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Economic Development Canada
Canadian Intellectual Property Office

CA 3106653 A1 2020/01/23

(21) 3 106 653

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) **A1**

(86) **Date de dépôt PCT/PCT Filing Date**: 2019/07/17
(87) **Date publication PCT/PCT Publication Date**: 2020/01/23
(85) **Entrée phase nationale/National Entry**: 2021/01/15
(86) **N° demande PCT/PCT Application No.**: US 2019/042245
(87) **N° publication PCT/PCT Publication No.**: 2020/018695
(30) **Priorité/Priority**: 2018/07/18 (US62/700,178)

(51) **Cl.Int./Int.Cl.** *C07K 16/30* (2006.01), *A61K 39/00* (2006.01), *A61P 35/00* (2006.01), *C07K 14/725* (2006.01)
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(54) **Titre** : RECEPTEURS CHIMERIQUES DE STEAP1 ET PROCEDES D'UTILISATION ASSOCIEES
(54) **Title**: CHIMERIC RECEPTORS TO STEAP1 AND METHODS OF USE THEREOF

(57) **Abrégé/Abstract**:

Antigen binding molecules, chimeric receptors, and engineered immune cells to STEAP1 are disclosed in accordance with the invention. The invention further relates to vectors, compositions, and methods of treatment and/or detection using the STEAP1 antigen binding molecules and engineered immune cells.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 January 2020 (23.01.2020)

(10) International Publication Number
WO 2020/018695 A1

(51) **International Patent Classification:**
C07K 16/30 (2006.01) *C07K 14/725* (2006.01)
A61K 39/00 (2006.01) *A61P 35/00* (2006.01)

(21) **International Application Number:**
PCT/US2019/042245

(22) **International Filing Date:**
17 July 2019 (17.07.2019)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
62/700,178 18 July 2018 (18.07.2018) US

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *with international search report (Art. 21(3))*

WO 2020/018695 A1

(54) Title: CHIMERIC RECEPTORS TO STEAP1 AND METHODS OF USE THEREOF

(57) **Abstract:** Antigen binding molecules, chimeric receptors, and engineered immune cells to STEAP1 are disclosed in accordance with the invention. The invention further relates to vectors, compositions, and methods of treatment and/or detection using the STEAP1 antigen binding molecules and engineered immune cells.

CHIMERIC RECEPTORS TO STEAP1 AND METHODS OF USE THEREOF

BACKGROUND OF THE INVENTION

[0001] Prostate cancer is the most frequently diagnosed cancer in men aside from skin cancer. With an estimated 28,170 deaths in 2012, prostate cancer is the second-leading cause of cancer death in men. Hormonal therapy, chemotherapy, radiation, or a combination of these treatments is used to treat more advanced disease. Despite the above identified advances in prostate cancer therapy, there is a great need for additional therapeutic agents capable of effectively inhibiting prostate cancer progression including in androgen receptor inhibitor naive prostate cancer.

[0002] Engineered immune cells have been shown to possess desired qualities in therapeutic treatments, particularly in oncology. Two main types of engineered immune cells are those that contain chimeric antigen receptors (termed "CARs" or "CAR-Ts") and T-cell receptors ("TCRs"). These engineered cells are engineered to endow them with antigen specificity while retaining or enhancing their ability to recognize and kill a target cell. Chimeric antigen receptors may comprise, for example, (i) an antigen-specific component ("antigen binding molecule"), (ii) one or more costimulatory domains, and (iii) one or more activating domains. Each domain may be heterogeneous, that is, comprised of sequences derived from different protein chains. Chimeric antigen receptor-expressing immune cells (such as T cells) may be used in various therapies, including cancer therapies. It will be appreciated that costimulating polypeptides as defined herein may be used to enhance the activation of CAR-expressing cells against target antigens, and therefore increase the potency of adoptive immunotherapy.

[0003] T cells can be engineered to possess specificity to one or more desired targets. For example, T cells can be transduced with DNA or other genetic material encoding an antigen binding molecule, such as one or more single chain variable fragment ("scFv") of an antibody, in conjunction with one or more signaling molecules, and/or one or more activating domains, such as CD3 zeta.

[0004] In addition to the CAR-T cells' ability to recognize and destroy the targeted cells, successful T cell therapy benefits from the CAR-T cells' ability to persist and maintain the ability to proliferate in response to antigen.

[0005] A need exists to identify novel and improved therapies for treating STEAP1 related diseases and disorders.

SUMMARY OF THE INVENTION

[0006] The invention relates to engineered immune cells (such as CARs or TCRs), antigen binding molecules (including but not limited to, antibodies, scFvs, heavy and/or light chains, and CDRs of these antigen binding molecules) with specificity to STEAP1.

[0007] Chimeric antigen receptors of the invention typically comprise: (i) a STEAP1 specific antigen binding molecule, (ii) one or more costimulatory domain, and (iii) one or more activating domain. It will be appreciated that each domain may be heterogeneous, thus comprised of sequences derived from different protein chains.

[0008] In some embodiments, the invention relates to a chimeric antigen receptor comprising an antigen binding molecule that specifically binds to STEAP1, wherein the antigen binding molecule comprises at least one of: (a) a variable heavy chain CDR1 comprising an amino acid sequence differing from that of SEQ ID NOs:89, 99, 109, 119, 129, or 139 by not more than 3, 2, 1, or 0 amino acid residues; (b) a variable heavy chain CDR2 comprising an amino acid sequence differing from that of SEQ ID NOs:90, 100, 110, 120, 130, or 140 by not more than 3, 2, 1, or 0 amino acid residues; (c) a variable heavy chain CDR3 comprising an amino acid sequence differing from that of SEQ ID NOs:91, 101, 111, 121, 131, or 141 by not more than 3, 2, 1, or 0 amino acid residues; (d) a variable light chain CDR1 comprising an amino acid sequence differing from that of SEQ ID NOs:94, 104, 114, 124, 134, or 14 by not more than 3, 2, 1, or 0 amino acid residues; (e) a variable light chain CDR2 comprising an amino acid sequence differing from that of SEQ ID NOs:95, 105, 115, 125, 135, or 145 by not more than 3, 2, 1, or 0 amino acid residues; (f) a variable light chain CDR3 comprising an amino acid sequence differing from that of SEQ IDs:96, 106, 116, 126, 136, or 146 by not more than 3, 2, 1, or 0 amino acid residues.

[0009] In other embodiments, the chimeric antigen receptor further comprises at least one costimulatory domain. In further embodiments, the chimeric antigen receptor further comprises at least one activating domain.

[0010] In certain embodiments the costimulatory domain is a signaling region of CD28, CD28T, OX-40, 4-1BB/CD137, CD2, CD7, CD27, CD30, CD40, Programmed Death-1 (PD-1), inducible T cell costimulator (ICOS), lymphocyte function-associated antigen-1 (LFA-1, CDl-la/CD18), CD3 gamma, CD3 delta, CD3 epsilon, CD247, CD276 (B7-H3), LIGHT, (TNFSF14), NKG2C, Ig alpha (CD79a), DAP-10, Fc gamma receptor, MHC class 1 molecule, TNF receptor proteins, an Immunoglobulin protein, cytokine receptor, integrins, Signaling Lymphocytic Activation Molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, ICAM-1, B7-H3, CDS, ICAM-1, GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL-2R beta, IL-2R gamma, IL-7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CDl ld, ITGAE, CD103, ITGAL, CDl la, LFA-1, ITGAM, CDl lb, ITGAX, CDl lc, ITGBl, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRT AM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Lyl08), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, a ligand that specifically binds with CD83, or any combination thereof.

[0011] In some embodiments, the costimulatory domain is derived from 4-1BB. In other embodiments, the costimulatory domain is derived from OX40. See also Hombach *et al.*, Oncoimmunology. 2012 Jul. 1; 1(4): 458–466. In still other embodiments, the costimulatory domain comprises ICOS as described in Guedan *et al.*, August 14, 2014; Blood: 124 (7) and Shen *et al.*, Journal of Hematology & Oncology (2013) 6:33. In still other embodiments, the costimulatory domain comprises CD27 as described in Song *et al.*, Oncoimmunology. 2012 Jul. 1;1(4): 547–549.

[0012] In certain embodiments, the CD28 costimulatory domain comprises SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, or SEQ ID NO:8. In additional embodiments, the CD8 costimulatory domain comprises SEQ ID NO:14. In further embodiments, the activating domain comprises CD3, CD3 zeta, or CD3 zeta having the sequence set forth in SEQ ID NO:10.

[0013] In other embodiments, the invention relates to a chimeric antigen receptor wherein the costimulatory domain comprises SEQ ID NO:2 and the activating domain comprises SEQ ID NO:10.

[0014] The invention further relates to polynucleotides encoding the chimeric antigen receptors, and vectors comprising the polynucleotides. The vector can be, for example, a retroviral vector, a DNA vector, a plasmid, a RNA vector, an adenoviral vector, an adenovirus associated vector, a lentiviral vector, or any combination thereof. The invention further relates to immune cells comprising the vectors. In some embodiments, the lentiviral vector is a pGAR vector.

[0015] Exemplary immune cells include, but are not limited to T cells, tumor infiltrating lymphocytes (TILs), NK cells, TCR-expressing cells, dendritic cells, or NK-T cells. The T cells can be autologous, allogeneic, or heterologous. In other embodiments, the invention relates to pharmaceutical compositions comprising the immune cells of described herein.

[0016] In certain embodiments, the invention relates to antigen binding molecules (and chimeric antigen receptors comprising these molecules) comprising at least one of:

(a) a VH region differing from the amino acid sequence of the VH region of 2F3 by no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues and a VL region differing from the amino acid sequence of the VL region of 2F3 by no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues;

(b) a VH region differing from the amino acid sequence of the VH region of 11C2 by no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues and a VL region differing from the amino acid sequence of the VL region of 11C2 by no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues;

(c) a VH region differing from the amino acid sequence of the VH region of 1A1 by no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues and a VL region differing from the amino acid sequence of the VL region of 1A1 by no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues;

(d) a VH region differing from the amino acid sequence of the VH region of 7A4 by no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues and a VL region differing from the amino acid sequence of the VL region of 7A4 by no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues; and

(e) a VH region differing from the amino acid sequence of the VH region of 7A5 by no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues and a VL region differing from the amino acid sequence of the VL region of 7A5 by no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues;

(f) a VH region differing from the amino acid sequence of the VH region of 14C1 by no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues and a VL region differing from the amino acid sequence of the VL region of 14C1 by no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues;

and wherein the VH and VL region or regions are linked by at least one linker.

[0017] In other embodiments, the invention relates to antigen binding molecules (and chimeric antigen receptors comprising these molecules) wherein the linker comprises at least one of the scFv G4S linker and the scFv Whitlow linker.

[0018] In other embodiments, the invention relates to vectors encoding the polypeptides of the invention and to immune cells comprising these polypeptides. Preferred immune cells include T cells, tumor infiltrating lymphocytes (TILs), NK cells, TCR-expressing cells, dendritic cells, or NK-T cells. The T cells may be autologous, allogeneic, or heterologous.

[0019] In other embodiments, the invention relates to isolated polynucleotides encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to STEAP1, wherein the antigen binding molecule comprises a variable heavy (V_H) chain CDR3 comprising an amino acid sequence of SEQ ID NO:19 or SEQ ID NO:27. The polynucleotides may further comprise an activating domain. In preferred embodiments, the activating domain is CD3, more preferably CD3 zeta, more preferably the amino acid sequence set forth in SEQ ID NO:9.

[0020] In other embodiments, the invention includes a costimulatory domain, such as CD28, CD28T, OX40, 4-1BB/CD137, CD2, CD3 (alpha, beta, delta, epsilon, gamma, zeta), CD4, CD5, CD7, CD9, CD16, CD22, CD27, CD30, CD 33, CD37, CD40, CD 45, CD64, CD80, CD86, CD134, CD137, CD154, PD-1, ICOS, lymphocyte function-associated antigen-1 (LFA-1 (CDl la/CD18), CD247, CD276 (B7-H3), LIGHT (tumor necrosis factor superfamily member 14; TNFSF14), NKG2C, Ig alpha (CD79a), DAP-10, Fc gamma receptor, MHC class I molecule, TNF, TNFr, integrin, signaling lymphocytic activation molecule, BTLA, Toll ligand receptor, ICAM-1, B7-H3, CDS, ICAM-1, GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL-2R beta, IL-2R gamma, IL-7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CDl-ld, ITGAE, CD103, ITGAL, CDl-la, LFA-1, ITGAM, CDl-lb, ITGAX, CDl-lc, ITGBl, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRT AM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Lyl08), SLAM (SLAMF1,

CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, CD83 ligand, or fragments or combinations thereof. Preferred costimulatory domains are recited hereinbelow.

[0021] The invention further relates to methods of treating a disease or disorder in a subject in need thereof comprising administering to the subject the antigen binding molecules, the CARs, TCRs, polynucleotides, vectors, cells, or compositions according to the invention. Suitable diseases for treatment include, but are not limited to, prostate cancer, including metastatic castration resistant prostate cancer.

BRIEF DESCRIPTION OF THE FIGURES

[0022] FIG. 1, depicts flow cytometric analysis of STEAP1 cell surface expression on human cell lines.

[0023] FIG. 2, depicts CAR expression in primary human T cells electroporated with mRNA encoding for various CARs.

[0024] FIG. 3, depicts cytolytic activity of electroporated CAR T cells against multiple cell lines.

[0025] FIG. 4, comprising of FIGS. 3A, and 3B, depicts IFNγ, IL-2, and TNFα production by electroporated CAR T cells.

[0026] FIG. 5, depicts CAR expression in lentivirus transduced primary human T cells from two healthy donors.

[0027] FIG. 6, depicts the pGAR vector map.

DETAILED DESCRIPTION OF THE INVENTION

[0028] It will be appreciated that chimeric antigen receptors (CARs or CAR-Ts) and T cell receptors (TCRs) are genetically engineered receptors. These engineered receptors can be readily inserted into and expressed by immune cells, including T cells in accordance with techniques known in the art. With a CAR, a single receptor can be programmed to both recognize a specific antigen and, when bound to that antigen, activate the immune cell to attack and destroy the cell bearing that antigen. When these antigens exist on tumor cells, an immune cell that expresses the CAR can target and kill the tumor cell.

[0029] CARs can be engineered to bind to an antigen (such as a cell-surface antigen) by incorporating an antigen binding molecule that interacts with that targeted antigen. Preferably, the antigen binding molecule is an antibody fragment thereof, and more preferably one or more single chain antibody fragment ("scFv"). An scFv is a single chain antibody fragment having the variable regions of the heavy and light chains of an antibody linked together. See U.S. Patent Nos. 7,741,465, and 6,319,494 as well as Eshhar *et al.*, Cancer Immunol Immunotherapy (1997) 45: 131-136. An scFv retains the parent antibody's ability to specifically interact with target antigen. scFvs are preferred for use in chimeric antigen receptors because they can be engineered to be expressed as part of a single chain along with the other CAR components. *Id.* See also Krause *et al.*, J. Exp. Med., Volume 188, No. 4, 1998 (619–626); Finney *et al.*, *Journal of Immunology*, 1998, 161: 2791–2797. It will be appreciated that the antigen binding molecule is typically contained within the extracellular portion of the CAR such that it is capable of recognizing and binding to the antigen of interest. Bispecific and multispecific CARs are contemplated within the scope of the invention, with specificity to more than one target of interest.

[0030] **Costimulatory Domains**. Chimeric antigen receptors may incorporate costimulatory (signaling) domains to increase their potency. See U.S. Patent Nos. 7,741,465, and 6,319,494, as well as Krause *et al.* and Finney *et al.* (supra), Song *et al.*, Blood 119:696-706 (2012); Kalos *et al.*, Sci Transl. Med. 3:95 (2011); Porter *et al.*, N. Engl. J. Med. 365:725-33 (2011), and Gross *et al.*, Annu. Rev. Pharmacol. Toxicol. 56:59–83 (2016). For example, CD28 is a costimulatory protein found naturally on T-cells. The complete native amino acid sequence of CD28 is described in NCBI Reference Sequence: NP_006130.1. The complete native CD28 nucleic acid sequence is described in NCBI Reference Sequence: NM_006139.1.

[0031] Certain CD28 domains have been used in chimeric antigen receptors. In one embodiment, a novel CD28 extracellular domain, termed "CD28T", can be used, and has been unexpectedly found to provide certain benefits when utilized in a CAR construct.

[0032] The nucleotide sequence of the CD28T molecule, including the extracellular CD28T domain, and the CD28 transmembrane and intracellular domains is set forth in SEQ ID NO:1:

[0033] CTTGATAATGAAAAGTCAAACGGAACAATCATTCACGTGAAGGGCAA
GCACCTCTGTCCGTCACCCTTGTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTC
GTAGTGGGTGGAGTCCTCGCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCT

TCTGGGTTAGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGAATATGACTC
CACGCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATT
TCGCTGCCTATCGGAGC

[0034] The corresponding amino acid sequence is set forth in SEQ ID NO:2:

[0035] LDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTV AFIIFWVRSK RSRLLHSDYM NMTPRRPGPT RKHYQPYAPP RDFAAYRS

[0036] The nucleotide sequence of the extracellular portion of CD28T is set forth in SEQ ID NO:3:

[0037] CTTGATAATGAAAAGTCAAACGGAACAATCATTCACGTGAAGGGCAA GCACCTCTGTCCGTCACCCTTGTTCCCTGGTCCATCCAAGCCA

[0038] The corresponding amino acid sequence of the CD28T extracellular domain is set forth in SEQ ID NO:4: LDNEKSNGTI IHVKGKHLCP SPLFPGPSKP

[0039] The nucleotide sequence of the CD28 transmembrane domain is set forth in SEQ ID NO:5):

[0040] TTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCGCTTGTTACTCTCTGC TCGTCACCGTGGCTTTTATAATCTTCTGGGTT

[0041] The amino acid sequence of the CD28 transmembrane domain is set forth in

[0042] SEQ ID NO:6: FWVLVVVGGV LACYSLLVTV AFIIFWV

[0043] The nucleotide sequence of the CD28 intracellular signaling domain is set forth in SEQ ID NO:7:

[0044] AGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGAATATGACT CCACGCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCACCACCTAGAGA TTTCGCTGCCTATCGGAGC

[0045] The amino acid sequence of the CD28 intracellular signaling domain is set forth in SEQ ID NO:8: RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS

[0046] Additional CD28 sequences suitable for use in the invention include the CD28 nucleotide sequence set forth in SEQ ID NO:11:

[0047] ATTGAGGTGATGTATCCACCGCCTTACCTGGATAACGAAAAGAGTAAC GGTACCATCATTCACGTGAAAGGTAAACACCTGTGTCCTTCTCCCCTCTTCCCCGGGC CATCAAAGCCC

[0048] The corresponding amino acid sequence is set forth in SEQ ID NO:12:

[0049] IEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKP

[0050] Other suitable extracellular or transmembrane sequences can be derived from CD8. The nucleotide sequence of a suitable CD8 extracellular and transmembrane domain is set forth in SEQ ID NO:13:

[0051] GCTGCAGCATTGAGCAACTCAATAATGTATTTTAGTCACTTTGTACCAG TGTTCTTGCCGGCTAAGCCTACTACCACACCCGCTCCACGGCCACCTACCCCAGCTC CTACCATCGCTTCACAGCCTCTGTCCCTGCGCCCAGAGGCTTGCCGACCGGCCGCAG GGGGCGCTGTTCATACCAGAGGACTGGATTTCGCCTGCGATATCTATATCTGGGCAC CCCTGGCCGGAACCTGCGGCGTACTCCTGCTGTCCCTGGTCATCACGCTCTATTGTAA TCACAGGAAC

[0052] The corresponding amino acid sequence is set forth in SEQ ID NO:14:

[0053] AAALSNSIMYFSHFVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPA AGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCNHRN

[0054] Other suitable intracellular signaling sequences can be derived from 41-BB. The nucleotide sequence of a suitable 41-BB intracellular signaling domain is set forth in SEQ ID NO:15:

[0055] CGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAGCTGCTGTACATTTTC AAACAGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGACGGCTGCTCCTG CCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTG

[0056] The corresponding amino acid sequence is set forth in SEQ ID NO:16:

[0057] RFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL

[0058] Suitable costimulatory domains within the scope of the invention can be derived from, among other sources, CD28, CD28T, OX40, 4-1BB/CD137, CD2, CD3 (alpha, beta, delta, epsilon, gamma, zeta), CD4, CD5, CD7, CD9, CD16, CD22, CD27, CD30, CD 33, CD37, CD40, CD 45, CD64, CD80, CD86, CD134, CD137, CD154, PD-1, ICOS, lymphocyte function-associated antigen-1 (LFA-1 (CDl la/CD18), CD247, CD276 (B7-H3), LIGHT (tumor necrosis factor superfamily member 14; TNFSF14), NKG2C, Ig alpha (CD79a), DAP-10, Fc gamma receptor, MHC class I molecule, TNF, TNFr, integrin, signaling lymphocytic activation molecule, BTLA, Toll ligand receptor, ICAM-1, B7-H3, CDS, ICAM-1, GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL-2R beta, IL-2R gamma, IL-7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CDl-ld, ITGAE, CD103, ITGAL, CDl-la, LFA-1, ITGAM, CDl-lb, ITGAX, CDl-lc, ITGBl, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRT AM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Lyl08), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, CD83 ligand, or fragments or combinations thereof.

[0059] **Activating Domains**.

[0060] CD3 is an element of the T cell receptor on native T cells, and has been shown to be an important intracellular activating element in CARs. In a preferred embodiment, the CD3 is CD3 zeta, the nucleotide sequence of which is set forth in SEQ ID NO:9:

[0061] AGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGC
CAGAACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTT
GGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAAC
CCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCT
GAAATAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACC
AGGGACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGC
CACCTAGG

[0062] The corresponding amino acid of intracellular CD3 zeta is set forth in SEQ ID NO:10:

[0063] RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGK
PR
RKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM
QALPPR

DOMAIN ORIENTATION

[0064] Structurally, it will appreciated that these domains correspond to locations relative to the immune cell. Thus, these domains can be part of the (i) "hinge" or extracellular (EC) domain (EC), (ii) the transmembrane (TM) domain, and/or (iii) the intracellular (cytoplasmic) domain (IC). The intracellular component frequently comprises in part a member of the CD3 family, preferably CD3 zeta, which is capable of activating the T cell upon binding of the antigen binding molecule to its target. In one embodiment, the hinge domain is typically comprised of at least one costimulatory domain as defined herein.

[0065] It will also be appreciated that the hinge region may also contain some or all of a member of the immunoglobulin family such as IgG1, IgG2, IgG3, IgG4, IgA, IgD, IgE, IgM, or fragment thereof.

[0066] Exemplary CAR constructs in accordance with the invention are set forth in Table 1.

Table 1

Construct Name	scFv	Costimulatory Domain	Activating Domain
2F3-CD28T-CD28-41BB	2F3	CD28T, 4-1BB	CD3 zeta
2F3-CD28T-CD28	2F3	CD28T	CD3 zeta
2F3-CD28T-41BB	2F3	4-1BB	CD3 zeta
2F3-C8K-CD28	2F3	CD28T	CD3 zeta
2F3-C8K-41BB	2F3	4-1BB	CD3 zeta
11C2-CD28T-CD28-41BB	11C2	CD28T, 4-1BB	CD3 zeta
11C2-CD28T-CD28	11C2	CD28T	CD3 zeta

11C2-CD28T-41BB	11C2	4-1BB	CD3 zeta
11C2-C8K-CD28	11C2	CD28T	CD3 zeta
11C2-C8K-41BB	11C2	4-1BB	CD3 zeta
1A1-CD28T-CD28-41BB	1A1	CD28T, 4-1BB	CD3 zeta
1A1-CD28T-CD28	1A1	CD28T	CD3 zeta
1A1-CD28T-41BB	1A1	4-1BB	CD3 zeta
1A1-C8K-CD28	1A1	CD28T	CD3 zeta
1A1-C8K-41BB	1A1	4-1BB	CD3 zeta
7A4-CD28T-CD28-41BB	7A4	CD28T, 4-1BB	CD3 zeta
7A4-CD28T-CD28	7A4	CD28T	CD3 zeta
7A4-CD28T-41BB	7A4	4-1BB	CD3 zeta
7A4-C8K-CD28	7A4	CD28T	CD3 zeta
7A4-C8K-41BB	7A4	4-1BB	CD3 zeta
7A5-CD28T-CD28-41BB	7A5	CD28T, 4-1BB	CD3 zeta
7A5-CD28T-CD28	7A5	CD28T	CD3 zeta
7A5-CD28T-41BB	7A5	4-1BB	CD3 zeta
7A5-C8K-CD28	7A5	CD28T	CD3 zeta

7A5-C8K-41BB	7A5	4-1BB	CD3 zeta
14C1-CD28T-CD28-41BB	14C1	CD28T, 4-1BB	CD3 zeta
14C1-CD28T-CD28	14C1	CD28T	CD3 zeta
14C1-CD28T-41BB	14C1	4-1BB	CD3 zeta
14C1-C8K-CD28	14C1	CD28T	CD3 zeta
14C1-C8K-41BB	14C1	4-1BB	CD3 zeta

DOMAINS RELATIVE TO THE CELL

[0067] It will be appreciated that relative to the cell bearing the receptor, the engineered T cells of the invention comprise an antigen binding molecule (such as an scFv), an extracellular domain (which may comprise a “hinge” domain), a transmembrane domain, and an intracellular domain. The intracellular domain comprises at least in part an activating domain, preferably comprised of a CD3 family member such as CD3 zeta, CD3 epsilon, CD3 gamma, or portions thereof. It will further be appreciated that the antigen binding molecule (e.g., one or more scFvs) is engineered such that it is located in the extracellular portion of the molecule/construct, such that it is capable of recognizing and binding to its target or targets.

[0068] **Extracellular Domain.** The extracellular domain is beneficial for signaling and for an efficient response of lymphocytes to an antigen. Extracellular domains of particular use in this invention may be derived from (*i.e.*, comprise) CD28, CD28T, CD8, OX-40, 4-1BB/CD137, CD2, CD7, CD27, CD30, CD40, programmed death-1 (PD-1), inducible T cell costimulator (ICOS), lymphocyte function-associated antigen-1 (LFA-1, CDl-la/CD18), CD3 gamma, CD3 delta, CD3 epsilon, CD247, CD276 (B7-H3), LIGHT, (TNFSF14), NKG2C, Ig alpha (CD79a), DAP-10, Fc gamma receptor, MHC class 1 molecule, TNF receptor proteins, an Immunoglobulin protein, cytokine receptor, integrins, Signaling Lymphocytic Activation Molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, ICAM-1, B7-H3, CDS, ICAM-1, GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL-2R beta, IL-2R gamma, IL-7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CDl ld, ITGAE, CD103, ITGAL, CDl la, LFA-1, ITGAM, CDl lb, ITGAX, CDl lc, ITGBl, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRT AM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Lyl08), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, a ligand that specifically binds with CD83, or any combination thereof. The extracellular domain may be derived either from a natural or from a synthetic source.

[0069] As described herein, extracellular domains often comprise a hinge portion. This is a portion of the extracellular domain, sometimes referred to as a “spacer” region. A variety of hinges can be employed in accordance with the invention, including costimulatory molecules as discussed above, as well as immunoglobulin (Ig) sequences or other suitable molecules to achieve the desired special distance from the target cell. In some embodiments, the entire extracellular region comprises a hinge region. In some embodiments, the hinge region comprises CD28T, or the EC domain of CD28.

[0070] **Transmembrane Domain.** The CAR can be designed to comprise a transmembrane domain that is fused to the extracellular domain of the CAR. It can similarly be fused to the intracellular domain of the CAR. In one embodiment, the transmembrane domain that naturally is associated with one of the domains in a CAR is used. In some instances, the transmembrane domain can be selected or modified by amino acid substitution to avoid binding of such domains to the transmembrane domains of the same or different surface membrane proteins to minimize interactions with other members of the receptor complex. The transmembrane domain may be derived either from a natural or from a synthetic source. Where the source is natural, the domain may be derived from any membrane-bound or transmembrane protein. Transmembrane regions of particular use in this invention may be derived from (i.e. comprise) CD28, CD28T, CD8, OX-40, 4-1BB/CD137, CD2, CD7, CD27, CD30, CD40, programmed death-1 (PD-1), inducible T cell costimulator (ICOS), lymphocyte function-associated antigen-1 (LFA-1, CDl-la/CD18), CD3 gamma, CD3 delta, CD3 epsilon, CD247, CD276 (B7-H3), LIGHT, (TNFSF14), NKG2C, Ig alpha (CD79a), DAP-10, Fc gamma receptor, MHC class 1 molecule, TNF receptor proteins, an Immunoglobulin protein, cytokine receptor, integrins, Signaling Lymphocytic Activation Molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, ICAM-1, B7-H3, CDS, ICAM-1, GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL-2R beta, IL-2R gamma, IL-7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CDl ld, ITGAE, CD103, ITGAL, CDl la, LFA-1, ITGAM, CDl lb, ITGAX, CDl lc, ITGBl, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRT AM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Lyl08), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, a ligand that specifically binds with CD83, or any combination thereof.

[0071] Optionally, short linkers may form linkages between any or some of the extracellular, transmembrane, and intracellular domains of the CAR.

[0072] In one embodiment, the transmembrane domain in the CAR of the invention is a CD8 transmembrane domain. In one embodiment, the CD8 transmembrane domain comprises the transmembrane portion of the nucleic acid sequence of SEQ ID NO:13. In another embodiment, the CD8 transmembrane domain comprises the nucleic acid sequence that encodes the transmembrane amino acid sequence contained within SEQ ID NO:14.

[0073] In certain embodiments, the transmembrane domain in the CAR of the invention is the CD28 transmembrane domain. In one embodiment, the CD28 transmembrane domain comprises the nucleic acid sequence of SEQ ID NO:5. In one embodiment, the CD28 transmembrane domain comprises the nucleic acid sequence that encodes the amino acid sequence of SEQ ID NO:6. In another embodiment, the CD28 transmembrane domain comprises the amino acid sequence of SEQ ID NO:6.

[0074] **Intracellular (Cytoplasmic) Domain.** The intracellular (cytoplasmic) domain of the engineered T cells of the invention can provide activation of at least one of the normal effector functions of the immune cell. Effector function of a T cell, for example, may be cytolytic activity or helper activity including the secretion of cytokines.

[0075] It will be appreciated that suitable intracellular molecules include (*i.e.*, comprise), but are not limited to CD28, CD28T, CD8, OX-40, 4-1BB/CD137, CD2, CD7, CD27, CD30, CD40, programmed death-1 (PD-1), inducible T cell costimulator (ICOS), lymphocyte function-associated antigen-1 (LFA-1, CDl-la/CD18), CD3 gamma, CD3 delta, CD3 epsilon, CD247,

CD276 (B7-H3), LIGHT, (TNFSF14), NKG2C, Ig alpha (CD79a), DAP-10, Fc gamma receptor, MHC class 1 molecule, TNF receptor proteins, an Immunoglobulin protein, cytokine receptor, integrins, Signaling Lymphocytic Activation Molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, ICAM-1, B7-H3, CDS, ICAM-1, GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL-2R beta, IL-2R gamma, IL-7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CDl ld, ITGAE, CD103, ITGAL, CDl la, LFA-1, ITGAM, CDl lb, ITGAX, CDl lc, ITGBl, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRT AM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Lyl08), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, a ligand that specifically binds with CD83, or any combination thereof.

[0076] In a preferred embodiment, the cytoplasmic domain of the CAR can be designed to comprise the CD3 zeta signaling domain by itself or combined with any other desired cytoplasmic domain(s) useful in the context of the CAR of the invention. For example, the cytoplasmic domain of the CAR can comprise a CD3 zeta chain portion and a costimulatory signaling region.

[0077] The cytoplasmic signaling sequences within the cytoplasmic signaling portion of the CAR of the invention may be linked to each other in a random or specified order.

[0078] In one preferred embodiment, the cytoplasmic domain is designed to comprise the signaling domain of CD3 zeta and the signaling domain of CD28. In another embodiment, the cytoplasmic domain is designed to comprise the signaling domain of CD3 zeta and the signaling domain of 4-1BB, wherein the cytoplasmic CD28 comprises the nucleic acid sequence set forth in SEQ ID NO:15 and the amino acid sequence set forth in SEQ ID NO:16. . In another embodiment, the cytoplasmic domain in the CAR of the invention is designed to comprise a portion of CD28 and CD3 zeta, wherein the cytoplasmic CD28 comprises the nucleic acid sequence set forth in SEQ ID NO:7 and the amino acid sequence set forth in SEQ ID NO:8. The CD3 zeta nucleic acid sequence is set forth in SEQ ID NO:9, and the amino acid sequence is set forth in SEQ ID NO:8.

[0079] It will be appreciated that one preferred orientation of the CARs in accordance with the invention comprises an antigen binding domain (such as scFv) in tandem with a costimulatory domain and an activating domain. The costimulatory domain can comprise one or more of an extracellular portion, a transmembrane portion, and an intracellular portion. It will be further appreciated that multiple costimulatory domains can be utilized in tandem.

[0080] In some embodiments, nucleic acids are provided comprising a promoter operably linked to a first polynucleotide encoding an antigen binding molecule, at least one costimulatory molecule, and an activating domain.

[0081] In some embodiments, the nucleic acid construct is contained within a viral vector. In some embodiments, the viral vector is selected from the group consisting of retroviral vectors, murine leukemia virus vectors, SFG vectors, adenoviral vectors, lentiviral vectors, adeno-associated virus (AAV) vectors, Herpes virus vectors, and vaccinia virus vectors. In some embodiments, the nucleic acid is contained within a plasmid.

[0082] The invention further relates to isolated polynucleotides encoding the chimeric antigen receptors, and vectors comprising the polynucleotides. Any vector known in the art can be suitable for the present invention. In some embodiments, the vector is a viral vector. In some embodiments, the vector is a retroviral vector (such as pMSVG1), a DNA vector, a murine leukemia virus vector, an SFG vector, a plasmid, a RNA vector, an adenoviral vector, a baculoviral vector, an Epstein Barr viral vector, a papovaviral vector, a vaccinia viral vector, a herpes simplex viral vector, an adenovirus associated vector (AAV), a lentiviral vector (such as pGAR), or any combination thereof. The pGAR vector map is shown in FIGURE 6. The pGAR sequence is as follows:

CTGACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGC
GTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTCGCTTTCTTCCCTTCCT
TTCTCGCCACGTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGG
GTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAAACTTGATTAGGGTGATGG
TTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTCGCCCTTTGACGTTGGAGTCC
ACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTATCTCG
GTCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTCGGCCTATTGGTTAAAAAATG
AGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAATATTAACGCTTACAATTT
GCCATTCGCCATTCAGGCTGCGCAACTGTTGGGAAGGGCGATCGGTGCGGGCCTCTT
CGCTATTACGCCAGCTGGCGAAAGGGGGATGTGCTGCAAGGCGATTAAGTTGGGTA
ACGCCAGGGTTTTCCCAGTCACGACGTTGTAAAACGACGGCCAGTGAATTGTAATAC
GACTCACTATAGGGCGACCCGGGGATGGCGCGCCAGTAATCAATTACGGGGTCATT

AGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGCC
TGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCAT
AGTAACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGGTAAAC
TGCCCACTTGGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGT
CAATGACGGTAAATGGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTT
TCCTACTTGGCAGTACATCTACGTATTAGTCATCGCTATTACCATGCTGATGCGGTTT
TGGCAGTACATCAATGGGCGTGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTC
CACCCCATTGACGTCAATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCA
AAATGTCGTAACAACTCCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGTG
GGAGGTCTATATAAGCAGAGCTGGTTTAGTGAACCGGGGTCTCTCTGGTTAGACCAG
ATCTGAGCCTGGGAGCTCTCTGGCTAACTAGGGAACCCACTGCTTAAGCCTCAATAA
AGCTTGCCTTGAGTGCTTCAAGTAGTGTGTGCCCGTCTGTTGTGTGACTCTGGTAACT
AGAGATCCCTCAGACCCTTTTAGTCAGTGTGGAAAATCTCTAGCAGTGGCGCCCGAA
CAGGGACTTGAAAGCGAAAGGGAAACCAGAGGAGCTCTCTCGACGCAGGACTCGGC
TTGCTGAAGCGCGCACGGCAAGAGGCGAGGGGCGGCGACTGGTGAGTACGCCAAAA
ATTTTGACTAGCGGAGGCTAGAAGGAGAGAGATGGGTGCGAGAGCGTCAGTATTAA
GCGGGGGAGAATTAGATCGCGATGGGAAAAAATTCGGTTAAGGCCAGGGGGAAAG
AAAAAATATAAATTAAAACATATAGTATGGGCAAGCAGGGAGCTAGAACGATTCGC
AGTTAATCCTGGCCTGTTAGAAACATCAGAAGGCTGTAGACAAATACTGGGACAGC
TACAACCATCCCTTCAGACAGGATCAGAAGAACTTAGATCATTATATAATACAGTAG
CAACCCTCTATTGTGTGCATCAAAGGATAGAGATAAAAGACACCAAGGAAGCTTTA
GACAAGATAGAGGAAGAGCAAAACAAAAGTAAGACCACCGCACAGCAAGCCGCCG
CTGATCTTCAGACCTGGAGGAGGAGATATGAGGGACAATTGGAGAAGTGAATTATA
TAAATATAAAGTAGTAAAAATTGAACCATTAGGAGTAGCACCCACCAAGGCAAAGA
GAAGAGTGGTGCAGAGAGAAAAAAGAGCAGTGGGAATAGGAGCTTTGTTCCTTGGG
TTCTTGGGAGCAGCAGGAAGCACTATGGGCGCAGCGTCAATGACGCTGACGGTACA
GGCCAGACAATTATTGTCTGGTATAGTGCAGCAGCAGAACAATTTGCTGAGGGCTAT
TGAGGCGCAACAGCATCTGTTGCAACTCACAGTCTGGGGCATCAAGCAGCTCCAGG
CAAGAATCCTGGCTGTGGAAAGATACCTAAAGGATCAACAGCTCCTGGGGATTTGG
GGTTGCTCTGGAAAACTCATTTGCACCACTGCTGTGCCTTGGAATGCTAGTTGGAGT
AATAAATCTCTGGAACAGATTTGGAATCACACGACCTGGATGGAGTGGGACAGAGA
AATTAACAATTACACAAGCTTAATACACTCCTTAATTGAAGAATCGCAAAACCAGCA
AGAAAAGAATGAACAAGAATTATTGGAATTAGATAAATGGGCAAGTTTGTGGAATT

GGTTTAACATAACAAATTGGCTGTGGTATATAAAATTATTCATAATGATAGTAGGAG
GCTTGGTAGGTTTAAGAATAGTTTTTGCTGTACTTTCTATAGTGAATAGAGTTAGGCA
GGGATATTCACCATTATCGTTTCAGACCCACCTCCCAACCCCGAGGGGACCCGACAG
GCCCGAAGGAATAGAAGAAGAAGGTGGAGAGAGAGACAGAGACAGATCCATTCGA
TTAGTGAACGGATCTCGACGGTATCGGTTAACTTTTAAAAGAAAAGGGGGGATTGG
GGGGTACAGTGCAGGGGAAAGAATAGTAGACATAATAGCAACAGACATACAAACT
AAAGAATTACAAAAACAAATTACAAAATTCAAAATTTTATCGCGATCGCGGAATGA
AAGACCCCACCTGTAGGTTTGGCAAGCTAGCTTAAGTAACGCCATTTTGCAAGGCAT
GGAAAATACATAACTGAGAATAGAGAAGTTCAGATCAAGGTTAGGAACAGAGAGA
CAGCAGAATATGGGCCAAACAGGATATCTGTGGTAAGCAGTTCCTGCCCCGGCTCA
GGGCCAAGAACAGATGGTCCCCAGATGCGGTCCCGCCCTCAGCAGTTTCTAGAGAA
CCATCAGATGTTTCCAGGGTGCCCCAAGGACCTGAAATGACCCTGTGCCTTATTTG
AACTAACCAATCAGTTCGCTTCTCGCTTCTGTTCGCGCGCTTCTGCTCCCCGAGCTCA
ATAAAAGAGCCCACAACCCCTCACTCGGCGCGCCAGTCCTTCGAAGTAGATCTTTGT
CGATCCTACCATCCACTCGACACACCCGCCAGCGGCCGCTGCCAAGCTTCCGAGCTC
TCGAATTAATTCACGGTACCCACCATGGCCTAGGGAGACTAGTCGAATCGATATCAA
CCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACTATGTTGCTCCTT
TTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCCCGTAT
GGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTGCTGTCTCTTTATGAGGAGTTGT
GGCCCGTTGTCAGGCAACGTGGCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCCA
CTGGTTGGGGCATTGCCACCACCTGTCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCT
CCCTATTGCCACGGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGC
TCGGCTGTTGGGCACTGACAATTCCGTGGTGTTGTCGGGGAAGCTGACGTCCTTTTC
ATGGCTGCTCGCCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCCTTCTGCTACGTC
CCTTCGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGGCCTGCTGCCGGCTCTGCGGC
CTCTTCCGCGTCTTCGCCTTCGCCCTCAGACGAGTCGGATCTCCCTTTGGGCCGCCTC
CCCGCCTGGTTAATTAAAGTACCTTTAAGACCAATGACTTACAAGGCAGCTGTAGAT
CTTAGCCACTTTTTAAAAGAAAAGGGGGGACTGGAAGGGCGAATTCACTCCCAACG
AAGACAAGATCTGCTTTTTGCTTGTACTGGGTCTCTCTGGTTAGACCAGATCTGAGCC
TGGGAGCTCTCTGGCTAACTAGGGAACCCACTGCTTAAGCCTCAATAAAGCTTGCCT
TGAGTGCTTCAAGTAGTGTGTGCCCGTCTGTTGTGTGACTCTGGTAACTAGAGATCC
CTCAGACCCTTTTAGTCAGTGTGGAAAATCTCTAGCAGGCATGCCAGACATGATAAG
ATACATTGATGAGTTTGGACAAACCACAACTAGAATGCAGTGAAAAAAATGCTTTAT

TTGTGAAATTTGTGATGCTATTGCTTTATTTGTAACCATTATAAGCTGCAATAAACAA
GTTAACAACAACAATTGCATTCATTTTATGTTTCAGGTTCAGGGGGAGGTGTGGGAG
GTTTTTTGGCGCGCCATCGTCGAGGTTCCCTTTAGTGAGGGTTAATTGCGAGCTTGGC
GTAATCATGGTCATAGCTGTTTCCTGTGTGAAATTGTTATCCGCTCACAATTCCACAC
AACATACGAGCCGGAAGCATAAAGTGTAAAGCCTGGGGTGCCTAATGAGTGAGCTA
ACTCACATTAATTGCGTTGCGCTCACTGCCCGCTTTCCAGTCGGGAAACCTGTCGTGC
CAGCTGCATTAATGAATCGGCCAACGCGCGGGGAGAGGCGGTTTGCGTATTGGGCG
CTCTTCCGCTTCCTCGCTCACTGACTCGCTGCGCTCGGTCGTTCGGCTGCGGCGAGCG
GTATCAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGGATAACGC
AGGAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGCCAGGAACCGTAAAAAGGCC
GCGTTGCTGGCGTTTTTCCATAGGCTCCGCCCCCCTGACGAGCATCACAAAAATCGA
CGCTCAAGTCAGAGGTGGCGAAACCCGACAGGACTATAAAGATACCAGGCGTTTCC
CCCTGGAAGCTCCCTCGTGCGCTCTCCTGTTCCGACCCTGCCGCTTACCGGATACCTG
TCCGCCTTTCTCCCTTCGGGAAGCGTGGCGCTTTCTCATAGCTCACGCTGTAGGTATC
TCAGTTCGGTGTAGGTCGTTCGCTCCAAGCTGGGCTGTGTGCACGAACCCCCCGTTC
AGCCCGACCGCTGCGCCTTATCCGGTAACTATCGTCTTGAGTCCAACCCGGTAAGAC
ACGACTTATCGCCACTGGCAGCAGCCACTGGTAACAGGATTAGCAGAGCGAGGTAT
GTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGCCTAACTACGGCTACACTAGAAG
AACAGTATTTGGTATCTGCGCTCTGCTGAAGCCAGTTACCTTCGGAAAAAGAGTTGG
TAGCTCTTGATCCGGCAAACAAACCACCGCTGGTAGCGGTGGTTTTTTTGTTTGCAA
GCAGCAGATTACGCGCAGAAAAAAAGGATCTCAAGAAGATCCTTTGATCTTTTCTAC
GGGGTCTGACGCTCAGTGGAACGAAAACTCACGTTAAGGGATTTTGGTCATGAGATT
ATCAAAAAGGATCTTCACCTAGATCCTTTTAAATTAAAAATGAAGTTTTAAATCAAT
CTAAAGTATATATGAGTAAACTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGC
ACCTATCTCAGCGATCTGTCTATTTCGTTCATCCATAGTTGCCTGACTCCCCGTCGTG
TAGATAACTACGATACGGGAGGGCTTACCATCTGGCCCCAGTGCTGCAATGATACCG
CGAGACCCACGCTCACCGGCTCCAGATTTATCAGCAATAAACCAGCCAGCCGGAAG
GGCCGAGCGCAGAAGTGGTCCTGCAACTTTATCCGCCTCCATCCAGTCTATTAATTG
TTGCCGGGAAGCTAGAGTAAGTAGTTCGCCAGTTAATAGTTTGCGCAACGTTGTTGC
CATTGCTACAGGCATCGTGGTGTCACGCTCGTCGTTTGGTATGGCTTCATTCAGCTCC
GGTTCCCAACGATCAAGGCGAGTTACATGATCCCCCATGTTGTGCAAAAAAGCGGTT
AGCTCCTTCGGTCCTCCGATCGTTGTCAGAAGTAAGTTGGCCGCAGTGTTATCACTC
ATGGTTATGGCAGCACTGCATAATTCTCTTACTGTCATGCCATCCGTAAGATGCTTTT

CTGTGACTGGTGAGTACTCAACCAAGTCATTCTGAGAATAGTGTATGCGGCGACCGAGTTGCTCTTGCCCGGCGTCAATACGGGATAATACCGCGCCACATAGCAGAACTTTAAAAGTGCTCATCATTGGAAAACGTTCTTCGGGGCGAAAACTCTCAAGGATCTTACCGCTGTTGAGATCCAGTTCGATGTAACCCACTCGTGCACCCAACTGATCTTCAGCATCTTTTACTTTCACCAGCGTTTCTGGGTGAGCAAAAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCGACACGGAAATGTTGAATACTCATACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATTGTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATAAACAAATAGGGGTTCCGCGCACATTTCCCCGAAAAGTGCCAC (SEQ ID NO:147)

[0083] Suitable additional exemplary vectors include e.g., pBABE-puro, pBABE-neo largeTcDNA, pBABE-hygro-hTERT, pMKO.1 GFP, MSCV-IRES-GFP, pMSCV PIG (Puro IRES GFP empty plasmid), pMSCV-loxp-dsRed-loxp-eGFP-Puro-WPRE, MSCV IRES Luciferase, pMIG, MDH1-PGK-GFP_2.0, TtRMPVIR, pMSCV-IRES-mCherry FP, pRetroX GFP T2A Cre, pRXTN, pLncEXP, and pLXIN-Luc.

[0084] In some embodiments, the engineered immune cell is a T cell, tumor infiltrating lymphocyte (TIL), NK cell, TCR-expressing cell, dendritic cell, or NK-T cell. In some embodiments, the cell is obtained or prepared from peripheral blood. In some embodiments, the cell is obtained or prepared from peripheral blood mononuclear cells (PBMCs). In some embodiments, the cell is obtained or prepared from bone marrow. In some embodiments, the cell is obtained or prepared from umbilical cord blood. In some embodiments, the cell is a human cell. In some embodiments, the cell is transfected or transduced by the nucleic acid vector using a method selected from the group consisting of electroporation, sonoporation, biolistics (e.g., Gene Gun), lipid transfection, polymer transfection, nanoparticles, or polyplexes.

[0085] In some embodiments, chimeric antigen receptors are expressed in the engineered immune cells that comprise the nucleic acids of the present application. These chimeric antigen receptors of the present application may comprise, in some embodiments, (i) an antigen binding molecule (such as an scFv), (ii) a transmembrane region, and (iii) a T cell activation molecule or region.

ANTIGEN BINDING MOLECULES

[0086] Antigen binding molecules are within the scope of the invention.

[0087] An "antigen binding molecule" as used herein means any protein that binds a specified target antigen. In the instant application, the specified target antigen is the STEAP1 protein or fragment thereof. Antigen binding molecules include, but are not limited to antibodies and binding parts thereof, such as immunologically functional fragments. Peptibodies (*i.e.*, Fc fusion molecules comprising peptide binding domains) are another example of suitable antigen binding molecules.

[0088] In some embodiments, the antigen binding molecule binds to an antigen on a tumor cell. In some embodiments, the antigen binding molecule binds to an antigen on a cell involved in a hyperproliferative disease or to a viral or bacterial antigen. In certain embodiments, the antigen binding molecule binds to STEAP1. In further embodiments, the antigen binding molecule is an antibody of fragment thereof, including one or more of the complementarity determining regions (CDRs) thereof. In further embodiments, the antigen binding molecule is a single chain variable fragment (scFv).

[0089] The term "immunologically functional fragment" (or "fragment") of an antigen binding molecule is a species of antigen binding molecule comprising a portion (regardless of how that portion is obtained or synthesized) of an antibody that lacks at least some of the amino acids present in a full-length chain but which is still capable of specifically binding to an antigen. Such fragments are biologically active in that they bind to the target antigen and can compete with other antigen binding molecules, including intact antibodies, for binding to a given epitope. In some embodiments, the fragments are neutralizing fragments. In some embodiments, the fragments can block or reduce the activity of STEAP1. In one aspect, such a fragment will retain at least one CDR present in the full-length light or heavy chain, and in some embodiments will comprise a single heavy chain and/or light chain or portion thereof. These fragments can be produced by recombinant DNA techniques, or can be produced by enzymatic or chemical cleavage of antigen binding molecules, including intact antibodies.

[0090] Immunologically functional immunoglobulin fragments include, but are not limited to, scFv fragments, Fab fragments (Fab', $F(ab')_2$, and the like), one or more CDR, a diabody (heavy chain variable domain on the same polypeptide as a light chain variable domain, connected via a short peptide linker that is too short to permit pairing between the two domains on the same chain), domain antibodies, and single-chain antibodies. These fragments can be derived from any mammalian source, including but not limited to human, mouse, rat, camelid or rabbit. As will be appreciated by one of skill in the art, an antigen binding molecule can include non-protein components.

[0091] Variants of the antigen binding molecules are also within the scope of the invention, e.g., variable light and/or variable heavy chains that each have at least 70-80%, 80-85%, 85-90%, 90-95%, 95-97%, 97-99%, or above 99% identity to the amino acid sequences of the sequences described herein. In some instances, such molecules include at least one heavy chain and one light chain, whereas in other instances the variant forms contain two identical light chains and two identical heavy chains (or subparts thereof). A skilled artisan will be able to determine suitable variants of the antigen binding molecules as set forth herein using well-known techniques. In certain embodiments, one skilled in the art can identify suitable areas of the molecule that may be changed without destroying activity by targeting regions not believed to be important for activity.

[0092] In certain embodiments, the polypeptide structure of the antigen binding molecules is based on antibodies, including, but not limited to, monoclonal antibodies, bispecific antibodies, minibodies, domain antibodies, synthetic antibodies (sometimes referred to herein as "antibody mimetics"), chimeric antibodies, humanized antibodies, human antibodies, antibody fusions (sometimes referred to herein as "antibody conjugates"), and fragments thereof, respectively. In some embodiments, the antigen binding molecule comprises or consists of avimers.

[0093] In some embodiments, an antigen binding molecule to STEAP1 is administered alone. In other embodiments, the antigen binding molecule to STEAP1 is administered as part of a CAR, TCR, or other immune cell. In such immune cells, the antigen binding molecule to STEAP1 can be under the control of the same promoter region, or a separate promoter. In certain embodiments, the genes encoding protein agents and/or an antigen binding molecule to STEAP1 can be in separate vectors.

[0094] The invention further provides for pharmaceutical compositions comprising an antigen binding molecule to STEAP1 together with a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant. In certain embodiments, pharmaceutical compositions will include more than one different antigen binding molecule to STEAP1. In certain embodiments, pharmaceutical compositions will include more than one antigen binding molecule to STEAP1 wherein the antigen binding molecules to STEAP1 bind more than one epitope. In some embodiments, the various antigen binding molecules will not compete with one another for binding to STEAP1.

[0095] In other embodiments, the pharmaceutical composition can be selected for parenteral delivery, for inhalation, or for delivery through the digestive tract, such as orally. The preparation of such pharmaceutically acceptable compositions is within the ability of one skilled in the art. In certain embodiments, buffers are used to maintain the composition at physiological pH or at a slightly lower pH, typically within a pH range of from about 5 to about 8. In certain embodiments, when parenteral administration is contemplated, a therapeutic composition can be in the form of a pyrogen-free, parenterally acceptable aqueous solution comprising a desired antigen binding molecule to STEAP1, with or without additional therapeutic agents, in a pharmaceutically acceptable vehicle. In certain embodiments, a vehicle for parenteral injection is sterile distilled water in which an antigen binding molecule to STEAP1, with or without at least one additional therapeutic agent, is formulated as a sterile, isotonic solution, properly preserved. In certain embodiments, the preparation can involve the formulation of the desired molecule with polymeric compounds (such as polylactic acid or polyglycolic acid), beads or liposomes that can provide for the controlled or sustained release of the product which can then be delivered via a depot injection. In certain embodiments, implantable drug delivery devices can be used to introduce the desired molecule.

[0096] In some embodiments, the antigen binding molecule is used as a diagnostic or validation tool. The antigen binding molecule can be used to assay the amount of STEAP1 present in a sample and/or subject. In some embodiments, the diagnostic antigen binding molecule is not neutralizing. In some embodiments, the antigen binding molecules disclosed herein are used or provided in an assay kit and/or method for the detection of STEAP1 in mammalian tissues or cells in order to screen/diagnose for a disease or disorder associated with changes in levels of STEAP1. The kit can comprise an antigen binding molecule that binds STEAP1, along with means for indicating the binding of the antigen binding molecule with STEAP1, if present, and optionally STEAP1 protein levels.

[0097] The antigen binding molecules will be further understood in view of the definitions and descriptions below.

[0098] An "Fc" region comprises two heavy chain fragments comprising the CH1 and CH2 domains of an antibody. The two heavy chain fragments are held together by two or more disulfide bonds and by hydrophobic interactions of the CH3 domains.

[0099] A "Fab fragment" comprises one light chain and the CH1 and variable regions of one heavy chain. The heavy chain of a Fab molecule cannot form a disulfide bond with another heavy chain molecule. A "Fab'" fragment" comprises one light chain and a portion of one heavy chain that contains the VH domain and the CH1 domain and also the region between the CH1 and CH2 domains, such that an interchain disulfide bond can be formed between the two heavy chains of two Fab' fragments to form an $F(ab')_2$ molecule. An "$F(ab')_2$ fragment" contains two light chains and two heavy chains containing a portion of the constant region between the CH1 and CH2 domains, such that an interchain disulfide bond is formed between the two heavy chains. An $F(ab')_2$ fragment thus is composed of two Fab' fragments that are held together by a disulfide bond between the two heavy chains.

[0100] The "Fv region" comprises the variable regions from both the heavy and light chains, but lacks the constant regions.

[0101] "Single chain variable fragment" ("scFv", also termed "single-chain antibody") refers to Fv molecules in which the heavy and light chain variable regions have been connected by a flexible linker to form a single polypeptide chain, which forms an antigen binding region. See PCT application WO88/01649 and U.S. Patent Nos. 4,946,778 and 5,260,203, the disclosures of which are incorporated by reference in their entirety.

[0102] A "bivalent antigen binding molecule" comprises two antigen binding sites. In some instances, the two binding sites have the same antigen specificities. Bivalent antigen binding molecules can be bispecific. A "multispecific antigen binding molecule" is one that targets more than one antigen or epitope. A "bispecific," "dual-specific" or "bifunctional" antigen binding molecule is a hybrid antigen binding molecule or antibody, respectively, having two different antigen binding sites. The two binding sites of a bispecific antigen binding molecule will bind to two different epitopes, which can reside on the same or different protein targets.

[0103] An antigen binding molecule is said to "specifically bind" its target antigen when the dissociation constant (K_d) is $\sim 1 \times 10^{-7}$ M. The antigen binding molecule specifically binds antigen with "high affinity" when the K_d is $1\text{-}5 \times 10^{-9}$ M, and with "very high affinity" when the K_d is $1\text{-}5 \times 10^{-10}$ M. In one embodiment, the antigen binding molecule has a K_d of 10^{-9} M. In one embodiment, the off-rate is $<1 \times 10^{-5}$. In other embodiments, the antigen binding molecules will bind to human STEAP1 with a K_d of between about 10^{-7} M and 10^{-13} M, and in yet another embodiment the antigen binding molecules will bind with a K_d $1.0\text{-}5 \times 10^{-10}$.

[0104] An antigen binding molecule is said to be "selective" when it binds to one target more tightly than it binds to a second target.

[0105] The term "antibody" refers to an intact immunoglobulin of any isotype, or a fragment thereof that can compete with the intact antibody for specific binding to the target antigen, and includes, for instance, chimeric, humanized, fully human, and bispecific antibodies. An "antibody" is a species of an antigen binding molecule as defined herein. An intact antibody will generally comprise at least two full-length heavy chains and two full-length light chains, but in some instances can include fewer chains such as antibodies naturally occurring in camelids which can comprise only heavy chains. Antibodies can be derived solely from a single source, or can be chimeric, that is, different portions of the antibody can be derived from two different antibodies as described further below. The antigen binding molecules, antibodies, or binding fragments can be produced in hybridomas, by recombinant DNA techniques, or by enzymatic or chemical cleavage of intact antibodies. Unless otherwise indicated, the term "antibody" includes, in addition to antibodies comprising two full-length heavy chains and two full-length light chains, derivatives, variants, fragments, and muteins thereof, examples of which are described below. Furthermore, unless explicitly excluded, antibodies include monoclonal antibodies, bispecific antibodies, minibodies, domain antibodies, synthetic antibodies (sometimes referred to herein as "antibody mimetics"), chimeric antibodies, humanized antibodies, human antibodies, antibody fusions (sometimes referred to herein as "antibody conjugates") and fragments thereof, respectively.

[0106] The variable regions typically exhibit the same general structure of relatively conserved framework regions (FR) joined by the 3 hypervariable regions (i.e., "CDRs"). The CDRs from the two chains of each pair typically are aligned by the framework regions, which can enable binding to a specific epitope. From N-terminal to C-terminal, both light and heavy chain variable regions typically comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. By convention, CDR regions in the heavy chain are typically referred to as HC CDR1, CDR2, and CDR3. The CDR regions in the light chain are typically referred to as LC CDR1, CDR2, and CDR3. The assignment of amino acids to each domain is typically in accordance with the definitions of Kabat (Seqs of Proteins of Immunological Interest (NIH, Bethesda, MD (1987 and 1991)), or Chothia (J. Mol. Biol., 196:901-917 (1987); Chothia *et al.*, Nature, 342:878-883 (1989)). Various methods of analysis can be employed to identify or approximate the CDR regions, including not only Kabat or Chothia, but also the AbM definition.

[0107] The term “light chain” includes a full-length light chain and fragments thereof having sufficient variable region sequence to confer binding specificity. A full-length light chain includes a variable region domain, V_L, and a constant region domain, C_L. The variable region domain of the light chain is at the amino-terminus of the polypeptide. Light chains include kappa chains and lambda chains.

[0108] The term “heavy chain” includes a full-length heavy chain and fragments thereof having sufficient variable region sequence to confer binding specificity. A full-length heavy chain includes a variable region domain, V_H, and three constant region domains, CH1, CH2, and CH3. The V_H domain is at the amino-terminus of the polypeptide, and the C_H domains are at the carboxyl-terminus, with the CH3 being closest to the carboxy-terminus of the polypeptide. Heavy chains can be of any isotype, including IgG (including IgG1, IgG2, IgG3 and IgG4 subtypes), IgA (including IgA1 and IgA2 subtypes), IgM and IgE.

[0109] The term “variable region” or “variable domain” refers to a portion of the light and/or heavy chains of an antibody, typically including approximately the amino-terminal 120 to 130 amino acids in the heavy chain and about 100 to 110 amino terminal amino acids in the light chain. The variable region of an antibody typically determines specificity of a particular antibody for its target.

[0110] Variability is not evenly distributed throughout the variable domains of antibodies; it is concentrated in sub-domains of each of the heavy and light chain variable regions. These subdomains are called “hypervariable regions” or "complementarity determining regions" (CDRs). The more conserved (i.e., non-hypervariable) portions of the variable domains are called the “framework” regions (FRM or FR) and provide a scaffold for the six CDRs in three dimensional space to form an antigen-binding surface. The variable domains of naturally occurring heavy and light chains each comprise four FRM regions (FR1, FR2, FR3, and FR4), largely adopting a β-sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases forming part of, the β -sheet structure. The hypervariable regions in each chain are held together in close proximity by the FRM and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site (see Kabat et al., loc. cit.).

[0111] The terms “CDR”, and its plural “CDRs”, refer to the complementarity determining region of which three make up the binding character of a light chain variable region (CDR-L1, CDR-L2 and CDR-L3) and three make up the binding character of a heavy chain variable region

(CDRH1, CDR-H2 and CDR-H3). CDRs contain most of the residues responsible for specific interactions of the antibody with the antigen and hence contribute to the functional activity of an antibody molecule: they are the main determinants of antigen specificity.

[0112] The exact definitional CDR boundaries and lengths are subject to different classification and numbering systems. CDRs may therefore be referred to by Kabat, Chothia, contact or any other boundary definitions, including the numbering system described herein. Despite differing boundaries, each of these systems has some degree of overlap in what constitutes the so called “hypervariable regions” within the variable sequences. CDR definitions according to these systems may therefore differ in length and boundary areas with respect to the adjacent framework region. See for example Kabat (an approach based on cross-species sequence variability), Chothia (an approach based on crystallographic studies of antigen-antibody complexes), and/or MacCallum (Kabat et al., loc. cit.; Chothia et al., J. MoI. Biol, 1987, 196: 901-917; and MacCallum et al., J. MoI. Biol, 1996, 262: 732). Still another standard for characterizing the antigen binding site is the AbM definition used by Oxford Molecular's AbM antibody modeling software. See, e.g., Protein Sequence and Structure Analysis of Antibody Variable Domains. In: Antibody Engineering Lab Manual (Ed.: Duebel, S. and Kontermann, R., Springer-Verlag, Heidelberg). To the extent that two residue identification techniques define regions of overlapping, but not identical regions, they can be combined to define a hybrid CDR. However, the numbering in accordance with the so-called Kabat system is preferred.

[0113] Typically, CDRs form a loop structure that can be classified as a canonical structure. The term “canonical structure” refers to the main chain conformation that is adopted by the antigen binding (CDR) loops. From comparative structural studies, it has been found that five of the six antigen binding loops have only a limited repertoire of available conformations. Each canonical structure can be characterized by the torsion angles of the polypeptide backbone. Correspondent loops between antibodies may, therefore, have very similar three dimensional structures, despite high amino acid sequence variability in most parts of the loops (Chothia and Lesk, J. MoI. Biol., 1987, 196: 901; Chothia et al., Nature, 1989, 342: 877; Martin and Thornton, J. MoI. Biol, 1996, 263: 800). Furthermore, there is a relationship between the adopted loop structure and the amino acid sequences surrounding it. The conformation of a particular canonical class is determined by the length of the loop and the amino acid residues residing at key positions within the loop, as well as within the conserved framework (i.e., outside of the loop). Assignment to a particular canonical class can therefore be made based on the presence of these key amino acid residues.

[0114] The term “canonical structure” may also include considerations as to the linear sequence of the antibody, for example, as catalogued by Kabat (Kabat et al., loc. cit.). The Kabat numbering scheme (system) is a widely adopted standard for numbering the amino acid residues of an antibody variable domain in a consistent manner and is the preferred scheme applied in the present invention as also mentioned elsewhere herein. Additional structural considerations can also be used to determine the canonical structure of an antibody. For example, those differences not fully reflected by Kabat numbering can be described by the numbering system of Chothia et al. and/or revealed by other techniques, for example, crystallography and two- or three-dimensional computational modeling. Accordingly, a given antibody sequence may be placed into a canonical class which allows for, among other things, identifying appropriate chassis sequences (e.g., based on a desire to include a variety of canonical structures in a library). Kabat numbering of antibody amino acid sequences and structural considerations as described by Chothia et al., loc. cit. and their implications for construing canonical aspects of antibody structure, are described in the literature. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known in the art. For a review of the antibody structure, see Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, eds. Harlow et al., 1988.

[0115] The CDR3 of the light chain and, particularly, the CDR3 of the heavy chain may constitute the most important determinants in antigen binding within the light and heavy chain variable regions. In some antibody constructs, the heavy chain CDR3 appears to constitute the major area of contact between the antigen and the antibody. In vitro selection schemes in which CDR3 alone is varied can be used to vary the binding properties of an antibody or determine which residues contribute to the binding of an antigen. Hence, CDR3 is typically the greatest source of molecular diversity within the antibody-binding site. H3, for example, can be as short as two amino acid residues or greater than 26 amino acids.

[0116] The term “neutralizing” refers to an antigen binding molecule, scFv, or antibody, respectively, that binds to a ligand and prevents or reduces the biological effect of that ligand. This can be done, for example, by directly blocking a binding site on the ligand or by binding to the ligand and altering the ligand's ability to bind through indirect means (such as structural or energetic alterations in the ligand). In some embodiments, the term can also denote an antigen binding molecule that prevents the protein to which it is bound from performing a biological function.

[0117] The term "target" or "antigen" refers to a molecule or a portion of a molecule capable of being bound by an antigen binding molecule. In certain embodiments, a target can have one or more epitopes.

[0118] The term "compete" when used in the context of antigen binding molecules that compete for the same epitope means competition between antigen binding molecules as determined by an assay in which the antigen binding molecule (e.g., antibody or immunologically functional fragment thereof) being tested prevents or inhibits (e.g., reduces) specific binding of a reference antigen binding molecule to an antigen. Numerous types of competitive binding assays can be used to determine if one antigen binding molecule competes with another, for example: solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (Stahli *et al.*, 1983, Methods in Enzymology 9:242-253); solid phase direct biotin-avidin EIA (Kirkland *et al.*, 1986, J. Immunol. 137:3614-3619), solid phase direct labeled assay, solid phase direct labeled sandwich assay (Harlow and Lane, 1988, Antibodies, A Laboratory Manual, Cold Spring Harbor Press); solid phase direct label RIA using 1-125 label (Morel *et al.*, 1988, Molec. Immunol. 25:7-15); solid phase direct biotin-avidin EIA (Cheung, *et al.*, 1990, Virology 176:546-552); and direct labeled RIA (Moldenhauer *et al.*, 1990, Scand. J. Immunol. 32:77-82). The term "epitope" includes any determinant capable of being bound by an antigen binding molecule, such as an scFv, antibody, or immune cell of the invention. An epitope is a region of an antigen that is bound by an antigen binding molecule that targets that antigen, and when the antigen is a protein, includes specific amino acids that directly contact the antigen binding molecule.

[0119] As used herein, the terms "label" or "labeled" refers to incorporation of a detectable marker, e.g., by incorporation of a radiolabeled amino acid or attachment to a polypeptide of biotin moieties that can be detected by marked avidin (e.g., streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or colorimetric methods). In certain embodiments, the label or marker can also be therapeutic. Various methods of labeling polypeptides and glycoproteins are known in the art and can be used.

[0120] In accordance with the invention, on-off or other types of control switch techniques may be incorporated herein. These techniques may employ the use of dimerization domains and optional activators of such domain dimerization. These techniques include, *e.g.*, those described by Wu *et al.*, *Science* 2014 350 (6258) utilizing FKBP/Rapalog dimerization systems in certain cells, the contents of which are incorporated by reference herein in their entirety. Additional dimerization technology is described in, *e.g.*, Fegan *et al. Chem. Rev.* 2010, *110,* 3315–3336 as well as U.S. Patent Nos. 5,830,462; 5,834,266; 5,869,337; and 6,165,787, the contents of which are also incorporated by reference herein in their entirety. Additional dimerization pairs may include cyclosporine-A/cyclophilin, receptor, estrogen/estrogen receptor (optionally using tamoxifen), glucocorticoids/glucocorticoid receptor, tetracycline/tetracycline receptor, vitamin D/vitamin D receptor. Further examples of dimerization technology can be found in *e.g.*, WO 2014/127261, WO 2015/090229, US 2014/0286987, US 2015/0266973, US 2016/0046700, U.S. Patent No. 8,486,693, US 2014/0171649, and US 2012/0130076, the contents of which are further incorporated by reference herein in their entirety.

METHODS OF TREATMENT

[0121] Using adoptive immunotherapy, native T cells can be (i) removed from a patient, (ii) genetically engineered to express a chimeric antigen receptor (CAR) that binds to at least one tumor antigen (iii) expanded *ex vivo* into a larger population of engineered T cells, and (iv) reintroduced into the patient. See e.g., U.S. Patent Nos. 7,741,465, and 6,319,494, Eshhar *et al.* (Cancer Immunol, supra); Krause *et al.* (supra); Finney *et al.* (supra). After the engineered T cells are reintroduced into the patient, they mediate an immune response against cells expressing the tumor antigen. See e.g., Krause *et al.*, J. Exp. Med., Volume 188, No. 4, 1998 (619–626). This immune response includes secretion of IL-2 and other cytokines by T cells, the clonal expansion of T cells recognizing the tumor antigen, and T cell-mediated specific killing of target-positive cells. See Hombach *et al.*, Journal of Immun. 167: 6123–6131 (2001).

[0122] In some aspects, the invention therefore comprises a method for treating or preventing a condition associated with undesired and/or elevated STEAP1 levels in a patient, comprising administering to a patient in need thereof an effective amount of at least one isolated antigen binding molecule, CAR, or TCR disclosed herein.

[0123] Methods are provided for treating diseases or disorders, including cancer. In some embodiments, the invention relates to creating a T cell-mediated immune response in a subject, comprising administering an effective amount of the engineered immune cells of the present application to the subject. In some embodiments, the T cell-mediated immune response is directed against a target cell or cells. In some embodiments, the engineered immune cell comprises a chimeric antigen receptor (CAR), or a T cell receptor (TCR). In some embodiments, the target cell is a tumor cell. In some aspects, the invention comprises a method for treating or preventing a malignancy, said method comprising administering to a subject in need thereof an effective amount of at least one isolated antigen binding molecule described herein. In some aspects, the invention comprises a method for treating or preventing a malignancy, said method comprising administering to a subject in need thereof an effective amount of at least one immune cell, wherein the immune cell comprises at least one chimeric antigen receptor, T cell receptor, and/or isolated antigen binding molecule as described herein.

[0124] In some aspects, the invention comprises a pharmaceutical composition comprising at least one antigen binding molecule as described herein and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition further comprises an additional active agent.

[0125] The antigen binding molecules, CARs, TCRs, immune cells, and the like of the invention can be used to treat STEAP1 expressing diseases including but not limited to prostate cancer, and in one preferred embodiment, in metastatic castration resistant prostate cancer.

[0126] It will be appreciated that target doses for CAR^+/ $CAR\text{-}T^+$/ TCR^+ cells can range from $1x10^6$ - $2x10^{10}$ cells/kg, preferably $2x10^6$ cells/kg, more preferably. It will be appreciated that doses above and below this range may be appropriate for certain subjects, and appropriate dose levels can be determined by the healthcare provider as needed. Additionally, multiple doses of cells can be provided in accordance with the invention.

[0127] Also provided are methods for reducing the size of a tumor in a subject, comprising administering to the subject an engineered cell of the present invention to the subject, wherein the cell comprises a chimeric antigen receptor, a T cell receptor, or a T cell receptor based chimeric antigen receptor comprising an antigen binding molecule binds to an antigen on the tumor. In some embodiments, the subject has a solid tumor, or a blood malignancy such as lymphoma or leukemia. In some embodiments, the engineered cell is delivered to a tumor bed. In some embodiments, the cancer is present in the bone marrow of the subject.

[0128] In some embodiments, the engineered cells are autologous T cells. In some embodiments, the engineered cells are allogeneic T cells. In some embodiments, the engineered cells are heterologous T cells. In some embodiments, the engineered cells of the present application are transfected or transduced *in vivo*. In other embodiments, the engineered cells are transfected or transduced *ex vivo*.

[0129] The methods can further comprise administering one or more chemotherapeutic agent. In certain embodiments, the chemotherapeutic agent is a lymphodepleting (preconditioning) chemotherapeutic. Beneficial preconditioning treatment regimens, along with correlative beneficial biomarkers are described in U.S. Provisional Patent Applications 62/262,143 and 62/167,750 which are hereby incorporated by reference in their entirety herein. These describe, *e.g.,* methods of conditioning a patient in need of a T cell therapy comprising administering to the patient specified beneficial doses of cyclophosphamide (between 200 mg/m^2/day and 2000 mg/m^2/day) and specified doses of fludarabine (between 20 mg/m^2/day and 900 mg/m^2/day). A preferred dose regimen involves treating a patient comprising administering daily to the patient about 500 mg/m^2/day of cyclophosphamide and about 60 mg/m^2/day of fludarabine for three days prior to administration of a therapeutically effective amount of engineered T cells to the patient.

[0130] In other embodiments, the antigen binding molecule, transduced (or otherwise engineered) cells (such as CARs or TCRs), and the chemotherapeutic agent are administered each in an amount effective to treat the disease or condition in the subject.

[0131] In certain embodiments, compositions comprising CAR-expressing immune effector cells disclosed herein may be administered in conjunction with any number of chemotherapeutic agents. Examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclophosphamide (CYTOXAN^{TM}); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide and trimethylolomelamine resume; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU);

folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, 5-FU; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK®; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2, 2',2"-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside (“Ara-C”); cyclophosphamide; thiotepa; taxoids, e.g. paclitaxel (TAXOL™, Bristol-Myers Squibb) and doxetaxel (TAXOTERE®, Rhone-Poulenc Rorer); chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; CPT-11; topoisomerase inhibitor RFS2000; difluoromethylomithine (DMFO); retinoic acid derivatives such as Targretin™ (bexarotene), Panretin™, (alitretinoin); ONTAK™ (denileukin diftitox); esperamicins; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included in this definition are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Combinations of chemotherapeutic agents are also administered where appropriate, including, but not limited to CHOP, i.e., Cyclophosphamide (Cytoxan®), Doxorubicin (hydroxydoxorubicin), Vincristine (Oncovin®), and Prednisone.

[0132] In some embodiments, the chemotherapeutic agent is administered at the same time or within one week after the administration of the engineered cell or nucleic acid. In other embodiments, the chemotherapeutic agent is administered from 1 to 4 weeks or from 1 week to 1 month, 1 week to 2 months, 1 week to 3 months, 1 week to 6 months, 1 week to 9 months, or 1 week to 12 months after the administration of the engineered cell or nucleic acid. In other embodiments, the chemotherapeutic agent is administered at least 1 month before administering the cell or nucleic acid. In some embodiments, the methods further comprise administering two or more chemotherapeutic agents.

[0133] A variety of additional therapeutic agents may be used in conjunction with the compositions described herein. For example, potentially useful additional therapeutic agents include PD-1 inhibitors such as nivolumab (Opdivo®), pembrolizumab (Keytruda®), pembrolizumab, pidilizumab, and atezolizumab, and CTLA-4 inhibitors, such as ipilimumab (Yervoy®).

[0134] Additional therapeutic agents suitable for use in combination with the invention include, but are not limited to, abiraterone acetate, apalutamide, bicalutamide, cabazitaxel, casodex (bicalutamide), degarelix, docetaxel, enzalutamide, Erleada® (apalutamide), flutamide, goserelin acetate, Jevtana® (cabazitaxel), leuprolide acetate, Lupron® (leuprolide acetate), Lupron Depot (leuprolide acetate), Lupron Depot-Ped (leuprolide acetate), mitoxantrone hydrochloride, Nilandron® (nilutamide), nilutamide, Provenge® (Sipuleucel-T), radium 223 dichloride, sipuleucel-T, taxotere (docetaxel), Viadur (leuprolide acetate), Xofigo (radium 223 dichloride), Xtandi (enzalutamide), Zoladex (goserelin acetate), or Zytiga (abiraterone acetate).

[0135] In additional embodiments, the composition comprising CAR-containing immune can be administered with an anti-inflammatory agent. Anti-inflammatory agents or drugs include, but are not limited to, steroids and glucocorticoids (including betamethasone, budesonide, dexamethasone, hydrocortisone acetate, hydrocortisone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone), nonsteroidal anti-inflammatory drugs (NSAIDS) including aspirin, ibuprofen, naproxen, methotrexate, sulfasalazine, leflunomide, anti-TNF medications, cyclophosphamide and mycophenolate. Exemplary NSAIDs include ibuprofen, naproxen, naproxen sodium, Cox-2 inhibitors, and sialylates. Exemplary analgesics include acetaminophen, oxycodone, tramadol of proporxyphene hydrochloride. Exemplary glucocorticoids include cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, or prednisone. Exemplary biological response modifiers include molecules directed against cell surface markers (e.g., CD4, CD5, etc.), cytokine inhibitors, such as the TNF antagonists, (e.g., etanercept (ENBREL®), adalimumab (HUMIRA®) and infliximab (REMICADE®), chemokine inhibitors and adhesion molecule inhibitors. The biological response modifiers include monoclonal antibodies as well as recombinant forms of molecules. Exemplary

DMARDs include azathioprine, cyclophosphamide, cyclosporine, methotrexate, penicillamine, leflunomide, sulfasalazine, hydroxychloroquine, Gold (oral (auranofin) and intramuscular) and minocycline.

[0136] In certain embodiments, the compositions described herein are administered in conjunction with a cytokine. "Cytokine" as used herein is meant to refer to proteins released by one cell population that act on another cell as intercellular mediators. Examples of cytokines are lymphokines, monokines, and traditional polypeptide hormones. Included among the cytokines are growth hormones such as human growth hormone, N-methionyl human growth hormone, and bovine growth hormone; parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prorelaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH); hepatic growth factor (HGF); fibroblast growth factor (FGF); prolactin; placental lactogen; mullerian-inhibiting substance; mouse gonadotropin-associated peptide; inhibin; activin; vascular endothelial growth factor; integrin; thrombopoietin (TPO); nerve growth factors (NGFs) such as NGF-beta; platelet-growth factor; transforming growth factors (TGFs) such as TGF-alpha and TGF-beta; insulin-like growth factor-I and -II; erythropoietin (EPO); osteoinductive factors; interferons such as interferon-alpha, beta, and -gamma; colony stimulating factors (CSFs) such as macrophage-CSF (M-CSF); granulocyte-macrophage-CSF (GM-CSF); and granulocyte-CSF (G-CSF); interleukins (ILs) such as IL-1, IL-1alpha, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12; IL-15, a tumor necrosis factor such as TNF-alpha or TNF-beta; and other polypeptide factors including LIF and kit ligand (KL). As used herein, the term cytokine includes proteins from natural sources or from recombinant cell culture, and biologically active equivalents of the native sequence cytokines.

[0137] In some aspects, the invention comprises an antigen binding molecule that binds to STEAP1 with a K_d that is smaller than 100 pM. In some embodiments, the antigen binding molecule binds with a K_d that is smaller than 10 pM. In other embodiments, the antigen binding molecule binds with a K_d that is less than 5 pM.

METHODS OF MAKING

[0138] A variety of known techniques can be utilized in making the polynucleotides, polypeptides, vectors, antigen binding molecules, immune cells, compositions, and the like according to the invention.

[0139] Prior to the *in vitro* manipulation or genetic modification of the immune cells described herein, the cells may be obtained from a subject. In some embodiments, the immune cells comprise T cells. T cells can be obtained from a number of sources, including peripheral blood mononuclear cells (PBMCs), bone marrow, lymph nodes tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion, spleen tissue, and tumors. In certain embodiments, T cells can be obtained from a unit of blood collected from the subject using any number of techniques known to the skilled person, such as FICOLL™ separation. Cells may preferably be obtained from the circulating blood of an individual by apheresis. The apheresis product typically contains lymphocytes, including T cells, monocytes, granulocytes, B cells, other nucleated white blood cells, red blood cells, and platelets. In certain embodiments, the cells collected by apheresis may be washed to remove the plasma fraction, and placed in an appropriate buffer or media for subsequent processing. The cells may be washed with PBS. As will be appreciated, a washing step may be used, such as by using a semiautomated flowthrough centrifuge -- for example, the Cobe™ 2991 cell processor, the Baxter CytoMate™, or the like. After washing, the cells may be resuspended in a variety of biocompatible buffers, or other saline solution with or without buffer. In certain embodiments, the undesired components of the apheresis sample may be removed.

[0140] In certain embodiments, T cells are isolated from PBMCs by lysing the red blood cells and depleting the monocytes, for example, using centrifugation through a PERCOLL™ gradient. A specific subpopulation of T cells, such as $CD28^+$, $CD4^+$, $CD8^+$, $CD45RA^+$, and $CD45RO^+$ T cells can be further isolated by positive or negative selection techniques known in the art. For example, enrichment of a T cell population by negative selection can be accomplished with a combination of antibodies directed to surface markers unique to the negatively selected cells. One method for use herein is cell sorting and/or selection via negative magnetic immunoadherence or flow cytometry that uses a cocktail of monoclonal antibodies directed to cell surface markers present on the cells negatively selected. For example, to enrich for $CD4^+$ cells by negative selection, a monoclonal antibody cocktail typically includes antibodies to CD14, CD20, CD11b, CD16, HLA-DR, and CD8. Flow cytometry and cell sorting may also be used to isolate cell populations of interest for use in the present invention.

[0141] PBMCs may be used directly for genetic modification with the immune cells (such as CARs or TCRs) using methods as described herein. In certain embodiments, after isolating the PBMCs, T lymphocytes can be further isolated and both cytotoxic and helper T lymphocytes can be sorted into naive, memory, and effector T cell subpopulations either before or after genetic modification and/or expansion.

[0142] In some embodiments, $CD8^+$ cells are further sorted into naive, central memory, and effector cells by identifying cell surface antigens that are associated with each of these types of $CD8^+$ cells. In some embodiments, the expression of phenotypic markers of central memory T cells include CD45RO, CD62L, CCR7, CD28, CD3, and CD127 and are negative for granzyme B. In some embodiments, central memory T cells are $CD45RO^+$, $CD62L^+$, $CD8^+$ T cells. In some embodiments, effector T cells are negative for CD62L, CCR7, CD28, and CD127, and positive for granzyme B and perforin. In certain embodiments, $CD4^+$ T cells are further sorted into subpopulations. For example, $CD4^+$ T helper cells can be sorted into naive, central memory, and effector cells by identifying cell populations that have cell surface antigens.

[0143] The immune cells, such as T cells, can be genetically modified following isolation using known methods, or the immune cells can be activated and expanded (or differentiated in the case of progenitors) *in vitro* prior to being genetically modified. In another embodiment, the immune cells, such as T cells, are genetically modified with the chimeric antigen receptors described herein (e.g., transduced with a viral vector comprising one or more nucleotide sequences encoding a CAR) and then are activated and/or expanded in vitro. Methods for activating and expanding T cells are known in the art and are described, for example, in U.S. Patent No. 6,905,874; U.S. Patent No. 6,867,041; U.S. Patent No. 6,797,514; and PCT WO2012/079000, the contents of which are hereby incorporated by reference in their entirety. Generally, such methods include contacting PBMC or isolated T cells with a stimulatory agent and costimulatory agent, such as anti-CD3 and anti-CD28 antibodies, generally attached to a bead or other surface, in a culture medium with appropriate cytokines, such as IL-2. Anti-CD3 and anti-CD28 antibodies attached to the same bead serve as a "surrogate" antigen presenting cell (APC). One example is The Dynabeads® system, a CD3/CD28 activator/stimulator system for physiological activation of human T cells.

[0144] In other embodiments, the T cells may be activated and stimulated to proliferate with feeder cells and appropriate antibodies and cytokines using methods such as those described in U.S. Patent No. 6,040,177; U.S. Patent No. 5,827,642; and WO2012129514, the contents of which are hereby incorporated by reference in their entirety.

[0145] Certain methods for making the constructs and engineered immune cells of the invention are described in PCT application PCT/US15/14520, the contents of which are hereby incorporated by reference in their entirety. Additional methods of making the constructs and cells can be found in U.S. provisional patent application no. 62/244036 the contents of which are hereby incorporated by reference in their entirety.

[0146] It will be appreciated that PBMCs can further include other cytotoxic lymphocytes such as NK cells or NKT cells. An expression vector carrying the coding sequence of a chimeric receptor as disclosed herein can be introduced into a population of human donor T cells, NK cells or NKT cells. Successfully transduced T cells that carry the expression vector can be sorted using flow cytometry to isolate CD3 positive T cells and then further propagated to increase the number of these CAR expressing T cells in addition to cell activation using anti-CD3 antibodies and IL-2 or other methods known in the art as described elsewhere herein. Standard procedures are used for cryopreservation of T cells expressing the CAR for storage and/or preparation for use in a human subject. In one embodiment, the *in vitro* transduction, culture and/or expansion of T cells are performed in the absence of non-human animal derived products such as fetal calf serum and fetal bovine serum.

[0147] For cloning of polynucleotides, the vector may be introduced into a host cell (an isolated host cell) to allow replication of the vector itself and thereby amplify the copies of the polynucleotide contained therein. The cloning vectors may contain sequence components generally include, without limitation, an origin of replication, promoter sequences, transcription initiation sequences, enhancer sequences, and selectable markers. These elements may be selected as appropriate by a person of ordinary skill in the art. For example, the origin of replication may be selected to promote autonomous replication of the vector in the host cell.

[0148] In certain embodiments, the present disclosure provides isolated host cells containing the vector provided herein. The host cells containing the vector may be useful in expression or cloning of the polynucleotide contained in the vector. Suitable host cells can include, without limitation, prokaryotic cells, fungal cells, yeast cells, or higher eukaryotic cells such as mammalian cells. Suitable prokaryotic cells for this purpose include, without limitation, eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobactehaceae such as Escherichia, e.g., E. coli, Enterobacter, Erwinia, Klebsiella, Proteus, Salmonella, e.g., Salmonella typhimurium, Serratia, e.g., Serratia marcescans, and Shigella, as well as Bacilli such as B. subtilis and B. licheniformis, Pseudomonas such as P. aeruginosa, and Streptomyces.

[0149] The vector can be introduced to the host cell using any suitable methods known in the art, including, without limitation, DEAE-dextran mediated delivery, calcium phosphate precipitate method, cationic lipids mediated delivery, liposome mediated transfection, electroporation, microprojectile bombardment, receptor-mediated gene delivery, delivery mediated by polylysine, histone, chitosan, and peptides. Standard methods for transfection and transformation of cells for expression of a vector of interest are well known in the art. In a further embodiment, a mixture of different expression vectors can be used in genetically modifying a donor population of immune effector cells wherein each vector encodes a different CAR as disclosed herein. The resulting transduced immune effector cells form a mixed population of engineered cells, with a proportion of the engineered cells expressing more than one different CARs.

[0150] In one embodiment, the invention provides a method of storing genetically engineered cells expressing CARs or TCRs which target a STEAP1 protein. This involves cryopreserving the immune cells such that the cells remain viable upon thawing. A fraction of the immune cells expressing the CARs can be cryopreserved by methods known in the art to provide a permanent source of such cells for the future treatment of patients afflicted with a malignancy. When needed, the cryopreserved transformed immune cells can be thawed, grown and expanded for more such cells.

[0151] As used herein, "cryopreserve" refers to the preservation of cells by cooling to sub-zero temperatures, such as (typically) 77 Kelvin or -196°C (the boiling point of liquid nitrogen). Cryoprotective agents are often used at sub-zero temperatures to prevent the cells being preserved from damage due to freezing at low temperatures or warming to room temperature. Cryopreservative agents and optimal cooling rates can protect against cell injury. Cryoprotective agents which can be used in accordance with the invention include but are not limited to: dimethyl sulfoxide (DMSO) (Lovelock & Bishop, Nature (1959); 183: 1394-1395; Ashwood-Smith, Nature (1961); 190: 1204-1205), glycerol, polyvinylpyrrolidine (Rinfret, Ann. N.Y. Acad. Sci. (1960); 85: 576), and polyethylene glycol (Sloviter & Ravdin, Nature (1962); 196: 48). The preferred cooling rate is 1° - 3°C/minute.

[0152] The term, "substantially pure," is used to indicate that a given component is present at a high level. The component is desirably the predominant component present in a composition. Preferably it is present at a level of more than 30%, of more than 50%, of more than 75%, of more than 90%, or even of more than 95%, said level being determined on a dry weight/dry weight basis with respect to the total composition under consideration. At very high levels (e.g. at levels of more than 90%, of more than 95% or of more than 99%) the component can be regarded as being in "pure form." Biologically active substances of the present invention (including polypeptides, nucleic acid molecules, antigen binding molecules, moieties) can be provided in a form that is substantially free of one or more contaminants with which the substance might otherwise be associated. When a composition is substantially free of a given contaminant, the contaminant will be at a low level (*e.g.*, at a level of less than 10%, less than 5%, or less than 1% on the dry weight/dry weight basis set out above).

[0153] In some embodiments, the cells are formulated by first harvesting them from their culture medium, and then washing and concentrating the cells in a medium and container system suitable for administration (a "pharmaceutically acceptable" carrier) in a treatment-effective amount. Suitable infusion media can be any isotonic medium formulation, typically normal saline, Normosol^{TM} R (Abbott) or Plasma-Lyte^{TM} A (Baxter), but also 5% dextrose in water or Ringer's lactate can be utilized. The infusion medium can be supplemented with human serum albumin.

[0154] Desired treatment amounts of cells in the composition is generally at least 2 cells (for example, at least 1 CD8$^+$ central memory T cell and at least 1 CD4$^+$ helper T cell subset) or is more typically greater than 10^2 cells, and up to 10^6, up to and including 10^8 or 10^9 cells and can be more than 10^{10} cells. The number of cells will depend upon the desired use for which the composition is intended, and the type of cells included therein. The density of the desired cells is typically greater than 10^6 cells/ml and generally is greater than 10^7 cells/ml, generally 10^8 cells/ml or greater. The clinically relevant number of immune cells can be apportioned into multiple infusions that cumulatively equal or exceed 10^5, 10^6, 10^7, 10^8, 10^9, 10^{10}, 10^{11}, or 10^{12} cells. In some aspects of the present invention, particularly since all the infused cells will be redirected to a particular target antigen (STEAP1), lower numbers of cells, in the range of 10^6/kilogram (10^6 - 10^{11} per patient) may be administered. CAR treatments may be administered multiple times at dosages within these ranges. The cells may be autologous, allogeneic, or heterologous to the patient undergoing therapy.

[0155] The CAR expressing cell populations of the present invention may be administered either alone, or as a pharmaceutical composition in combination with diluents and/or with other components such as IL-2 or other cytokines or cell populations. Pharmaceutical compositions of the present invention may comprise a CAR or TCR expressing cell population, such as T cells, as described herein, in combination with one or more pharmaceutically or physiologically acceptable carriers, diluents or excipients. Such compositions may comprise buffers such as neutral buffered saline, phosphate buffered saline and the like; carbohydrates such as glucose, mannose, sucrose or dextrans, mannitol; proteins; polypeptides or amino acids such as glycine; antioxidants; chelating agents such as EDTA or glutathione; adjuvants (e.g., aluminum hydroxide); and preservatives. Compositions of the present invention are preferably formulated for intravenous administration.

[0156] The pharmaceutical compositions (solutions, suspensions or the like), may include one or more of the following: sterile diluents such as water for injection, saline solution, preferably physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils such as synthetic mono- or diglycerides which may serve as the solvent or suspending medium, polyethylene glycols, glycerin, propylene glycol or other solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. An injectable pharmaceutical composition is preferably sterile.

[0157] It will be appreciated that adverse events may be minimized by transducing the immune cells (containing one or more CARs or TCRs) with a suicide gene. It may also be desired to incorporate an inducible “on” or “accelerator” switch into the immune cells. Suitable techniques include use of inducible caspase-9 (U.S. Appl. 2011/0286980) or a thymidine kinase, before, after or at the same time, as the cells are transduced with the CAR construct of the present invention. Additional methods for introducing suicide genes and/or “on” switches include TALENS, zinc fingers, RNAi, siRNA, shRNA, antisense technology, and other techniques known in the art.

[0158] It will be understood that descriptions herein are exemplary and explanatory only and are not restrictive of the invention as claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise.

[0159] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in this application, including but not limited to patents, patent applications, articles, books, and treatises, are hereby expressly incorporated by reference in their entirety for any purpose. As utilized in accordance with the present disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

[0160] In this application, the use of “or” means “and/or” unless stated otherwise. Furthermore, the use of the term “including”, as well as other forms, such as “includes” and “included”, is not limiting. Also, terms such as “element” or “component” encompass both elements and components comprising one unit and elements and components that comprise more than one subunit unless specifically stated otherwise.

[0161] The term “STEAP1 activity” includes any biological effect of STEAP1. In certain embodiments, STEAP1 activity includes the ability of STEAP1 to interact or bind to a substrate or receptor.

[0162] The term “polynucleotide”, “nucleotide”, or “nucleic acid” includes both single-stranded and double-stranded nucleotide polymers. The nucleotides comprising the polynucleotide can be ribonucleotides or deoxyribonucleotides or a modified form of either type of nucleotide. Said modifications include base modifications such as bromouridine and inosine derivatives, ribose modifications such as 2',3'-dideoxyribose, and internucleotide linkage modifications such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphoro-diselenoate, phosphoro-anilothioate, phoshoraniladate and phosphoroamidate.

[0163] The term “oligonucleotide” refers to a polynucleotide comprising 200 or fewer nucleotides. Oligonucleotides can be single stranded or double stranded, e.g., for use in the construction of a mutant gene. Oligonucleotides can be sense or antisense oligonucleotides. An oligonucleotide can include a label, including a radiolabel, a fluorescent label, a hapten or an antigenic label, for detection assays. Oligonucleotides can be used, for example, as PCR primers, cloning primers or hybridization probes.

[0164] The term “control sequence” refers to a polynucleotide sequence that can affect the expression and processing of coding sequences to which it is ligated. The nature of such control sequences can depend upon the host organism. In particular embodiments, control sequences for prokaryotes can include a promoter, a ribosomal binding site, and a transcription termination sequence. For example, control sequences for eukaryotes can include promoters comprising one or a plurality of recognition sites for transcription factors, transcription enhancer sequences, and transcription termination sequence. “Control sequences” can include leader sequences (signal peptides) and/or fusion partner sequences.

[0165] As used herein, “operably linked” means that the components to which the term is applied are in a relationship that allows them to carry out their inherent functions under suitable conditions.

[0166] The term “vector” means any molecule or entity (e.g., nucleic acid, plasmid, bacteriophage or virus) used to transfer protein coding information into a host cell. The term “expression vector” or “expression construct” refers to a vector that is suitable for transformation of a host cell and contains nucleic acid sequences that direct and/or control (in conjunction with the host cell) expression of one or more heterologous coding regions operatively linked thereto. An expression construct can include, but is not limited to, sequences that affect or control transcription, translation, and, if introns are present, affect RNA splicing of a coding region operably linked thereto.

[0167] The term “host cell” refers to a cell that has been transformed, or is capable of being transformed, with a nucleic acid sequence and thereby expresses a gene of interest. The term includes the progeny of the parent cell, whether or not the progeny is identical in morphology or in genetic make-up to the original parent cell, so long as the gene of interest is present.

[0168] The term “transformation” refers to a change in a cell's genetic characteristics, and a cell has been transformed when it has been modified to contain new DNA or RNA. For example, a cell is transformed where it is genetically modified from its native state by introducing new genetic material via transfection, transduction, or other techniques. Following transfection or transduction, the transforming DNA can recombine with that of the cell by physically integrating into a chromosome of the cell, or can be maintained transiently as an episomal element without being replicated, or can replicate independently as a plasmid. A cell is considered to have been “stably transformed” when the transforming DNA is replicated with the division of the cell.

[0169] The term “transfection” refers to the uptake of foreign or exogenous DNA by a cell. A number of transfection techniques are well known in the art and are disclosed herein. See, *e.g.*, Graham *et al.*, 1973, Virology 52:456; Sambrook *et al.*, 2001, Molecular Cloning: A Laboratory Manual, supra; Davis *et al.*, 1986, Basic Methods in Molecular Biology, Elsevier; Chu *et al.*, 1981, Gene 13:197.

[0170] The term “transduction” refers to the process whereby foreign DNA is introduced into a cell via viral vector. See Jones *et al.*, (1998). Genetics: principles and analysis. Boston: Jones & Bartlett Publ.

[0171] The terms "polypeptide" or "protein" refer to a macromolecule having the amino acid sequence of a protein, including deletions from, additions to, and/or substitutions of one or more amino acids of the native sequence. The terms "polypeptide" and "protein" specifically encompass STEAP1 antigen binding molecules, antibodies, or sequences that have deletions from, additions to, and/or substitutions of one or more amino acid of antigen-binding protein. The term "polypeptide fragment" refers to a polypeptide that has an amino-terminal deletion, a carboxyl-terminal deletion, and/or an internal deletion as compared with the full-length native protein. Such fragments can also contain modified amino acids as compared with the native protein. Useful polypeptide fragments include immunologically functional fragments of antigen binding molecules. Useful fragments include but are not limited to one or more CDR regions, variable domains of a heavy and/or light chain, a portion of other portions of an antibody chain, and the like.

[0172] The term "isolated" means (i) free of at least some other proteins with which it would normally be found, (ii) is essentially free of other proteins from the same source, *e.g.*, from the same species, (iii) separated from at least about 50 percent of polynucleotides, lipids, carbohydrates, or other materials with which it is associated in nature, (iv) operably associated (by covalent or noncovalent interaction) with a polypeptide with which it is not associated in nature, or (v) does not occur in nature.

[0173] A "variant" of a polypeptide (*e.g.*, an antigen binding molecule, or an antibody) comprises an amino acid sequence wherein one or more amino acid residues are inserted into, deleted from and/or substituted into the amino acid sequence relative to another polypeptide sequence. Variants include fusion proteins.

[0174] The term "identity" refers to a relationship between the sequences of two or more polypeptide molecules or two or more nucleic acid molecules, as determined by aligning and comparing the sequences. "Percent identity" means the percent of identical residues between the amino acids or nucleotides in the compared molecules and is calculated based on the size of the smallest of the molecules being compared. For these calculations, gaps in alignments (if any) are preferably addressed by a particular mathematical model or computer program (*i.e.*, an "algorithm").

[0175] To calculate percent identity, the sequences being compared are typically aligned in a way that gives the largest match between the sequences. One example of a computer program that can be used to determine percent identity is the GCG program package, which includes GAP (Devereux *et al.*, 1984, Nucl. Acid Res. 12:387; Genetics Computer Group, University of Wisconsin, Madison, Wis.). The computer algorithm GAP is used to align the two polypeptides or polynucleotides for which the percent sequence identity is to be determined. The sequences are aligned for optimal matching of their respective amino acid or nucleotide (the "matched span", as determined by the algorithm). In certain embodiments, a standard comparison matrix (see, Dayhoff *et al.*, 1978, Atlas of Protein Sequence and Structure 5:345-352 for the PAM 250 comparison matrix; Henikoff *et al.*, 1992, Proc. Natl. Acad. Sci. U.S.A. 89:10915-10919 for the BLOSUM 62 comparison matrix) is also used by the algorithm.

[0176] As used herein, the twenty conventional (e.g., naturally occurring) amino acids and their abbreviations follow conventional usage. *See* Immunology - A Synthesis (2nd Edition, Golub and Gren, Eds., Sinauer Assoc., Sunderland, Mass. (1991)), which is incorporated herein by reference for any purpose. Stereoisomers (e.g., D-amino acids) of the twenty conventional amino acids, unnatural amino acids such as alpha-, alpha-disubstituted amino acids, N-alkyl amino acids, lactic acid, and other unconventional amino acids can also be suitable components for polypeptides of the present invention. Examples of unconventional amino acids include: 4-hydroxyproline, .gamma.-carboxyglutamate, epsilon-N,N,N-trimethyllysine, e-N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, .sigma.-N-methylarginine, and other similar amino acids and imino acids (e.g., 4-hydroxyproline). In the polypeptide notation used herein, the left-hand direction is the amino terminal direction and the right-hand direction is the carboxy-terminal direction, in accordance with standard usage and convention.

[0177] Conservative amino acid substitutions can encompass non-naturally occurring amino acid residues, which are typically incorporated by chemical peptide synthesis rather than by synthesis in biological systems. These include peptidomimetics and other reversed or inverted forms of amino acid moieties. Naturally occurring residues can be divided into classes based on common side chain properties:

a) hydrophobic: norleucine, Met, Ala, Val, Leu, Ile;
b) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln;
c) acidic: Asp, Glu;
d) basic: His, Lys, Arg;

e) residues that influence chain orientation: Gly, Pro; and

f) aromatic: Trp, Tyr, Phe.

[0178] For example, non-conservative substitutions can involve the exchange of a member of one of these classes for a member from another class. Such substituted residues can be introduced, for example, into regions of a human antibody that are homologous with non-human antibodies, or into the non-homologous regions of the molecule.

[0179] In making changes to the antigen binding molecule, the costimulatory or activating domains of the engineered T cell, according to certain embodiments, the hydropathic index of amino acids can be considered. Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics. They are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5). See Kyte et al., J. Mol. Biol., 157:105-131 (1982). It is known that certain amino acids can be substituted for other amino acids having a similar hydropathic index or score and still retain a similar biological activity. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity, particularly where the biologically functional protein or peptide thereby created is intended for use in immunological embodiments, as in the present case. Exemplary amino acid substitutions are set forth in Table 2.

Table 2

Original Residues	Exemplary Substitutions	Preferred Substitutions
Ala	Val, Leu, Ile	Val
Arg	Lys, Gln, Asn	Lys
Asn	Gln	Gln
Asp	Glu	Glu
Cys	Ser, Ala	Ser
Gln	Asn	Asn
Glu	Asp	Asp
Gly	Pro, Ala	Ala
His	Asn, Gln, Lys, Arg	Arg

Ile	Leu, Val, Met, Ala, Phe, Norleucine	Leu
Leu	Norleucine, Ile, Val, Met, Ala, Phe	Ile
Lys	Arg, 1,4 Diamino-butyric	Arg
	Acid, Gln, Asn	
Met	Leu, Phe, Ile	Leu
Phe	Leu, Val, Ile, Ala,	Leu
	Tyr	
Pro	Ala	Gly
Ser	Thr, Ala, Cys	Thr
Thr	Ser	Ser
Trp	Tyr, Phe	Tyr
Tyr	Trp, Phe, Thr, Ser	Phe
Val	Ile, Met, Leu, Phe,	Leu
	Ala, Norleucine	

[0180] The term “derivative” refers to a molecule that includes a chemical modification other than an insertion, deletion, or substitution of amino acids (or nucleic acids). In certain embodiments, derivatives comprise covalent modifications, including, but not limited to, chemical bonding with polymers, lipids, or other organic or inorganic moieties. In certain embodiments, a chemically modified antigen binding molecule can have a greater circulating half-life than an antigen binding molecule that is not chemically modified. In some embodiments, a derivative antigen binding molecule is covalently modified to include one or more water soluble polymer attachments, including, but not limited to, polyethylene glycol, polyoxyethylene glycol, or polypropylene glycol.

[0181] Peptide analogs are commonly used in the pharmaceutical industry as non-peptide drugs with properties analogous to those of the template peptide. These types of non-peptide compound are termed “peptide mimetics” or “peptidomimetics.” Fauchere, J., Adv. Drug Res., 15:29 (1986); Veber & Freidinger, TINS, p.392 (1985); and Evans *et al.*, J. Med. Chem., 30:1229 (1987), which are incorporated herein by reference for any purpose.

[0182] The term "therapeutically effective amount" refers to the amount of a STEAP1 antigen binding molecule determined to produce a therapeutic response in a mammal. Such therapeutically effective amounts are readily ascertained by one of ordinary skill in the art.

[0183] The terms "patient" and "subject" are used interchangeably and include human and non-human animal subjects as well as those with formally diagnosed disorders, those without formally recognized disorders, those receiving medical attention, those at risk of developing the disorders, etc.

[0184] The term "treat" and "treatment" includes therapeutic treatments, prophylactic treatments, and applications in which one reduces the risk that a subject will develop a disorder or other risk factor. Treatment does not require the complete curing of a disorder and encompasses embodiments in which one reduces symptoms or underlying risk factors. The term "prevent" does not require the 100% elimination of the possibility of an event. Rather, it denotes that the likelihood of the occurrence of the event has been reduced in the presence of the compound or method.

[0185] Standard techniques can be used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (e.g., electroporation, lipofection). Enzymatic reactions and purification techniques can be performed according to manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures can be generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. See, e.g., Sambrook *et al.*, Molecular Cloning: A Laboratory Manual (2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)), which is incorporated herein by reference for any purpose.

[0186] The following sequences will further exemplify the invention.

[0187] CD28T DNA Extracellular, transmembrane, intracellular

CTTGATAATGAAAAGTC
AACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACC
CTTGTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGT
GGAGTCCTCGCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCT
TCTGGGTTAGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGA

ATATGACTCCACGCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTT ACGCACCACCTAGAGATTTCGCTGCCTATCGGAGC (SEQ ID NO:1)

[0188] CD28T Extracellular, transmembrane, intracellular AA:
LDNEKSNGTI IHVKGKHLCP SPLFPGPSKP FWVLVVVGGV LACYSLLVTV AFIIFWVRSK RSRLLHSDYM NMTPRRPGPT RKHYQPYAPP RDFAAYRS (SEQ ID NO:2)

CD28T DNA - Extracellular

[0189] CTTGATAATGAAAAGTCAAACGGAACAATCATTCACGTGAAGGGCAA GCACCTCTGTCCGTCACCCTTGTTCCCTGGTCCATCCAAGCCA (SEQ ID NO:3)

[0190] CD28T AA - Extracellular
LDNEKSNGTI IHVKGKHLCP SPLFPGPSKP (SEQ ID NO:4)

[0191] CD28 DNA Transmembrane Domain
TTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCGCTTGTTACTCTCTGC TCGTCACCGTGGCTTTTATAATCTTCTGGGTT (SEQ ID NO:5)

[0192] CD28 AA Transmembrane Domain:
FWVLVVVGGV LACYSLLVTV AFIIFWV (SEQ ID NO:6)

[0193] CD28 DNA Intracellular Domain:
AGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGAATATGACT CCACGCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCACCA CCTAGAGATTTCGCTGCCTATCGGAGC (SEQ ID NO:7)

[0194] CD28 AA Intracellular Domain
RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS (SEQ ID NO:8)

[0195] CD3 zeta DNA
AGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGC CAGAACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTA TGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCA

AACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAGCTGCAG
AAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGA
GCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCA
CTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCAC
CTAGG (SEQ ID NO:9)

[0196] CD3 zeta AA
RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGK
PRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTA
TKDTYDALHMQALPPR (SEQ ID NO:10)

[0197] CD28 DNA
ATTGAGGTGATGTATCCACCGCCTTACCTGGATAACGAAAAGAGTAAC
GGTACCATCATTCACGTGAAAGGTAAACACCTGTGTCCTTCTCCCCTCT
TCCCCGGGCCATCAAAGCCC (SEQ ID NO:11)

[0198] CD28 AA
IEVMYPPPYL DNEKSNGTII HVKGKHLCPS PLFPGPSKP (SEQ ID NO:12)

[0199] CD8 DNA extracellular & transmembrane domain
GCTGCAGCATTGAGCAACTCAATAATGTATTTTAGTCACTTTGTACCAG
TGTTCTTGCCGGCTAAGCCTACTACCACACCCGCTCCACGGCCACCTAC
CCCAGCTCCTACCATCGCTTCACAGCCTCTGTCCCTGCGCCCAGAGGCT
TGCCGACCGGCCGCAGGGGGCGCTGTTCATACCAGAGGACTGGATTTC
GCCTGCGATATCTATATCTGGGCACCCCTGGCCGGAACCTGCGGCGTA
CTCCTGCTGTCCCTGGTCATCACGCTCTATTGTAATCACAGGAAC (SEQ ID NO:13)

[0200] CD8 AA extracellular & transmembrane Domain
AAALSNSIMYFSHFVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPA
AGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCNHRN (SEQ ID NO:14)

[0201] 4-1BB DNA intracellular domain

CGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAGCTGCTGTACATTTTCAAACAGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGACGGCTGCTCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTG (SEQ ID NO:15)

[0202] 4-1BB AA intracellular Domain

RFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL (SEQ ID NO:16)

[0203] Clone 2F3 HC DNA

CAGGTTCAGCTGCAGCAGTCTGGAGCTGAGATGATGAAGCCTGGGGCCTCAGTGAAGATATCCTGCAAGGCTACTGGCTACACATTCAGTACCTACTGGATAGAGTGGGTAAAGCAGAGGCCTGGACATGGCCTTGAGTGGATTGGAGAGATTTTACCTGGAAGTGGTAATACTGACTTCAATGAGAAGTTCAAGGGCAAGGCCACATTCACTGCAGATACATCCTCCGACACAGCCTACATGCATCTCAGCAGCCTGACATCTGAGGACTCTGCCGTCTATTACTGTACAAGATGGGGGTACTACGGTACTAGGGGGTACTTCAATGTCTGGGGCGCAGGGTCCACGGTCACCGTCTCCTCA (SEQ ID NO: 87)

[0204] Clone 2F3 HC AA – CDRs Underlined

QVQLVQSGAEVKKPGASVKVSCKASGYTFSTYWIEWVRQAPGQRLEWMGEILPGSGNTDFNEKFQGRVTFTADTSSDTAYMELSSLRSEDTAVYYCTRWGYYGTRGYFNVWGQGTLVTVSS (SEQ ID NO: 88)

[0205] Clone 2F3 HC AA CDR1: TYWIE (SEQ ID NO: 89)

[0206] Clone 2F3 HC AA CDR2: EILPGSGNTDFNEKFQG (SEQ ID NO: 90)

[0207] Clone 2F3 HC AA CDR3: WGYYGTRGYFNV (SEQ ID NO: 91)

[0208] Clone 2F3 LC DNA

CAAATTGTTCTCACCCAGTCTCCAGCAATCATGTCTGCATCTCCAGGGGAGAAGGTCACCATAACGTGCAGTGCCAGCTCAAGTGTAAGTTACATGCACTGGTTCCAGCAGAAGCCAGGCACTTCTCCCAAACTCTGGATTTATAGCACCTCCAACCTGGCTTCTGGAGTCCCTGCTCGCTTCAGTGGCAGTGGATCTGGGACCTCTTACTCTCTCACAATCAGCCGAATGGAGGCTGAAGATGCTGCCACTTATTACTGCCAGCAAAGGCGTAGTTTCCCGTACACGTTCGGAGGGGGGACCAAGCTGGAAATTAAA (SEQ ID NO: 92)

[0209] Clone 2F3 LC AA (CDRs Underlined)

EIVLTQSPATLSLSPGERATLSCRASSSVSYMHWFQQKPGQAPRLLIYSTSNLASGIPARFSGSGSGTDYTLTISSLEPEDFAVYYCQQRRSFPYTFGQGTKLEIK (SEQ ID NO: 93)

[0210] Clone 2F3 LC CDR1 AA: RASSSVSYMH (SEQ ID NO: 94)

[0211] Clone 2F3 LC CDR2 AA: STSNLAS (SEQ ID NO: 95)

[0212] Clone 2F3 LC CDR3 AA: QQRRSFPYT (SEQ ID NO: 96)

[0213] Clone 11C2 HC DNA

CAGATCCAGTTGGTGCAGTCTGGACCTGAACTGAAGAAGCCTGGAGAGACAGTCAAGATCTCCTGCAAGGCTTCTGGATATACCTTCACAAACTATGGAATGAACTGGGTGAAGCAGGCTCCAGGAAAGGGTTTACAGTGGATGGGCTGGATGAACACTTATACTGGAGAGCCAACATATGCTGATGACTTCAAGGGACGGTTTGCCTTCTCTTTGGAAACCTCTGCCAGAACTGTCTCTTTGGACATCAACGACCTCAAAAATGAGGACACGGCTACATATTTCTGTACAAGAGCAGGGGGACAACTCAGGCCCGGGGCTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA (SEQ ID NO:97)

[0214] Clone 11C2 HC AA (CDRs underlined)

QLVQSGAEVKKPGATVKISCKASGYTFTNYGMNWVQQAPGQGLEWMGWMNTYTGEPTYADKFQGRVTFTLDTSARTVYMELSSLRSEDTAVYFCARAGGQLRPGAMDYWGQGTMVTVSS (SEQ ID NO:98)

[0215] Clone 11C2 HC AA CDR1: NYGMN (SEQ ID NO:99)

[0216] Clone 11C2 HC AA CDR2: WMNTYTGEPTYADKFQG (SEQ ID NO:100)

[0217] Clone 11C2 HC AA CDR3: AGGQLRPGAMDY (SEQ ID NO:101)

[0218] Clone 11C2 LC DNA

GACATTGTGCTGACCCAATCTCCAGCTTCTTTGGCTGTGTCTCTAGGGCAGAGGGCCACCATCTCCTGCAAGGCCAGCCAAAGTGTTGATTATGATGGTGATAGTTTTATGAACTGGTACCAACAGAAACCAGGACAGCCACCCAAACTCCTCATCTATGTTGCATCCAATCTAGAATCTGGGATCCCAGACAGGTTTAGTGGCAGTGGGTCTGGGACAGACTTCACCCTCAACATCCATCCTGTGGAGGAGGAGGATGCTGCAACCTATTATTGTCAGCAAAGTAATGAGGAACCTCCGACGTTCGGTGGAGGCACCAAGCTGGAAATCAAA (SEQ ID NO: 102)

[0219] Clone 11C2 LC AA (CDRs underlined)

[0220] DIVLTQTPLSLSVTPGQPASISCKASQSVDYDGDSFMNWYLQKPGQPPQLLIYVASNLESGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCQQSNEEPPTFGQGTKLEIK (SEQ ID NO: 103)

[0221] Clone 11C2 LC AA CDR1: KASQSVDYDGDSFMN (SEQ ID NO: 104)

[0222] Clone 11C2 LC AA CDR2: VASNLES (SEQ ID NO: 105)

[0223] Clone 11C2 LHC AA CDR3: QQSNEEPPT (SEQ ID NO: 106)

[0224] Clone 1A1 HC DNA

[0225] CAGATACAACTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGTAGCGTCTGGATTCACCTTCAAGAACTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATTTGGTATGATGGAAGTAATGAATACTATGGAGACCCCGTGAAGGGCCGATTCACCATCTCCAGAGACAACTCCAAGAACATGTTGTATCTGCAAATGAACAGCCTGAGAGCCGATGACACGGCTGTGTATTACTGTGCGAGGTCGGGAATAGCAGTGGCTGGGGCCTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA (SEQ ID NO: 107)

[0226] Clone 1A1 HC AA (CDRs underlined)

[0227] QVQLVQSGAEVKKPGASVKVSCKASGYTFTTYWMHWVRQAPGQGLEWMGEINPSSGRTNYNEKFKTRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAKLGPGPQYYAMDYWGQGTMVTVSS (SEQ ID NO: 108)

[0228] Clone 1A1 HC AA CDR1: TYWMH (SEQ ID NO: 109)

[0229] Clone 1A1 HC AA CDR2: EINPSSGRTNYNEKFKT (SEQ ID NO: 110)

[0230] Clone 1A1 HC AA CDR3: LGPGPQYYAMDY (SEQ ID NO: 111)

[0231] Clone 1A1 LC DNA

[0232] GAAATTGTGTTGACGCAGTCTCCAGACACCCTGTCTTTGTCTCCAGGGGAAAAAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCAGCTTCTTGGCCTGGTACCAGCAGAAACCTGGACAGGCTCCCAGTCTCCTCATCTATGTTGCATCCAGAAGGGCCGCTGGCATCCCTGACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATTTTGGAATGTTTTACTGTCAACACTATGGTAGGACACCATTCACTTTCGGCCCTGGGACCAAAGTGGATATCAAACGA (SEQ ID NO: 112)

[0233] Clone 1A1 LC AA (CDRs underlined)

[0234] DIQMTQSPSSLSASVGDRVTITCHASQNINVWLSWYQQKPGKAPKLLIYKASKLHTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGQSYPWTFGQGTKLEIK (SEQ ID NO:113)

[0235] Clone 1A1 LC AA CDR1: HASQNINVWLS (SEQ ID NO: 114)

[0236] Clone 1A1 LC AA CDR2: KASKLHT (SEQ ID NO: 115)

[0237] Clone 1A1 LC AA CDR3: QQGQSYPWT (SEQ ID NO: 116)

[0238] Clone 7A4 HC DNA

[0239] CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATACACCTTCACCGGCTACTATATACACTGGGTGCGACAGGCCCCTGAACAAGGGCTTGAGTGGATGGGATGGATCAACCCTAACAGTGGTGGCACAAACTATGCACAGAAGTTTCAGGGCAGGGTCACCATGGCCAGGGACACGTCCATCAGCACAGTTTACATGGACCTGAGCAGGCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGAATACGCGGTGGTAACTCGGTCTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA (SEQ ID NO: 117)

[0240] Clone 7A4 HC AA (CDRs underlined)

[0241] QVQLVQSGAEVKKPGASVKVSCKASGYSFTSYDINWVRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSISTAYMELSSLRSEDTAVYYCGRAGYYYYFGMDVWGQGTTVTVSS (SEQ ID NO: 118)

[0242] Clone 7A4 HC AA CDR1: SYDIN (SEQ ID NO: 119)

[0243] Clone 7A4 HC AA CDR2: WMNPNSGNTGYAQKFQG (SEQ ID NO: 120)

[0244] Clone 7A4 HC AA CDR3: AGYYYYFGMDV (SEQ ID NO: 121)

[0245] Clone 7A4 LC DNA

[0246] GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGGGCCACCATCAACTGCAAGTCCACCCAGAGTATTTTATACACCTCCAACAATAAGAACTTCTTAGCTTGGTACCAGCAGAAACCAGGGCAGCCTCCTAAACTGCTCATTTCCTGGGCATCTATCCGGGAATCCGGGGTCCCTGACCGATTCAGTGGCAGCGGGTCTGGGACAGATTTCGCTCTCACCATCAGCAGCCTGCAGGCTGAAGATGTGGCAGTTTATTACTGTCAACAATATTTTAGTACTATGTTCAGTTTTGGCCAGGGGACCAAGCTGGAGATCAAACGA (SEQ ID NO: 122)

[0247] Clone 7A4 LC AA (CDRs underlined)

[0248] EIVLTQSPGTLSLSPGERATLSCRAGQSVTSSSFAWYQQKPGQAPRLLIYQTSTRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGGSRSFGQGTKVELKR (SEQ ID NO: 123)

[0249] Clone 7A4 LC AA CDR1: RAGQSVTSSSFA (SEQ ID NO: 124)

[0250] Clone 7A4 LC AA CDR2: QTSTRAT (SEQ ID NO: 125)

[0251] Clone 7A4 LC AA CDR3: QQYGGSRS (SEQ ID NO: 126)

[0252] Clone 7A5 HC DNA

[0253] CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGTAGTGGTGCATACTACTGGACTTGGATCCGCCAGCACCCAGGGAAGGGCCTGGAGTGGATTGGGTACATCCATTACAGTGGGAGCACCTACTCCAACCCGTCCCTCAAGAGTCGAATTACCATATCGTTAGACACGTCTAAGAACCAGTTCTCCCTGAAGCTGAACTCTGTGACTGCCGCGGACACGGCCGTGTATTACTGTGCGAGACAAGAGGACTACGGTGGTTTGTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTTTCCTCA (SEQ ID NO: 127)

[0254] Clone 7A5 HC AA (CDRs underlined)

[0255] QVQLVQSGAEVKKPGASVKVSCKASGYSFTSYDINWVRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSISTAYMELSSLRSEDTAVYYCGRAGYYYYFGMDVWGQGTTVTVSS (SEQ ID NO: 128)

[0256] Clone 7A5 HC AA CDR1: SYDIN (SEQ ID NO: 129)

[0257] Clone 7A5 HC AA CDR2: WMNPNSGNTGYAQKFQG (SEQ ID NO: 130)

[0258] Clone 7A5 HC AA CDR3: AGYYYYFGMDV (SEQ ID NO: 131)

[0259]

[0260] Clone 7A5 LC DNA

[0261] GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTGTCTCCAGGGGAAAGAATCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTACCACCGACTTAGCCTGGTACCAGCAGATGCCTGGACAGGCTCCCCGGCTCCTCATCTATGATGCTTCCACCAGGGCCACTGGTTTCCCAGCCAGATTCAGTGGCAGTGGGTCTGGGACAGACTTCACGCTCACCATCAGCAGCCTGCAGGCTGAAGATTTTGCAGTTTATTACTGTCAACATTATAAAACCTGGCCTCTCACTTTCGGCGGAGGGACTAAGGTGGAGATCAAACGA (SEQ ID NO: 132)

[0262] Clone 7A5 LC AA (CDRs underlined)

[0263] EIVLTQSPGTLSLSPGERATLSCRAGQSVTSSSLAWYQQKPGQAPRLLIYQTSTRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGGSRAFGQGTKVELKR (SEQ ID NO: 133)

[0264] Clone 7A5 LC AA CDR1: RAGQSVTSSSLA (SEQ ID NO: 134)

[0265] Clone 7A5 LC AA CDR2: QTSTRAT (SEQ ID NO: 135)

[0266] Clone 7A5 LC AA CDR3: QQYGGSRA (SEQ ID NO: 136)

[0267] Clone 14C11 HC DNA

[0268] CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGTAGTGGTGCATACTACTGGACTTGGATCCGCCAGCACCCAGGGAAGGGCCTGGAGTGGATTGGGTACATCCATTACAGTGGGAGCACCTACTCCAACCCGTCCCTCAAGAGTCGAATTACCATATCGTTAGACACGTCTAAGAACCAGTTCTCCCTGAAGCTGAACTCTGTGACTGCCGCGGACACGGCCGTGTATTACTGTGCGAGACAAGAGGACTACGGTGGTTTGTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTTTCCTCA (SEQ ID NO: 137)

[0269] Clone 14C11 HC AA (CDRs underlined)

[0270] QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPNSGGTNSAQKFQGRVTMTRDTSISTAYMELNRLRSDDTAVYYCARGWLQTYYFDNWGQGTLVTVSS (SEQ ID NO: 138)

[0271] Clone 14C11 HC AA CDR1: GYYMH (SEQ ID NO: 139)

[0272] Clone 14C1 HC AA CDR2: WINPNSGGTNSAQKFQG (SEQ ID NO: 140)

[0273] Clone 14C1 HC AA CDR3: GWLQTYYFDN (SEQ ID NO: 141)

[0274]

[0275] Clone 14C11 LC DNA

[0276] GAAATAGTGATGACGCAGTCTCCAGCCACCCTGTCTGTGTCTCCAGGGGAAAGAATCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTACCACCGACTTAGCCTGGTACCAGCAGATGCCTGGACAGGCTCCCCGGCTCCTCATCTATGATGCTTCCACCAGGGCCACTGGTTTCCCAGCCAGATTCAGTGGCAGTGGGTCTGGGACAGACTTCACGCTCACCATCAGCAGCCTGCAGGCTGAAGATTTTGCAGTTTATTACTGTCAACATTATAAAACCTGGCCTCTCACTTTCGGCGGAGGGACTAAGGTGGAGATCAAACGA (SEQ ID NO: 142)

[0277] Clone 14C11 LC AA (CDRs underlined)

[0278] DIVMTQSPDSLAVSLGERATIYCKSSQTVLTSSNNKNFLAWYQQKLGQPPKLLISWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAIYYCQHYYTSPLTFGGGTKVEIKR (SEQ ID NO: 143)

[0279] Clone 14C11 LC AA CDR1: TVLTSSNNKNFLA (SEQ ID NO: 144)

[0280] Clone 14C1 LC AA CDR2: WASTRES (SEQ ID NO: 145)

[0281] Clone 14C1 LC AA CDR3: QHYYTSPLT (SEQ ID NO: 146)

[0282] Construct S1-2F3-CD28T-CD28-41BB DNA (signal sequence in bold)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAGAAGCCCGGA
GCCAGCGTGAAGGTGAGCTGCAAAGCCAGCGGCTACACCTTCTCCACCTACTGG
ATCGAGTGGGTGAGACAGGCCCCGGACAGAGGCTGGAATGGATGGGAGAGATC
CTGCCCGGCAGCGGCAACACCGACTTCAACGAGAAGTTCCAGGGCAGAGTGACC
TTCACCGCCGATACCAGCAGCGACACCGCCTACATGGAACTGAGCAGCCTGAGA
AGCGAGGATACCGCCGTCTACTACTGCACCAGATGGGGCTACTACGGCACCAGG
GGCTATTTCAACGTGTGGGGCCAGGGAACCCTCGTGACCGTGAGCAGCGGAGGC
GGAGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGAGATTGTGCTGACC
CAGAGCCCTGCTACACTGAGCCTGAGCCCCGGCGAGAGAGCCACACTGAGCTGC
AGAGCCAGCAGCAGCGTGAGCTACATGCACTGGTTCCAGCAAAAGCCCGGCCAG
GCCCCTAGGCTGCTGATCTACAGCACATCCAACCTGGCCAGCGGCATCCCTGCCA
GATTCAGCGGTTCTGGCTCCGGCACCGACTACACCCTGACCATCTCCAGCCTGGA
GCCCGAGGACTTTGCCGTGTATTACTGCCAGCAGAGGAGGAGCTTCCCCTACACA
TTCGGCCAGGGCACCAAACTGGAGATCAAGGCCGCTGCCCTTGATAATGAAAAG
TCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTTGT
TCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCGC
TTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTAGATCCAAAA
GAAGCCGCCTGCTCCATAGCGATTACATGAATATGACTCCACGCCGCCCTGGCCC
CACAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATTTCGCTGCCTATCGG
AGCCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCTGCTGTACATTTTCAAAC
AGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGACGGCTGCTCCTGCC
GCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGAAGTTTTCCAGAT
CTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCA
ACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGAC
CCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAAT
GAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGA
GAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGC
TACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAA
GAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGA
AGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCC
GCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCC
TGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTG

GCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCC
TGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTG
TACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGAT
GCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTGT
GAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATA
AGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCG
AACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGC
TGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGAT
GGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCC
AAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCG
TGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCG
ACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGT
AGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:17)

[0283] Construct S1-2F3-CD28T-CD28-41BB AA (signal sequence in bold; CDRs underlined)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFSTYWI
EWVRQAPGQRLEWMGEILPGSGNTDFNEKFQGRVTFTADTSSDTAYMELSSLRSED
TAVYYCTRWGYYGTRGYFNVWGQGTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPA
TLSLSPGERATLSCRASSSVSYMHWFQQKPGQAPRLLIYSTSNLASGIPARFSGSGSGT
DYTLTISSLEPEDFAVYYCQQRRSFPYTFGQGTKLEIKAAALDNEKSNGTIIHVKGKH
LCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTP
RRPGPTRKHYQPYAPPRDFAAYRSRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGC
SCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRD
PEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTAT
KDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRL
LLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSV
TFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRV
CEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRW
ADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPV
VTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:18)

[0284] Construct S1-2F3-CD28T-CD28 DNA (signal sequence in bold)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAGAAGCCCGGA
GCCAGCGTGAAGGTGAGCTGCAAAGCCAGCGGCTACACCTTCTCCACCTACTGG
ATCGAGTGGGTGAGACAGGCCCCCGGACAGAGGCTGGAATGGATGGGAGAGAT
CCTGCCCGGCAGCGGCAACACCGACTTCAACGAGAAGTTCCAGGGCAGAGTGAC
CTTCACCGCCGATACCAGCAGCGACACCGCCTACATGGAACTGAGCAGCCTGAG
AAGCGAGGATACCGCCGTCTACTACTGCACCAGATGGGGCTACTACGGCACCAG
GGGCTATTTCAACGTGTGGGGCCAGGGAACCCTCGTGACCGTGAGCAGCGGAGG
CGGAGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGAGATTGTGCTGAC
CCAGAGCCCTGCTACACTGAGCCTGAGCCCCGGCGAGAGAGCCACACTGAGCTG
CAGAGCCAGCAGCAGCGTGAGCTACATGCACTGGTTCCAGCAAAAGCCCGGCCA
GGCCCCTAGGCTGCTGATCTACAGCACATCCAACCTGGCCAGCGGCATCCCTGCC
AGATTCAGCGGTTCTGGCTCCGGCACCGACTACACCCTGACCATCTCCAGCCTGG
AGCCCGAGGACTTTGCCGTGTATTACTGCCAGCAGAGGAGGAGCTTCCCCTACAC
ATTCGGCCAGGGCACCAAACTGGAGATCAAGGCCGCTGCCCTTGATAATGAAAA
GTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTTG
TTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCG
CTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTAGATCCAAA
AGAAGCCGCCTGCTCCATAGCGATTACATGAATATGACTCCACGCCGCCCTGGCC
CCACAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATTTCGCTGCCTATCG
GAGCAGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCA
GAACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTT
GGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAA
ACCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCT
ATTCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGT
TTGTACCAGGGACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGC
AAGCCCTGCCACCTAGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATCT
CTCCTTACATGTGGGGACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGCC
ACGGGAAGGGCTATGGATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGT
CTCTCGGAGGCGCTAAGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTGA
ATGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAAC
CAGACAGTCTGTGAACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAG
CCACCGAGCCTTGCAAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGC

CCCCTGTGTCGAAGCCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:19)

[0285] Construct S1-2F3-CD28T-CD28 AA (signal sequence in bold; CDRs underlined)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFSTYWIEWVRQAPGQRLEWMGEILPGSGNTDFNEKFQGRVTFTADTSSDTAYMELSSLRSEDTAVYYCTRWGYYGTRGYFNVWGQGTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPATLSLSPGERATLSCRASSSVSYMHWFQQKPGQAPRLLIYSTSNLASGIPARFSGSGSGTDYTLTISSLEPEDFAVYYCQQRRSFPYTFGQGTKLEIKAAALDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:20)

[0286] Construct S1-2F3-CD28T-41BB DNA (signal sequence in bold)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCGCACGCCCGCAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAGAAGCCCGGAGCCAGCGTGAAGGTGAGCTGCAAAGCCAGCGGCTACACCTTCTCCACCTACTGGATCGAGTGGGTGAGACAGGCCCCCGGACAGAGGCTGGAATGGATGGGAGAGAT

CCTGCCCGGCAGCGGCAACACCGACTTCAACGAGAAGTTCCAGGGCAGAGTGAC
CTTCACCGCCGATACCAGCAGCGACACCGCCTACATGGAACTGAGCAGCCTGAG
AAGCGAGGATACCGCCGTCTACTACTGCACCAGATGGGGCTACTACGGCACCAG
GGGCTATTTCAACGTGTGGGGCCAGGGAACCCTCGTGACCGTGAGCAGCGGAGG
CGGAGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGAGATTGTGCTGAC
CCAGAGCCCTGCTACACTGAGCCTGAGCCCCGGCGAGAGAGCCACACTGAGCTG
CAGAGCCAGCAGCAGCGTGAGCTACATGCACTGGTTCCAGCAAAAGCCCGGCCA
GGCCCCTAGGCTGCTGATCTACAGCACATCCAACCTGGCCAGCGGCATCCCTGCC
AGATTCAGCGGTTCTGGCTCCGGCACCGACTACACCCTGACCATCTCCAGCCTGG
AGCCCGAGGACTTTGCCGTGTATTACTGCCAGCAGAGGAGGAGCTTCCCCTACAC
ATTCGGCCAGGGCACCAAACTGGAGATCAAGGCCGCTGCCCTTGATAATGAAAA
GTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTTG
TTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCG
CTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTCGCTTTTCCG
TCGTTAAGCGGGGGAGAAAAAAGCTGCTGTACATTTTCAAACAGCCGTTTATGA
GGCCGGTCCAAACGACTCAGGAAGAGGACGGCTGCTCCTGCCGCTTTCCTGAGG
AGGAGGAGGGCGGGTGCGAACTGAGGGTGAAGTTTTCCAGATCTGCAGATGCAC
CAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGACGCA
GGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGATGGGTG
GCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAG
GATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAGAAG
GGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGAAGGATAC
TTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAAGAGAAGTGGCAG
CGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGAAGAAAATCCGGG
GCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCCGCGACTGCTTCT
CCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCCTGTCCAACGGGC
CTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTCG
CACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCCTGGATTCAGTGAC
ATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTGTACCGAATGTGTG
GGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGATGCAGTGTGCAGAT
GTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTGTGAGGCCTGCCGGG
TGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGCAAAACACAGT
ATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCGAACCACGTCGACCC

TTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGAGAGAGTGTAC
GCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGATCACCCGGAG
CACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAGAACCGGAGGC
CCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTC
ATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCGACAATCTGATTCCT
GTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCT
TTAAGAGATGACCTAGGTAA (SEQ ID NO:21)

[0287] Construct S1-2F3-CD28T-41BB AA (signal sequence in bold; CDRs underlined)
MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFSTYWI
EWVRQAPGQRLEWMGEILPGSGNTDFNEKFQGRVTFTADTSSDTAYMELSSLRSED
TAVYYCTRWGYYGTRGYFNVWGQGTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPA
TLSLSPGERATLSCRASSSVSYMHWFQQKPGQAPRLLIYSTSNLASGIPARFSGSGSGT
DYTLTISSLEPEDFAVYYCQQRRSFPYTFGQGTKLEIKAAALDNEKSNGTIIHVKGKH
LCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRFSVVKRGRKKLLYIFKQ
PFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLG
RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRR
GKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGP
MGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQ
PCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAY
GYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPC
TVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIAS
TVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID
NO:22)

[0288] Construct S1-2F3-C8K-CD28 DNA (signal sequence in bold)
ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAGAAGCCCGGA
GCCAGCGTGAAGGTGAGCTGCAAAGCCAGCGGCTACACCTTCTCCACCTACTGG
ATCGAGTGGGTGAGACAGGCCCCCGGACAGAGGCTGGAATGGATGGGAGAGAT
CCTGCCCGGCAGCGGCAACACCGACTTCAACGAGAAGTTCCAGGGCAGAGTGAC
CTTCACCGCCGATACCAGCAGCGACACCGCCTACATGGAACTGAGCAGCCTGAG
AAGCGAGGATACCGCCGTCTACTACTGCACCAGATGGGGCTACTACGGCACCAG

GGGCTATTTCAACGTGTGGGGCCAGGGAACCCTCGTGACCGTGAGCAGCGGAGG
CGGAGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGAGATTGTGCTGAC
CCAGAGCCCTGCTACACTGAGCCTGAGCCCCGGCGAGAGAGCCACACTGAGCTG
CAGAGCCAGCAGCAGCGTGAGCTACATGCACTGGTTCCAGCAAAAGCCCGGCCA
GGCCCCTAGGCTGCTGATCTACAGCACATCCAACCTGGCCAGCGGCATCCCTGCC
AGATTCAGCGGTTCTGGCTCCGGCACCGACTACACCCTGACCATCTCCAGCCTGG
AGCCCGAGGACTTTGCCGTGTATTACTGCCAGCAGAGGAGGAGCTTCCCCTACAC
ATTCGGCCAGGGCACCAAACTGGAGATCAAGGCCGCTGCCTTCGTGCCTGTTTTT
CTGCCCGCGAAACCCACAACTACCCCCGCCCCTCGGCCCCCAACTCCTGCACCAA
CTATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCATGCCGCCCCGCGGCAGG
CGGCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGATATTTATATCTGGGCC
CCCCTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTGGTGATTACCCTCTACT
GCAACCACAGAAACAGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGA
ATATGACTCCACGCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCAC
CACCTAGAGATTTCGCTGCCTATCGGAGCAGGGTGAAGTTTTCCAGATCTGCAGA
TGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGG
ACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGAT
GGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAGCTGCA
GAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGA
GAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGAAG
GATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAAGAGAAGT
GGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGAAGAAAAT
CCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCCGCGACTG
CTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCCTGTCCAA
CGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTGGCGAGGG
CGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCCTGGATTCA
GTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTGTACCGAAT
GTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGATGCAGTGTG
CAGATGTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTGTGAGGCCTG
CCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGCAAAA
CACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCGAACCACGT
CGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGAGAGA
GTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGATCAC

CCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAGAACC
GGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGTGAC
GACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCGACAATCT
GATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCCTAC
ATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:23)

[0289] Construct S1-2F3-C8K-CD28 AA (signal sequence in bold; CDRs underlined)
MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFSTYWI
EWVRQAPGQRLEWMGEILPGSGNTDFNEKFQGRVTFTADTSSDTAYMELSSLRSED
TAVYYCTRWGYYGTRGYFNVWGQGTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPA
TLSLSPGERATLSCRASSSVSYMHWFQQKPGQAPRLLIYSTSNLASGIPARFSGSGSGT
DYTLTISSLEPEDFAVYYCQQRRSFPYTFGQGTKLEIKAAAFVPVFLPAKPTTTPAPRP
PTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITL
YCNHRNRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSAD
APAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQK
DKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSG
EGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYT
HSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQS
MSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEEC
PDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDS
TAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVG
LVAYIAFKR (SEQ ID NO:24)

[0290] Construct S1-2F3-C8K-41BB DNA (signal sequence in bold)
ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAGAAGCCCGGA
GCCAGCGTGAAGGTGAGCTGCAAAGCCAGCGGCTACACCTTCTCCACCTACTGG
ATCGAGTGGGTGAGACAGGCCCCCGGACAGAGGCTGGAATGGATGGGAGAGAT
CCTGCCCGGCAGCGGCAACACCGACTTCAACGAGAAGTTCCAGGGCAGAGTGAC
CTTCACCGCCGATACCAGCAGCGACACCGCCTACATGGAACTGAGCAGCCTGAG
AAGCGAGGATACCGCCGTCTACTACTGCACCAGATGGGGCTACTACGGCACCAG
GGGCTATTTCAACGTGTGGGGCCAGGGAACCCTCGTGACCGTGAGCAGCGGAGG
CGGAGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGAGATTGTGCTGAC

CCAGAGCCCTGCTACACTGAGCCTGAGCCCCGGCGAGAGAGCCACACTGAGCTG
CAGAGCCAGCAGCAGCGTGAGCTACATGCACTGGTTCCAGCAAAAGCCCGGCCA
GGCCCCTAGGCTGCTGATCTACAGCACATCCAACCTGGCCAGCGGCATCCCTGCC
AGATTCAGCGGTTCTGGCTCCGGCACCGACTACACCCTGACCATCTCCAGCCTGG
AGCCCGAGGACTTTGCCGTGTATTACTGCCAGCAGAGGAGGAGCTTCCCCTACAC
ATTCGGCCAGGGCACCAAACTGGAGATCAAGGCCGCTGCCTTCGTGCCTGTTTTT
CTGCCCGCGAAACCCACAACTACCCCCGCCCCTCGGCCCCCAACTCCTGCACCAA
CTATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCATGCCGCCCCGCGGCAGG
CGGCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGATATTTATATCTGGGCC
CCCCTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTGGTGATTACCCTCTACT
GCAACCACAGAAACCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCTGCTGT
ACATTTTCAAACAGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGACG
GCTGCTCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGA
AGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGT
ATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCA
GAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAG
GGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATA
GGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGG
ACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCA
CCTAGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGT
GGGGACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGC
TATGGATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGC
GCTAAGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAA
GCCTGTAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCT
GTGAACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCC
TTGCAAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTC
GAAGCCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACT
ACCGGGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCA
GTTGCCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACA
GCGACGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATA
CCGAACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAG
ATCCCTGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACA
GCCCCGAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCT

ACAGTTGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACG
CGGGGCACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGG
TCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID
NO:25)

[0291] Construct S1-2F3-C8K-41BB AA (signal sequence in bold; CDRs underlined)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFSTYWI
EWVRQAPGQRLEWMGEILPGSGNTDFNEKFQGRVTFTADTSSDTAYMELSSLRSED
TAVYYCTRWGYYGTRGYFNVWGQGTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPA
TLSLSPGERATLSCRASSSVSYMHWFQQKPGQAPRLLIYSTSNLASGIPARFSGSGSGT
DYTLTISSLEPEDFAVYYCQQRRSFPYTFGQGTKLEIKAAAFVPVFLPAKPTTTPAPRP
PTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITL
YCNHRNRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKF
SRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLY
NELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRA
KRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEAC
PTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTEC
VGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNT
VCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTP
PEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILA
AVVVGLVAYIAFKR (SEQ ID NO:26)

[0292] Construct S1-11C2-CD28T-CD28-41BB DNA (signal sequence in bold)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGGAGATTCAGCTGGTGCAGAGCGGCGCCGAGGTGAAAAAGCCCGGA
GCCACCGTGAAGATCAGCTGCAAGGCCAGCGGCTACACATTCACCAACTACGGC
ATGAACTGGGTGCAACAGGCCCCCGGCCAGGGACTGGAGTGGATGGGCTGGATG
AACACATACACCGGCGAGCCCACCTACGCCGACAAGTTCCAGGGCAGGGTGACA
TTCACACTCGATACCAGCGCCAGAACCGTGTATATGGAACTGAGCAGCCTGAGG
AGCGAGGACACCGCTGTGTACTTCTGCGCAAGGGCTGGAGGCCAGCTGAGACCT
GGCGCTATGGACTACTGGGGCCAGGGCACCATGGTGACCGTGAGCTCCGGAGGC
GGAGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGACATCGTGCTGACC

CAGACACCTCTCTCCCTGTCCGTGACCCCCGGACAGCCTGCCTCCATTTCCTGTA
AGGCCTCCCAGAGCGTGGACTATGACGGCGACAGCTTCATGAACTGGTACCTGC
AGAAGCCCGGACAACCCCCCCAGCTGCTGATCTACGTGGCCAGCAACCTGGAGT
CCGGCGTGCCTGACAGGTTTTCCGGCTCCGGCAGCGGCACCGACTTCACCCTGAA
GATCAGCAGGGTGGAAGCCGAGGACGTGGGCGTGTACTACTGCCAGCAGAGCAA
CGAGGAGCCCCCTACCTTCGGACAGGGCACCAAGCTGGAGATCAAGGCCGCTGC
CCTTGATAATGAAAAGTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCT
CTGTCCGTCACCCTTGTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAG
TGGGTGGAGTCCTCGCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTC
TGGGTTAGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGAATATGACTC
CACGCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCACCACCTAGAG
ATTTCGCTGCCTATCGGAGCCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCT
GCTGTACATTTTCAAACAGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGA
GGACGGCTGCTCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAG
GGTGAAGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCA
ACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAA
GCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCC
AGGAGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTG
AAATAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTAC
CAGGGACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCC
CTGCCACCTAGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTT
ACATGTGGGGACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGA
AGGGCTATGGATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCG
GAGGCGCTAAGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTT
GCAAAGCCTGTAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGA
CAGTCTGTGAACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCAC
CGAGCCTTGCAAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCC
TGTGTCGAAGCCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAGGAC
GAAACTACCGGGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTC
GTGTTCAGTTGCCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGACGGA
ACCTACAGCGACGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCG
AGGATACCGAACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCG
AGGAGATCCCTGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACA

GTACAGCCCCGAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:27)

[0293] <u>Construct S1-11C2-CD28T-CD28-41BB AA (signal sequence in bold; CDRs underlined)</u>

MALPVTALLLPLALLLHAARPEIQLVQSGAEVKKPGATVKISCKASGYTFTNYGMNWVQQAPGQGLEWMGWMNTYTGEPTYADKFQGRVTFTLDTSARTVYMELSSLRSEDTAVYFCARAGGQLRPGAMDYWGQGTMVTVSSGGGGSGGGGSGGGGSDIVLTQTPLSLSVTPGQPASISCKASQSVDYDGDSFMNWYLQKPGQPPQLLIYVASNLESGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCQQSNEEPPTFGQGTKLEIKAAALDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:28)

[0294] <u>Construct S1-11C2-CD28T-CD28 DNA (signal sequence in bold)</u>

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCGCACGCCCGGAGATTCAGCTGGTGCAGAGCGGCGCCGAGGTGAAAAAGCCCGGAGCCACCGTGAAGATCAGCTGCAAGGCCAGCGGCTACACATTCACCAACTACGGCATGAACTGGGTGCAACAGGCCCCCGGCCAGGGACTGGAGTGGATGGGCTGGATGAACACATACACCGGCGAGCCCACCTACGCCGACAAGTTCCAGGGCAGGGTGACATTCACACTCGATACCAGCGCCAGAACCGTGTATATGGAACTGAGCAGCCTGAGGAGCGAGGACACCGCTGTGTACTTCTGCGCAAGGGCTGGAGGCCAGCTGAGACCT

GGCGCTATGGACTACTGGGGCCAGGGCACCATGGTGACCGTGAGCTCCGGAGGC
GGAGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGACATCGTGCTGACC
CAGACACCTCTCTCCCTGTCCGTGACCCCCGGACAGCCTGCCTCCATTTCCTGTA
AGGCCTCCCAGAGCGTGGACTATGACGGCGACAGCTTCATGAACTGGTACCTGC
AGAAGCCCGGACAACCCCCCCAGCTGCTGATCTACGTGGCCAGCAACCTGGAGT
CCGGCGTGCCTGACAGGTTTTCCGGCTCCGGCAGCGGCACCGACTTCACCCTGAA
GATCAGCAGGGTGGAAGCCGAGGACGTGGGCGTGTACTACTGCCAGCAGAGCAA
CGAGGAGCCCCCTACCTTCGGACAGGGCACCAAGCTGGAGATCAAGGCCGCTGC
CCTTGATAATGAAAAGTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCT
CTGTCCGTCACCCTTGTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAG
TGGGTGGAGTCCTCGCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTC
TGGGTTAGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGAATATGACTC
CACGCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCACCACCTAGAG
ATTTCGCTGCCTATCGGAGCAGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGC
GTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGA
AGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAA
ACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGATAA
GATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGGAA
AAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGAAGGATACTTATG
ACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAAGAGAAGTGGCAGCGGGG
AGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGAAGAAAATCCGGGGCCTA
TGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCCGCGACTGCTTCTCCTGCT
GTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCCTGTCCAACGGGCCTCTAC
ACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTCGCACAA
CCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCCTGGATTCAGTGACATTCA
GCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTGTACCGAATGTGTGGGCCT
TCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGATGCAGTGTGCAGATGTGCC
TATGGATATTACCAGGACGAAACTACCGGGCGGTGTGAGGCCTGCCGGGTGTGT
GAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGCAAAACACAGTATGT
GAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCGAACCACGTCGACCCTTGC
TTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGAGAGAGTGTACGCGC
TGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGATCACCCGGAGCACA
CCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAGAACCGGAGGCCCCT

CCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTCATG
GGATCCTCACAACCAGTCGTGACGCGGGGCACAACCGACAATCTGATTCCTGTCT
ACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCTTTAA
GAGATGACCTAGGTAA (SEQ ID NO:29)

[0295] Construct S1-11C2-CD28T-CD28 AA (signal sequence in bold; CDRs underlined)
MALPVTALLLPLALLLHAARPEIQLVQSGAEVKKPGATVKISCKASGYTFTNYGM
NWVQQAPGQGLEWMGWMNTYTGEPTYADKFQGRVTFTLDTSARTVYMELSSLRS
EDTAVYFCARAGGQLRPGAMDYWGQGTMVTVSSGGGGSGGGGSGGGGSDIVLTQ
TPLSLSVTPGQPASISCKASQSVDYDGDSFMNWYLQKPGQPPQLLIYVASNLESGVP
DRFSGSGSGTDFTLKISRVEAEDVGVYYCQQSNEEPPTFGQGTKLEIKAAALDNEKS
NGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRL
LHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQLY
NELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGM
KGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDV
EENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLG
EGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAV
CRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHV
DPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPE
QDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ
ID NO:30)

[0296] Construct S1-11C2-CD28T-41BB DNA (signal sequence in bold)
ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGGAGATTCAGCTGGTGCAGAGCGGCGCCGAGGTGAAAAAGCCCGGA
GCCACCGTGAAGATCAGCTGCAAGGCCAGCGGCTACACATTCACCAACTACGGC
ATGAACTGGGTGCAACAGGCCCCCGGCCAGGGACTGGAGTGGATGGGCTGGATG
AACACATACACCGGCGAGCCCACCTACGCCGACAAGTTCCAGGGCAGGGTGACA
TTCACACTCGATACCAGCGCCAGAACCGTGTATATGGAACTGAGCAGCCTGAGG
AGCGAGGACACCGCTGTGTACTTCTGCGCAAGGGCTGGAGGCCAGCTGAGACCT
GGCGCTATGGACTACTGGGGCCAGGGCACCATGGTGACCGTGAGCTCCGGAGGC
GGAGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGACATCGTGCTGACC
CAGACACCTCTCTCCCTGTCCGTGACCCCCGGACAGCCTGCCTCCATTTCCTGTA

AGGCCTCCCAGAGCGTGGACTATGACGGCGACAGCTTCATGAACTGGTACCTGC
AGAAGCCCGGACAACCCCCCCAGCTGCTGATCTACGTGGCCAGCAACCTGGAGT
CCGGCGTGCCTGACAGGTTTTCCGGCTCCGGCAGCGGCACCGACTTCACCCTGAA
GATCAGCAGGGTGGAAGCCGAGGACGTGGGCGTGTACTACTGCCAGCAGAGCAA
CGAGGAGCCCCCTACCTTCGGACAGGGCACCAAGCTGGAGATCAAGGCCGCTGC
CCTTGATAATGAAAAGTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCT
CTGTCCGTCACCCTTGTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAG
TGGGTGGAGTCCTCGCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTC
TGGGTTCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCTGCTGTACATTTTCA
AACAGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGACGGCTGCTCCT
GCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGAAGTTTTCCA
GATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGC
TCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGG
ACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATA
ATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAG
GAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACT
GCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCA
AGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGG
AAGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCC
CGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGC
CTGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTT
GGCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGC
CTGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTT
GTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGA
TGCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTG
TGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGAT
AAGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGC
GAACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCA
GCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAG
ATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTAC
CCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGG
CGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAAC

CGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTG
GTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:31)

[0297] Construct S1-11C2-CD28T-41BB AA (signal sequence in bold; CDRs underlined)

MALPVTALLLPLALLLHAARPEIQLVQSGAEVKKPGATVKISCKASGYTFTNYGM
NWVQQAPGQGLEWMGWMNTYTGEPTYADKFQGRVTFTLDTSARTVYMELSSLRS
EDTAVYFCARAGGQLRPGAMDYWGQGTMVTVSSGGGGSGGGGSGGGGSDIVLTQ
TPLSLSVTPGQPASISCKASQSVDYDGDSFMNWYLQKPGQPPQLLIYVASNLESGVP
DRFSGSGSGTDFTLKISRVEAEDVGVYYCQQSNEEPPTFGQGTKLEIKAAALDNEKS
NGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRFSVVKR
GRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQ
NQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYS
EIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTC
GDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKA
CNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEA
DDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDE
ANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEP
EAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFK
R (SEQ ID NO:32)

[0298] Construct S1-11C2-C8K-CD28 DNA (signal sequence in bold)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGGAGATTCAGCTGGTGCAGAGCGGCGCCGAGGTGAAAAAGCCCGGA
GCCACCGTGAAGATCAGCTGCAAGGCCAGCGGCTACACATTCACCAACTACGGC
ATGAACTGGGTGCAACAGGCCCCCGGCCAGGGACTGGAGTGGATGGGCTGGATG
AACACATACACCGGCGAGCCCACCTACGCCGACAAGTTCCAGGGCAGGGTGACA
TTCACACTCGATACCAGCGCCAGAACCGTGTATATGGAACTGAGCAGCCTGAGG
AGCGAGGACACCGCTGTGTACTTCTGCGCAAGGGCTGGAGGCCAGCTGAGACCT
GGCGCTATGGACTACTGGGGCCAGGGCACCATGGTGACCGTGAGCTCCGGAGGC
GGAGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGACATCGTGCTGACC
CAGACACCTCTCTCCCTGTCCGTGACCCCCGGACAGCCTGCCTCCATTTCCTGTA
AGGCCTCCCAGAGCGTGGACTATGACGGCGACAGCTTCATGAACTGGTACCTGC

AGAAGCCCGGACAACCCCCCCAGCTGCTGATCTACGTGGCCAGCAACCTGGAGT
CCGGCGTGCCTGACAGGTTTTCCGGCTCCGGCAGCGGCACCGACTTCACCCTGAA
GATCAGCAGGGTGGAAGCCGAGGACGTGGGCGTGTACTACTGCCAGCAGAGCAA
CGAGGAGCCCCCTACCTTCGGACAGGGCACCAAGCTGGAGATCAAGGCCGCTGC
CTTCGTGCCTGTTTTTCTGCCCGCGAAACCCACAACTACCCCCGCCCCTCGGCCCC
CAACTCCTGCACCAACTATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCATG
CCGCCCCGCGGCAGGCGGCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGA
TATTTATATCTGGGCCCCCCTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTG
GTGATTACCCTCTACTGCAACCACAGAAACAGATCCAAAAGAAGCCGCCTGCTC
CATAGCGATTACATGAATATGACTCCACGCCGCCCTGGCCCCACAAGGAAACAC
TACCAGCCTTACGCACCACCTAGAGATTTCGCTGCCTATCGGAGCAGGGTGAAGT
TTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATA
ACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAG
GACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGT
CTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGC
ATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACT
CAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCT
AGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGG
GACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATG
GATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTA
AGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTG
TAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGA
ACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGC
AAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAG
CCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCG
GGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTG
CCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGA
CGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGA
ACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCC
TGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCC
GAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGT
TGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGG

CACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTG
GGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:33)

[0299] Construct S1-11C2-C8K-CD28 AA (signal sequence in bold; CDRs underlined)

MALPVTALLLPLALLLHAARPEIQLVQSGAEVKKPGATVKISCKASGYTFTNYGM
NWVQQAPGQGLEWMGWMNTYTGEPTYADKFQGRVTFTLDTSARTVYMELSSLRS
EDTAVYFCARAGGQLRPGAMDYWGQGTMVTVSSGGGGSGGGGSGGGGSDIVLTQ
TPLSLSVTPGQPASISCKASQSVDYDGDSFMNWYLQKPGQPPQLLIYVASNLESGVP
DRFSGSGSGTDFTLKISRVEAEDVGVYYCQQSNEEPPTFGQGTKLEIKAAAFVPVFLP
AKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGT
CGVLLLSLVITLYCNHRNRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAA
YRSRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRK
NPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM
QALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSL
GGAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATE
PCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFS
CQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPG
RWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLI
PVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:34)

[0300] Construct S1-11C2-C8K-41BB DNA (signal sequence in bold)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGGAGATTCAGCTGGTGCAGAGCGGCGCCGAGGTGAAAAAGCCCGGA
GCCACCGTGAAGATCAGCTGCAAGGCCAGCGGCTACACATTCACCAACTACGGC
ATGAACTGGGTGCAACAGGCCCCCGGCCAGGGACTGGAGTGGATGGGCTGGATG
AACACATACACCGGCGAGCCCACCTACGCCGACAAGTTCCAGGGCAGGGTGACA
TTCACACTCGATACCAGCGCCAGAACCGTGTATATGGAACTGAGCAGCCTGAGG
AGCGAGGACACCGCTGTGTACTTCTGCGCAAGGGCTGGAGGCCAGCTGAGACCT
GGCGCTATGGACTACTGGGGCCAGGGCACCATGGTGACCGTGAGCTCCGGAGGC
GGAGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGACATCGTGCTGACC
CAGACACCTCTCTCCCTGTCCGTGACCCCCGGACAGCCTGCCTCCATTTCCTGTA
AGGCCTCCCAGAGCGTGGACTATGACGGCGACAGCTTCATGAACTGGTACCTGC
AGAAGCCCGGACAACCCCCCCAGCTGCTGATCTACGTGGCCAGCAACCTGGAGT

CCGGCGTGCCTGACAGGTTTTCCGGCTCCGGCAGCGGCACCGACTTCACCCTGAA
GATCAGCAGGGTGGAAGCCGAGGACGTGGGCGTGTACTACTGCCAGCAGAGCAA
CGAGGAGCCCCCTACCTTCGGACAGGGCACCAAGCTGGAGATCAAGGCCGCTGC
CTTCGTGCCTGTTTTTCTGCCCGCGAAACCCACAACTACCCCCGCCCCTCGGCCCC
CAACTCCTGCACCAACTATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCATG
CCGCCCCGCGGCAGGCGGCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGA
TATTTATATCTGGGCCCCCCTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTG
GTGATTACCCTCTACTGCAACCACAGAAACCGCTTTTCCGTCGTTAAGCGGGGGA
GAAAAAAGCTGCTGTACATTTTCAAACAGCCGTTTATGAGGCCGGTCCAAACGA
CTCAGGAAGAGGACGGCTGCTCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGGGT
GCGAACTGAGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGG
GCCAGAACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACG
TTTTGGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGA
AAAAACCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAA
GCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGA
CGGTTTGTACCAGGGACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCAC
ATGCAAGCCCTGCCACCTAGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGG
ATCTCTCCTTACATGTGGGGACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGG
CGCCACGGGAAGGGCTATGGATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGC
GTGTCTCTCGGAGGCGCTAAGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCG
GTGAATGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGC
TAACCAGACAGTCTGTGAACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTC
TCAGCCACCGAGCCTTGCAAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGT
CCGCCCCCTGTGTCGAAGCCGATGATGCAGTGTGCAGATGTGCCTATGGATATTA
CCAGGACGAAACTACCGGGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTC
TGGCCTCGTGTTCAGTTGCCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCC
AGACGGAACCTACAGCGACGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCAC
CGTCTGCGAGGATACCGAACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGC
TGAGTGCGAGGAGATCCCTGGGAGATGGATCACCCGGAGCACACCTCCTGAGGG
ATCAGACAGTACAGCCCCGAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGA
CCTGATCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAA
CCAGTCGTGACGCGGGGCACAACCGACAATCTGATTCCTGTCTACTGTAGCATCT

TGGCAGCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAG
GTAA (SEQ ID NO:35)

[0301] Construct S1-11C2-C8K-41BB AA (signal sequence in bold; CDRs underlined)
MALPVTALLLPLALLLHAARPEIQLVQSGAEVKKPGATVKISCKASGYTFTNYGM
NWVQQAPGQGLEWMGWMNTYTGEPTYADKFQGRVTFTLDTSARTVYMELSSLRS
EDTAVYFCARAGGQLRPGAMDYWGQGTMVTVSSGGGGSGGGGSGGGGSDIVLTQ
TPLSLSVTPGQPASISCKASQSVDYDGDSFMNWYLQKPGQPPQLLIYVASNLESGVP
DRFSGSGSGTDFTLKISRVEAEDVGVYYCQQSNEEPPTFGQGTKLEIKAAAFVPVFLP
AKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGT
CGVLLLSLVITLYCNHRNRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEE
EEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGK
PRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDA
LHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLLG
VSLGGAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVS
ATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSG
LVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECE
EIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTT
DNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:36)

[0302] Construct S2-1A1-CD28T-CD28-41BB DNA (signal sequence in bold)
ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCCGGCGCCGAAGTGAAGAAGCCCGGAG
CCAGCGTGAAGGTGAGCTGCAAGGCCTCCGGCTACACCTTCACCACCTACTGGAT
GCACTGGGTCAGACAGGCTCCCGGACAGGGCCTGGAATGGATGGGCGAAATCAA
CCCCTCCTCCGGCAGGACCAACTACAACGAGAAGTTCAAGACCAGGGTGACCAT
GACCAGGGACACCAGCACCAGCACCGTGTACATGGAGCTGTCCAGCCTGAGGAG
CGAGGACACCGCCGTGTACTACTGTGCCAAGCTGGGACCCGGCCCCCAGTACTA
TGCCATGGACTACTGGGGCCAAGGCACCATGGTGACCGTGAGCAGCGGAGGCGG
AGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGACATCCAGATGACCCA
GAGCCCCTCCAGCCTGTCCGCTAGCGTGGGCGACAGGGTCACCATTACCTGCCAC
GCCAGCCAGAACATCAACGTGTGGCTGAGCTGGTATCAGCAGAAACCCGGCAAG
GCTCCCAAGCTGCTGATCTACAAGGCCAGCAAGCTGCACACCGGCGTGCCCAGC

AGGTTTAGCGGTTCTGGCTCCGGCACCGACTTCACCCTCACCATCAGCAGCCTGC
AGCCCGAAGACTTCGCTACCTACTACTGCCAGCAGGGACAAAGCTACCCCTGGA
CCTTCGGCCAGGGAACCAAGCTGGAAATCAAGGCCGCTGCCCTTGATAATGAAA
AGTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTT
GTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTC
GCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTAGATCCAA
AAGAAGCCGCCTGCTCCATAGCGATTACATGAATATGACTCCACGCCGCCCTGGC
CCCACAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATTTCGCTGCCTATC
GGAGCCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAGCTGCTGTACATTTTCAA
ACAGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGACGGCTGCTCCTG
CCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGAAGTTTTCCAG
ATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCT
CAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGG
ACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATA
ATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAG
GAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACT
GCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCA
AGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGG
AAGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCC
CGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGC
CTGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTT
GGCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGC
CTGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTT
GTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGA
TGCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTG
TGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGAT
AAGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGC
GAACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCA
GCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAG
ATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTAC
CCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGG
CGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAAC

CGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTG
GTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:37)

[0303] Construct S2-1A1-CD28T-CD28-41BB AA (signal sequence in bold; CDRs underlined)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTTYW
MHWVRQAPGQGLEWMGEINPSSGRTNYNEKFKTRVTMTRDTSTSTVYMELSSLRSE
DTAVYYCAKLGPGPQYYAMDYWGQGTMVTVSSGGGGSGGGGSGGGGSDIQMTQS
PSSLSASVGDRVTITCHASQNINVWLSWYQQKPGKAPKLLIYKASKLHTGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQGQSYPWTFGQGTKLEIKAAALDNEKSNGTIIH
VKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDY
MNMTPRRPGPTRKHYQPYAPPRDFAAYRSRFSVVKRGRKKLLYIFKQPFMRPVQTT
QEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLD
KRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLY
QGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGR
AMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTV
CEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETT
GRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTER
QLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTT
VMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:38)

[0304] Construct S2-1A1-CD28T-CD28 DNA (signal sequence in bold)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCCGGCGCCGAAGTGAAGAAGCCCGGAG
CCAGCGTGAAGGTGAGCTGCAAGGCCTCCGGCTACACCTTCACCACCTACTGGAT
GCACTGGGTCAGACAGGCTCCCGGACAGGGCCTGGAATGGATGGGCGAAATCAA
CCCCTCCTCCGGCAGGACCAACTACAACGAGAAGTTCAAGACCAGGGTGACCAT
GACCAGGGACACCAGCACCAGCACCGTGTACATGGAGCTGTCCAGCCTGAGGAG
CGAGGACACCGCCGTGTACTACTGTGCCAAGCTGGGACCCGGCCCCCAGTACTA
TGCCATGGACTACTGGGGCCAAGGCACCATGGTGACCGTGAGCAGCGGAGGCGG
AGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGACATCCAGATGACCCA
GAGCCCCTCCAGCCTGTCCGCTAGCGTGGGCGACAGGGTCACCATTACCTGCCAC
GCCAGCCAGAACATCAACGTGTGGCTGAGCTGGTATCAGCAGAAACCCGGCAAG

GCTCCCAAGCTGCTGATCTACAAGGCCAGCAAGCTGCACACCGGCGTGCCCAGC
AGGTTTAGCGGTTCTGGCTCCGGCACCGACTTCACCCTCACCATCAGCAGCCTGC
AGCCCGAAGACTTCGCTACCTACTACTGCCAGCAGGGACAAAGCTACCCCTGGA
CCTTCGGCCAGGGAACCAAGCTGGAAATCAAGGCCGCTGCCCTTGATAATGAAA
AGTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTT
GTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTC
GCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTAGATCCAA
AAGAAGCCGCCTGCTCCATAGCGATTACATGAATATGACTCCACGCCGCCCTGGC
CCCACAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATTTCGCTGCCTATC
GGAGCAGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCC
AGAACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTT
TGGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAA
AACCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCC
TATTCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGG
TTTGTACCAGGGACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATG
CAAGCCCTGCCACCTAGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATC
TCTCCTTACATGTGGGGACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGC
CACGGGAAGGGCTATGGATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTG
TCTCTCGGAGGCGCTAAGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTG
AATGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAA
CCAGACAGTCTGTGAACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCA
GCCACCGAGCCTTGCAAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCG
CCCCCTGTGTCGAAGCCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCA
GGACGAAACTACCGGGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGG
CCTCGTGTTCAGTTGCCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGA
CGGAACCTACAGCGACGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGT
CTGCGAGGATACCGAACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGA
GTGCGAGGAGATCCCTGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATC
AGACAGTACAGCCCCGAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCT
GATCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCA
GTCGTGACGCGGGGCACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGG
CAGCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTA
A (SEQ ID NO:39)

[0305] Construct S2-1A1-CD28T-CD28 AA (signal sequence in bold; CDRs underlined)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTTYWMHWVRQAPGQGLEWMGEINPSSGRTNYNEKFKTRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAKLGPGPQYYAMDYWGQGTMVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCHASQNINVWLSWYQQKPGKAPKLLIYKASKLHTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGQSYPWTFGQGTKLEIKAAALDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:40)

[0306] Construct S2-1A1-CD28T-41BB DNA (signal sequence in bold)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCGCACGCCCGCAGGTGCAGCTGGTGCAGTCCGGCGCCGAAGTGAAGAAGCCCGGAGCCAGCGTGAAGGTGAGCTGCAAGGCCTCCGGCTACACCTTCACCACCTACTGGATGCACTGGGTCAGACAGGCTCCCGGACAGGGCCTGGAATGGATGGGCGAAATCAACCCCTCCTCCGGCAGGACCAACTACAACGAGAAGTTCAAGACCAGGGTGACCATGACCAGGGACACCAGCACCAGCACCGTGTACATGGAGCTGTCCAGCCTGAGGAGCGAGGACACCGCCGTGTACTACTGTGCCAAGCTGGGACCCGGCCCCCAGTACTATGCCATGGACTACTGGGGCCAAGGCACCATGGTGACCGTGAGCAGCGGAGGCGGAGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGACATCCAGATGACCCAGAGCCCCTCCAGCCTGTCCGCTAGCGTGGGCGACAGGGTCACCATTACCTGCCACGCCAGCCAGAACATCAACGTGTGGCTGAGCTGGTATCAGCAGAAACCCGGCAAGGCTCCCAAGCTGCTGATCTACAAGGCCAGCAAGCTGCACACCGGCGTGCCCAGCAGGTTTAGCGGTTCTGGCTCCGGCACCGACTTCACCCTCACCATCAGCAGCCTGCAGCCCGAAGACTTCGCTACCTACTACTGCCAGCAGGGACAAAGCTACCCCTGGACCTTCGGCCAGGGAACCAAGCTGGAAATCAAGGCCGCTGCCCTTGATAATGAAA

AGTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTT
GTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTC
GCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTCGCTTTTCC
GTCGTTAAGCGGGGGAGAAAAAGCTGCTGTACATTTTCAAACAGCCGTTTATG
AGGCCGGTCCAAACGACTCAGGAAGAGGACGGCTGCTCCTGCCGCTTTCCTGAG
GAGGAGGAGGGCGGGTGCGAACTGAGGGTGAAGTTTTCCAGATCTGCAGATGCA
CCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGACGC
AGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGATGGGT
GGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAGCTGCAGAA
GGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAGAA
GGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGAAGGATA
CTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAAGAGAAGTGGCA
GCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGAAGAAAATCCGG
GGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCCGCGACTGCTTC
TCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCCTGTCCAACGGG
CCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTC
GCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCCTGGATTCAGTGA
CATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTGTACCGAATGTGT
GGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGATGCAGTGTGCAGA
TGTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTGTGAGGCCTGCCGG
GTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGCAAAACACA
GTATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCGAACCACGTCGAC
CCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGAGAGAGTGT
ACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGATCACCCGG
AGCACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAGAACCGGAG
GCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGTGACGACAG
TCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCGACAATCTGATTC
CTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCCTACATCGC
CTTTAAGAGATGACCTAGGTAA (SEQ ID NO:41)

[0307] Construct S2-1A1-CD28T-41BB AA (signal sequence in bold; CDRs underlined)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTTYW
MHWVRQAPGQGLEWMGEINPSSGRTNYNEKFKTRVTMTRDTSTSTVYMELSSLRSE

DTAVYYCAKLGPGPQYYAMDYWGQGTMVTVSSGGGGSGGGGSGGGGSDIQMTQS
PSSLSASVGDRVTITCHASQNINVWLSWYQQKPGKAPKLLIYKASKLHTGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQGQSYPWTFGQGTKLEIKAAALDNEKSNGTIIH
VKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRFSVVKRGRKKL
LYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYN
ELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMK
GERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVE
ENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGE
GVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVC
RCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVD
PCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQ
DLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ
ID NO:42)

[0308] Construct S2-1A1-C8K-CD28 DNA (signal sequence in bold)
ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCCGGCGCCGAAGTGAAGAAGCCCGGAG
CCAGCGTGAAGGTGAGCTGCAAGGCCTCCGGCTACACCTTCACCACCTACTGGAT
GCACTGGGTCAGACAGGCTCCCGGACAGGGCCTGGAATGGATGGGCGAAATCAA
CCCCTCCTCCGGCAGGACCAACTACAACGAGAAGTTCAAGACCAGGGTGACCAT
GACCAGGGACACCAGCACCAGCACCGTGTACATGGAGCTGTCCAGCCTGAGGAG
CGAGGACACCGCCGTGTACTACTGTGCCAAGCTGGGACCCGGCCCCCAGTACTA
TGCCATGGACTACTGGGGCCAAGGCACCATGGTGACCGTGAGCAGCGGAGGCGG
AGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGACATCCAGATGACCCA
GAGCCCCTCCAGCCTGTCCGCTAGCGTGGGCGACAGGGTCACCATTACCTGCCAC
GCCAGCCAGAACATCAACGTGTGGCTGAGCTGGTATCAGCAGAAACCCGGCAAG
GCTCCCAAGCTGCTGATCTACAAGGCCAGCAAGCTGCACACCGGCGTGCCCAGC
AGGTTTAGCGGTTCTGGCTCCGGCACCGACTTCACCCTCACCATCAGCAGCCTGC
AGCCCGAAGACTTCGCTACCTACTACTGCCAGCAGGGACAAAGCTACCCCTGGA
CCTTCGGCCAGGGAACCAAGCTGGAAATCAAGGCCGCTGCCTTCGTGCCTGTTTT
TCTGCCCGCGAAACCCACAACTACCCCCGCCCCTCGGCCCCCAACTCCTGCACCA
ACTATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCATGCCGCCCCGCGGCAG
GCGGCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGATATTTATATCTGGGC

CCCCCTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTGGTGATTACCCTCTAC
TGCAACCACAGAAACAGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATG
AATATGACTCCACGCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCA
CCACCTAGAGATTTCGCTGCCTATCGGAGCAGGGTGAAGTTTTCCAGATCTGCAG
ATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGG
GACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAG
ATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAGCTG
CAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCG
GAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGA
AGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAAGAGAA
GTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGAAGAAA
ATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCCGCGAC
TGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCCTGTCC
AACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTGGCGAG
GGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCCTGGATT
CAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTGTACCGA
ATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGATGCAGTG
TGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTGTGAGGCC
TGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGCAAA
ACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCGAACCACG
TCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGAGAG
AGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGATCA
CCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAGAAC
CGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGTGAC
GACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCGACAATCT
GATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCCTAC
ATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:43)

[0309] Construct S2-1A1-C8K-CD28 AA (signal sequence in bold; CDRs underlined)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTTYW
MHWVRQAPGQGLEWMGEINPSSGRTNYNEKFKTRVTMTRDTSTSTVYMELSSLRSE
DTAVYYCAKLGPGPQYYAMDYWGQGTMVTVSSGGGGSGGGGSGGGGSDIQMTQS
PSSLSASVGDRVTITCHASQNINVWLSWYQQKPGKAPKLLIYKASKLHTGVPSRFSG

SGSGTDFTLTISSLQPEDFATYYCQQGQSYPWTFGQGTKLEIKAAAFVPVFLPAKPTT
TPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLL
LSLVITLYCNHRNRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRV
KFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEG
LYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
AKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEA
CPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTE
CVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQN
TVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRST
PPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSIL
AAVVVGLVAYIAFKR (SEQ ID NO:44)

[0310] Construct S2-1A1-C8K-41BB DNA (signal sequence in bold)
ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCCGGCGCCGAAGTGAAGAAGCCCGGAG
CCAGCGTGAAGGTGAGCTGCAAGGCCTCCGGCTACACCTTCACCACCTACTGGAT
GCACTGGGTCAGACAGGCTCCCGGACAGGGCCTGGAATGGATGGGCGAAATCAA
CCCCTCCTCCGGCAGGACCAACTACAACGAGAAGTTCAAGACCAGGGTGACCAT
GACCAGGGACACCAGCACCAGCACCGTGTACATGGAGCTGTCCAGCCTGAGGAG
CGAGGACACCGCCGTGTACTACTGTGCCAAGCTGGGACCCGGCCCCCAGTACTA
TGCCATGGACTACTGGGGCCAAGGCACCATGGTGACCGTGAGCAGCGGAGGCGG
AGGATCTGGTGGCGGTGGTTCTGGCGGCGGAGGCTCCGACATCCAGATGACCCA
GAGCCCCTCCAGCCTGTCCGCTAGCGTGGGCGACAGGGTCACCATTACCTGCCAC
GCCAGCCAGAACATCAACGTGTGGCTGAGCTGGTATCAGCAGAAACCCGGCAAG
GCTCCCAAGCTGCTGATCTACAAGGCCAGCAAGCTGCACACCGGCGTGCCCAGC
AGGTTTAGCGGTTCTGGCTCCGGCACCGACTTCACCCTCACCATCAGCAGCCTGC
AGCCCGAAGACTTCGCTACCTACTACTGCCAGCAGGGACAAAGCTACCCCTGGA
CCTTCGGCCAGGGAACCAAGCTGGAAATCAAGGCCGCTGCCTTCGTGCCTGTTTT
TCTGCCCGCGAAACCCACAACTACCCCCGCCCCTCGGCCCCCAACTCCTGCACCA
ACTATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCATGCCGCCCCGCGGCAG
GCGGCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGATATTTATATCTGGGC
CCCCCTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTGGTGATTACCCTCTAC
TGCAACCACAGAAACCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAGCTGCTG

TACATTTTCAAACAGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGAC
GGCTGCTCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTG
AAGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTG
TATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGC
AGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGA
GGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAAT
AGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGG
GACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCC
ACCTAGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATG
TGGGGACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGG
CTATGGATGGCCCGCGACTGCTTCTCCTGCTGTTGGGCGTGTCTCTCGGAGG
CGCTAAGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAA
GCCTGTAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCT
GTGAACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCC
TTGCAAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTC
GAAGCCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACT
ACCGGGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCA
GTTGCCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACA
GCGACGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATA
CCGAACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAG
ATCCCTGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACA
GCCCCGAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCT
ACAGTTGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACG
CGGGGCACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGG
TCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:45)

[0311] Construct S2-1A1-C8K-41BB AA (signal sequence in bold; CDRs underlined)
MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTTYW
MHWVRQAPGQGLEWMGEINPSSGRTNYNEKFKTRVTMTRDTSTSTVYMELSSLRSE
DTAVYYCAKLGPGPQYYAMDYWGQGTMVTVSSGGGGSGGGGSGGGGSDIQMTQS
PSSLSASVGDRVTITCHASQNINVWLSWYQQKPGKAPKLLIYKASKLHTGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQGQSYPWTFGQGTKLEIKAAAFVPVFLPAKPTT

TPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLL
LSLVITLYCNHRNRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGC
ELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKN
PQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQ
ALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSLG
GAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEP
CKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFS
CQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPG
RWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLI
PVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:46)

[0312] Construct S2-7A4-CD28T-CD28-41BB DNA (signal sequence in bold)
ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG
CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACAGCTTCACCAGTTATGATAT
CAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGGTGGATGAA
CCCGAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCAT
GACCAGGGACACCTCCATAAGCACAGCCTACATGGAACTGAGCAGCCTGAGATC
TGAGGACACGGCCGTGTATTACTGTGGGAGAGCCGGTTACTACTACTACTTCGGT
ATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTATCCTCAGGAGGCGGCGGT
TCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGAAATTGTGTTGACGCAGTCT
CCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCG
GTCAGAGTGTTACCAGCAGCTCCTTTGCTTGGTACCAACAGAAACCTGGCCAGGC
TCCCAGGCTCCTCATCTATCAGACATCCACCAGGGCCACTGGCATCCCAGACAGG
TTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGACTGGAGC
CTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTGGCTCACGGTCGTTCGG
CCAAGGGACCAAGGTGGAACTCAAACGAGCCGCTGCCCTTGATAATGAAAAGTC
AAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTTGTTC
CCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCGCTT
GTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTAGATCCAAAAGA
AGCCGCCTGCTCCATAGCGATTACATGAATATGACTCCACGCCGCCCTGGCCCCA
CAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATTTCGCTGCCTATCGGA
GCCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCTGCTGTACATTTTCAAACA

GCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGACGGCTGCTCCTGCCG
CTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGAAGTTTTCCAGATC
TGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAA
CCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCC
TGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGA
GCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGA
GCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTAC
GAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAAGAG
AAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGAAGA
AAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCCGCG
ACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCCTGT
CCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTGGCG
AGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCCTGG
ATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTGTAC
CGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGATGCA
GTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTGTGAG
GCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGC
AAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCGAAC
CACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGA
GAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGA
TCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAG
AACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGT
GACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCGACAA
TCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCC
TACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:47)

[0313] Construct S2-7A4-CD28T-CD28-41BB AA (signal sequence in bold; CDRs underlined)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYSFTSYDI
NWVRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSISTAYMELSSLRS
EDTAVYYCGRAGYYYYFGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSP
GTLSLSPGERATLSCRAGQSVTSSSFAWYQQKPGQAPRLLIYQTSTRATGIPDRFSGS
GSGTDFTLTISRLEPEDFAVYYCQQYGGSRSFGQGTKVELKRAAALDNEKSNGTIIHV

KGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYM
NMTPRRPGPTRKHYQPYAPPRDFAAYRSRFSVVKRGRKKLLYIFKQPFMRPVQTTQE
EDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKR
RGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQG
LSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAM
DGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEP
CLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRC
EACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLR
ECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVM
GSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:48)

[0314] Construct S2-7A4-CD28T-CD28 DNA (signal sequence in bold)
ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG
CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACAGCTTCACCAGTTATGATAT
CAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGGTGGATGAA
CCCGAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCAT
GACCAGGGACACCTCCATAAGCACAGCCTACATGGAACTGAGCAGCCTGAGATC
TGAGGACACGGCCGTGTATTACTGTGGGAGAGCCGGTTACTACTACTACTTCGGT
ATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTATCCTCAGGAGGCGGCGGT
TCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGAAATTGTGTTGACGCAGTCT
CCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCG
GTCAGAGTGTTACCAGCAGCTCCTTTGCTTGGTACCAACAGAAACCTGGCCAGGC
TCCCAGGCTCCTCATCTATCAGACATCCACCAGGGCCACTGGCATCCCAGACAGG
TTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGACTGGAGC
CTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTGGCTCACGGTCGTTCGG
CCAAGGGACCAAGGTGGAACTCAAACGAGCCGCTGCCCTTGATAATGAAAAGTC
AAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTTGTTC
CCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCGCTT
GTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTAGATCCAAAAGA
AGCCGCCTGCTCCATAGCGATTACATGAATATGACTCCACGCCGCCCTGGCCCCA
CAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATTTCGCTGCCTATCGGA
GCAGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGA

ACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGG
ACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAC
CCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTAT
TCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTT
GTACCAGGGACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCA
AGCCCTGCCACCTAGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCT
CCTTACATGTGGGGACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGCCAC
GGGAAGGGCTATGGATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCT
CTCGGAGGCGCTAAGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTGAA
TGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAACC
AGACAGTCTGTGAACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAGC
CACCGAGCCTTGCAAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCC
CCCTGTGTCGAAGCCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAGG
ACGAAACTACCGGGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCC
TCGTGTTCAGTTGCCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGACG
GAACCTACAGCGACGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTCT
GCGAGGATACCGAACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGT
GCGAGGAGATCCCTGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAG
ACAGTACAGCCCCGAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGA
TCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGT
CGTGACGCGGGGCACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCA
GCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA
(SEQ ID NO:49)

[0315] Construct S2-7A4-CD28T-CD28 AA (signal sequence in bold; CDRs underlined)
MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYSFTSYDI
NWVRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSISTAYMELSSLRS
EDTAVYYCGRAGYYYYFGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSP
GTLSLSPGERATLSCRAGQSVTSSSFAWYQQKPGQAPRLLIYQTSTRATGIPDRFSGS
GSGTDFTLTISRLEPEDFAVYYCQQYGGSRSFGQGTKVELKRAAALDNEKSNGTIIHV
KGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYM
NMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQLYNELNLGR
REEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRG

KGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGPM
GAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQP
CGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYG
YYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCT
VCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIAST
VAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:50)

[0316] Construct S2-7A4-CD28T-41BB DNA (signal sequence in bold)
ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG
CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACAGCTTCACCAGTTATGATAT
CAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGGTGGATGAA
CCCGAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCAT
GACCAGGGACACCTCCATAAGCACAGCCTACATGGAACTGAGCAGCCTGAGATC
TGAGGACACGGCCGTGTATTACTGTGGGAGAGCCGGTTACTACTACTACTTCGGT
ATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTATCCTCAGGAGGCGGCGGT
TCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGAAATTGTGTTGACGCAGTCT
CCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCG
GTCAGAGTGTTACCAGCAGCTCCTTTGCTTGGTACCAACAGAAACCTGGCCAGGC
TCCCAGGCTCCTCATCTATCAGACATCCACCAGGGCCACTGGCATCCCAGACAGG
TTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGACTGGAGC
CTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTGGCTCACGGTCGTTCGG
CCAAGGGACCAAGGTGGAACTCAAACGAGCCGCTGCCCTTGATAATGAAAAGTC
AAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTTGTTC
CCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCGCTT
GTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTCGCTTTTCCGTC
GTTAAGCGGGGGAGAAAAAAGCTGCTGTACATTTTCAAACAGCCGTTTATGAGG
CCGGTCCAAACGACTCAGGAAGAGGACGGCTGCTCCTGCCGCTTTCCTGAGGAG
GAGGAGGGCGGGTGCGAACTGAGGGTGAAGTTTTCCAGATCTGCAGATGCACCA
GCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGACGCAGG
GAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGC
AAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGAT

AAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGG
AAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGAAGGATACTTA
TGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAAGAGAAGTGGCAGCGG
GGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGAAGAAAATCCGGGGCC
TATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCCGCGACTGCTTCTCCT
GCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCCTGTCCAACGGGCCTC
TACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTCGCAC
AACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCCTGGATTCAGTGACATT
CAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTGTACCGAATGTGTGGGC
CTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGATGCAGTGTGCAGATGTG
CCTATGGATATTACCAGGACGAAACTACCGGGCGGTGTGAGGCCTGCCGGGTGT
GTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGCAAAACACAGTAT
GTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCGAACCACGTCGACCCTT
GCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGAGAGAGTGTACGC
GCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGATCACCCGGAGCA
CACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAGAACCGGAGGCCC
CTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTCAT
GGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCGACAATCTGATTCCTGT
CTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCTTT
AAGAGATGACCTAGGTAA (SEQ ID NO:51)

[0317] Construct S2-7A4-CD28T-41BB AA (signal sequence in bold; CDRs underlined)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYSFTSYDI
NWVRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSISTAYMELSSLRS
EDTAVYYCGRAGYYYYFGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSP
GTLSLSPGERATLSCRAGQSVTSSSFAWYQQKPGQAPRLLIYQTSTRATGIPDRFSGS
GSGTDFTLTISRLEPEDFAVYYCQQYGGSRSFGQGTKVELKRAAALDNEKSNGTIIHV
KGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRFSVVKRGRKKLL
YIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNE
LNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKG
ERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEE
NPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGE
GVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVC

RCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVD
PCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQ
DLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:52)

[0318] Construct S2-7A4-C8K-CD28 DNA (signal sequence in bold)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG
CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACAGCTTCACCAGTTATGATAT
CAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGGTGGATGAA
CCCGAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCAT
GACCAGGGACACCTCCATAAGCACAGCCTACATGGAACTGAGCAGCCTGAGATC
TGAGGACACGGCCGTGTATTACTGTGGGAGAGCCGGTTACTACTACTACTTCGGT
ATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTATCCTCAGGAGGCGGCGGT
TCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGAAATTGTGTTGACGCAGTCT
CCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCG
GTCAGAGTGTTACCAGCAGCTCCTTTGCTTGGTACCAACAGAAACCTGGCCAGGC
TCCCAGGCTCCTCATCTATCAGACATCCACCAGGGCCACTGGCATCCCAGACAGG
TTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGACTGGAGC
CTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTGGCTCACGGTCGTTCGG
CCAAGGGACCAAGGTGGAACTCAAACGAGCCGCTGCCTTCGTGCCTGTTTTTCTG
CCCGCGAAACCCACAACTACCCCCGCCCCTCGGCCCCCAACTCCTGCACCAACTA
TCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCATGCCGCCCCGCGGCAGGCGG
CGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGATATTTATATCTGGGCCCCC
CTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTGGTGATTACCCTCTACTGCA
ACCACAGAAACAGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGAATA
TGACTCCACGCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCACCAC
CTAGAGATTTCGCTGCCTATCGGAGCAGGGTGAAGTTTTCCAGATCTGCAGATGC
ACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGACG
CAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGATGG
GTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAGCTGCAGA
AGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAGA
AGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGAAGGAT

ACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:53)

[0319] Construct S2-7A4-C8K-CD28 AA (signal sequence in bold; CDRs underlined)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYSFTSYDINWVRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSISTAYMELSSLRSEDTAVYYCGRAGYYYYFGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSLSPGERATLSCRAGQSVTSSSFAWYQQKPGQAPRLLIYQTSTRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGGSRSFGQGTKVELKRAAAFVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCNHRNRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTP

PEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILA
AVVVGLVAYIAFKR (SEQ ID NO:54)

[0320] Construct S2-7A4-C8K-41BB DNA (signal sequence in bold)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG
CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACAGCTTCACCAGTTATGATAT
CAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGGTGGATGAA
CCCGAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCAT
GACCAGGGACACCTCCATAAGCACAGCCTACATGGAACTGAGCAGCCTGAGATC
TGAGGACACGGCCGTGTATTACTGTGGGAGAGCCGGTTACTACTACTACTTCGGT
ATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTATCCTCAGGAGGCGGCGGT
TCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGAAATTGTGTTGACGCAGTCT
CCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCG
GTCAGAGTGTTACCAGCAGCTCCTTTGCTTGGTACCAACAGAAACCTGGCCAGGC
TCCCAGGCTCCTCATCTATCAGACATCCACCAGGGCCACTGGCATCCCAGACAGG
TTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGACTGGAGC
CTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTGGCTCACGGTCGTTCGG
CCAAGGGACCAAGGTGGAACTCAAACGAGCCGCTGCCTTCGTGCCTGTTTTTCTG
CCCGCGAAACCCACAACTACCCCCGCCCCTCGGCCCCCAACTCCTGCACCAACTA
TCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCATGCCGCCCCGCGGCAGGCGG
CGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGATATTTATATCTGGGCCCCC
CTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTGGTGATTACCCTCTACTGCA
ACCACAGAAACCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCTGCTGTACA
TTTTCAAACAGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGACGGCT
GCTCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGAAGT
TTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATA
ACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAG
GACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGT
CTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGC
ATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACT
CAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCT
AGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGG

GACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATG
GATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTA
AGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTG
TAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGA
ACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGC
AAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAG
CCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCG
GGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTG
CCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGA
CGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGA
ACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCC
TGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCC
GAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGT
TGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGG
CACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTG
GGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:55)

[0321] Construct S2-7A4-C8K-41BB AA (signal sequence in bold; CDRs underlined)
MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYSFTSYDI
NWVRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSISTAYMELSSLRS
EDTAVYYCGRAGYYYYFGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSP
GTLSLSPGERATLSCRAGQSVTSSSFAWYQQKPGQAPRLLIYQTSTRATGIPDRFSGS
GSGTDFTLTISRLEPEDFAVYYCQQYGGSRSFGQGTKVELKRAAAFVPVFLPAKPTTT
PAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL
SLVITLYCNHRNRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCE
LRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNP
QEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA
LPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSLGG
AKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPC
KPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSC
QDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPGR
WITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIP
VYCSILAAVVVGLVAYIAFKR (SEQ ID NO:56)

[0322] Construct S2-7A5-CD28T-CD28-41BB DNA (signal sequence in bold)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG
CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACAGCTTCACCAGTTATGATAT
CAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGGTGGATGAA
CCCGAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCAT
GACCAGGGACACCTCCATAAGCACAGCCTACATGGAACTGAGCAGCCTGAGATC
TGAGGACACGGCCGTGTATTACTGTGGGAGAGCCGGTTACTACTACTACTTCGGT
ATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTATCCTCAGGAGGCGGCGGT
TCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGAAATTGTGTTGACGCAGTCT
CCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCG
GTCAGAGTGTTACCAGCAGCTCCTTAGCTTGGTACCAGCAGAAACCTGGCCAGG
CTCCCAGGCTCCTCATCTATCAGACATCCACCAGGGCCACTGGCATCCCAGACAG
GTTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGACTGGAG
CCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTGGCTCACGGGCGTTCG
GCCAAGGGACCAAGGTGGAACTCAAACGAGCCGCTGCCCTTGATAATGAAAAGT
CAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTTGTT
CCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCGCT
TGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTAGATCCAAAAG
AAGCCGCCTGCTCCATAGCGATTACATGAATATGACTCCACGCCGCCCTGGCCCC
ACAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATTTCGCTGCCTATCGG
AGCCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCTGCTGTACATTTTCAAAC
AGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGACGGCTGCTCCTGCC
GCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGAAGTTTTCCAGAT
CTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCA
ACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGAC
CCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAAT
GAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGA
GAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGC
TACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAA
GAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGA
AGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCC
GCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCC

TGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:57)

[0323] Construct S2-7A5-CD28T-CD28-41BB AA (signal sequence in bold; CDRs underlined)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYSFTSYDINWVRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSISTAYMELSSLRSEDTAVYYCGRAGYYYYFGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSLSPGERATLSCRAGQSVTSSSLAWYQQKPGQAPRLLIYQTSTRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGGSRAFGQGTKVELKRAAALDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:58)

[0324] Construct S2-7A5-CD28T-CD28 DNA (signal sequence in bold)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG
CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACAGCTTCACCAGTTATGATAT
CAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGGTGGATGAA
CCCGAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCAT
GACCAGGGACACCTCCATAAGCACAGCCTACATGGAACTGAGCAGCCTGAGATC
TGAGGACACGGCCGTGTATTACTGTGGGAGAGCCGGTTACTACTACTACTTCGGT
ATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTATCCTCAGGAGGCGGCGGT
TCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGAAATTGTGTTGACGCAGTCT
CCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCG
GTCAGAGTGTTACCAGCAGCTCCTTAGCTTGGTACCAGCAGAAACCTGGCCAGG
CTCCCAGGCTCCTCATCTATCAGACATCCACCAGGGCCACTGGCATCCCAGACAG
GTTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGACTGGAG
CCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTGGCTCACGGGCGTTCG
GCCAAGGGACCAAGGTGGAACTCAAACGAGCCGCTGCCCTTGATAATGAAAAGT
CAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTTGTT
CCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCGCT
TGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTAGATCCAAAAG
AAGCCGCCTGCTCCATAGCGATTACATGAATATGACTCCACGCCGCCCTGGCCCC
ACAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATTTCGCTGCCTATCGG
AGCAGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCAG
AACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTG
GACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAA
CCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTA
TTCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTT
TGTACCAGGGACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCA
AGCCCTGCCACCTAGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCT
CCTTACATGTGGGGACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGCCAC
GGGAAGGGCTATGGATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCT
CTCGGAGGCGCTAAGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTGAA
TGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAACC
AGACAGTCTGTGAACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAGC

CACCGAGCCTTGCAAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCC
CCCTGTGTCGAAGCCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAGG
ACGAAACTACCGGGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCC
TCGTGTTCAGTTGCCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGACG
GAACCTACAGCGACGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTCT
GCGAGGATACCGAACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGT
GCGAGGAGATCCCTGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAG
ACAGTACAGCCCCGAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGA
TCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGT
CGTGACGCGGGGCACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCA
GCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA
(SEQ ID NO:59)

[0325] Construct S2-7A5-CD28T-CD28 AA (signal sequence in bold; CDRs underlined)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYSFTSYDI
NWVRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSISTAYMELSSLRS
EDTAVYYCGRAGYYYYFGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSP
GTLSLSPGERATLSCRAGQSVTSSSLAWYQQKPGQAPRLLIYQTSTRATGIPDRFSGS
GSGTDFTLTISRLEPEDFAVYYCQQYGGSRAFGQGTKVELKRAAALDNEKSNGTIIH
VKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDY
MNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQLYNELNL
GRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERR
RGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGP
MGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQ
PCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAY
GYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPC
TVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIAS
TVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID
NO:60)

[0326] Construct S2-7A5-CD28T-41BB DNA (signal sequence in bold)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG

CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACAGCTTCACCAGTTATGATAT
CAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGGTGGATGAA
CCCGAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCAT
GACCAGGGACACCTCCATAAGCACAGCCTACATGGAACTGAGCAGCCTGAGATC
TGAGGACACGGCCGTGTATTACTGTGGGAGAGCCGGTTACTACTACTACTTCGGT
ATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTATCCTCAGGAGGCGGCGGT
TCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGAAATTGTGTTGACGCAGTCT
CCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCG
GTCAGAGTGTTACCAGCAGCTCCTTAGCTTGGTACCAGCAGAAACCTGGCCAGG
CTCCCAGGCTCCTCATCTATCAGACATCCACCAGGGCCACTGGCATCCCAGACAG
GTTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGACTGGAG
CCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTGGCTCACGGGCGTTCG
GCCAAGGGACCAAGGTGGAACTCAAACGAGCCGCTGCCCTTGATAATGAAAAGT
CAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTTGTT
CCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCGCT
TGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTCGCTTTTCCGTC
GTTAAGCGGGGGAGAAAAAAGCTGCTGTACATTTTCAAACAGCCGTTTATGAGG
CCGGTCCAAACGACTCAGGAAGAGGACGGCTGCTCCTGCCGCTTTCCTGAGGAG
GAGGAGGGCGGGTGCGAACTGAGGGTGAAGTTTTCCAGATCTGCAGATGCACCA
GCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGACGCAGG
GAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGC
AAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGAT
AAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGG
AAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGAAGGATACTTA
TGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAAGAGAAGTGGCAGCGG
GGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGAAGAAAATCCGGGGCC
TATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCCGCGACTGCTTCTCCT
GCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCCTGTCCAACGGGCCTC
TACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTCGCAC
AACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCCTGGATTCAGTGACATT
CAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTGTACCGAATGTGTGGGC
CTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGATGCAGTGTGCAGATGTG
CCTATGGATATTACCAGGACGAAACTACCGGGCGGTGTGAGGCCTGCCGGGTGT

GTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGCAAAACACAGTAT
GTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCGAACCACGTCGACCCTT
GCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGAGAGAGTGTACGC
GCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGATCACCCGGAGCA
CACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAGAACCGGAGGCCC
CTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTCAT
GGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCGACAATCTGATTCCTGT
CTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCTTT
AAGAGATGACCTAGGTAA (SEQ ID NO:61)

[0327] Construct S2-7A5-CD28T-41BB AA (signal sequence in bold; CDRs underlined)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYSFTSYDI
NWVRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSISTAYMELSSLRS
EDTAVYYCGRAGYYYYFGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSP
GTLSLSPGERATLSCRAGQSVTSSSLAWYQQKPGQAPRLLIYQTSTRATGIPDRFSGS
GSGTDFTLTISRLEPEDFAVYYCQQYGGSRAFGQGTKVELKRAAALDNEKSNGTIIH
VKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRFSVVKRGRKKL
LYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYN
ELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMK
GERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVE
ENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGE
GVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVC
RCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVD
PCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQ
DLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ
ID NO:62)

[0328] Construct S2-7A5-C8K-CD28 DNA (signal sequence in bold)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG
CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACAGCTTCACCAGTTATGATAT
CAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGGTGGATGAA
CCCGAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCAT

GACCAGGGACACCTCCATAAGCACAGCCTACATGGAACTGAGCAGCCTGAGATC
TGAGGACACGGCCGTGTATTACTGTGGGAGAGCCGGTTACTACTACTACTTCGGT
ATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTATCCTCAGGAGGCGGCGGT
TCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGAAATTGTGTTGACGCAGTCT
CCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCG
GTCAGAGTGTTACCAGCAGCTCCTTAGCTTGGTACCAGCAGAAACCTGGCCAGG
CTCCCAGGCTCCTCATCTATCAGACATCCACCAGGGCCACTGGCATCCCAGACAG
GTTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGACTGGAG
CCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTGGCTCACGGGCGTTCG
GCCAAGGGACCAAGGTGGAACTCAAACGAGCCGCTGCCTTCGTGCCTGTTTTTCT
GCCCGCGAAACCCACAACTACCCCCGCCCCTCGGCCCCCAACTCCTGCACCAACT
ATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCATGCCGCCCCGCGGCAGGCG
GCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGATATTTATATCTGGGCCCC
CCTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTGGTGATTACCCTCTACTGC
AACCACAGAAACAGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGAAT
ATGACTCCACGCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCACCA
CCTAGAGATTTCGCTGCCTATCGGAGCAGGGTGAAGTTTTCCAGATCTGCAGATG
CACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGAC
GCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGATG
GGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAGCTGCAG
AAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAG
AAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGAAGG
ATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAAGAGAAGTG
GCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGAAGAAAATC
CGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCCGCGACTGC
TTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCCTGTCCAAC
GGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTGGCGAGGGC
GTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCCTGGATTCAG
TGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTGTACCGAATG
TGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGATGCAGTGTGC
AGATGTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTGTGAGGCCTGC
CGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGCAAAAC
ACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCGAACCACGTC

GACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:63)

[0329] Construct S2-7A5-C8K-CD28 AA (signal sequence in bold; CDRs underlined)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYSFTSYDINWVRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSISTAYMELSSLRSEDTAVYYCGRAGYYYYFGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSLSPGERATLSCRAGQSVTSSSLAWYQQKPGQAPRLLIYQTSTRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGGSRAFGQGTKVELKRAAAFVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCNHRNRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:64)

[0330] Construct S2-7A5-C8K-41BB DNA (signal sequence in bold)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCGCACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACAGCTTCACCAGTTATGATATCAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGGTGGATGAACCCGAACAGTGGTAACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCATGACCAGGGACACCTCCATAAGCACAGCCTACATGGAACTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGGGAGAGCCGGTTACTACTACTACTTCGGT

ATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTATCCTCAGGAGGCGGCGGT
TCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGAAATTGTGTTGACGCAGTCT
CCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCG
GTCAGAGTGTTACCAGCAGCTCCTTAGCTTGGTACCAGCAGAAACCTGGCCAGG
CTCCCAGGCTCCTCATCTATCAGACATCCACCAGGGCCACTGGCATCCCAGACAG
GTTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGACTGGAG
CCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTGGCTCACGGGCGTTCG
GCCAAGGGACCAAGGTGGAACTCAAACGAGCCGCTGCCTTCGTGCCTGTTTTCT
GCCCGCGAAACCCACAACTACCCCCGCCCCTCGGCCCCCAACTCCTGCACCAACT
ATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCATGCCGCCCCGCGGCAGGCG
GCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGATATTTATATCTGGGCCCC
CCTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTGGTGATTACCCTCTACTGC
AACCACAGAAACCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCTGCTGTAC
ATTTTCAAACAGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGACGGC
TGCTCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGAAG
TTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATA
ACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAG
GACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGT
CTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGC
ATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACT
CAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCT
AGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGG
GACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATG
GATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTA
AGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTG
TAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGA
ACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGC
AAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAG
CCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCG
GGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTG
CCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGA
CGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGA
ACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCC

TGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCC
GAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGT
TGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGG
CACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTG
GGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:65)

[0331] <u>Construct S2-7A5-C8K-41BB AA (signal sequence in bold; CDRs underlined)</u>

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYSFTSYDI
NWVRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRDTSISTAYMELSSLRS
EDTAVYYCGRAGYYYYFGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSP
GTLSLSPGERATLSCRAGQSVTSSSLAWYQQKPGQAPRLLIYQTSTRATGIPDRFSGS
GSGTDFTLTISRLEPEDFAVYYCQQYGGSRAFGQGTKVELKRAAAFVPVFLPAKPTT
TPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLL
LSLVITLYCNHRNRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGC
ELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKN
PQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQ
ALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSLG
GAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEP
CKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFS
CQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPG
RWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLI
PVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:66)

[0332] <u>Construct S2-14C1-CD28T-CD28-41BB DNA (signal sequence in bold)</u>

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG
CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACACCTTCACCGGCTACTATAT
GCACTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAA
CCCTAATAGTGGTGGCACAAACTCTGCACAGAAGTTTCAGGGCAGGGTCACCAT
GACCAGGGACACGTCCATCAGTACAGCCTACATGGAGCTGAACAGGCTGAGATC
TGACGACACGGCCGTTTATTACTGTGCGAGAGGATGGCTACAGACGTACTACTTT
GACAACTGGGGCCAGGGAACCCTGGTCACCGTATCCTCAGGAGGCGGCGGTTCA
GGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGACATCGTGATGACCCAGTCTCCA

GACTCCCTGGCTGTGTCTCTGGGCGAGAGGGCCACCATCTACTGCAAGTCCAGCC
AGACTGTTTTGACCAGCTCCAACAATAAGAACTTCTTAGCTTGGTACCAACAGAA
ACTAGGACAGCCTCCTAAGCTGCTCATTTCCTGGGCCTCTACCCGGGAATCCGGG
GTCCCTGACCGATTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCA
GCAGCCTGCAGGCTGAAGATGTGGCAATTTATTACTGTCAGCACTATTATACTAG
TCCACTCACTTTCGGCGGCGGGACCAAGGTGGAGATCAAACGAGCCGCTGCCCT
TGATAATGAAAAGTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTG
TCCGTCACCCTTGTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGG
GTGGAGTCCTCGCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGG
GTTAGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGAATATGACTCCAC
GCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATT
TCGCTGCCTATCGGAGCCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCTGCT
GTACATTTTCAAACAGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGA
CGGCTGCTCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGT
GAAGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACT
GTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCG
CAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGG
AGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAA
TAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAG
GGACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGC
CACCTAGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACAT
GTGGGGACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGG
GCTATGGATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAG
GCGCTAAGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAA
AGCCTGTAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGT
CTGTGAACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAG
CCTTGCAAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTG
TCGAAGCCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAA
CTACCGGGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTT
CAGTTGCCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTA
CAGCGACGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGA
TACCGAACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGA
GATCCCTGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTAC

AGCCCCGAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTC
TACAGTTGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGAC
GCGGGGCACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTG
GTCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:67)

[0333] Construct S2-14C1-CD28T-CD28-41BB AA (signal sequence in bold; CDRs underlined)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTGYY
MHWVRQAPGQGLEWMGWINPNSGGTNSAQKFQGRVTMTRDTSISTAYMELNRLRS
DDTAVYYCARGWLQTYYFDNWGQGTLVTVSSGGGGSGGGGSGGGGSDIVMTQSP
DSLAVSLGERATIYCKSSQTVLTSSNNKNFLAWYQQKLGQPPKLLISWASTRESGVP
DRFSGSGSGTDFTLTISSLQAEDVAIYYCQHYYTSPLTFGGGTKVEIKRAAALDNEKS
NGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRL
LHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRFSVVKRGRKKLLYIFKQPFMR
PVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREE
YDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKG
HDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGA
GATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQPCG
ANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYY
QDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCTVC
EDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVA
GVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:68)

[0334] Construct S2-14C1-CD28T-CD28 DNA (signal sequence in bold)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG
CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACACCTTCACCGGCTACTATAT
GCACTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAA
CCCTAATAGTGGTGGCACAAACTCTGCACAGAAGTTTCAGGGCAGGGTCACCAT
GACCAGGGACACGTCCATCAGTACAGCCTACATGGAGCTGAACAGGCTGAGATC
TGACGACACGGCCGTTTATTACTGTGCGAGAGGATGGCTACAGACGTACTACTTT

GACAACTGGGGCCAGGGAACCCTGGTCACCGTATCCTCAGGAGGCGGCGGTTCA
GGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGACATCGTGATGACCCAGTCTCCA
GACTCCCTGGCTGTGTCTCTGGGCGAGAGGGCCACCATCTACTGCAAGTCCAGCC
AGACTGTTTTGACCAGCTCCAACAATAAGAACTTCTTAGCTTGGTACCAACAGAA
ACTAGGACAGCCTCCTAAGCTGCTCATTTCCTGGGCCTCTACCCGGGAATCCGGG
GTCCCTGACCGATTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCA
GCAGCCTGCAGGCTGAAGATGTGGCAATTTATTACTGTCAGCACTATTATACTAG
TCCACTCACTTTCGGCGGCGGGACCAAGGTGGAGATCAAACGAGCCGCTGCCCT
TGATAATGAAAAGTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTG
TCCGTCACCCTTGTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGG
GTGGAGTCCTCGCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGG
GTTAGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGAATATGACTCCAC
GCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATT
TCGCTGCCTATCGGAGCAGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGCGTA
TCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGA
GTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACC
AAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGATAAGAT
GGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAG
GGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGAAGGATACTTATGACG
CTCTCCACATGCAAGCCCTGCCACCTAGGGCCAAGAGAAGTGGCAGCGGGGAGG
GCCGGGGATCTCTCCTTACATGTGGGGACGTGGAAGAAAATCCGGGGCCTATGG
GTGCCGGCGCCACGGGAAGGGCTATGGATGGCCCGCGACTGCTTCTCCTGCTGTT
GTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCCTGTCCAACGGGCCTCTACACT
CACTCCGGTGAATGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTCGCACAACCTT
GTGGTGCTAACCAGACAGTCTGTGAACCATGCCTGGATTCAGTGACATTCAGCGA
TGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTGTACCGAATGTGTGGGCCTTCAG
TCCATGTCCGCCCCCTGTGTCGAAGCCGATGATGCAGTGTGCAGATGTGCCTATG
GATATTACCAGGACGAAACTACCGGGCGGTGTGAGGCCTGCCGGGTGTGTGAAG
CCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGCAAAACACAGTATGTGAGG
AGTGTCCAGACGGAACCTACAGCGACGAGGCGAACCACGTCGACCCTTGCTTGC
CGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGAGAGAGTGTACGCGCTGGG
CAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGATCACCCGGAGCACACCTC
CTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAGAACCGGAGGCCCCTCCAG

AGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTCATGGGATC
CTCACAACCAGTCGTGACGCGGGGCACAACCGACAATCTGATTCCTGTCTACTGT
AGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGAT
GACCTAGGTAA (SEQ ID NO:69)

[0335] Construct S2-14C1-CD28T-CD28 AA (signal sequence in bold; CDRs underlined)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTGYY
MHWVRQAPGQGLEWMGWINPNSGGTNSAQKFQGRVTMTRDTSISTAYMELNRLRS
DDTAVYYCARGWLQTYYFDNWGQGTLVTVSSGGGGSGGGGSGGGGSDIVMTQSP
DSLAVSLGERATIYCKSSQTVLTSSNNKNFLAWYQQKLGQPPKLLISWASTRESGVP
DRFSGSGSGTDFTLTISSLQAEDVAIYYCQHYYTSPLTFGGGTKVEIKRAAALDNEKS
NGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRL
LHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQLY
NELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGM
KGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDV
EENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLG
EGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAV
CRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHV
DPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPE
QDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ
ID NO:70)

[0336] Construct S2-14C1-CD28T-41BB DNA (signal sequence in bold)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG
CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACACCTTCACCGGCTACTATAT
GCACTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAA
CCCTAATAGTGGTGGCACAAACTCTGCACAGAAGTTTCAGGGCAGGGTCACCAT
GACCAGGGACACGTCCATCAGTACAGCCTACATGGAGCTGAACAGGCTGAGATC
TGACGACACGGCCGTTTATTACTGTGCGAGAGGATGGCTACAGACGTACTACTTT
GACAACTGGGGCCAGGGAACCCTGGTCACCGTATCCTCAGGAGGCGGCGGTTCA
GGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGACATCGTGATGACCCAGTCTCCA
GACTCCCTGGCTGTGTCTCTGGGCGAGAGGGCCACCATCTACTGCAAGTCCAGCC

AGACTGTTTTGACCAGCTCCAACAATAAGAACTTCTTAGCTTGGTACCAACAGAA
ACTAGGACAGCCTCCTAAGCTGCTCATTTCCTGGGCCTCTACCCGGGAATCCGGG
GTCCCTGACCGATTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCA
GCAGCCTGCAGGCTGAAGATGTGGCAATTTATTACTGTCAGCACTATTATACTAG
TCCACTCACTTTCGGCGGCGGGACCAAGGTGGAGATCAAACGAGCCGCTGCCCT
TGATAATGAAAAGTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTCTG
TCCGTCACCCTTGTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGTGG
GTGGAGTCCTCGCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGG
GTTCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCTGCTGTACATTTTCAAAC
AGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGACGGCTGCTCCTGCC
GCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGAAGTTTTCCAGAT
CTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCA
ACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGAC
CCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAAT
GAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGA
GAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGC
TACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAA
GAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGA
AGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCC
GCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCC
TGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTG
GCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCC
TGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTG
TACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGAT
GCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTGT
GAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATA
AGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCG
AACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGC
TGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGAT
GGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCC
AAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCG
TGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCG

ACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGT
AGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:71)

[0337] Construct S2-14C1-CD28T-41BB AA (signal sequence in bold; CDRs underlined)
MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTGYY
MHWVRQAPGQGLEWMGWINPNSGGTNSAQKFQGRVTMTRDTSISTAYMELNRLRS
DDTAVYYCARGWLQTYYFDNWGQGTLVTVSSGGGGSGGGGSGGGGSDIVMTQSP
DSLAVSLGERATIYCKSSQTVLTSSNNKNFLAWYQQKLGQPPKLLISWASTRESGVP
DRFSGSGSGTDFTLTISSLQAEDVAIYYCQHYYTSPLTFGGGTKVEIKRAAALDNEKS
NGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRFSVVKR
GRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQ
NQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYS
EIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTC
GDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKA
CNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEA
DDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDE
ANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEP
EAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFK
R (SEQ ID NO:72)

[0338] Construct S2-14C1-C8K-CD28 DNA (signal sequence in bold)
ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
CACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGG
CCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACACCTTCACCGGCTACTATAT
GCACTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAA
CCCTAATAGTGGTGGCACAAACTCTGCACAGAAGTTTCAGGGCAGGGTCACCAT
GACCAGGGACACGTCCATCAGTACAGCCTACATGGAGCTGAACAGGCTGAGATC
TGACGACACGGCCGTTTATTACTGTGCGAGAGGATGGCTACAGACGTACTACTTT
GACAACTGGGGCCAGGGAACCCTGGTCACCGTATCCTCAGGAGGCGGCGGTTCA
GGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGACATCGTGATGACCCAGTCTCCA
GACTCCCTGGCTGTGTCTCTGGGCGAGAGGGCCACCATCTACTGCAAGTCCAGCC
AGACTGTTTTGACCAGCTCCAACAATAAGAACTTCTTAGCTTGGTACCAACAGAA
ACTAGGACAGCCTCCTAAGCTGCTCATTTCCTGGGCCTCTACCCGGGAATCCGGG

GTCCCTGACCGATTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCA
GCAGCCTGCAGGCTGAAGATGTGGCAATTTATTACTGTCAGCACTATTATACTAG
TCCACTCACTTTCGGCGGCGGGACCAAGGTGGAGATCAAACGAGCCGCTGCCTT
CGTGCCTGTTTTTCTGCCCGCGAAACCCACAACTACCCCCGCCCCTCGGCCCCCA
ACTCCTGCACCAACTATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCATGCC
GCCCCGCGGCAGGCGGCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGATA
TTTATATCTGGGCCCCCCTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTGGT
GATTACCCTCTACTGCAACCACAGAAACAGATCCAAAAGAAGCCGCCTGCTCCA
TAGCGATTACATGAATATGACTCCACGCCGCCCTGGCCCCACAAGGAAACACTA
CCAGCCTTACGCACCACCTAGAGATTTCGCTGCCTATCGGAGCAGGGTGAAGTTT
TCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAAC
GAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGA
CGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCT
CTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCAT
GAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCA
GCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAG
GGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGA
CGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGA
TGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAG
GAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTA
ACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAAC
CATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAA
GCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCC
GATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCGGG
CGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCC
AGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGAC
GAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAA
CGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCT
GGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCCG
AGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTT
GCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGGC
ACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGG
GCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:73)

[0339] Construct S2-14C1-C8K-CD28 AA (signal sequence in bold; CDRs underlined)

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPNSGGTNSAQKFQGRVTMTRDTSISTAYMELNRLRSDDTAVYYCARGWLQTYYFDNWGQGTLVTVSSGGGGSGGGGSGGGGSDIVMTQSPDSLAVSLGERATIYCKSSQTVLTSSNNKNFLAWYQQKLGQPPKLLISWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAIYYCQHYYTSPLTFGGGTKVEIKRAAAFVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCNHRNRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:74)

[0340] Construct S2-14C1-C8K-41BB DNA (signal sequence in bold)

ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCGCACGCCCGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTGTCCTGCAAGGCTTCTGGATACACCTTCACCGGCTACTATATGCACTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAACCCTAATAGTGGTGGCACAAACTCTGCACAGAAGTTTCAGGGCAGGGTCACCATGACCAGGGACACGTCCATCAGTACAGCCTACATGGAGCTGAACAGGCTGAGATCTGACGACACGGCCGTTTATTACTGTGCGAGAGGATGGCTACAGACGTACTACTTTGACAACTGGGGCCAGGGAACCCTGGTCACCGTATCCTCAGGAGGCGGCGGTTCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGGGCCACCATCTACTGCAAGTCCAGCCAGACTGTTTTGACCAGCTCCAACAATAAGAACTTCTTAGCTTGGTACCAACAGAAACTAGGACAGCCTCCTAAGCTGCTCATTTCCTGGGCCTCTACCCGGGAATCCGGGGTCCCTGACCGATTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGATGTGGCAATTTATTACTGTCAGCACTATTATACTAGTCCACTCACTTTCGGCGGCGGGACCAAGGTGGAGATCAAACGAGCCGCTGCCTT

CGTGCCTGTTTTTCTGCCCGCGAAACCCACAACTACCCCCGCCCCTCGGCCCCCAACTCCTGCACCAACTATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCATGCCGCCCCGCGGCAGGCGGCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGATATTTATATCTGGGCCCCCCTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTGGTGATTACCCTCTACTGCAACCACAGAAACCGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAAGCTGCTGTACATTTTCAAACAGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAGGACGGCTGCTCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGGGCCAAGAGAAGTGGCAGCGGGGAGGGCCGGGGATCTCTCCTTACATGTGGGGACGTGGAAGAAAATCCGGGGCCTATGGGTGCCGGCGCCACGGGAAGGGCTATGGATGGCCCGCGACTGCTTCTCCTGCTGTTGTTGGGCGTGTCTCTCGGAGGCGCTAAGGAGGCCTGTCCAACGGGCCTCTACACTCACTCCGGTGAATGTTGCAAAGCCTGTAACCTTGGCGAGGGCGTCGCACAACCTTGTGGTGCTAACCAGACAGTCTGTGAACCATGCCTGGATTCAGTGACATTCAGCGATGTTGTCTCAGCCACCGAGCCTTGCAAGCCTTGTACCGAATGTGTGGGCCTTCAGTCCATGTCCGCCCCCTGTGTCGAAGCCGATGATGCAGTGTGCAGATGTGCCTATGGATATTACCAGGACGAAACTACCGGGCGGTGTGAGGCCTGCCGGGTGTGTGAAGCCGGCTCTGGCCTCGTGTTCAGTTGCCAGGATAAGCAAAACACAGTATGTGAGGAGTGTCCAGACGGAACCTACAGCGACGAGGCGAACCACGTCGACCCTTGCTTGCCGTGCACCGTCTGCGAGGATACCGAACGCCAGCTGAGAGAGTGTACGCGCTGGGCAGACGCTGAGTGCGAGGAGATCCCTGGGAGATGGATCACCCGGAGCACACCTCCTGAGGGATCAGACAGTACAGCCCCGAGTACCCAAGAACCGGAGGCCCCTCCAGAGCAGGACCTGATCGCTTCTACAGTTGCTGGCGTGGTGACGACAGTCATGGGATCCTCACAACCAGTCGTGACGCGGGGCACAACCGACAATCTGATTCCTGTCTACTGTAGCATCTTGGCAGCCGTGGTCGTGGGCCTGGTAGCCTACATCGCCTTTAAGAGATGACCTAGGTAA (SEQ ID NO:75)

[0341] <u>Construct S2-14C1-C8K-41BB AA (signal sequence in bold; CDRs underlined)</u>

MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPNSGGTNSAQKFQGRVTMTRDTSISTAYMELNRLRSDDTAVYYCARGWLQTYYFDNWGQGTLVTVSSGGGGSGGGGSGGGGSDIVMTQSPDSLAVSLGERATIYCKSSQTVLTSSNNKNFLAWYQQKLGQPPKLLISWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAIYYCQHYYTSPLTFGGGTKVEIKRAAAFVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCNHRNRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRAKRSGSGEGRGSLLTCGDVEENPGPMGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKR (SEQ ID NO:76)

[0342] <u>Human STEAP1 NM_012449 (NP_036581) AA</u>

[0343] MESRKDITNQEELWKMKPRRNLEEDDYLHKDTGETSMLKRPVLLHLHQTAHADEFDCPSELQHTQELFPQWHLPIKIAAIIASLTFLYTLLREVIHPLATSHQQYFYKIPILVINKVLPMVSITLLALVYLPGVIAAIVQLHNGTKYKKFPHWLDKWMLTRKQFGLLSFFFAVLHAIYSLSYPMRRSYRYKLLNWAYQQVQQNKEDAWIEHDVWRMEIYVSLGIVGLAILALLAVTSIPSVSDSLTWREFHYIQSKLGIVSLLLGTIHALIFAWNKWIDIKQFVWYTPPTFMIAVFLPIVVLIFKSILFLPCLRKKILKIRHGWEDVTKINKTEICSQL (SEQ ID NO:77)

[0344] <u>CAR Signal Peptide DNA</u>
ATGGCACTCCCCGTAACTGCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCGCACGCCCG (SEQ ID NO:78)

[0345] <u>CAR Signal Peptide</u>: MALPVTALLLPLALLLHAARP (SEQ ID NO:79)

[0346] <u>scFv G4S linker DNA</u>

GGCGGTGGAGGCTCCGGAGGGGGGGGCTCTGGCGGAGGGGGCTCC (SEQ ID NO:80)

[0347] scFv G4s linker: GGGGSGGGGSGGGGS (SEQ ID NO:81)

[0348] scFv Whitlow linker DNA
GGGTCTACATCCGGCTCCGGGAAGCCCGGAAGTGGCGAAGGTAGTACAAAGGGG (SEQ ID NO:82)

[0349] scFv Whitlow linker: GSTSGSGKPGSGEGSTKG (SEQ ID NO:83)

[0350] 4-1BB Nucleic Acid Sequence (intracellular domain)
AAGCGCGGCAGGAAGAAGCTCCTCTACATTTTTAAGCAGCCTTTTATGAGGCCCGTACAGACAACACAGGAGGAAGATGGCTGTAGCTGCAGATTTCCCGAGGAGGAGGAAGGTGGGTGCGAGCTG (SEQ ID NO:84)

[0351] 4-1BB AA (intracellular domain)
KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL (SEQ ID NO:85)

[0352] OX40 AA
RRDQRLPPDAHKPPGGGSFRTPIQEEQADAHSTLAKI (SEQ ID NO:86)

INCORPORATION BY REFERENCE

[0353] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. However, the citation of a reference herein should not be construed as an acknowledgement that such reference is prior art to the present invention. To the extent that any of the definitions or terms provided in the references incorporated by reference differ from the terms and discussion provided herein, the present terms and definitions control.

EQUIVALENTS

[0354] The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The foregoing description and examples detail certain preferred embodiments of the invention and describe the best mode contemplated by the inventors. It will be appreciated, however, that no matter how detailed the foregoing may appear in text, the invention may be practiced in many ways and the invention should be construed in accordance with the appended claims and any equivalents thereof.

[0355] The following examples, including the experiments conducted and results achieved, are provided for illustrative purposes only and are not to be construed as limiting the present invention.

EXAMPLE 1

[0356] PNT-2, LNCaP, PC-3, 22Rv1, C4-2B, and DU145 cell lines were cultured in RPMI1640 (Lonza) + 10% FBS (Corning) + 1X Penicillin Streptomycin L-Glutamine (Corning) (R10) medium and maintained at a cell density between 0.5-2.0 x 10^6 cells/ml. PNT-2 and DU145 are negative control cell lines. To examine cell surface STEAP1 expression, cells were incubated with an anti-STEAP1 antibody (2F3) or an IgG1 isotype control antibody (BD Pharmingen) in stain buffer (BD Pharmingen) for 30 minutes at 4°C. Cells were then washed and resuspended in stain buffer with propidium iodide (BD Pharmingen) prior to data acquisition. STEAP1 expression on target cells is shown in FIGURE 1.

EXAMPLE 2

[0357] Plasmids encoding a T7 promoter, CAR construct and a beta globin stabilizing sequence were linearized by overnight digestion of 10 µgDNA with EcoRI and BamHI (NEB). DNA was then digested for 2 hours at 50°C with proteinase K (Thermo Fisher, 600 U/ml) purified with phenol/chloroform and precipitated by adding sodium acetate and two volumes of ethanol. Pellets were then dried, resuspended in RNAse/DNAse-free water and quantified using NanoDrop. One µg of the linear DNA was then used for in vitro transcription using the mMESSAGE mMACHINE T7 Ultra (Thermo Fisher) following the manufacturer's instructions. RNA was further purified using the MEGAClear Kit (Thermo Fisher) following the manufacturer's instructions and quantified using NanoDrop. mRNA integrity was assesed using mobility on an agarose gel. PBMCs were isolated from healthy donor leukopaks (Hemacare) using ficoll-paque density centrifugation per manufacturer's instructions. PBMCs were stimulated using OKT3 (50 ng/ml, Miltenyi Biotec) in R10 medium + IL-2 (300 IU/ml, Proleukin®, Prometheus® Therapeutics and Diagnostics). Seven days post-stimulation, T cells were washed twice in Opti-MEM medium (Thermo Fisher Scientific) and resuspended at a final concentration of $2.5x10^7$ cells/ml in Opti-MEM medium. Ten µg of mRNA was used per electroporation. Electroporation of cells was performed using a Gemini X2 system (Harvard Apparatus BTX) to deliver a single 400 V pulse for 0.5 ms in 2 mm cuvettes (Harvard Apparatus BTX). Cells were immediately transferred to R10 + IL-2 medium and allowed to recover for 6 hours. To examine CAR expression, T cells were stained with LNGFR or biotinylated Protein L (Thermo Scientific) in stain buffer (BD Pharmingen) for 30 minutes at 4°C. Cells were then washed and stained with anti-LNGFR-PE or PE Streptavidin (BD Pharmingen) in stain buffer for 30 minutes at 4°C. Cells were then washed and resuspended in stain buffer with propidium iodide (BD Pharmingen) prior to data acquisition. Expression of STEAP1 CARs in electroporated T cells is shown in FIGURE 2.

EXAMPLE 3

[0358] To examine cytolytic activity in electroporated STEAP1 CAR T cells, effector cells were cultured with target cells at a 1:1 E:T ratio in R10 medium. Sixteen hours post-coculture, supernatants were analyzed by Luminex (EMD Millipore) and target cell viability was assessed by flow cytometric analysis of propidium iodide (PI) uptake by CD3-negative cells. Cytolytic activity of electroporated CAR T cells is shown in FIGURE 3 and cytokine production is shown in FIGURE 4.

EXAMPLE 4

[0359] To assess CAR T cell proliferation in response to STEAP1 expressing target cells, T cells were labeled with CFSE prior to co-culture with target cells at a 1:1 E:T ratio in R10 medium. Five days later, T cell proliferation was assessed by flow cytometric analysis of CFSE dilution. Proliferation of STEAP1 CAR T cells is shown in FIGURE 5.

What is Claimed

1. A chimeric antigen receptor comprising an antigen binding molecule that specifically binds to STEAP1, wherein the antigen binding molecule comprises:
   a) a variable heavy chain CDR1 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NOs:89, 99, 109, 119, 129, or 139; or
   b) a variable heavy chain CDR2 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NOs:90, 100, 110, 120, 130, or 140; or
   c) a variable heavy chain CDR3 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NOs:91, 101, 111, 121, 131, or 141; or
   d) a variable light chain CDR1 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NOs:94, 104, 114, 124, 134, or 144; or
   e) a variable light chain CDR2 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NOs:95, 105, 115, 125, 135, or 145; or
   f) a variable light chain CDR3 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ IDs:96, 106, 116, 126, 136, or 146; or
   g) a variable heavy chain CDR1 comprising an amino acid sequence of a variable heavy chain CDR1 sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1; or
   h) a variable heavy chain CDR2 comprising an amino acid sequence of a variable heavy chain CDR2 sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1; or
   i) a variable heavy chain CDR3 comprising an amino acid sequence of a variable heavy chain CDR3 sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1; or

j) a variable light chain CDR1 comprising an amino acid sequence of a variable light chain CDR1 sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1; or

k) a variable light chain CDR2 comprising an amino acid sequence of a variable light chain CDR2 sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1; or

l) a variable light chain CDR3 comprising an amino acid sequence of a variable light chain CDR3 sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1; or

m) a variable heavy chain sequence differing by not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 residues from the variable heavy chain sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1; or

n) a variable light chain sequence differing by not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 residues from the variable light chain sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1.

2. The chimeric antigen receptor according to claim 1 further comprising at least one costimulatory domain.

3. The chimeric antigen receptor according to claim 1 further comprising at least one activating domain.

4. The chimeric antigen receptor according to claim 2 wherein the costimulatory domain is a signaling region of CD28, OX-40, 4-1BB/CD137, CD2, CD7, CD27, CD30, CD40, programmed death-1 (PD-1), inducible T cell costimulator (ICOS), lymphocyte function-associated antigen-1 (LFA-1 (CDl la/CD18), CD3 gamma, CD3 delta, CD3 epsilon, CD247, CD276 (B7-H3), LIGHT, (TNFSF14), NKG2C, Ig alpha (CD79a), DAP-10, Fc gamma receptor, MHC class I molecule, TNF receptor proteins, an Immunoglobulin protein, cytokine receptor, integrins, Signaling Lymphocytic Activation Molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, ICAM-1, B7-H3, CDS, ICAM-1, GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL-2R beta, IL-2R gamma, IL-7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CDl ld, ITGAE, CD103, ITGAL, CDl la, LFA-1, ITGAM, CDl lb, ITGAX, CDl lc, ITGBl, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4

(CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRT AM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Lyl08), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, a ligand that specifically binds with CD83, or any combination thereof.

5. The chimeric antigen receptor according to claim 4 wherein the costimulatory domain comprises CD28.
6. The chimeric antigen receptor according to claim 5 wherein the CD28 costimulatory domain comprises a sequence that differs at no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues from the sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, or SEQ ID NO:8.
7. The chimeric antigen receptor according to claim 3 wherein the CD8 costimulatory domain comprises a sequence that differs at no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues from the sequence of SEQ ID NO:14.
8. The chimeric antigen receptor according to claim 3 wherein the activating domain comprises CD3.
9. The chimeric antigen receptor according to claim 7 wherein the CD3 comprises CD3 zeta.
10. The chimeric antigen receptor according to claim 8 wherein the CD3 zeta comprises a sequence that differs at no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues from the sequence of SEQ ID NO:10.
11. The chimeric antigen receptor according to claim 1 wherein the costimulatory domain comprises a sequence that differs at no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues from the sequence of SEQ ID NO:2 and the activating domain comprises a sequence that differs at no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues from the sequence of SEQ ID NO:10.
12. A polynucleotide encoding the chimeric antigen receptor of claim 1.
13. A vector comprising the polynucleotide of claim 12.
14. The vector according to claim 13 which is a retroviral vector, a DNA vector, a plasmid, a RNA vector, an adenoviral vector, an adenovirus associated vector, a lentiviral vector, or any combination thereof.
15. An immune cell comprising the vector of claim 13.

16. The immune cell according to claim 15, wherein the immune cell is a T cell, tumor infiltrating lymphocyte (TIL), NK cell, TCR-expressing cell, dendritic cell, or NK-T cell.

17. The immune cell according to claim 16, wherein the cell is an autologous T cell.

18. The immune cell according to claim 16, wherein the cell is an allogeneic T cell.

19. The immune cell of claim 15, wherein the vector is introduced into a cell that is isolated from a patient's body or that is grown from a sample taken from a patient's body.

20. The immune cell of claim 15, wherein the vector is introduced into a cell that is isolated from a donor's body or that is grown from a sample taken from a patient's body.

21. A pharmaceutical composition comprising an immune cell of claim 15.

22. A chimeric antigen receptor comprising:

    (a) a VH region of clone 2F3 and a VL region of clone 2F3;

    (b) a VH region of clone 11C2 and a VL region of clone 11C2;

    (c) a VH region of clone 1A1 and a VL region of clone 1A1;

    (d) a VH region of clone 7A4 and a VL region of clone 7A4;

    (e) a VH region of clone 7A5 and a VL region of clone 7A5; or

    (f) a VH region of clone 14C1 and a VL region of clone 14C1,

    wherein the VH and VL region is linked by at least one linker.

23. The chimeric antigen receptor according to claim 22, wherein the linker comprises the scFv G4S linker or the scFv Whitlow linker.

24. The chimeric antigen receptor according to claim 22, further comprising a costimulatory domain.

25. The chimeric antigen receptor according to claim 22, further comprising an activating domain.

26. The chimeric antigen receptor according to claim 24 wherein the costimulatory domain is a signaling region of CD28, OX-40, 4-1BB/CD137, CD2, CD7, CD27, CD30, CD40, programmed death-1 (PD-1), inducible T cell costimulator (ICOS), lymphocyte function-associated antigen-1 (LFA-1 (CDl la/CD18), CD3 gamma, CD3 delta, CD3 epsilon, CD247, CD276 (B7-H3), LIGHT, (TNFSF14), NKG2C, Ig alpha (CD79a), DAP-10, Fc gamma receptor, MHC class I molecule, TNF receptor proteins, an Immunoglobulin protein, cytokine

receptor, integrins, Signaling Lymphocytic Activation Molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, ICAM-1, B7-H3, CDS, ICAM-1, GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL-2R beta, IL-2R gamma, IL-7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CDl ld, ITGAE, CD103, ITGAL, CDl la, LFA-1, ITGAM, CDl lb, ITGAX, CDl lc, ITGBl, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRT AM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Lyl08), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, a ligand that specifically binds with CD83, or any combination thereof.

27. An immune cell comprising the chimeric antigen receptor of claim 22.

28. The immune cell according to claim 27, wherein the immune cell is a T cell, tumor infiltrating lymphocyte (TIL), NK cell, TCR-expressing cell, dendritic cell, or NK-T cell.

29. The T cell of claim 28 that is an autologous T cell.

30. The T cell of claim 29 that is an allogeneic T cell.

31. A pharmaceutical composition comprising the cell of claim 27.

32. An isolated polynucleotide comprising a sequence encoding the chimeric antigen receptor of claim 22.

33. A vector comprising the polynucleotide according to claim 32.

34. An immune cell comprising the vector of claim 33.

35. The immune cell according to claim 34, wherein the immune cell is a T cell, tumor infiltrating lymphocyte (TIL), NK cell, TCR-expressing cell, dendritic cell, or NK-T cell.

36. The T cell of claim 35 that is an autologous T cell.

37. The T cell of claim 35 that is an allogeneic T cell.

38. An isolated polypeptide comprising the amino acid sequence of construct 2F3-CD28T-CD28-41BB, construct 2F3-CD28T-CD28, construct 2F3-CD28T-41BB, construct 2F3-C8K-CD28, construct 2F3-C8K-41BB, construct 11C2-CD28T-CD28-41BB, construct 11C2-CD28T-CD28, construct 11C2-CD28T-41BB, construct 11C2-C8K-CD28, construct 11C2-C8K-

41BB, construct 1A1-CD28T-CD28-41BB, construct 1A1-CD28T-CD28, construct 1A1-CD28T-41BB, construct 1A1-C8K-CD28, construct 1A1-C8K-41BB, construct 7A4-CD28T-CD28-41BB, construct 7A4-CD28T-CD28, construct 7A4-CD28T-41BB, construct 7A4-C8K-CD28, construct 7A4-C8K-41BB, construct 7A5-CD28T-CD28-41BB, construct 7A5-CD28T-CD28, construct 7A5-CD28T-41BB, construct 7A5-C8K-CD28, construct 7A5-C8K-41BB, construct 14C1-CD28T-CD28-41BB, construct 14C1-CD28T-CD28, construct 14C1-CD28T-41BB, construct 14C1-C8K-CD28, or construct 14C1-C8K-41BB2F3 CD28.

39. A vector encoding the polypeptide of claim 38.

40. An immune cell comprising the polypeptide of claim 38.

41. The immune cell according to claim 40, wherein the immune cell is a T cell, tumor infiltrating lymphocyte (TIL), NK cell, TCR-expressing cell, dendritic cell, or NK-T cell.

42. The T cell of claim 41 that is an autologous T cell.

43. The T cell of claim 41 that is an allogeneic T cell.

44. An isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to STEAP1, wherein the antigen binding molecule comprises a variable heavy chain CDR3 comprising the amino acid sequence of a variable heavy chain CDR3 of clone 2F3, clone 11C2, clone 1A1, clone 7A4, clone 7A5, or clone 14C1.

45. The polynucleotide according to claim 44 further comprising an activating domain.

46. The polynucleotide according to claim 45 wherein the activating domain is CD3.

47. The polynucleotide according to claim 46 wherein the CD3 is CD3 zeta.

48. The polynucleotide according to claim 47 wherein the CD3 zeta comprises the amino acid sequence set forth in SEQ ID NO:9.

49. The polynucleotide according to claim 44 further comprising a costimulatory domain.

50. The polynucleotide according to claim 49 wherein the costimulatory domain is a signaling region of CD28, OX-40, 4-1BB/CD137, CD2, CD7, CD27, CD30, CD40, programmed death-1 (PD-1), inducible T cell costimulator (ICOS), lymphocyte function-associated antigen-1 (LFA-1 (CDl la/CD18), CD3 gamma, CD3 delta, CD3 epsilon, CD247, CD276 (B7-H3), LIGHT, (TNFSF14), NKG2C, Ig alpha (CD79a), DAP-10, Fc gamma receptor, MHC class I

molecule, TNF receptor proteins, an Immunoglobulin protein, cytokine receptor, integrins, Signaling Lymphocytic Activation Molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, ICAM-1, B7-H3, CDS, ICAM-1, GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL-2R beta, IL-2R gamma, IL-7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CDl ld, ITGAE, CD103, ITGAL, CDl la, LFA-1, ITGAM, CDl lb, ITGAX, CDl lc, ITGBl, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRT AM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Lyl08), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, a ligand that specifically binds with CD83, or any combination thereof.

51. The polynucleotide according to claim 50 wherein the CD28 costimulatory domain encodes the amino acid sequence set forth in SEQ ID NO 2.
52. A vector comprising the polynucleotide of claim 41.
53. An immune cell comprising the vector of claim 49.
54. The immune cell of claim 50, wherein the immune cell is a T cell, tumor infiltrating lymphocyte (TIL), NK cell, TCR-expressing cell, dendritic cell, or NK-T cell.
55. The T cell of claim 51 that is an autologous T cell.
56. The T cell of claim 51 that is an allogeneic T cell.
57. An isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR), said CAR or TCR comprising an antigen binding molecule that specifically binds to STEAP1, wherein the antigen binding molecule comprises:
    a. a variable heavy chain sequence differing by not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 residues from the variable heavy chain sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1; and/or
    b. a variable light chain sequence differing by not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 residues from the variable light chain sequence of clone 2F3, clone 11C2, clone 1A1, clone 7A4, or clone 7A5, or clone 14C1.
58. The polynucleotide according to claim 54 further comprising an activating domain.

59. The polynucleotide according to claim 55 wherein the activating domain is CD3.

60. The polynucleotide according to claim 56 wherein the CD3 is CD3 zeta.

61. The polynucleotide according to claim 60 wherein the CD3 zeta comprises the amino acid sequence set forth in SEQ ID NO:9.

62. The polynucleotide according to claim 57 further comprising a costimulatory domain.

63. The polynucleotide according to claim 62 wherein the costimulatory domain is a signaling region of CD28, OX-40, 4-1BB/CD137, CD2, CD7, CD27, CD30, CD40, programmed death-1 (PD-1), inducible T cell costimulator (ICOS), lymphocyte function-associated antigen-1 (LFA-1 (CDl la/CD18), CD3 gamma, CD3 delta, CD3 epsilon, CD247, CD276 (B7-H3), LIGHT, (TNFSF14), NKG2C, Ig alpha (CD79a), DAP-10, Fc gamma receptor, MHC class I molecule, TNF receptor proteins, an Immunoglobulin protein, cytokine receptor, integrins, Signaling Lymphocytic Activation Molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, ICAM-1, B7-H3, CDS, ICAM-1, GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL-2R beta, IL-2R gamma, IL-7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CDl ld, ITGAE, CD103, ITGAL, CDl la, LFA-1, ITGAM, CDl lb, ITGAX, CDl lc, ITGBl, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRT AM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, a ligand that specifically binds with CD83, or any combination thereof.

64. The polynucleotide according to claim 63 wherein the CD28 costimulatory domain comprises the nucleotide sequence set forth in SEQ ID NO 3.

65. The polynucleotide according to claim 64 wherein the CD28 costimulatory domain comprises the nucleotide sequence set forth in SEQ ID NO 1.

66. An isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to STEAP1, wherein the antigen binding molecule heavy chain comprises CDR1 (SEQ ID NO:89), CDR2 (SEQ ID

NO:90), and CDR3 (SEQ ID NO:91) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:94), CDR2 (SEQ ID NO:95), and CDR3 (SEQ ID NO:96).

67. An isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to STEAP1, wherein the antigen binding molecule heavy chain comprises CDR1 (SEQ ID NO:99), CDR2 (SEQ ID NO:100), and CDR3 (SEQ ID NO:101) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:104), CDR2 (SEQ ID NO:105), and CDR3 (SEQ ID NO:106).

68. An isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to STEAP1, wherein the antigen binding molecule heavy chain comprises CDR1 (SEQ ID NO:109), CDR2 (SEQ ID NO:110), and CDR3 (SEQ ID NO:111) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:114), CDR2 (SEQ ID NO:115), and CDR3 (SEQ ID NO:116).

69. An isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to STEAP1, wherein the antigen binding molecule heavy chain comprises CDR1 (SEQ ID NO:119), CDR2 (SEQ ID NO:120), and CDR3 (SEQ ID NO:121) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:124), CDR2 (SEQ ID NO:125), and CDR3 (SEQ ID NO:126).

70. An isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to STEAP1, wherein the antigen binding molecule heavy chain comprises CDR1 (SEQ ID NO:129), CDR2 (SEQ ID NO:130), and CDR3 (SEQ ID NO:131) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:134), CDR2 (SEQ ID NO:135), and CDR3 (SEQ ID NO:136).

71. An isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to STEAP1, wherein the antigen binding molecule heavy chain comprises CDR1 (SEQ ID NO:139), CDR2 (SEQ ID NO:140), and CDR3 (SEQ ID NO:141) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:144), CDR2 (SEQ ID NO:145), and CDR3 (SEQ ID NO:146).

72. A method of treating a disease or disorder in a subject in need thereof comprising administering to the subject the polynucleotide according to claim 12, 44, 57, 66, 67, 68, 69, 70, or 71.

73. A method of treating a disease or disorder in a subject in need thereof comprising administering to the subject the polypeptide according to claim 38.

74. A method of treating a disease or disorder in a subject in need thereof comprising administering to the subject the chimeric antigen receptor according to claim 1 or 22.

75. A method of treating a disease or disorder in a subject in need thereof comprising administering to the subject the cell according to claim 15, 27, 34, 40, or 53.

76. A method of treating a disease or disorder in a subject in need thereof comprising administering to the subject the pharmaceutical composition according to claim 21 or 31.

77. The method according to any of claims 72, 73, 74, 75, or 76, wherein the disease or disorder is cancer.

78. The method according to claim 77 wherein the cancer is prostate cancer.

79. The method according to claim 78, wherein the cancer is metastatic castration resistant prostate cancer.

FIG. 1

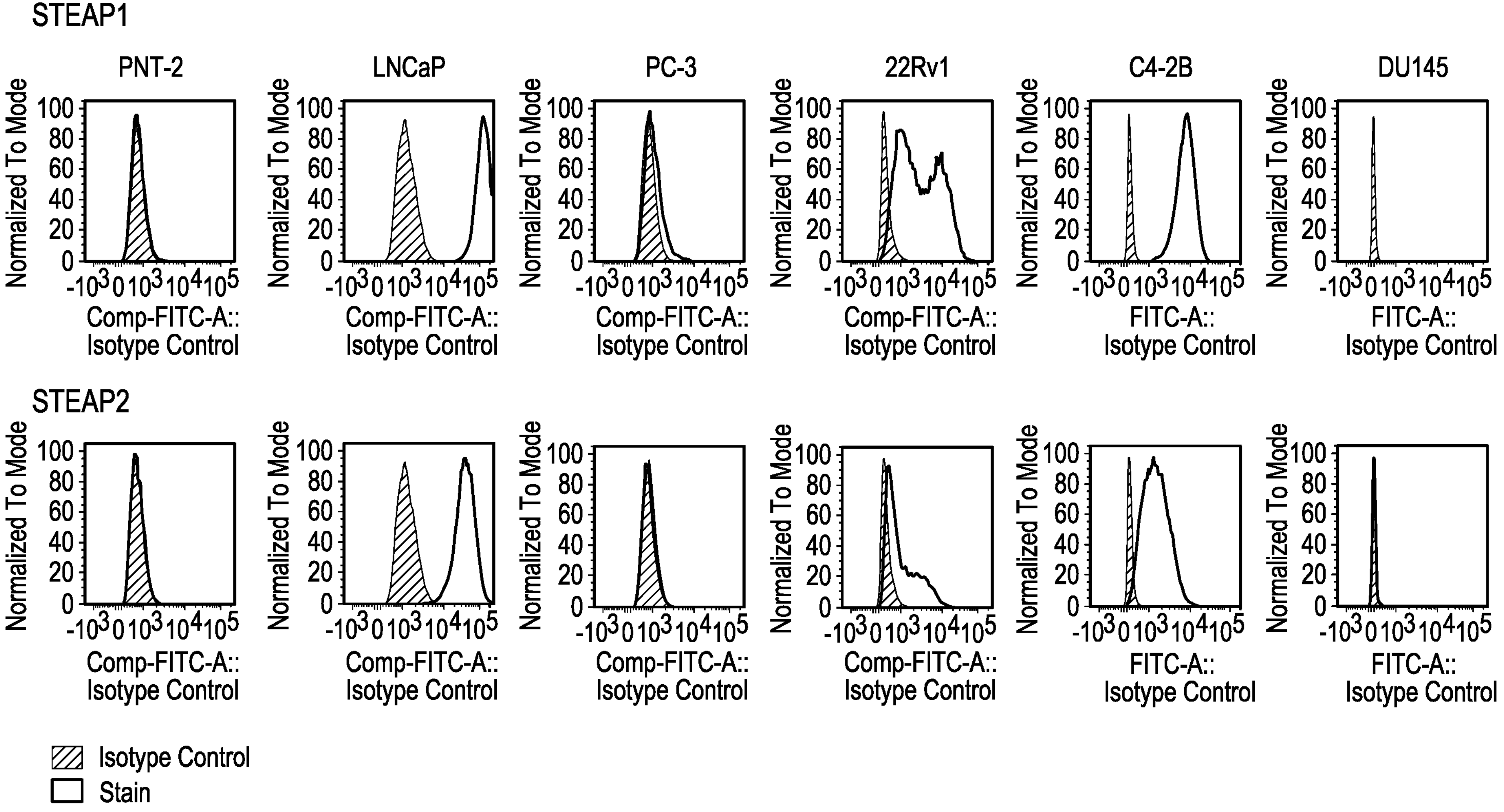

STEAP1
PNT-2
LNCaP
PC-3
22Rv1
C4-2B
DU145
STEAP2
Normalized To Mode
100
80
60
40
20
0
-10^3 0 10^3 10^4 10^5
Comp-FITC-A:: Isotype Control
FITC-A:: Isotype Control
▨ Isotype Control
☐ Stain

FIG. 2

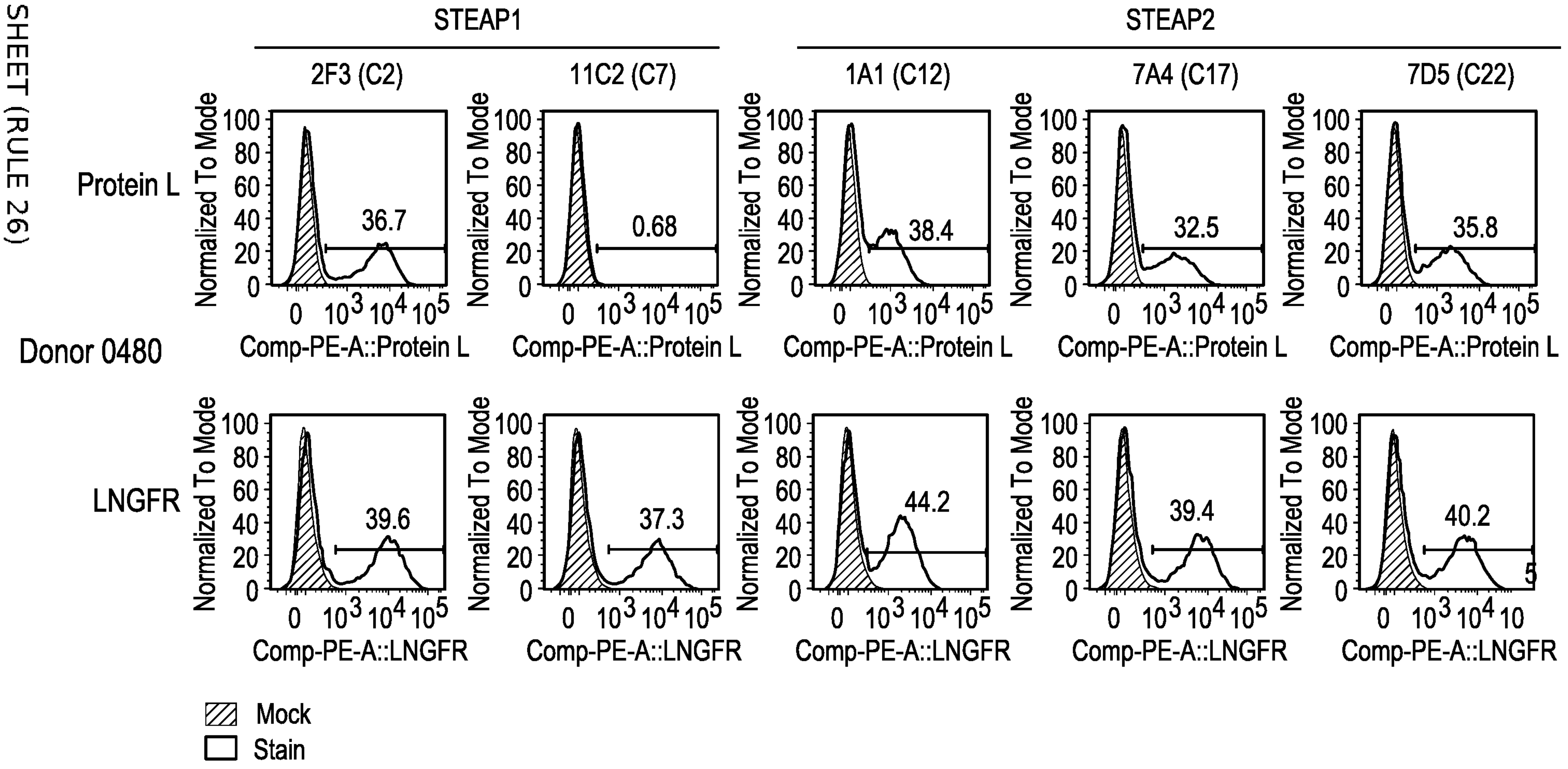

STEAP1
STEAP2
2F3 (C2)
11C2 (C7)
1A1 (C12)
7A4 (C17)
7D5 (C22)
Protein L
Donor 0480
LNGFR
Normalized To Mode
100
80
60
40
20
0
0
10^3
10^4
10^5
Comp-PE-A::Protein L
Comp-PE-A::LNGFR
36.7
0.68
38.4
32.5
35.8
39.6
37.3
44.2
39.4
40.2
Mock
Stain

FIG. 2 Cont'd

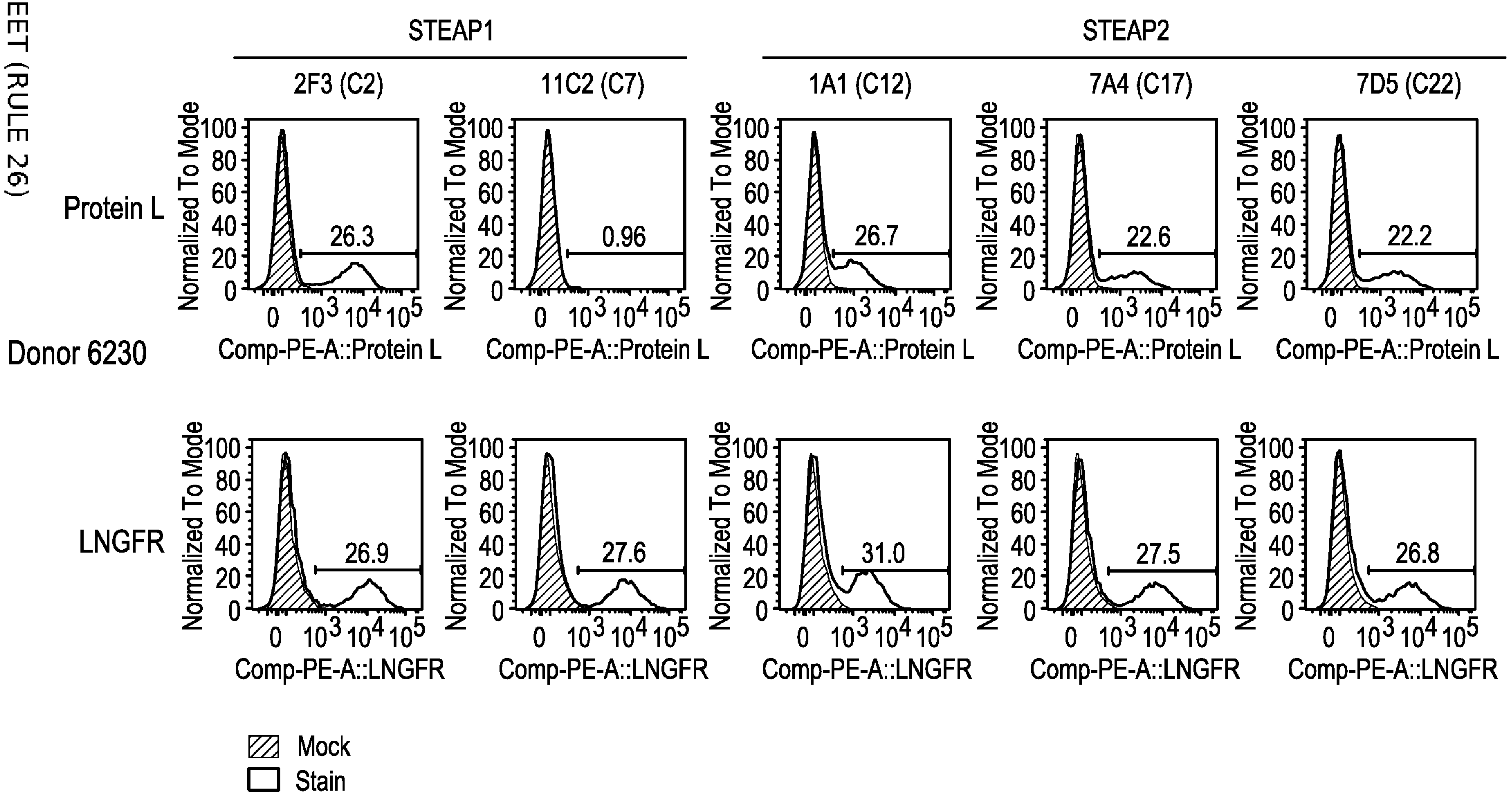

STEAP1
STEAP2
2F3 (C2)
11C2 (C7)
1A1 (C12)
7A4 (C17)
7D5 (C22)
Protein L
Donor 6230
LNGFR
Normalized To Mode
100
80
60
40
20
0
0
10^3
10^4
10^5
Comp-PE-A::Protein L
Comp-PE-A::LNGFR
26.3
0.96
26.7
22.6
22.2
26.9
27.6
31.0
27.5
26.8
▨ Mock
☐ Stain

FIG. 3

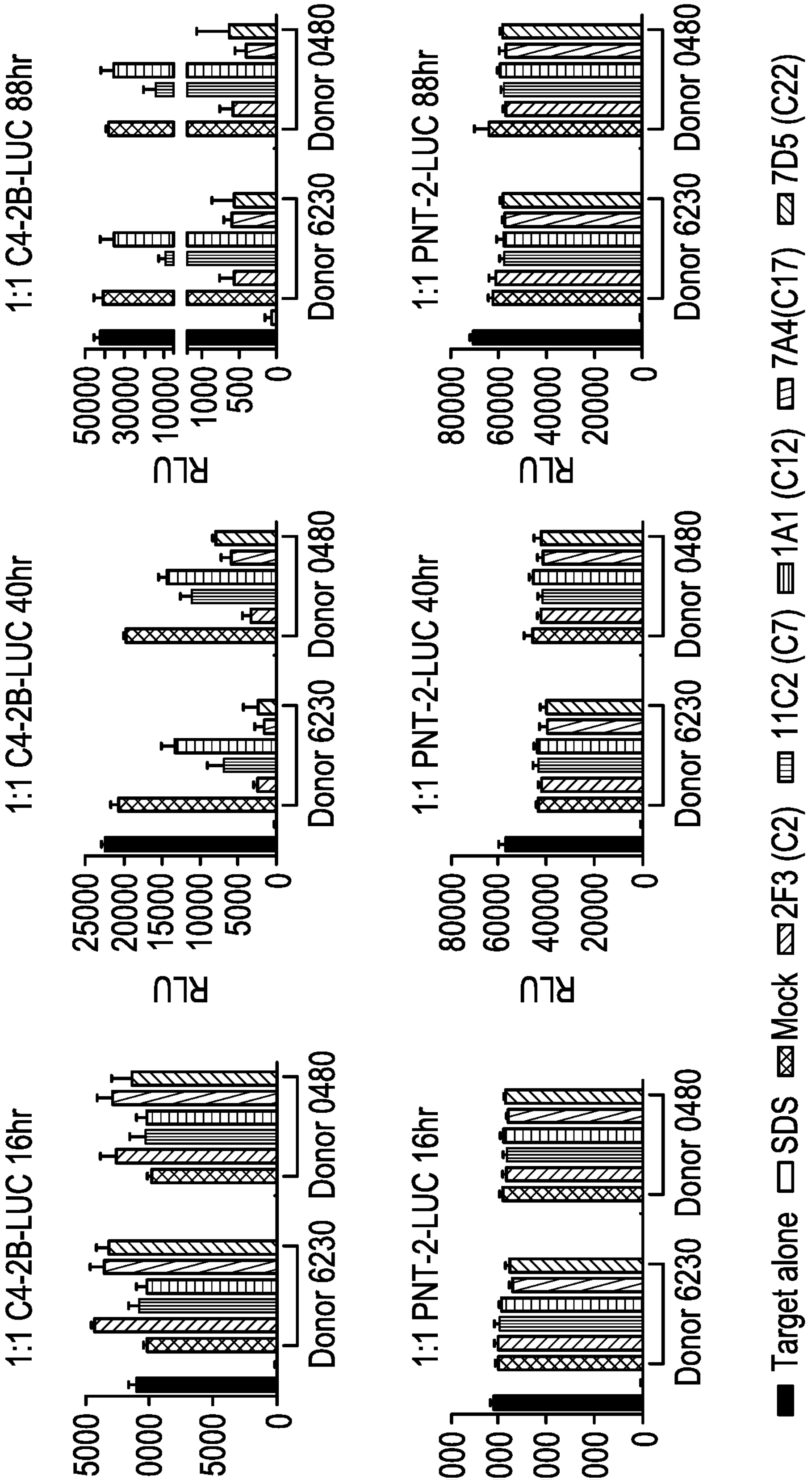

1:1 C4-2B-LUC 16hr
RLU
15000
10000
5000
0
Donor 6230
Donor 0480
1:1 C4-2B-LUC 40hr
RLU
25000
20000
15000
10000
5000
0
Donor 6230
Donor 0480
1:1 C4-2B-LUC 88hr
RLU
50000
30000
10000
1000
500
0
Donor 6230
Donor 0480
1:1 PNT-2-LUC 16hr
RLU
40000
30000
20000
10000
0
Donor 6230
Donor 0480
1:1 PNT-2-LUC 40hr
RLU
80000
60000
40000
20000
0
Donor 6230
Donor 0480
1:1 PNT-2-LUC 88hr
RLU
80000
60000
40000
20000
0
Donor 6230
Donor 0480
■ Target alone
☐ SDS
▨ Mock
▨ 2F3 (C2)
▥ 11C2 (C7)
▤ 1A1 (C12)
▥ 7A4(C17)
▨ 7D5 (C22)

FIG. 4

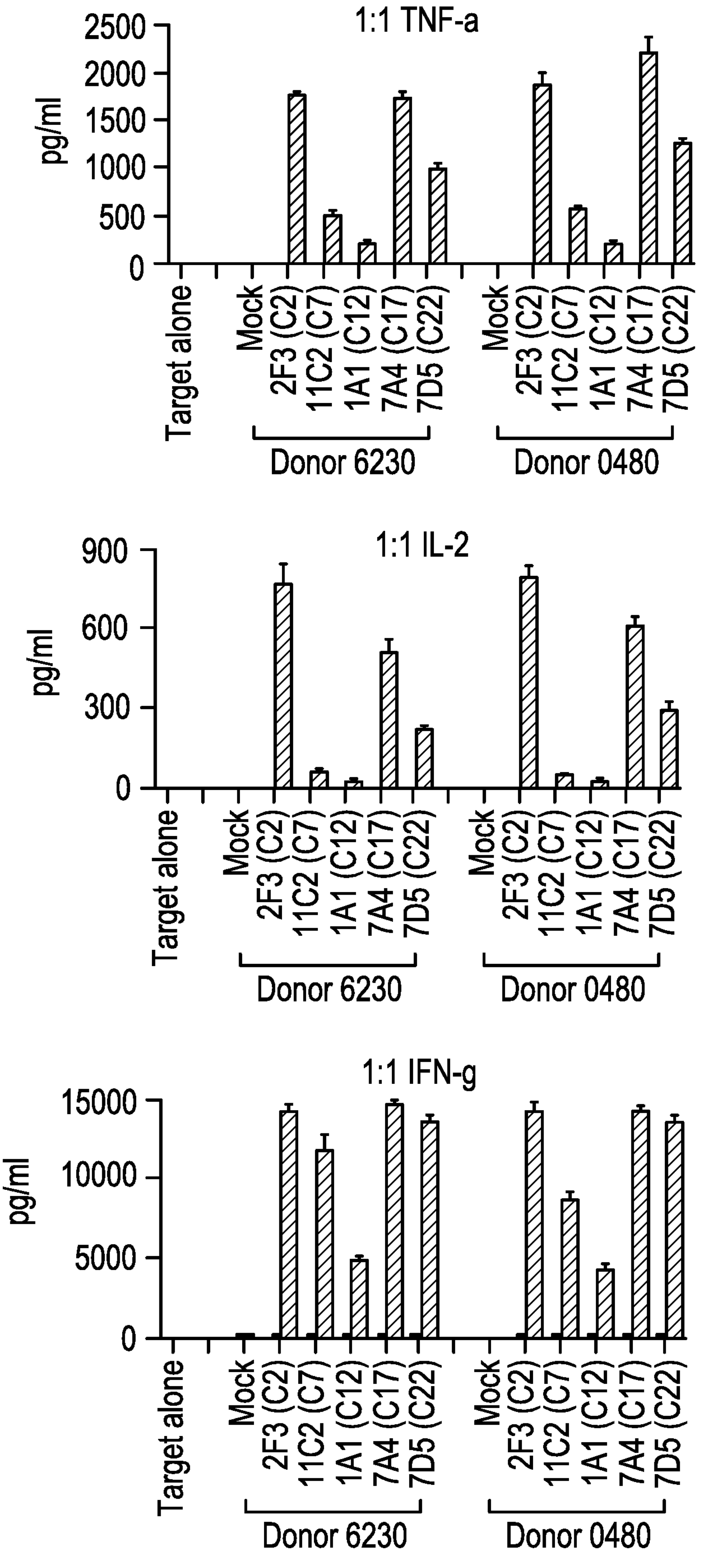

1:1 TNF-a
pg/ml
2500
2000
1500
1000
500
0
1:1 IL-2
900
600
300
0
1:1 IFN-g
15000
10000
5000
0
Target alone
Mock
2F3 (C2)
11C2 (C7)
1A1 (C12)
7A4 (C17)
7D5 (C22)
Donor 6230
Donor 0480
T cells alone
PNT-2-LUC
C4-2B-LUC

FIG. 5

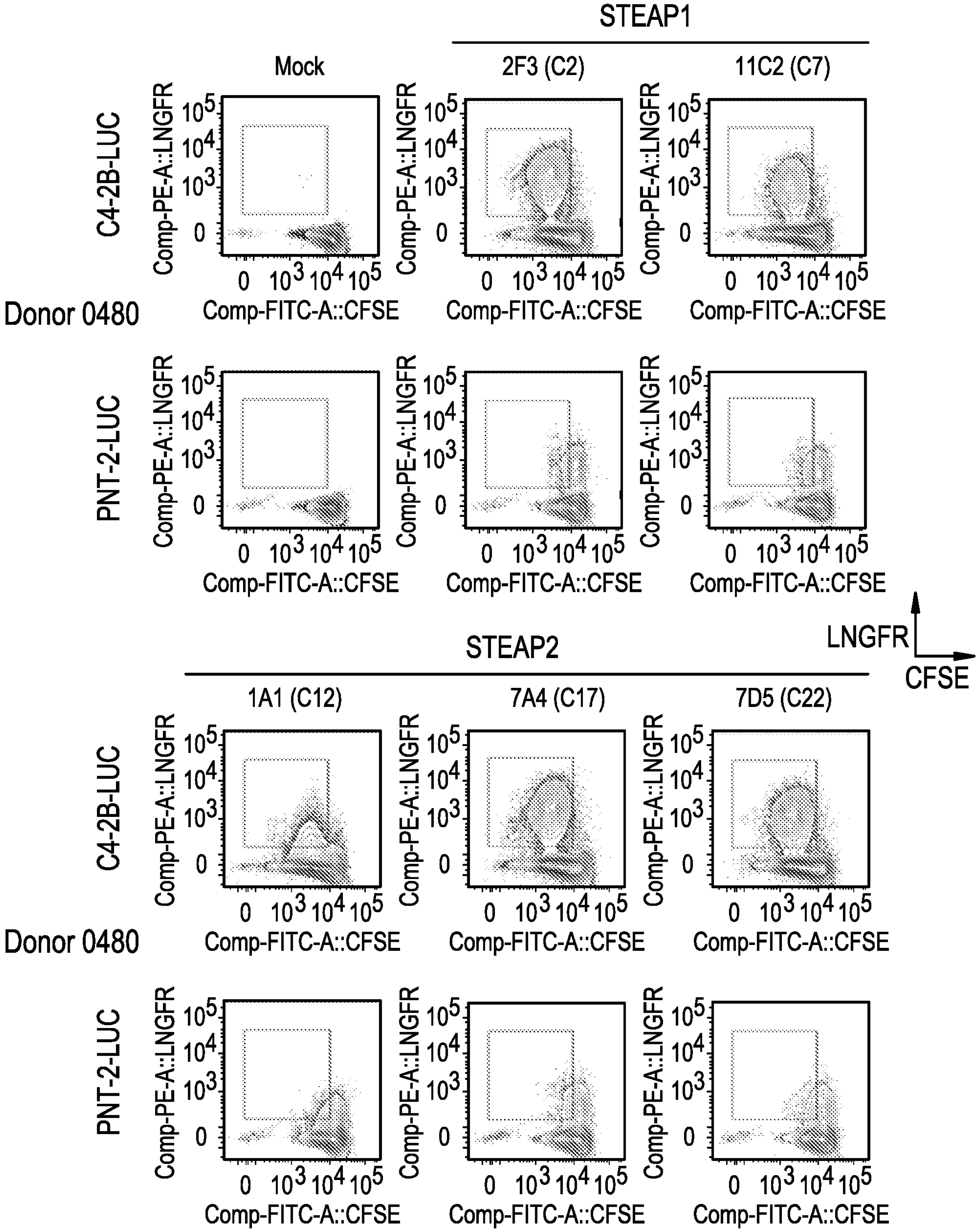

STEAP1
Mock
2F3 (C2)
11C2 (C7)
C4-2B-LUC
Donor 0480
PNT-2-LUC
Comp-PE-A::LNGFR
Comp-FITC-A::CFSE
0
10^3
10^4
10^5
STEAP2
1A1 (C12)
7A4 (C17)
7D5 (C22)
C4-2B-LUC
Donor 0480
PNT-2-LUC
LNGFR
CFSE

FIG. 5 Cont'd

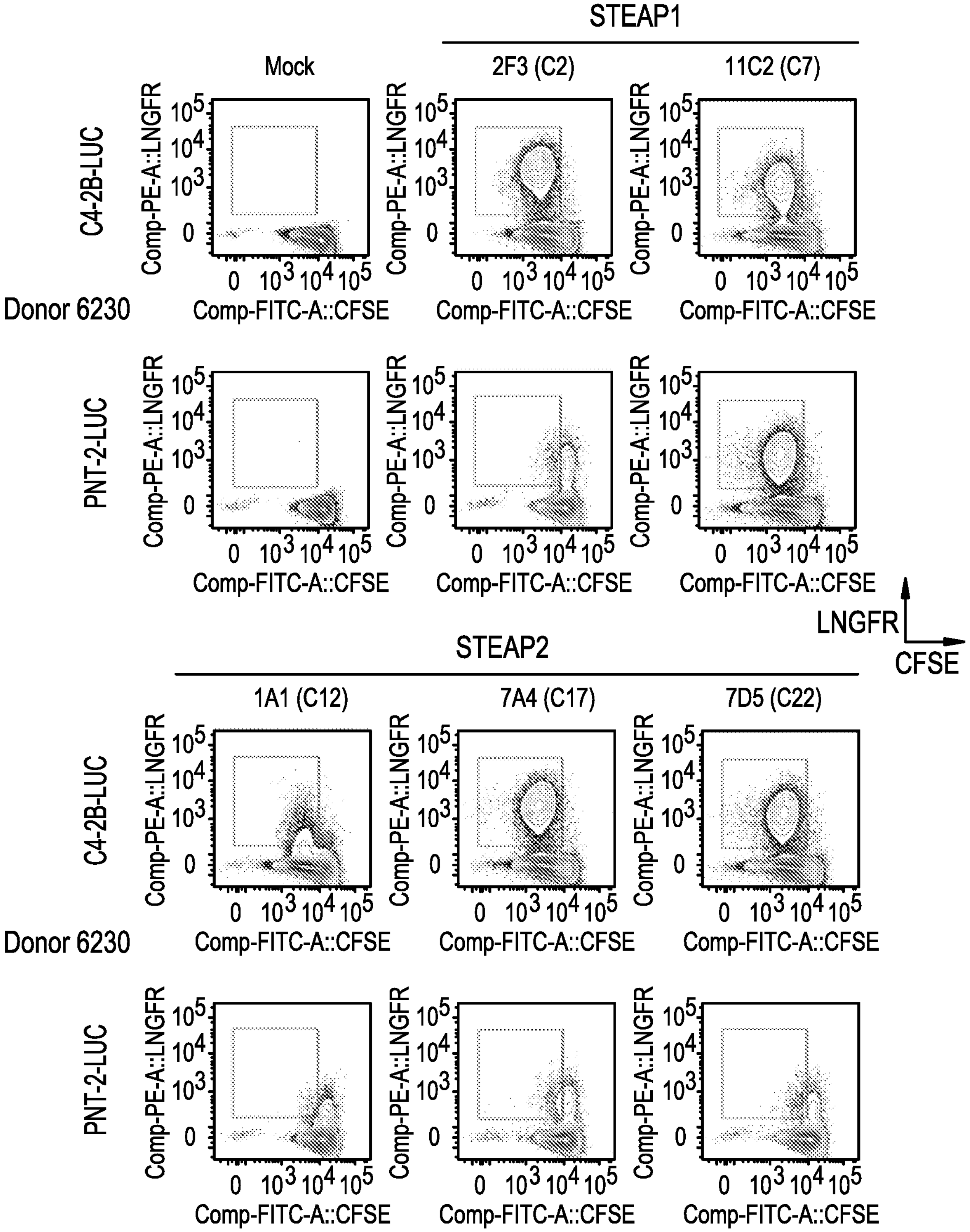
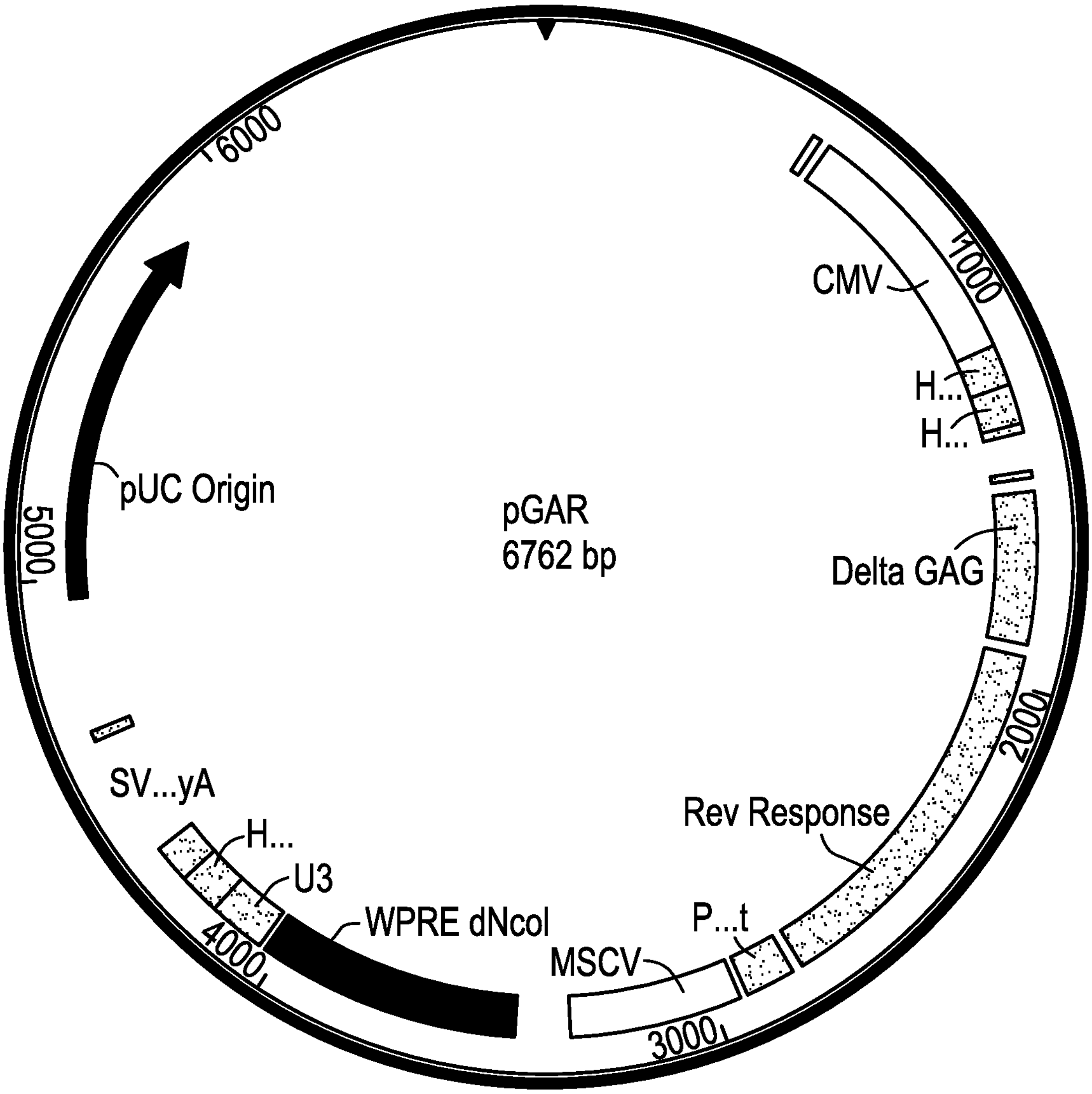

STEAP1
Mock
2F3 (C2)
11C2 (C7)
C4-2B-LUC
PNT-2-LUC
Donor 6230
Comp-PE-A::LNGFR
Comp-FITC-A::CFSE
0
10^3
10^4
10^5
LNGFR
CFSE
STEAP2
1A1 (C12)
7A4 (C17)
7D5 (C22)
C4-2B-LUC
PNT-2-LUC
Donor 6230

FIG. 6


pGAR
6762 bp
CMV
1000
H...
H...
Delta GAG
2000
Rev Response
P...t
MSCV
3000
WPRE dNcoI
U3
H...
4000
SV...yA
5000
pUC Origin
6000