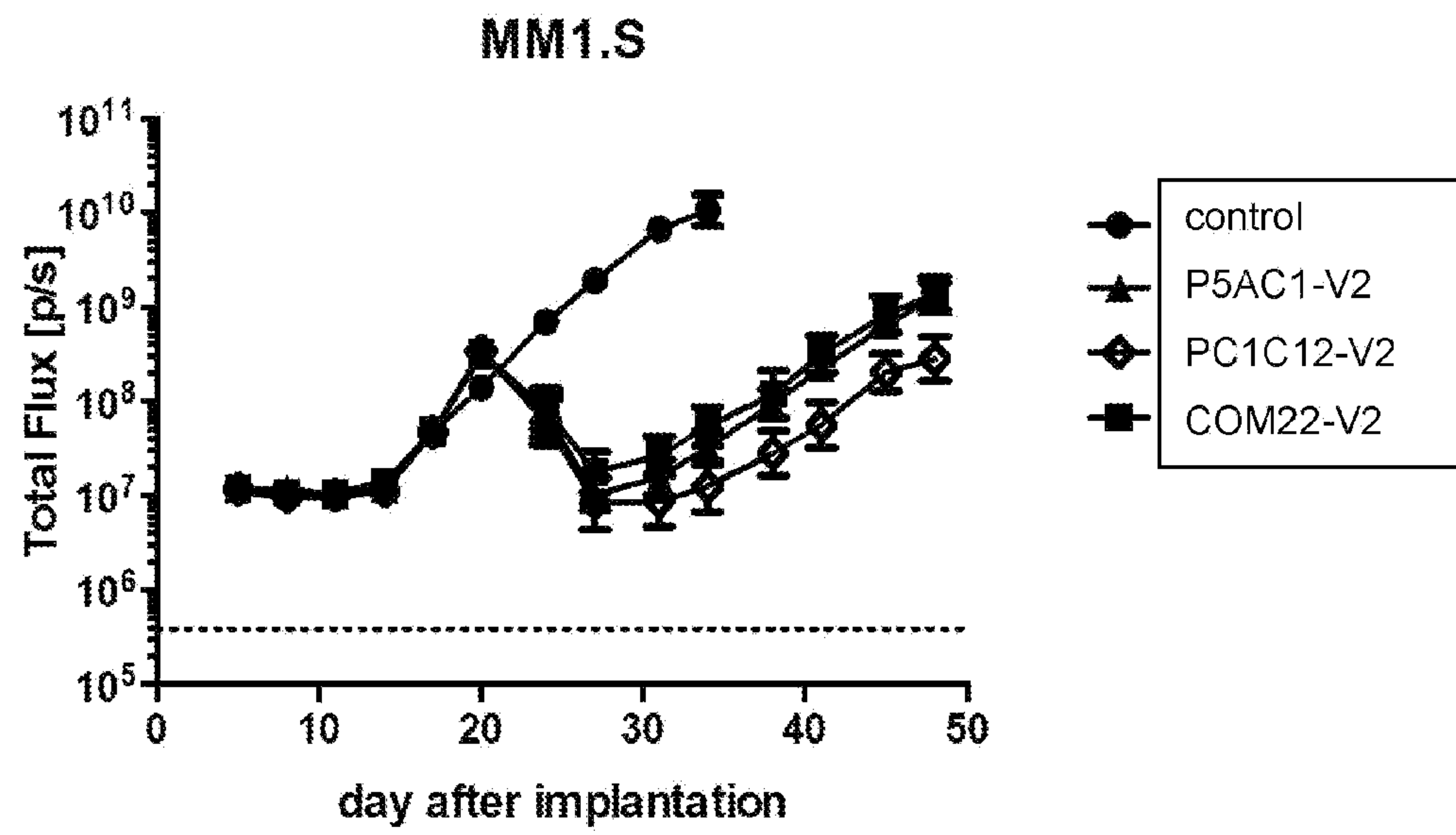


FIG. 1

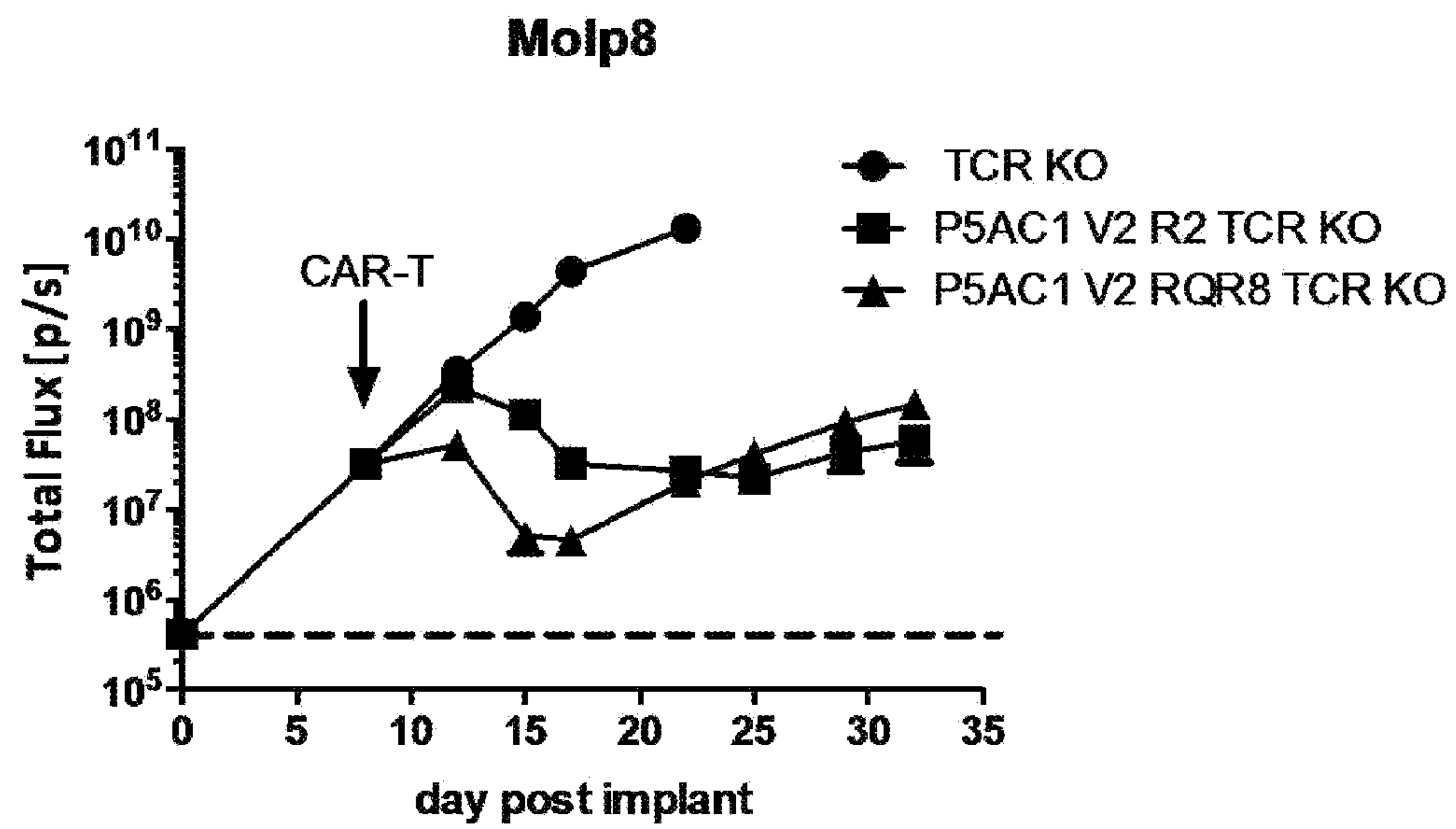


FIG. 2