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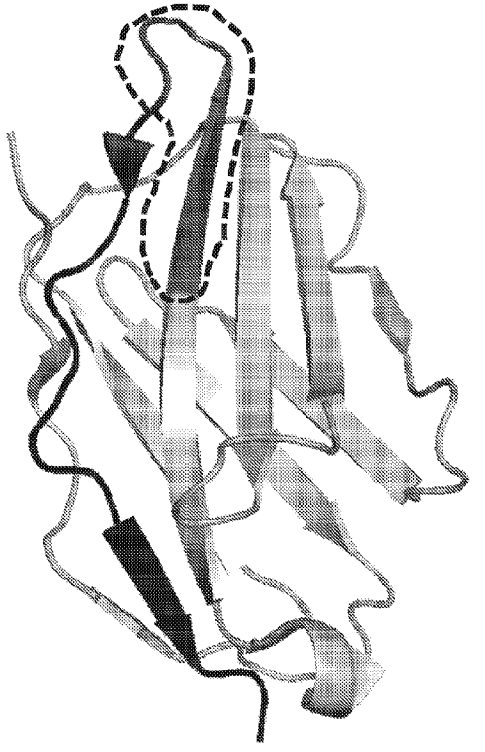
(54) Titre : RECEPTEURS ANTIGENIQUES CHIMERIQUES ET RECEPTEURS DE LYMPHOCYTES T ET LEURS PROCEDES D'UTILISATION

(54) Title: CHIMERIC ANTIGEN AND T CELL RECEPTORS AND METHODS OF USE

FIG. 1B



(57) Abrégé/Abstract:
The invention provides a chimeric antigen receptor (CAR) or a T cell receptor (TCR) comprising extracellular domain disclosed herein. Some aspects of the invention relate to a polynucleotide encoding a chimeric antigen receptor (CAR) or a T cell receptor (TCR) comprising the extracellular domain disclosed herein. Other aspects of the invention relate to cells comprising the CAR or the TCR and their use in a T cell therapy.

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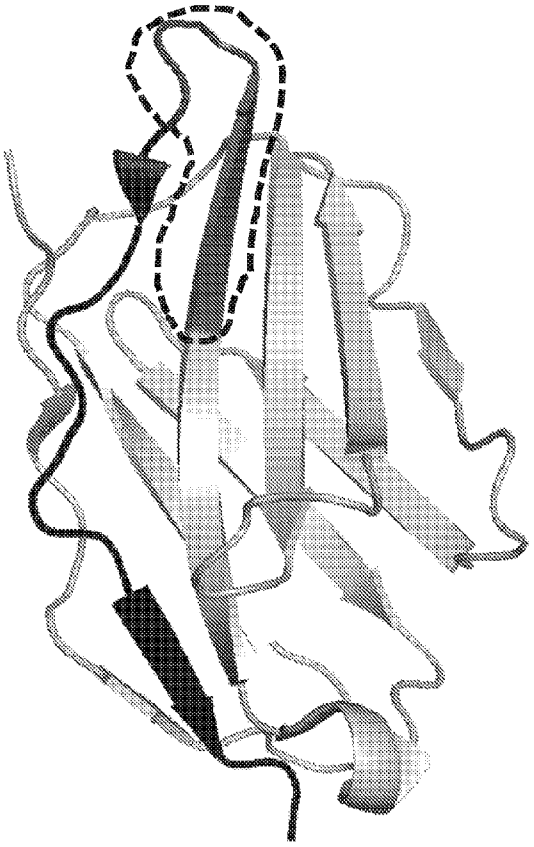
(54) Title: CHIMERIC ANTIGEN AND T CELL RECEPTORS AND METHODS OF USE

FIG. 1B



(57) Abstract: The invention provides a chimeric antigen receptor (CAR) or a T cell receptor (TCR) comprising extracellular domain disclosed herein. Some aspects of the invention relate to a polynucleotide encoding a chimeric antigen receptor (CAR) or a T cell receptor (TCR) comprising the extracellular domain disclosed herein. Other aspects of the invention relate to cells comprising the CAR or the TCR and their use in a T cell therapy.

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CHIMERIC ANTIGEN AND T CELL RECEPTORS AND METHODS OF USE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/317,258, filed April 1, 2016, which is hereby incorporated by reference in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on March 30, 2017, is named K-1031_02_SL.txt and is 414,963 bytes in size.

BACKGROUND OF THE INVENTION

[0003] Human cancers are by their nature comprised of normal cells that have undergone a genetic or epigenetic conversion to become abnormal cancer cells. In doing so, cancer cells begin to express proteins and other antigens that are distinct from those expressed by normal cells. These aberrant tumor antigens can be used by the body's innate immune system to specifically target and kill cancer cells. However, cancer cells employ various mechanisms to prevent immune cells, such as T and B lymphocytes, from successfully targeting cancer cells.

[0004] Current therapies T cell therapies rely on enriched or modified human T cells to target and kill cancer cells in a patient. To increase the ability of T cells to target and kill a particular cancer cell, methods have been developed to engineer T cells to express constructs which direct T cells to a particular target cancer cell. Chimeric antigen receptors (CARs) and engineered T cell receptors (TCRs), which comprise binding domains capable of interacting with a particular tumor antigen, allow T cells to target and kill cancer cells that express the particular tumor antigen.

[0005] A need exists for improved CARs and TCRs for targeting and killing cancer cells.

SUMMARY OF THE INVENTION

[0006] The present invention addresses this need by providing compositions and methods comprising genetically engineered immune cells that express antigen receptors (CARs) or T cell receptors (TCRs) which specifically target and kill cancer cells.

[0007] A CAR may comprise, for example, (i) an antigen-specific component ("antigen binding molecule"), (ii) one or more costimulatory domains (which includes a hinge domain), and (iii) one or more activating domains. Each domain may be heterogeneous, that is, comprised of sequences derived from different protein chains. CAR-expressing immune cells (such as T cells) may be used in various therapies, including cancer therapies.

[0008] As described in more detail below, including the Examples section, CARs comprising a costimulatory domain which includes a truncated hinge domain ("THD") provides unexpectedly superior properties when compared to a CAR comprising a costimulatory domain which includes a complete hinge domain ("CHD"). Polynucleotides encoding such CARs can be transduced into T cells and the CARs are expressed in T cells, *e.g.*, a patient's own T cells. When the transduced T cells are transplanted back to a patient, the CARS direct the T cells to recognize and bind an epitope present on the surface of cancer cells, thus, allowing binding of cancer cells rather than non-cancerous cells. This binding leads to activation of cytolytic mechanisms in the T cell that specifically kill the bound cancer cells. Prior to the present invention, it was unknown that a CARs comprising a THD is superior to a CAR comprising a CHD. Thus, the present invention satisfies an unmet need that exists for novel and improved therapies for treating cancer.

[0009] An aspect of the present invention is an isolated polynucleotide encoding a chimeric antigen receptor (CAR) or a T cell receptor (TCR), which comprises (i) an antigen binding molecule, (ii) a costimulatory domain, and (iii) an activating domain. The costimulatory domain may comprise an extracellular domain, a transmembrane domain, and an intracellular domain, wherein the extracellular domain comprises a truncated hinge domain consisting essentially of or consisting of (i) an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to amino acids 123 to 152 of SEQ ID NO: 1 and, optionally, (ii) one to six amino acids.

[0010] In some embodiments, the one to six amino acids are heterologous amino acids.

[0011] In some embodiments, the truncated hinge domain consists essentially of or consists of an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to amino acids 123 to 152 of SEQ ID NO: 1.

[0012] In some embodiments, the amino acid sequence is encoded by a nucleotide sequence at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 2.

[0013] In some embodiments, the transmembrane domain is a transmembrane domain of 4-1BB/CD137, an alpha chain of a T cell receptor, a beta chain of a T cell receptor, CD3 epsilon, CD4, CD5, CD8 alpha, CD9, CD16, CD19, CD22, CD33, CD37, CD45, CD64, CD80, CD86, CD134, CD137, CD154, or a zeta chain of a T cell receptor, or any combination thereof.

[0014] In some embodiments, the transmembrane domain comprises an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 5.

[0015] In some embodiments, the transmembrane domain is encoded by a nucleotide sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 4.

[0016] In some embodiments, the intracellular domain comprises a signaling region of 4-1BB/CD137, activating NK cell receptors, B7-H3, BAFFR, BLAME (SLAMF8), BTLA, CD100 (SEMA4D), CD103, CD160 (BY55), CD18, CD19, CD19a, CD2, CD247, CD27, CD276 (B7-H3), CD29, CD3 delta, CD3 epsilon, CD3 gamma, CD30, CD4, CD40, CD49a, CD49D, CD49f, CD69, CD7, CD84, CD8alpha, CD8beta, CD96 (Tactile), CDl la, CDl lb, CDl lc, CDl ld, CDS, CEACAM1, CRT AM, cytokine receptors, DAP-10, DNAM1 (CD226), Fc gamma receptor, GADS, GITR, HVEM (LIGHTR), IA4, ICAM-1, ICAM-1, Ig alpha (CD79a), IL2R beta, IL2R gamma, IL7R alpha, Immunoglobulin-like proteins, inducible T cell costimulator (ICOS), integrins, ITGA4, ITGA4, ITGA6, ITGAD, ITGAE, ITGAL, ITGAM, ITGAX, ITGB2, ITGB7, ITGBl, KIRDS2, LAT, LFA-1, LFA-1, a ligand that specifically binds with CD83, LIGHT, LIGHT (tumor necrosis factor superfamily member 14; TNFSF14), LTBR, Ly9 (CD229), lymphocyte function-associated antigen-1 (LFA-1 (CDl la/CD18), MHC class I molecule, NKG2C, NKG2D, NKp30, NKp44, NKp46, NKp80 (KLRF1), OX-40,

PAG/Cbp, programmed death-1 (PD-1), PSGL1, SELPLG (CD162), signaling lymphocytic activation molecules (SLAM proteins), SLAM (SLAMF1; CD150; IPO-3), SLAMF4 (CD244; 2B4), SLAMF6 (NTB-A; Lyl08), SLAMF7, SLP-76, TNF receptor proteins, TNFR2, a Toll ligand receptor, TRANCE/RANKL, VLA1, or VLA-6, or a combination thereof.

[0017] In some embodiments, the intracellular domain comprises a 4-1BB/CD137 signaling region.

[0018] In some embodiments, the intracellular domain comprises an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 7.

[0019] In some embodiments, the intracellular domain comprises an amino acid sequence encoded by a nucleotide sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 6.

[0020] In some embodiments, the antigen binding molecule comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises 3 complementarity determining regions (CDRs) and the VL comprises 3 CDRs.

[0021] In some embodiments, the antigen binding molecule specifically binds an antigen selected from the group consisting of 5T4, alphafetoprotein, B cell maturation antigen (BCMA), CA-125, carcinoembryonic antigen, CD19, CD20, CD22, CD23, CD30 , CD33, CD56, CD123, CD138, c-Met, CSPG4, C-type lectin-like molecule 1 (CLL-1), EGFRvIII, epithelial tumor antigen, ERBB2, FLT3, folate binding protein, GD2, GD3, HER1-HER2 in combination, HER2-HER3 in combination, HER2/Neu, HERV-K, HIV-1 envelope glycoprotein gp41, HIV-1 envelope glycoprotein gpl20, IL-llRalpha, kappa chain, lambda chain, melanoma-associated antigen, mesothelin, MUC-1, mutated p53, mutated ras, prostate-specific antigen, ROR1, or VEGFR2, or a combination thereof.

[0022] In some embodiments, the antigen binding molecule specifically binds BCMA, CLL-1, or FLT3.

[0023] In some embodiments, the activation domain comprises an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 9 or SEQ ID NO: 251.

[0024] In some embodiments, the activation domain is encoded by a nucleotide sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 8.

[0025] In some embodiments, the CAR or TCR further comprises a leader peptide.

[0026] In some embodiments, the leader peptide comprises an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 11.

[0027] In some embodiments, the leader peptide is encoded by a nucleotide sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 10.

[0028] Another aspect of the present invention is a vector comprising the polynucleotide of an above aspect or embodiment.

[0029] In some embodiments, the vector is an adenoviral vector, an adenovirus-associated vector, a DNA vector, a lentiviral vector, a plasmid, a retroviral vector, or an RNA vector, or any combination thereof.

[0030] Yet another aspect of the present invention is a polypeptide encoded by the polynucleotide of an above aspect or embodiment or the vector of an above aspect or embodiment.

[0031] In another aspect, the present invention is a cell comprising the polynucleotide of an above aspect or embodiment, the vector of an above aspect or embodiment, or the polypeptide of an above aspect or embodiment, or any combination thereof.

[0032] In some embodiments, the cell is a T cell.

[0033] In some embodiments, the T cell is an allogeneic T cell, an autologous T cell, an engineered autologous T cell (eACT™), or a tumor-infiltrating lymphocyte (TIL).

[0034] In some embodiments, the T cell is a CD4+ T cell.

[0035] In some embodiments, the T cell is a CD8+ T cell.

[0036] In some embodiments, the T cell is an *in vitro* cell.

[0037] In some embodiments, the T cell is an autologous T cell.

[0038] An aspect of the present invention is a composition comprising the polynucleotide of an above aspect or embodiment, comprising the vector of an above aspect or

embodiment, comprising the polypeptide of an above aspect or embodiment, or comprising the cell of an above aspect or embodiment.

[0039] In some embodiments, the composition is formulated to be delivered to a subject, optionally, comprising at least one pharmaceutically-acceptable excipient.

[0040] Another aspect of the present invention is a method of making a cell expressing a CAR or TCR comprising transducing a cell with the polynucleotide of an above aspect or embodiment under suitable conditions.

[0041] In some embodiments, the method further comprises isolating the cell.

[0042] Yet another aspect of the present invention is a method of inducing an immunity against a tumor comprising administering to a subject an effective amount of a cell comprising the polynucleotide of an above aspect or embodiment, comprising the vector of an above aspect or embodiment, or the polypeptide of an above aspect or embodiment, or any combination thereof.

[0043] In another aspect, the present invention is a method of treating a cancer in a subject in need thereof comprising administering to the subject the polynucleotide of an above aspect or embodiment, the vector of an above aspect or embodiment, the polypeptide of an above aspect or embodiment, the cell of an above aspect or embodiment, or the composition of an above aspect or embodiment.

[0044] In some embodiments, the cancer is a hematologic cancer.

[0045] In some embodiments, the cancer is of the white blood cells.

[0046] In some embodiments, the cancer is of the plasma cells.

[0047] In some embodiments, the cancer is leukemia, lymphoma, or myeloma.

[0048] In some embodiments, the cancer is acute lymphoblastic leukemia (ALL) (including non T cell ALL), acute myeloid leukemia, B cell prolymphocytic leukemia, B-cell acute lymphoid leukemia ("BALL"), blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myeloid leukemia, chronic or acute leukemia, diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), hairy cell leukemia, Hodgkin's Disease, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, monoclonal gammapathy of undetermined significance (MGUS), multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma (NHL), plasma cell proliferative disorder (including asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), plasmablastic lymphoma, plasmacytoid dendritic cell

neoplasm, plasmacytomas (including plasma cell dyscrasia; solitary myeloma; solitary plasmacytoma; extramedullary plasmacytoma; and multiple plasmacytoma), POEMS syndrome (also known as Crow-Fukase syndrome; Takatsuki disease; and PEP syndrome), primary mediastinal large B cell lymphoma (PMBC), small cell- or a large cell-follicular lymphoma, splenic marginal zone lymphoma (SMZL), systemic amyloid light chain amyloidosis, T-cell acute lymphoid leukemia ("TALL"), T-cell lymphoma, transformed follicular lymphoma, or Waldenstrom macroglobulinemia, or a combination thereof.

[0049] Generally, the present invention relates to Engineered Autologous Cell Therapy, abbreviated as "eACT™," also known as adoptive cell transfer. eACT™, is a process by which a patient's own T cells are collected and subsequently genetically engineered to recognize and target one or more antigens expressed on the cell surface of one or more specific cancer cells. T cells may be engineered to express, for example, a CAR or TCR. CAR positive (CAR+) T cells are engineered to express a CAR. CARs may comprise, *e.g.*, an extracellular single chain variable fragment (scFv) with specificity for a particular tumor antigen, which is directly or indirectly linked to an intracellular signaling part comprising at least one costimulatory domain, which is directly or indirectly linked to at least one activating domain; the components may be arranged in any order. The costimulatory domain may be derived from a costimulatory protein known in the art, *e.g.*, SEQ ID NO: 1, and the activating domain may be derived from, *e.g.*, any form of CD3-zeta. In some embodiments, the CAR is designed to have two, three, four, or more costimulatory domains. In some embodiments, a CAR is engineered such that the costimulatory domain is expressed as a separate polypeptide chain. Examples of CAR T cell therapies and constructs are described in U.S. Patent Publication Nos. 2013/0287748, 2014/0227237, 2014/0099309, and 2014/0050708; International Patent Publications Nos. WO2012033885, WO2012079000, WO2014127261, WO2014186469, WO2015080981, WO2015142675, WO2016044745, and WO2016090369; and Sadelain *et al*, *Cancer Discovery*, 3: 388-398 (2013), each of which is incorporated by reference in its entirety.

[0050] Any aspect or embodiment described herein may be combined with any other aspect or embodiment as disclosed herein. While the present invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the present invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

[0051] The patent and scientific literature referred to herein establishes the knowledge that is available to those with skill in the art. All United States patents and published or unpublished United States patent applications cited herein are incorporated by reference. All published foreign patents and patent applications cited herein are hereby incorporated by reference. All other published references, dictionaries, documents, manuscripts and scientific literature cited herein are hereby incorporated by reference.

[0052] Other features and advantages of the invention will be apparent from the Drawings and the following Detailed Description, including the Examples, and the claims.

BRIEF DESCRIPTION OF THE FIGURES

[0053] The above and further features will be more clearly appreciated from the following detailed description when taken in conjunction with the accompanying drawings. The drawings however are for illustration purposes only; not for limitation.

[0054] FIG. 1A shows a costimulatory protein having the amino acid sequence of SEQ ID NO: 1. The costimulatory protein's hinge domain (solid underline), transmembrane domain (dotted underline), and signaling domain (dashed underline) are labeled. A novel truncated hinge domain ("THD") is bolded. FIGs. 1B and 1C provide ribbon diagrams of the extracellular domain of the costimulatory protein having the amino acid sequence of SEQ ID NO: 1. FIG. 1B shows an example of a region within the amino acid sequence of SEQ ID NO: 1 used to derive one embodiment of a hinge region in the context of CAR, i.e., a region containing amino acids 114 to 152 of SEQ ID NO: 1 (herein referred to as a complete hinge domain or "CHD"; it is marked in black and dark grey). FIG. 1C shows the THD which contain amino acids 123 to 152 of SEQ ID NO: 1 (marked in black). In FIG. 1B, the portion of the hinge region that is excluded from FIG. 1C is marked dark grey and circled.

[0055] FIGs. 2A-2H show CLUTSTAL W (2.83) multiple sequence alignments of eight example binding molecules disclosed herein. FIG. 2A shows a sequence alignment of example anti-CLL-1 binding molecules comprising a VH domain. CDRs and framework regions FRs are shown, as determined by Chothia numbering (FIG. 2A). FIG. 2B is a table providing the SEQ ID NO for each VH and CDR illustrated in FIG. 2A. FIG. 2C shows a sequence alignment of example anti-CLL-1 binding molecules comprising a VL domain. CDRs and FRs are shown, as determined by Chothia numbering (FIG. 2C). FIG. 2D is a

table providing the SEQ ID NO for each VH and CDR sequence illustrated in FIG. 2C. FIG. 2E shows a sequence alignment of example anti-BCMA binding molecules comprising a VH domain. Complementarity determining regions (CDRs) and framework regions (FRs) are shown, as determined by Chothia numbering (FIG. 2E). FIG. 2F is a table providing the SEQ ID NO for each VH and CDR illustrated in FIG. 2E. FIG. 2G shows a sequence alignment of example anti-BCMA binding molecules comprising a VL domain. CDRs and FRs are shown, as determined by Chothia numbering (FIG. 2G). FIG. 2H is a table providing the SEQ ID NO for each VH and CDR sequence illustrated in FIG. 2G.

[0056] FIG. 3 depicts CAR expression in primary human T cells electroporated with mRNA encoding for various CARs. Data obtained from CAR having a complete hinge domain ("CHD") is shown and data obtained from CAR having a truncated hinge domain ("THD") is shown.

[0057] FIGs. 4A-4X show IFNγ, IL-2, and TNFα production by electroporated anti-FLT3 CAR T cells following 16 hours of co-culture with the indicated target cell lines. FIGs. 4A-4B, 4G-4H, 4M-4N, and 4S-4T show IFNγ production following co-culture with Namalwa, EoL-1, HL60, and MV4;11 target cells, respectively. FIGs. 4C-4D, 4I-4J, 4O-4P, and 4U-4V show IL-2 production following co-culture with Namalwa, EoL-1, HL60, and MV4;11 target cells, respectively. FIGs. 4E-4F, 4K-4L, 4Q-4R, and 4W-4X show TNFα production following co-culture with Namalwa, EoL-1, HL60, and MV4;11 target cells, respectively.

[0058] FIGs. 5A-5H show cytolytic activity of electroporated anti-FLT3 CAR T cells against Namalwa (FIGs. 5A-5B), EoL1 (FIGs. 5C-5D), HL60 (FIGs. 5E-5F), and MV4;11 (FIGs. 5G-5H) target cell lines following 16 hours of co-culture.

[0059] FIGs. 6A-6B depict CAR expression in lentivirus transduced primary human T cells from two healthy donors.

[0060] FIGs. 7A-7F show IFNγ (FIGs. 7A-7B), TNFα (FIGs. 7C-7D), and IL-2 (FIGs. 7E-7F) production by lentivirus transduced CAR T cells from two healthy donors following 16 hours of co-culture with the indicated target cell lines.

[0061] FIGs. 8A-8D show the average cytolytic activity over time from two healthy donors expressing the anti-FLT3 CAR constructs co-cultured with Namalwa (FIG. 8A), EoL1 (FIG. 8B), MV4;11 (FIG. 8C), and HL60 (FIG. 8D) target cell lines for 16, 40, 64, 88, or 112 hours.

[0062] FIGs. 9A-9B depict proliferation of CFSE-labeled lentivirus transduced CAR T cells from two healthy donors following 5 days of co-culture with CD3-CD28 beads or the indicated target cell lines.

[0063] FIGs. 10A-10D depict CAR expression in lentivirus transduced primary human T cells used for *in vivo* studies. FIGs. 10E-10F show graphical representations of measured bioluminescence imaging of labeled acute myeloid leukemia (AML) cells following intravenous injection of either control (mock) or anti-FLT3 CAR T cells (10E3-CHD, 10E3-THD, or 8B5-THD) in a xenogeneic model, performed in duplicate. FIG. 10G provides the p-values for the respective data points in FIG. 10E. FIGs. 10H-10K show survival curves of mice injected with mock or 10E3-CHD (FIG. 10H), mock or 10E3-THD (FIG. 10I), mock or 8B5-THD (FIG. 10J), or 10E3-THD or 8B5-THD (FIG. 10K) CAR T cells.

[0064] FIGs. 11A-11B shows CLL-1 CAR expression determined by protein L 6 hours post mRNA electroporation.

[0065] FIGs. 12A-12C show the results from a cytokine release assay from different CLL-1 CAR-T cell constructs 24 hours after mRNA electroporation. IL-2 (FIG. 12A), IFNγ (FIG. 12B), and TNFα (FIG. 12C) production levels are shown for controls (target alone, mock, GFP, and CD19 CAR T cells) and anti-CLL-1 CAR T cells (24C1_HL-THD, 24C1_HL_CHD, 24C8_HL-CHD, and 24C8_HL_THD) co-cultured with Namalwa, MV4;11, U937, HL60, and EoL-1 cells, as indicated.

[0066] FIGs. 13A-13E show cytolytic activity of different CLL-1 CAR-T cell constructs 24 hours after mRNA electroporation. T cells electroporated with control constructs (mock, GFP, and CD19 CAR) or anti-CLL-1 CAR constructs (24C8_HL-CHD and 24C8_HL_THD) were co-cultured with Namalwa (FIG. 13A), MV;411 (FIG. 13B), EoL-1 (FIG. 13C), HL-60 (FIG. 13D), and U937 target cells, and the percent of specific lysis of each target cell line was determined.

[0067] FIGs. 14A-14C show the results from a cytokine release assay from different transduced anti-CLL-1 CAR T cells 16 hours after co-culture with different cell lines. IFNγ (FIG. 14A), IL-2 (FIG. 14B), and TNFα (FIG. 14C) production levels are shown for controls (target alone and mock) and transduced anti-CLL-1 CAR T cells (10E3_THD and 24C1_LH_THD) co-cultured with Namalwa, HL-60, or MV4;11 target cells, as indicated.

[0068] FIGs. 15A-15C show cytolytic activity from anti-CLL-1 CAR T cells (C1_24C1_LH_THD) 16 hours and 40 hours after co-culture with Namalwa (FIG. 15A), MV4;11 (FIG. 15B), or HL-60 (FIG. 15C) target cells.

[0069] FIGs 16A-16F shows IFNγ, TNFα, and IL-2 production by lentivirus transduced CAR T cells from two healthy donors following 16 hours of co-cultured with EoL-1 (Black), NCI-H929 (light grey), or MM1S (grey) target cell lines. FIGs. 16A and 16B show the IFNγ (pg/ml; y-axis) production in lentivirus transduced CAR T cells from a first donor (FIG. 6A) and a second donor (FIG. 16B). FIGs. 16C and 16D show the TNFα (pg/ml; y-axis) production in lentivirus transduced CAR T cells from a first donor (FIG. 16C) and a second donor (FIG. 16D). FIGs. 16E and 16F show the IL-2 production (pg/ml; y-axis) in lentivirus transduced CAR T cells from a first donor (FIG. 16E) and a second donor (FIG. 16F).

[0070] FIGs. 17A-17F show the average cytolytic activity (as a percentage of viable target cells remaining; y-axis) over time from two healthy donors expressing the indicated CARs co-cultured with EoL1 (FIGs. 17A and 17B), NCI-H929 (FIGs. 17C and 17D), or MM1S (FIGs. 17E and 17F) target cells for 16 hours, 40 hours, 64 hours, 88 hours, or 112 hours. FIGs. 17A and 17B show the average cytolytic activity of transduced CAR T cells from a first donor (FIG. 17A) and a second donor (FIG. 17B) co-cultured with EoL1 target cells for 16 hours, 40 hours, 64 hours, 88 hours, or 112 hours. FIGs. 17C and 17D show the average cytolytic activity of transduced CAR T cells from a first donor (FIG. 17C) and a second donor (FIG. 17D) co-cultured with NCI-H929 target cells for 16 hours, 40 hours, 64 hours, 88 hours, or 112 hours. FIGs. 17E and 17F show the average cytolytic activity of transduced CAR T cells from a first donor (FIG. 17E) and a second donor (FIG. 17F) co-cultured with MM1S target cells for 16 hours, 40 hours, 64 hours, 88 hours, or 112 hours.

[0071] FIGs. 18A and 18B show proliferation of CFSE-labeled lentivirus transduced CAR T cells from a first healthy donor (FIG. 18A) and a second healthy donor (FIG. 18B) following 6 days of co-culture with CD3-CD28 beads (top row), EoL-1 (second row), NCI-H929 (third row), or MM1S (bottom row) target cell lines.

[0072] FIG 19A and FIG. 19B are graphs showing thermostability of chimeric antigen receptors (CARs) of the present invention. FIG. 19A: In a phosphate-buffered saline (PBS) solution, a CAR comprising an extracellular domain with a truncated hinge domain ("THD") has a higher melting temperature relative to a CAR comprising an extracellular domain with a complete hinge domain ("CHD"). FIG. 19B: In the presence of 50 mM NaCl, a CAR comprising an extracellular domain with a THD has a higher melting temperature relative to a CAR comprising an extracellular domain with a CHD.

DETAILED DESCRIPTION OF THE INVENTION

[0073] The present invention relates to novel polypeptides comprising a novel truncated hinge domain ("THD") and polynucleotides encoding the same. Some aspects of the invention relate to a polynucleotide encoding a chimeric antigen receptor (CAR) or a T cell receptor (TCR) comprising the THD disclosed herein. The present invention also provides vectors (*e.g.*, viral vectors) comprising such polynucleotides and compositions comprising such vectors. The present invention further provides polynucleotides encoding such CARs or TCRs and compositions comprising such polynucleotides. The present invention additionally provides engineered cells (*e.g.*, T cells) comprising such polynucleotides and/or transduced with such viral vectors and compositions comprising such engineered cells. The present invention provides compositions (*e.g.*, pharmaceutical compositions) including a plurality of engineered T cells. The present invention provides methods for manufacturing such engineered T cells and compositions and uses (*e.g.*, in treating a melanoma) of such engineered T cells and compositions. And, the present invention provides a method of inducing an immunity against a tumor comprising administering to a subject an effective amount of a cell comprising a polynucleotide, a vector, or a polypeptide of the present invention. Other aspects of the invention relate to cells comprising the CAR or the TCR and their use in a T cell therapy, *e.g.*, an autologous cell therapy (eACT™), for the treatment of a patient suffering from a cancer.

DEFINITIONS

[0074] In order for the present invention to be more readily understood, certain terms are first defined below. Additional definitions for the following terms and other terms are set forth throughout the Specification.

[0075] As used in this Specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

[0076] Unless specifically stated or obvious from context, as used herein, the term "or" is understood to be inclusive and covers both "or" and "and".

[0077] The term "and/or" where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term "and/or" as used in a phrase such as "A and/or B" herein is intended to include A and B; A or B; A (alone); and B (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or

C" is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0078] The terms "*e.g.*," and "*i.e.*" as used herein, are used merely by way of example, without limitation intended, and should not be construed as referring only those items explicitly enumerated in the specification.

[0079] The terms "or more", "at least", "more than", and the like, *e.g.*, "at least one" are understood to include but not be limited to at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149 or 150, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000 or more than the stated value. Also included is any greater number or fraction in between.

[0080] Conversely, the term "no more than" includes each value less than the stated value. For example, "no more than 100 nucleotides" includes 100, 99, 98, 97, 96, 95, 94, 93, 92, 91, 90, 89, 88, 87, 86, 85, 84, 83, 82, 81, 80, 79, 78, 77, 76, 75, 74, 73, 72, 71, 70, 69, 68, 67, 66, 65, 64, 63, 62, 61, 60, 59, 58, 57, 56, 55, 54, 53, 52, 51, 50, 49, 48, 47, 46, 45, 44, 43, 42, 41, 40, 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, and 0 nucleotides. Also included is any lesser number or fraction in between.

[0081] The terms "plurality", "at least two", "two or more", "at least second", and the like, are understood to include but not limited to at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149 or 150, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000 or more. Also included is any greater number or fraction in between.

[0082] Throughout the specification the word "comprising," or variations such as "comprises" or "comprising," will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps. It is understood that wherever aspects are described herein with the language "comprising," otherwise analogous aspects described in terms of "consisting of" and/or "consisting essentially of" are also provided.

[0083] Unless specifically stated or evident from context, as used herein, the term "about" refers to a value or composition that is within an acceptable error range for the particular value or composition as determined by one of ordinary skill in the art, which will depend in part on how the value or composition is measured or determined, *i.e.*, the limitations of the measurement system. For example, "about" or "comprising essentially of" can mean within one or more than one standard deviation per the practice in the art. "About" or "comprising essentially of" can mean a range of up to 10% (*i.e.*, ±10%). Thus, "about" can be understood to be within 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, 0.05%, 0.01%, or 0.001% greater or less than the stated value. For example, about 5 mg can include any amount between 4.5 mg and 5.5 mg. Furthermore, particularly with respect to biological systems or processes, the terms can mean up to an order of magnitude or up to 5-fold of a value. When particular values or compositions are provided in the instant disclosure, unless otherwise stated, the meaning of "about" or "comprising essentially of" should be assumed to be within an acceptable error range for that particular value or composition.

[0084] As described herein, any concentration range, percentage range, ratio range or integer range is to be understood to be inclusive of the value of any integer within the recited range and, when appropriate, fractions thereof (such as one-tenth and one-hundredth of an integer), unless otherwise indicated.

[0085] Units, prefixes, and symbols used herein are provided using their Système International de Unites (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range.

[0086] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, Juo, "The Concise Dictionary of Biomedicine and Molecular Biology", 2nd ed., (2001), CRC Press; "The Dictionary of Cell & Molecular Biology", 5th ed., (2013), Academic Press; and "The Oxford Dictionary Of Biochemistry And

Molecular Biology", Cammack *et al.* eds., 2nd ed, (2006), Oxford University Press, provide those of skill in the art with a general dictionary for many of the terms used in this disclosure.

[0087] "Administering" refers to the physical introduction of an agent to a subject, using any of the various methods and delivery systems known to those skilled in the art. Exemplary routes of administration for the formulations disclosed herein include intravenous, intramuscular, subcutaneous, intraperitoneal, spinal or other parenteral routes of administration, for example by injection or infusion. The phrase "parenteral administration" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intralymphatic, intralesional, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion, as well as *in vivo* electroporation. In some embodiments, the formulation is administered via a non-parenteral route, *e.g.,* orally. Other non-parenteral routes include a topical, epidermal or mucosal route of administration, for example, intranasally, vaginally, rectally, sublingually or topically. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

[0088] The term "antibody" (Ab) includes, without limitation, a glycoprotein immunoglobulin which binds specifically to an antigen. In general, and antibody can comprise at least two heavy (H) chains and two light (L) chains interconnected by disulfide bonds, or an antigen-binding molecule thereof. Each H chain comprises a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region comprises three constant domains, CH1, CH2 and CH3. Each light chain comprises a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region is comprises one constant domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL comprises three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the Abs may mediate the binding of the immunoglobulin to

host tissues or factors, including various cells of the immune system (*e.g.*, effector cells) and the first component (C1q) of the classical complement system.

[0089] Antibodies can include, for example, monoclonal antibodies, recombinantly produced antibodies, monospecific antibodies, multispecific antibodies (including bispecific antibodies), human antibodies, engineered antibodies, humanized antibodies, chimeric antibodies, immunoglobulins, synthetic antibodies, tetrameric antibodies comprising two heavy chain and two light chain molecules, an antibody light chain monomer, an antibody heavy chain monomer, an antibody light chain dimer, an antibody heavy chain dimer, an antibody light chain- antibody heavy chain pair, intrabodies, antibody fusions (sometimes referred to herein as "antibody conjugates"), heteroconjugate antibodies, single domain antibodies, monovalent antibodies, single chain antibodies or single-chain Fvs (scFv), camelized antibodies, affybodies, Fab fragments, $F(ab')_2$ fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies (including, e.g., anti-anti-Id antibodies), minibodies, domain antibodies, synthetic antibodies (sometimes referred to herein as "antibody mimetics"), and antigen-binding fragments of any of the above. In certain embodiments, antibodies described herein refer to polyclonal antibody populations.

[0090] An immunoglobulin may derive from any of the commonly known isotypes, including but not limited to IgA, secretory IgA, IgG, IgE and IgM. IgG subclasses are also well known to those in the art and include but are not limited to human IgG1, IgG2, IgG3 and IgG4. "Isotype" refers to the Ab class or subclass (*e.g.*, IgM or IgG1) that is encoded by the heavy chain constant region genes. The term "antibody" includes, by way of example, both naturally occurring and non-naturally occurring Abs; monoclonal and polyclonal Abs; chimeric and humanized Abs; human or nonhuman Abs; wholly synthetic Abs; and single chain Abs. A nonhuman Ab may be humanized by recombinant methods to reduce its immunogenicity in man. Where not expressly stated, and unless the context indicates otherwise, the term "antibody" also includes an antigen-binding fragment or an antigen-binding portion of any of the aforementioned immunoglobulins, and includes a monovalent and a divalent fragment or portion, and a single chain Ab.

[0091] An "antigen binding molecule," "antigen binding portion," or "antibody fragment" refers to any molecule that comprises the antigen binding parts (e.g., CDRs) of the antibody from which the molecule is derived. An antigen binding molecule can include the antigenic complementarity determining regions (CDRs). Examples of antibody fragments include, but are not limited to, Fab, Fab', F(ab')2, and Fv fragments, dAb, linear antibodies,

scFv antibodies, and multispecific antibodies formed from antigen binding molecules. Peptibodies (i.e., Fc fusion molecules comprising peptide binding domains) are another example of suitable antigen binding molecules. 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 BCMA, CLL-1, or FLT3. In further embodiments, the antigen binding molecule is an antibody fragment that specifically binds to the antigen, 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). In some embodiments, the antigen binding molecule comprises or consists of avimers.

[0092] As used herein, the term "variable region" or "variable domain" is used interchangeably and are common in the art. The variable region typically refers to a portion of an antibody, generally, a portion of a light or heavy chain, typically about the amino-terminal 110 to 120 amino acids in the mature heavy chain and about 90 to 115 amino acids in the mature light chain, which differ extensively in sequence among antibodies and are used in the binding and specificity of a particular antibody for its particular antigen. The variability in sequence is concentrated in those regions called complementarity determining regions (CDRs) while the more highly conserved regions in the variable domain are called framework regions (FR). Without wishing to be bound by any particular mechanism or theory, it is believed that the CDRs of the light and heavy chains are primarily responsible for the interaction and specificity of the antibody with antigen. In certain embodiments, the variable region is a human variable region. In certain embodiments, the variable region comprises rodent or murine CDRs and human framework regions (FRs). In particular embodiments, the variable region is a primate (*e.g.*, non-human primate) variable region. In certain embodiments, the variable region comprises rodent or murine CDRs and primate (*e.g.*, non-human primate) framework regions (FRs).

[0093] The terms "VL" and "VL domain" are used interchangeably to refer to the light chain variable region of an antibody or an antigen-binding molecule thereof.

[0094] The terms "VH" and "VH domain" are used interchangeably to refer to the heavy chain variable region of an antibody or an antigen-binding molecule thereof.

[0095] A number of definitions of the CDRs are commonly in use: Kabat numbering, Chothia numbering, AbM numbering, or contact numbering. The AbM definition is a

compromise between the two used by Oxford Molecular' s AbM antibody modelling software. The contact definition is based on an analysis of the available complex crystal structures.

[0096] Table 1. CDR Numbering

Loop	Kabat	AbM	Chothia	Contact
L1	L24--L34	L24--L34	L24--L34	L30--L36
L2	L50--L56	L50--L56	L50--L56	L46--L55
L3	L89--L97	L89--L97	L89--L97	L89--L96
H1	H31--H35B (Kabat Numbering)	H26--H35B	H26--H32..34	H30--H35B
H1	H31--H35 (Chothia Numbering)	H26--H35	H26--H32	H30--H35
H2	H50--H65	H50--H58	H52--H56	H47--H58
H3	H95--H102	H95--H102	H95--H102	H93--H101

[0097] The term "Kabat numbering" and like terms are recognized in the art and refer to a system of numbering amino acid residues in the heavy and light chain variable regions of an antibody, or an antigen-binding molecule thereof. In certain aspects, the CDRs of an antibody can be determined according to the Kabat numbering system (*see*, *e.g.*, Kabat EA & Wu TT (1971) Ann NY Acad Sci 190: 382-391 and Kabat EA *et al.*, (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). Using the Kabat numbering system, CDRs within an antibody heavy chain molecule are typically present at amino acid positions 31 to 35, which optionally can include one or two additional amino acids, following 35 (referred to in the Kabat numbering scheme as 35A and 35B) (CDR1), amino acid positions 50 to 65 (CDR2), and amino acid positions 95 to 102 (CDR3). Using the Kabat numbering system, CDRs within an antibody light chain molecule are typically present at amino acid positions 24 to 34 (CDR1), amino acid positions 50 to 56 (CDR2), and amino acid positions 89 to 97 (CDR3). In a specific

embodiment, the CDRs of the antibodies described herein have been determined according to the Kabat numbering scheme.

[0098] In certain aspects, the CDRs of an antibody can be determined according to the Chothia numbering scheme, which refers to the location of immunoglobulin structural loops (*see*, *e.g.*, Chothia C & Lesk AM, (1987), J Mol Biol 196: 901-917; Al-Lazikani B *et al.*, (1997) J Mol Biol 273: 927-948; Chothia C *et al.*, (1992) J Mol Biol 227: 799-817; Tramontano A *et al.*, (1990) J Mol Biol 215(1): 175-82; and U.S. Patent No. 7,709,226). Typically, when using the Kabat numbering convention, the Chothia CDR-H1 loop is present at heavy chain amino acids 26 to 32, 33, or 34, the Chothia CDR-H2 loop is present at heavy chain amino acids 52 to 56, and the Chothia CDR-H3 loop is present at heavy chain amino acids 95 to 102, while the Chothia CDR-L1 loop is present at light chain amino acids 24 to 34, the Chothia CDR-L2 loop is present at light chain amino acids 50 to 56, and the Chothia CDR-L3 loop is present at light chain amino acids 89 to 97. The end of the Chothia CDR-HI loop when numbered using the Kabat numbering convention varies between H32 and H34 depending on the length of the loop (this is because the Kabat numbering scheme places the insertions at H35A and H35B; if neither 35A nor 35B is present, the loop ends at 32; if only 35A is present, the loop ends at 33; if both 35A and 35B are present, the loop ends at 34). In a specific embodiment, the CDRs of the antibodies described herein have been determined according to the Chothia numbering scheme.

[0099] As used herein, the terms "constant region" and "constant domain" are interchangeable and have a meaning common in the art. The constant region is an antibody portion, *e.g.*, a carboxyl terminal portion of a light and/or heavy chain which is not directly involved in binding of an antibody to antigen but which can exhibit various effector functions, such as interaction with the Fc receptor. The constant region of an immunoglobulin molecule generally has a more conserved amino acid sequence relative to an immunoglobulin variable domain.

[0100] As used herein, the term "heavy chain" when used in reference to an antibody can refer to any distinct type, *e.g.*, alpha (α), delta (δ), epsilon (ε), gamma (γ) and mu (μ), based on the amino acid sequence of the constant domain, which give rise to IgA, IgD, IgE, IgG and IgM classes of antibodies, respectively, including subclasses of IgG, *e.g.*, IgG_1, IgG_2, IgG_3 and IgG_4.

[0101] As used herein, the term "light chain" when used in reference to an antibody can refer to any distinct type, *e.g.*, kappa (κ) or lambda (λ) based on the amino acid sequence

of the constant domains. Light chain amino acid sequences are well known in the art. In specific embodiments, the light chain is a human light chain.

[0102] "Binding affinity" generally refers to the strength of the sum total of non-covalent interactions between a single binding site of a molecule (*e.g.*, an antibody) and its binding partner (*e.g.*, an antigen). Unless indicated otherwise, as used herein, "binding affinity" refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (*e.g.*, antibody and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (K_D). Affinity can be measured and/or expressed in a number of ways known in the art, including, but not limited to, equilibrium dissociation constant (K_D), and equilibrium association constant (K_A). The K_D is calculated from the quotient of k_{off}/k_{on}, whereas K_A is calculated from the quotient of k_{on}/k_{off}. k_{on} refers to the association rate constant of, *e.g.*, an antibody to an antigen, and k_{off} refers to the dissociation of, *e.g.*, an antibody to an antigen. The k_{on} and k_{off} can be determined by techniques known to one of ordinary skill in the art, such as BIACORE® or KinExA.

[0103] As used herein, a "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). In certain embodiments, one or more amino acid residues within a CDR(s) or within a framework region(s) of an antibody or antigen-binding molecule thereof can be replaced with an amino acid residue with a similar side chain.

[0104] As, used herein, the term "heterologous" means from any source other than naturally occurring sequences. For example, a heterologous sequence included as a part of a costimulatory protein having the amino acid sequence of SEQ ID NO: 1, e.g., the corresponding human costimulatory protein, is amino acids that do not naturally occur as, i.e., do not align with, the wild type human costimulatory protein. For example, a heterologous nucleotide sequence refers to a nucleotide sequence other than that of the wild type human costimulatory protein-encoding sequence.

[0105] As used herein, an "epitope" is a term in the art and refers to a localized region of an antigen to which an antibody can specifically bind. An epitope can be, for example, contiguous amino acids of a polypeptide (linear or contiguous epitope) or an epitope can, for example, come together from two or more non-contiguous regions of a polypeptide or polypeptides (conformational, non-linear, discontinuous, or non-contiguous epitope). In certain embodiments, the epitope to which an antibody binds can be determined by, *e.g.*, NMR spectroscopy, X-ray diffraction crystallography studies, ELISA assays, hydrogen/deuterium exchange coupled with mass spectrometry (*e.g.*, liquid chromatography electrospray mass spectrometry), array-based oligo-peptide scanning assays, and/or mutagenesis mapping (*e.g.*, site-directed mutagenesis mapping). For X-ray crystallography, crystallization may be accomplished using any of the known methods in the art (*e.g.*, Giegé R *et al.*, (1994) Acta Crystallogr D Biol Crystallogr 50(Pt 4): 339-350; McPherson A (1990) Eur J Biochem 189: 1-23; Chayen NE (1997) Structure 5: 1269-1274; McPherson A (1976) J Biol Chem 251: 6300-6303). Antibody:antigen crystals may be studied using well known X-ray diffraction techniques and may be refined using computer software such as X-PLOR (Yale University, 1992, distributed by Molecular Simulations, Inc.; see e.g. Meth Enzymol (1985) volumes 114 & 115, eds Wyckoff HW *et al.*,; U.S. 2004/0014194), and BUSTER (Bricogne G (1993) Acta Crystallogr D Biol Crystallogr 49(Pt 1): 37-60; Bricogne G (1997) Meth Enzymol 276A: 361-423, ed Carter CW; Roversi P *et al.*, (2000) Acta Crystallogr D Biol Crystallogr 56(Pt 10): 1316-1323). Mutagenesis mapping studies may be accomplished using any method known to one of skill in the art. *See*, *e.g.*, Champe M *et al.*, (1995) J Biol Chem 270: 1388-1394 and Cunningham BC & Wells JA (1989) Science 244: 1081-1085 for a description of mutagenesis techniques, including alanine scanning mutagenesis techniques.

[0106] As used herein, an antigen binding molecule, an antibody, or an antigen binding molecule thereof "cross-competes" with a reference antibody or an antigen binding molecule thereof if the interaction between an antigen and the first binding molecule, an antibody, or an antigen binding molecule thereof blocks, limits, inhibits, or otherwise reduces the ability of the reference binding molecule, reference antibody, or an antigen binding molecule thereof to interact with the antigen. Cross competition can be complete, *e.g.*, binding of the binding molecule to the antigen completely blocks the ability of the reference binding molecule to bind the antigen, or it can be partial, *e.g.*, binding of the binding molecule to the antigen reduces the ability of the reference binding molecule to bind the antigen. In certain embodiments, an antigen binding molecule that cross-competes with a reference antigen binding molecule binds

the same or an overlapping epitope as the reference antigen binding molecule. In other embodiments, the antigen binding molecule that cross-competes with a reference antigen binding molecule binds a different epitope as the reference antigen binding molecule. 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).

[0107] As used herein, the terms "immunospecifically binds," "immunospecifically recognizes," "specifically binds," and "specifically recognizes" are analogous terms in the context of antibodies and refer to molecules that bind to an antigen (*e.g.*, epitope or immune complex) as such binding is understood by one skilled in the art. For example, a molecule that specifically binds to an antigen may bind to other peptides or polypeptides, generally with lower affinity as determined by, *e.g.*, immunoassays, BIACORE®, KinExA 3000 instrument (Sapidyne Instruments, Boise, ID), or other assays known in the art. In a specific embodiment, molecules that specifically bind to an antigen bind to the antigen with a K_A that is at least 2 logs, 2.5 logs, 3 logs, 4 logs or greater than the K_A when the molecules bind to another antigen.

[0108] In another embodiment, molecules that specifically bind to an antigen bind with a dissociation constant (K_d) of about 1 x 10^{-7} M. In some embodiments, the antigen binding molecule specifically binds an antigen with "high affinity" when the K_d is about 1 x 10^{-9} M to about 5 x 10^{-9} M. In some embodiments, the antigen binding molecule specifically binds an antigen with "very high affinity" when the K_d is 1 x 10^{-10} M to about 5 x 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 less than about 1 x 10^{-5}. In other embodiments, the antigen binding molecule binds human BCMA with a K_d of between about 1 x 10^{-7} M and about 1 x 10^{-13} M. In yet another embodiment, the antigen binding molecule binds human BCMA with a K_d of about l x 10^{-10} M to about 5 x 10^{-10} M.

[0109] In a specific embodiment, provided herein is an antibody or an antigen binding molecule thereof that binds to a target human antigen, *e.g.,* human BCMA or human CLL-1, with higher affinity than to another species of the target antigen, *e.g.*, a non-human BCMA or a non-human CLL-1. In certain embodiments, provided herein is an antibody or an antigen binding molecule t thereof that binds to the target human antigen, *e.g.*, human BCMA or human CLL-1, with a 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70% or higher affinity than to another species of the target antigen as measured by, *e.g.*, a radioimmunoassay, surface plasmon resonance, or kinetic exclusion assay. In a specific embodiment, an antibody or an antigen binding molecule thereof described herein, which binds to a target human antigen, will bind to another species of the target antigen with less than 10%, 15%, or 20% of the binding of the antibody or an antigen binding molecule thereof to the human antigen as measured by, *e.g.*, a radioimmunoassay, surface plasmon resonance, or kinetic exclusion assay.

[0110] An "antigen" refers to any molecule that provokes an immune response or is capable of being bound by an antibody or an antigen binding molecule. The immune response may involve either antibody production, or the activation of specific immunologically-competent cells, or both. A person of skill in the art would readily understand that any macromolecule, including virtually all proteins or peptides, can serve as an antigen. An antigen can be endogenously expressed, *i.e.* expressed by genomic DNA, or can be recombinantly expressed. An antigen can be specific to a certain tissue, such as a cancer cell, or it can be broadly expressed. In addition, fragments of larger molecules can act as antigens. In one embodiment, antigens are tumor antigens. In one particular embodiment, the antigen is all or a fragment of BCMA, FLT3, or CLL-1.

[0111] The term "neutralizing" refers to an antigen binding molecule, scFv, antibody, or a fragment thereof, that binds to a ligand and prevents or reduces the biological effect of that ligand. In some embodiments, the antigen binding molecule, scFv, antibody, or a fragment thereof, directly blocking a binding site on the ligand or otherwise alters the ligand's ability to bind through indirect means (such as structural or energetic alterations in the ligand). In some embodiments, the antigen binding molecule, scFv, antibody, or a fragment thereof prevents the protein to which it is bound from performing a biological function.

[0112] As used herein, the term "BCMA" refers to B cell maturation antigen, which can include, but is not limited to, native BCMA, an isoform of BCMA, or an interspecies BCMA homolog of BCMA. BCMA (also known as TNFRSF17, CD269, and TNFRSF13A) is

a member of the tumor necrosis factor (TNF)-receptor superfamily. BCMA is expressed on the surface of multiple myeloma cells, while highly restricted to plasma cells and a subset of mature B cells in healthy tissue. The amino acid sequence of human BCMA (hBCMA) is provided in NCBI Accession Q02223.2 (GI:313104029). As used herein, BCMA includes human BCMA and non-human BCMA homologs, as well as variants, fragments, or post-transnationally modified forms thereof, including, but not limited to, N- and O-linked glycosylated forms of BCMA. BCMA proteins may further include fragments comprising all or a portion of the extracellular domain of BCMA (*e.g.*, all or a portion of amino acids 1-54 of hBCMA).

[0113] As used herein, the term "CLL-1" refers to C-type lectin-like molecule-1, which can include, but is not limited to native CLL-1, an isoform of CLL-1, or an interspecies CLL-1 homolog of CLL-1. CLL-1 (also known as C-type lectin domain family 12 member A, CLEC12A, dendritic cell-associated lectin 2, DCAL-2, myeloid inhibitory C-type lectin-like receptor, and MICL) is a cell surface receptor that modulates signaling cascades and mediates tyrosine phosphorylation of target MAP kinases. CLL-1 expression is observed, *e.g.*, in acute myeloid leukemia (AML) cells. The amino acid sequence of human CLL-1 (hCLL-1) is provided in UniProtKB/Swiss-Prot Accession No. Q5QGZ9.3 (GI:308153619). As used herein, CLL-1 includes human CLL-1 and non-human CLL-1 homologs, as well as variants, fragments, or post-transnationally modified forms thereof, including, but not limited to, N- and O-linked glycosylated forms of CLL-1.

[0114] As used herein the term "FLT3" refers to Fms-like tyrosine kinase 3 (FLT-3), which can include, but is not limited to native FLT3, an isoform of FLT3, or an interspecies FLT3 homolog of FLT3. FLT3 (also known as Cluster of differentiation antigen 135 (CD135), receptor-type tyrosine-protein kinase FLT3, FMS-related tyrosine kinase 3, stem cell tyrosine kinase 1, FL cytokine receptor, growth factor receptor tyrosine kinase type III, STK1, or fetal liver kinase-2 (Flk2)) is a cytokine receptor which belongs to the receptor tyrosine kinase class III. CD135 is the receptor for the cytokine Flt3 ligand (FLT3L). FLT3 is expressed on the surface of various hematopoietic progenitor cells and on the surface of acute myeloid leukemia (AML) cells. The amino acid sequence of human FLT3 (hFLT3) is provided in UniProtKB/Swiss-Prot Accession No. P36888 (GI:156630887). As used herein, FLT3 includes human FLT3 and non-human FLT3 homologs, as well as variants, fragments, or post-transnationally modified forms thereof, including, but not limited to, N- and O-linked glycosylated forms of FLT3.

[0115] The term "autologous" refers to any material derived from the same individual to which it is later to be re-introduced. For example, the engineered autologous cell therapy (eACT™) method described herein involves collection of lymphocytes from a patient, which are then engineered to express, *e.g.*, a CAR construct, and then administered back to the same patient.

[0116] The term "allogeneic" refers to any material derived from one individual which is then introduced to another individual of the same species, *e.g.*, allogeneic T cell transplantation.

[0117] The terms "transduction" and "transduced" refer to the process whereby foreign DNA is introduced into a cell via viral vector (*see* Jones et al., "Genetics: principles and analysis," Boston: Jones & Bartlett Publ. (1998)). In some embodiments, the vector is a retroviral vector, a DNA vector, 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, a lentiviral vector, or any combination thereof.

[0118] As used herein, the term "truncated" refers to anything less than the whole. For example, a truncated hinge domain (alternatively referred to herein as "THD") amino acid sequence can include any amino acid sequence shorter than the full length or complete hinge domain ("CHD"). In some embodiments, a THD consists essentially of or consists of amino acids 118-152, 119-152, 120-152, 121-152, 122-152, 123-152, 124-152, 125-152, 126-152, 127-152, 128-152, 129-152, or 130-152, of SEQ ID NO: 1. In one embodiment, the THD consists essentially of or consists of the amino acid sequence of SEQ ID NO: 3, which consists of amino acids 123 to 152 of SEQ ID NO: 1.

[0119] A "cancer" refers to a broad group of various diseases characterized by the uncontrolled growth of abnormal cells in the body. Unregulated cell division and growth results in the formation of malignant tumors that invade neighboring tissues and may also metastasize to distant parts of the body through the lymphatic system or bloodstream. A "cancer" or "cancer tissue" can include a tumor. Examples of cancers that can be treated by the methods of the present invention include, but are not limited to, cancers of the immune system including lymphoma, leukemia, myeloma, and other leukocyte malignancies. In some embodiments, the methods of the present invention can be used to reduce the tumor size of a tumor derived from, for example, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes,

carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, multiple myeloma, Hodgkin's Disease, non-Hodgkin's lymphoma (NHL), primary mediastinal large B cell lymphoma (PMBC), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), transformed follicular lymphoma, splenic marginal zone lymphoma (SMZL), cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, chronic or acute leukemia, acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia (ALL) (including non T cell ALL), chronic lymphocytic leukemia (CLL), solid tumors of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers including those induced by asbestos, other B cell malignancies, and combinations of said cancers. In one particular embodiment, the cancer is multiple myeloma. The particular cancer can be responsive to chemo- or radiation therapy or the cancer can be refractory. A refractory cancer refers to a cancer that is not amendable to surgical intervention and the cancer is either initially unresponsive to chemo- or radiation therapy or the cancer becomes unresponsive over time.

[0120] An “anti-tumor effect” as used herein, refers to a biological effect that can present as a decrease in tumor volume, a decrease in the number of tumor cells, a decrease in tumor cell proliferation, a decrease in the number of metastases, an increase in overall or progression-free survival, an increase in life expectancy, or amelioration of various physiological symptoms associated with the tumor. An anti-tumor effect can also refer to the prevention of the occurrence of a tumor, *e.g.*, a vaccine.

[0121] A “cytokine,” as used herein, refers to a non-antibody protein that is released by one cell in response to contact with a specific antigen, wherein the cytokine interacts with a second cell to mediate a response in the second cell. A cytokine can be endogenously expressed by a cell or administered to a subject. Cytokines may be released by immune cells, including macrophages, B cells, T cells, and mast cells to propagate an immune response. Cytokines can induce various responses in the recipient cell. Cytokines can include homeostatic cytokines, chemokines, pro-inflammatory cytokines, effectors, and acute-phase proteins. For example, homeostatic cytokines, including interleukin (IL) 7 and IL-15, promote immune cell survival

and proliferation, and pro-inflammatory cytokines can promote an inflammatory response. Examples of homeostatic cytokines include, but are not limited to, IL-2, IL-4, IL-5, IL-7, IL-10, IL-12p40, IL-12p70, IL-15, and interferon (IFN) gamma. Examples of pro-inflammatory cytokines include, but are not limited to, IL-1a, IL-1b, IL-6, IL-13, IL-17a, tumor necrosis factor (TNF)-alpha, TNF-beta, fibroblast growth factor (FGF) 2, granulocyte macrophage colony-stimulating factor (GM-CSF), soluble intercellular adhesion molecule 1 (sICAM-1), soluble vascular adhesion molecule 1 (sVCAM-1), vascular endothelial growth factor (VEGF), VEGF-C, VEGF-D, and placental growth factor (PLGF). Examples of effectors include, but are not limited to, granzyme A, granzyme B, soluble Fas ligand (sFasL), and perforin. Examples of acute phase-proteins include, but are not limited to, C-reactive protein (CRP) and serum amyloid A (SAA).

[0122] "Chemokines" are a type of cytokine that mediates cell chemotaxis, or directional movement. Examples of chemokines include, but are not limited to, IL-8, IL-16, eotaxin, eotaxin-3, macrophage-derived chemokine (MDC or CCL22), monocyte chemotactic protein 1 (MCP-1 or CCL2), MCP-4, macrophage inflammatory protein 1α (MIP-1α, MIP-1a), MIP-1β (MIP-1b), gamma-induced protein 10 (IP-10), and thymus and activation regulated chemokine (TARC or CCL17).

[0123] A "therapeutically effective amount," "effective dose," "effective amount," or "therapeutically effective dosage" of a therapeutic agent, *e.g.,* engineered CAR T cells, is any amount that, when used alone or in combination with another therapeutic agent, protects a subject against the onset of a disease or promotes disease regression evidenced by a decrease in severity of disease symptoms, an increase in frequency and duration of disease symptom-free periods, or a prevention of impairment or disability due to the disease affliction. The ability of a therapeutic agent to promote disease regression can be evaluated using a variety of methods known to the skilled practitioner, such as in human subjects during clinical trials, in animal model systems predictive of efficacy in humans, or by assaying the activity of the agent in *in vitro* assays.

[0124] The term "lymphocyte" as used herein includes natural killer (NK) cells, T cells, or B cells. NK cells are a type of cytotoxic (cell toxic) lymphocyte that represent a major component of the inherent immune system. NK cells reject tumors and cells infected by viruses. It works through the process of apoptosis or programmed cell death. They were termed "natural killers" because they do not require activation in order to kill cells. T-cells play a major role in cell-mediated-immunity (no antibody involvement). Its T-cell receptors (TCR) differentiate

themselves from other lymphocyte types. The thymus, a specialized organ of the immune system, is primarily responsible for the T cell's maturation. There are six types of T-cells, namely: Helper T-cells (*e.g.,* CD4+ cells), Cytotoxic T-cells (also known as TC, cytotoxic T lymphocyte, CTL, T-killer cell, cytolytic T cell, CD8+ T-cells or killer T cell), Memory T-cells ((i) stem memory T_{SCM} cells, like naive cells, are CD45RO−, CCR7+, CD45RA+, CD62L+ (L-selectin), CD27+, CD28+ and IL-7Rα+, but they also express large amounts of CD95, IL-2Rβ, CXCR3, and LFA-1, and show numerous functional attributes distinctive of memory cells); (ii) central memory T_{CM} cells express L-selectin and the CCR7, they secrete IL-2, but not IFNγ or IL-4, and (iii) effector memory T_{EM} cells, however, do not express L-selectin or CCR7 but produce effector cytokines like IFNγ and IL-4), Regulatory T-cells (Tregs, suppressor T cells, or CD4+CD25+ regulatory T cells), Natural Killer T-cells (NKT) and Gamma Delta T-cells. B-cells, on the other hand, play a principal role in humoral immunity (with antibody involvement). It makes antibodies and antigens and performs the role of antigen-presenting cells (APCs) and turns into memory B-cells after activation by antigen interaction. In mammals, immature B-cells are formed in the bone marrow, where its name is derived from.

[0125] The term "genetically engineered" or "engineered" refers to a method of modifying the genome of a cell, including, but not limited to, deleting a coding or non-coding region or a portion thereof or inserting a coding region or a portion thereof. In some embodiments, the cell that is modified is a lymphocyte, *e.g.*, a T cell, which can either be obtained from a patient or a donor. The cell can be modified to express an exogenous construct, such as, *e.g.*, a chimeric antigen receptor (CAR) or a T cell receptor (TCR), which is incorporated into the cell's genome.

[0126] An "immune response" refers to the action of a cell of the immune system (for example, T lymphocytes, B lymphocytes, natural killer (NK) cells, macrophages, eosinophils, mast cells, dendritic cells and neutrophils) and soluble macromolecules produced by any of these cells or the liver (including Abs, cytokines, and complement) that results in selective targeting, binding to, damage to, destruction of, and/or elimination from a vertebrate's body of invading pathogens, cells or tissues infected with pathogens, cancerous or other abnormal cells, or, in cases of autoimmunity or pathological inflammation, normal human cells or tissues.

[0127] The term "immunotherapy" refers to the treatment of a subject afflicted with, or at risk of contracting or suffering a recurrence of, a disease by a method comprising inducing, enhancing, suppressing or otherwise modifying an immune response. Examples of

immunotherapy include, but are not limited to, T cell therapies. T cell therapy can include adoptive T cell therapy, tumor-infiltrating lymphocyte (TIL) immunotherapy, autologous cell therapy, engineered autologous cell therapy (eACT™), and allogeneic T cell transplantation. However, one of skill in the art would recognize that the conditioning methods disclosed herein would enhance the effectiveness of any transplanted T cell therapy. Examples of T cell therapies are described in U.S. Patent Publication Nos. 2014/0154228 and 2002/0006409, U.S. Patent No. 5,728,388, and International Publication No. WO 2008/081035.

[0128] The T cells of the immunotherapy can come from any source known in the art. For example, T cells can be differentiated *in vitro* from a hematopoietic stem cell population, or T cells can be obtained from a subject. T cells can be obtained from, *e.g.*, peripheral blood mononuclear cells (PBMCs), bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion, spleen tissue, and tumors. In addition, the T cells can be derived from one or more T cell lines available in the art. T cells can also be obtained from a unit of blood collected from a subject using any number of techniques known to the skilled artisan, such as FICOLL™ separation and/or apheresis. Additional methods of isolating T cells for a T cell therapy are disclosed in U.S. Patent Publication No. 2013/0287748, which is herein incorporated by references in its entirety.

[0129] The term "engineered Autologous Cell Therapy," which can be abbreviated as "eACT™," also known as adoptive cell transfer, is a process by which a patient's own T cells are collected and subsequently genetically altered to recognize and target one or more antigens expressed on the cell surface of one or more specific tumor cells or malignancies. T cells can be engineered to express, for example, chimeric antigen receptors (CAR) or T cell receptor (TCR). CAR positive (+) T cells are engineered to express an extracellular single chain variable fragment (scFv) with specificity for a particular tumor antigen linked to an intracellular signaling part comprising at least one costimulatory domain and at least one activating domain. The costimulatory domain can be derived from a naturally-occurring costimulatory domain, e.g., having the amino acid sequence of SEQ ID NO: 1, or a variant thereof, *e.g.*, a variant having a truncated hinge domain ("THD"), and the activating domain can be derived from, *e.g.*, CD3-zeta. In certain embodiments, the CAR is designed to have two, three, four, or more costimulatory domains. The CAR scFv can be designed to target, for example, CD19, which is a transmembrane protein expressed by cells in the B cell lineage, including all normal B cells and B cell malignances, including but not limited to NHL, CLL, and non-T cell ALL. In some embodiments, the CAR is engineered such that the costimulatory domain is expressed as a

separate polypeptide chain. Example CAR T cell therapies and constructs are described in U.S. Patent Publication Nos. 2013/0287748, 2014/0227237, 2014/0099309, and 2014/0050708, and these references are incorporated by reference in their entirety.

[0130] A "patient" as used herein includes any human who is afflicted with a cancer (*e.g.*, a lymphoma or a leukemia). The terms "subject" and "patient" are used interchangeably herein.

[0131] As used herein, the term "*in vitro* cell" refers to any cell which is cultured *ex vivo*. In particular, an *in vitro* cell can include a T cell.

[0132] The terms "peptide," "polypeptide," and "protein" are used interchangeably, and refer to a compound comprised of amino acid residues covalently linked by peptide bonds. A protein or peptide contains at least two amino acids, and no limitation is placed on the maximum number of amino acids that can comprise a protein's or peptide's sequence. Polypeptides include any peptide or protein comprising two or more amino acids joined to each other by peptide bonds. As used herein, the term refers to both short chains, which also commonly are referred to in the art as peptides, oligopeptides and oligomers, for example, and to longer chains, which generally are referred to in the art as proteins, of which there are many types. "Polypeptides" include, for example, biologically active fragments, substantially homologous polypeptides, oligopeptides, homodimers, heterodimers, variants of polypeptides, modified polypeptides, derivatives, analogs, fusion proteins, among others. The polypeptides include natural peptides, recombinant peptides, synthetic peptides, or a combination thereof.

[0133] "Stimulation," as used herein, refers to a primary response induced by binding of a stimulatory molecule with its cognate ligand, wherein the binding mediates a signal transduction event. A "stimulatory molecule" is a molecule on a T cell, *e.g.*, the T cell receptor (TCR)/CD3 complex, that specifically binds with a cognate stimulatory ligand present on an antigen present cell. A "stimulatory ligand" is a ligand that when present on an antigen presenting cell (*e.g.*, an APC, a dendritic cell, a B-cell, and the like) can specifically bind with a stimulatory molecule on a T cell, thereby mediating a primary response by the T cell, including, but not limited to, activation, initiation of an immune response, proliferation, and the like. Stimulatory ligands include, but are not limited to, an anti-CD3 antibody (such as OKT3), an MHC Class I molecule loaded with a peptide, a superagonist anti-CD2 antibody, and a superagonist anti-CD28 antibody.

[0134] A "costimulatory signal," as used herein, refers to a signal, which in combination with a primary signal, such as TCR/CD3 ligation, leads to a T cell response, such as, but not limited to, proliferation and/or upregulation or down regulation of key molecules.

[0135] A "costimulatory ligand" as used herein, includes a molecule on an antigen presenting cell that specifically binds a cognate co-stimulatory molecule on a T cell. Binding of the costimulatory ligand provides a signal that mediates a T cell response, including, but not limited to, proliferation, activation, differentiation, and the like. A costimulatory ligand induces a signal that is in addition to the primary signal provided by a stimulatory molecule, for instance, by binding of a T cell receptor (TCR)/CD3 complex with a major histocompatibility complex (MHC) molecule loaded with peptide. A co-stimulatory ligand can include, but is not limited to, 3/TR6, 4-1BB ligand, agonist or antibody that binds Toll ligand receptor , B7-1 (CD80), B7-2 (CD86), CD30 ligand, CD40, CD7, CD70, CD83, herpes virus entry mediator (HVEM), human leukocyte antigen G (HLA-G), ILT4, immunoglobulin-like transcript (ILT) 3, inducible costimulatory ligand (ICOS-L), intercellular adhesion molecule (ICAM), ligand that specifically binds with B7-H3. , lymphotoxin beta receptor, MHC class I chain-related protein A (MICA), MHC class I chain-related protein B (MICB), OX40 ligand, PD-L2, or programmed death (PD) L1. A co-stimulatory ligand includes, without limitation, an antibody that specifically binds with a co-stimulatory molecule present on a T cell, such as, but not limited to, 4-1BB, B7-H3, CD2, CD27, CD28, CD30, CD40, CD7, ICOS, ligand that specifically binds with CD83, lymphocyte function-associated antigen-1 (LFA-1), natural killer cell receptor C (NKG2C), OX40, PD-1, or tumor necrosis factor superfamily member 14 (TNFSF14 or LIGHT).

[0136] A "costimulatory molecule" is a cognate binding partner on a T cell that specifically binds with a costimulatory ligand, thereby mediating a costimulatory response by the T cell, such as, but not limited to, proliferation. Costimulatory molecules include, but are not limited to, A "costimulatory molecule" is a cognate binding partner on a T cell that specifically binds with a costimulatory ligand, thereby mediating a costimulatory response by the T cell, such as, but not limited to, proliferation. Costimulatory molecules include, but are not limited to, 4-1BB/CD137, B7-H3, BAFFR, BLAME (SLAMF8), BTLA, CD 33, CD 45, CD100 (SEMA4D), CD103, CD134, CD137, CD154, CD16, CD160 (BY55), CD18, CD19, CD19a, CD2, CD22, CD247, CD27, CD276 (B7-H3), CD28, CD29, CD3 (alpha; beta; delta; epsilon; gamma; zeta), CD30, CD37, CD4, CD4, CD40, CD49a, CD49D, CD49f, CD5, CD64, CD69, CD7, CD80, CD83 ligand, CD84, CD86, CD8alpha, CD8beta, CD9, CD96 (Tactile),

CDl-la, CDl-lb, CDl-lc, CDl-ld, CDS, CEACAM1, CRT AM, DAP-10, DNAM1 (CD226), Fc gamma receptor, GADS, GITR, HVEM (LIGHTR), IA4, ICAM-1, ICAM-1, ICOS, Ig alpha (CD79a), IL2R beta, IL2R gamma, IL7R alpha, integrin, ITGA4, ITGA4, ITGA6, ITGAD, ITGAE, ITGAL, ITGAM, ITGAX, ITGB2, ITGB7, ITGBl, KIRDS2, LAT, LFA-1, LFA-1, LIGHT, LIGHT (tumor necrosis factor superfamily member 14; TNFSF14), LTBR, Ly9 (CD229), lymphocyte function-associated antigen-1 (LFA-1 (CDl la/CD18), MHC class I molecule, NKG2C, NKG2D, NKp30, NKp44, NKp46, NKp80 (KLRF1), OX40, PAG/Cbp, PD-1, PSGL1, SELPLG (CD162), signaling lymphocytic activation molecule, SLAM (SLAMF1; CD150; IPO-3), SLAMF4 (CD244; 2B4), SLAMF6 (NTB-A; Lyl08), SLAMF7, SLP-76, TNF, TNFr, TNFR2, Toll ligand receptor, TRANCE/RANKL, VLA1, or VLA-6, or fragments, truncations, or combinations thereof.

[0137] The terms "reducing" and "decreasing" are used interchangeably herein and indicate any change that is less than the original. "Reducing" and "decreasing" are relative terms, requiring a comparison between pre- and post- measurements. "Reducing" and "decreasing" include complete depletions.

[0138] "Treatment" or "treating" of a subject refers to any type of intervention or process performed on, or the administration of an active agent to, the subject with the objective of reversing, alleviating, ameliorating, inhibiting, slowing down or preventing the onset, progression, development, severity or recurrence of a symptom, complication or condition, or biochemical indicia associated with a disease. In one embodiment, "treatment" or "treating" includes a partial remission. In another embodiment, "treatment" or "treating" includes a complete remission.

[0139] 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.

[0140] Various aspects of the invention are described in further detail in the following subsections.

I. Chimeric Antigen Receptors and T Cell Receptors

[0141] 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.

[0142] One aspect of the present invention is directed to polynucleotides encoding chimeric antigen receptors (CARs) or T cell receptors (TCRs) comprising a costimulatory domain comprising a novel extracellular domain comprising a truncated hinge domain ("THD"), and engineered T cells comprising a costimulatory domain comprising the novel THD. The costimulatory domain can further comprise a transmembrane domain and/or an intracellular domain. In some embodiments, a CAR or TCR encoded by the polynucleotide of the present invention further comprises an antigen binding molecule that specifically binds to a target antigen. In some embodiments, the CAR or TCR encoded by the polynucleotide further comprises an activating domain. In one particular embodiment, the CAR or TCR encoded by the polynucleotide comprises (i) an antigen binding molecule that specifically binds to a target antigen, (ii) a costimulatory domain comprising an extracellular domain, a transmembrane domain, and an intracellular domain, and (iii) an activating domain, wherein the extracellular domain comprises, consists essentially of, or consists of a THD described herein, e.g., SEQ ID NO: 3.

[0143] In some embodiments, an 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. In other embodiments, multiple costimulatory domains can be utilized in tandem.

I.A. Costimulatory Domain.

[0144] Chimeric antigen receptors incorporates 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). The costimulatory protein having the amino acid sequence of SEQ ID NO: 1 is a costimulatory protein found naturally on T-cells. The complete native amino acid sequence of this costimulatory protein is described in NCBI Reference Sequence: NP_006130.1. See Figure 1A. The complete native nucleic acid sequence of this costimulatory protein is described in NCBI Reference Sequence: NM_006139.1.

[0145] ***Novel Extracellular Domain***: The present disclosure shows that a novel extracellular domain of a costimulatory protein and comprising a truncated hinge domain ("THD") can improve one or more properties of a CAR or a TCR. In some embodiments, the THD domain is a truncated version of a complete hinge domain ("CHD"). In certain embodiments, the isolated polynucleotide encoding a THD comprises (i) an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to amino acids 123 to 152 of SEQ ID NO: 1, wherein the THD domain does not contain amino acids 1 to 122 of SEQ ID NO: 1.

[0146] In other embodiments, the THD consists essentially of or consists of an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to amino acids 123 to 152 of SEQ ID NO: 1. In other embodiments, the THD consists essentially of or consists of an amino acid sequence encoded by a nucleotide sequence at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 3.

[0147] In some embodiments, the isolated polynucleotide encoding a THD consists essentially of or consists of (i) an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to amino acids 123 to 152 of SEQ ID NO: 1 and (ii) optionally ± one amino acid, ± two amino acids, ± three amino acids, ± four amino acids, ± five amino acids, or ± six amino acids. In some embodiments, the isolated

polynucleotide encoding a THD consists essentially of or consists of (i) an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to amino acids 123 to 152 of SEQ ID NO: 1 and (ii) optionally one or two amino acids, one to three amino acids, one to four amino acids, one to five amino acids, or one to six amino acids. The one to six amino acids that can be added or deleted from the amino acid sequence in the THD can be at either the N-terminus, at the C-terminus, or both the N-terminus and the C-terminus.

[0148] In some embodiments, the isolated polynucleotide encoding a THD consists essentially of or consists of (i) an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to amino acids 123 to 152 of SEQ ID NO: 1 and (ii) one additional N-terminal amino acid, two additional N-terminal amino acids, three additional N-terminal amino acids, four additional N-terminal amino acids, five additional N-terminal amino acids, or six additional N-terminal amino acids.

[0149] In some embodiments, the additional amino acids can be N-terminal amino acids. In some embodiments, the additional amino acids can be heterologous. In other embodiments, the additional amino acids are part of the naturally occurring costimulatory protein sequence.

[0150] In some embodiments, the THD consists essentially of or consists of an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to amino acids 123 to 152 of SEQ ID NO: 1, amino acids 122 to 152 of SEQ ID NO: 1, amino acids 121 to 152 of SEQ ID NO: 1, amino acids 120 to 152 of SEQ ID NO: 1, amino acids 119 to 152 of SEQ ID NO: 1, amino acids 118 to 152 of SEQ ID NO: 1, or amino acids 117 to 152 of SEQ ID NO: 1.

[0151] In other embodiments, the THD consists essentially of or consists of an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to amino acids 124 to 152 of SEQ ID NO: 1, amino acids 125 to 152 of SEQ ID NO: 1, amino acids 126 to 152 of SEQ ID NO: 1, amino acids 127 to 152 of SEQ ID NO: 1, amino acids 128 to 152 of SEQ ID NO: 1, amino acids 129 to 152 of SEQ ID NO: 1, or amino acids 130 to 152 of SEQ ID NO: 1.

[0152] In some embodiments, the THD does not comprise amino acids 1-116 of SEQ ID NO: 1. In some embodiments, the THD does not comprise amino acids 1-117 of SEQ ID NO: 1. In some embodiments, the THD does not comprise amino acids 1-118 of SEQ ID NO: 1. In some embodiments, the THD does not comprise amino acids 1-119 of SEQ ID NO: 1. In some embodiments, the THD does not comprise amino acids 1-120 of SEQ ID NO: 1. In some embodiments, the THD does not comprise amino acids 1-121 of SEQ ID NO: 1. In some embodiments, the THD does not comprise amino acids 1-122 of SEQ ID NO: 1. In some embodiments, the THD does not comprise amino acids 1-123 of SEQ ID NO: 1. In some embodiments, the THD does not comprise amino acids 1-124 of SEQ ID NO: 1. In some embodiments, the THD does not comprise amino acids 1-125 of SEQ ID NO: 1. In some embodiments, the THD does not comprise amino acids 1-126 of SEQ ID NO: 1. In some embodiments, the THD does not comprise amino acids 1-127 of SEQ ID NO: 1. In some embodiments, the THD does not comprise amino acids 1-128 of SEQ ID NO: 1. In some embodiments, the THD does not comprise amino acids 1-129 of SEQ ID NO: 1.

[0153] The corresponding amino acid sequence of the THD is set forth in SEQ ID NO. 3 LDNEKSNGTI IHVKGKHLCP SPLFPGPSKP. A nucleotide sequence encoding the extracellular portion of THD is set forth in SEQ ID NO. 2 CTTGATAATGAAAAGTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTC TGTCCGTCACCCTTGTTCCCTGGTCCATCCAAGCCA.

[0154] In certain embodiments, the polynucleotide encoding a costimulatory domain in a CAR or TCR comprises a nucleotide sequence at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 3, wherein the nucleotide sequence encodes a THD and wherein the CAR or TCR does not comprise amino acids 1 to 122 of SEQ ID NO: 1.

[0155] In one particular embodiment, the THD consists essentially of or consists of an amino acid sequence at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence of SEQ ID NO: 3. In a specific embodiment, the polynucleotide encoding THD consists essentially of or consists of a nucleotide sequence at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%,

at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the nucleotide sequence of SEQ ID NO: 2.

[0156] In some embodiments, the THD further comprises some or all of a member of the immunoglobulin family such as IgG1, IgG2, IgG3, IgG4, IgA, IgD, IgE, IgM, or fragment thereof.

[0157] In some embodiments, the THD is derived from a human complete hinge domain ("CHD"), e.g., from the costimulatory protein having the amino acid sequence of SEQ ID NO: 1. In other embodiments, the THD is derived from a rodent, murine, or primate (*e.g.*, non-human primate) CHD of a costimulatory protein. In some embodiments, the THD is derived from a chimeric CHD of a costimulatory protein.

[0158] ***Transmembrane Domain:*** The costimulatory domain for the CAR or TCR of the invention can further comprise a transmembrane domain and/or an intracellular signaling domain. The transmembrane domain can be designed to be 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 can be derived either from a natural or from a synthetic source. Where the source is natural, the domain can be derived from any membrane-bound or transmembrane protein. Transmembrane regions of particular use in this invention can be derived from (i.e., comprise) 4-1BB/CD137, activating NK cell receptors, an Immunoglobulin protein, B7-H3, BAFFR, BLAME (SLAMF8), BTLA, CD100 (SEMA4D), CD103, CD160 (BY55), CD18, CD19, CD19a, CD2, CD247, CD27, CD276 (B7-H3), CD28, CD29, CD3 delta, CD3 epsilon, CD3 gamma, CD30, CD4, CD40, CD49a, CD49D, CD49f, CD69, CD7, CD84, CD8alpha, CD8beta, CD96 (Tactile), CDl la, CDl lb, CDl lc, CDl ld, CDS, CEACAM1, CRT AM, cytokine receptor, DAP-10, DNAM1 (CD226), Fc gamma receptor, GADS, GITR, HVEM (LIGHTR), IA4, ICAM-1, ICAM-1, Ig alpha (CD79a), IL-2R beta, IL-2R gamma, IL-7R alpha, inducible T cell costimulator (ICOS), integrins, ITGA4, ITGA4, ITGA6, ITGAD, ITGAE, ITGAL, ITGAM, ITGAX, ITGB2, ITGB7, ITGBl, KIRDS2, LAT, LFA-1, LFA-1, a ligand that specifically binds with CD83,, LIGHT, LIGHT, LTBR, Ly9 (CD229), lymphocyte function-associated antigen-1 (LFA-1; CDl-la/CD18), MHC class 1 molecule, NKG2C, NKG2D, NKp30, NKp44, NKp46, NKp80 (KLRF1), OX-40, PAG/Cbp,

programmed death-1 (PD-1), PSGL1, SELPLG (CD162), Signaling Lymphocytic Activation Molecules (SLAM proteins), SLAM (SLAMF1; CD150; IPO-3), SLAMF4 (CD244; 2B4), SLAMF6 (NTB-A; Ly108), SLAMF7, SLP-76, TNF receptor proteins, TNFR2, TNFSF14, a Toll ligand receptor, TRANCE/RANKL, VLA1, or VLA-6, or a fragment, truncation, or a combination thereof.

[0159] Optionally, short linkers can form linkages between any or some of the extracellular, transmembrane, and intracellular domains of the CAR.

[0160] In one specific embodiment, the nucleotide sequence of the costimulatory protein's transmembrane domain is set forth in SEQ ID NO. 4: TTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCGCTTGTTACTCTCTGCTCGTCAC CGTGGCTTTTATAATCTTCTGGGTT

[0161] In one embodiment, the polynucleotide encoding a transmembrane domain within a costimulatory domain comprises a nucleotide sequence at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the nucleotide sequence of SEQ ID NO: 4.

[0162] The amino acid sequence of the costimulatory protein's transmembrane domain is set forth in SEQ ID NO. 5: FWVLVVVGGV LACYSLLVTV AFIIFWV.

[0163] In one particular embodiment, the transmembrane domain within a costimulatory domain comprises an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence of SEQ ID NO: 5.

[0164] In another embodiment, the transmembrane domain is derived from (i.e., comprises) CD8. In one embodiment, the nucleotide sequence of the CD8 extracellular domain and transmembrane domain is set forth in SEQ ID NO: 238 GCTGCAGCATTGAGCAACTCAATAATGTATTTTAGTCACTTTGTACCAGTGTTCTT GCCGGCTAAGCCTACTACCACACCCGCTCCACGGCCACCTACCCCAGCTCCTACC ATCGCTTCACAGCCTCTGTCCCTGCGCCCAGAGGCTTGCCGACCGGCCGCAGGGG GCGCTGTTCATACCAGAGGACTGGATTTCGCCTGCGATATCTATATCTGGGCACC CCTGGCCGGAACCTGCGGCGTACTCCTGCTGTCCCTGGTCATCACGCTCTATTGT AATCACAGGAAC.

[0165] In some embodiments, the polynucleotide encoding a transmembrane domain within a costimulatory domain comprises a nucleotide sequence at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the nucleotide sequence of the CD8 transmembrane domain.

[0166] The amino acid sequence of the CD8 extracellular domain and transmembrane domain is set forth in SEQ ID NO. 239 AAALSNSIMYFSHFVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVH TRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCNHRN.

[0167] In one particular embodiment, the transmembrane domain within a costimulatory domain comprises an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence of the CD8 transmembrane domain.

[0168] ***Intracellular (signaling) Domain*:** The intracellular (signaling) domain of the engineered T cells of the invention can provide signaling to an activating domain, which then activates at least one of the normal effector functions of the immune cell. Effector function of a T cell, for example, can be cytolytic activity or helper activity including the secretion of cytokines.

[0169] In certain embodiments, suitable intracellular signaling domain include (*i.e.*, comprise), but are not limited to 4-1BB/CD137, activating NK cell receptors, an Immunoglobulin protein, B7-H3, BAFFR, BLAME (SLAMF8), BTLA, CD100 (SEMA4D), CD103, CD160 (BY55), CD18, CD19, CD19a, CD2, CD247, CD27, CD276 (B7-H3), CD28, CD29, CD3 delta, CD3 epsilon, CD3 gamma, CD30, CD4, CD40, CD49a, CD49D, CD49f, CD69, CD7, CD84, CD8alpha, CD8beta, CD96 (Tactile), CDl la, CDl lb, CDl lc, CDl ld, CDS, CEACAM1, CRT AM, cytokine receptor, DAP-10, DNAM1 (CD226), Fc gamma receptor, GADS, GITR, HVEM (LIGHTR), IA4, ICAM-1, ICAM-1, Ig alpha (CD79a), IL-2R beta, IL-2R gamma, IL-7R alpha, inducible T cell costimulator (ICOS), integrins, ITGA4, ITGA4, ITGA6, ITGAD, ITGAE, ITGAL, ITGAM, ITGAX, ITGB2, ITGB7, ITGBl, KIRDS2, LAT, LFA-1, LFA-1, ligand that specifically binds with CD83,, LIGHT, LIGHT, LTBR, Ly9 (CD229), Lyl08), lymphocyte function-associated antigen-1 (LFA-1; CDl-la/CD18), MHC class 1 molecule, NKG2C, NKG2D, NKp30, NKp44, NKp46, NKp80 (KLRF1), OX-40,

PAG/Cbp, programmed death-1 (PD-1), PSGL1, SELPLG (CD162), Signaling Lymphocytic Activation Molecules (SLAM proteins), SLAM (SLAMF1; CD150; IPO-3), SLAMF4 (CD244; 2B4), SLAMF6 (NTB-A, SLAMF7, SLP-76, TNF receptor proteins, TNFR2, TNFSF14, a Toll ligand receptor, TRANCE/RANKL, VLA1, or VLA-6, or a fragment, truncation, or a combination thereof.

[0170] An example of a nucleotide sequence encoding the intracellular signaling domain is set forth in SEQ ID NO. 6: AGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGAATATGACTCCACGC CGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATTTCG CTGCCTATCGGAGC

[0171] In one embodiment, the polynucleotide encoding an intracellular signaling domain within a costimulatory domain comprises a nucleotide sequence at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the nucleotide sequence of SEQ ID NO: 6.

[0172] An example of an intracellular signaling domain is set forth in SEQ ID NO. 7: RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS.

[0173] In one particular embodiment, the intracellular signaling domain within a costimulatory domain comprises an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence of SEQ ID NO: 7.

[0174] In some embodiments, the costimulatory domain comprises, consists essentially of, or consists of the extracellular THD, and the costimulatory proteins' s transmembrane and intracellular domains. For example, a nucleotide sequence encoding a costimulatory domain is set forth in SEQ ID NO. 240: CTTGATAATGAAAAGTCAAACGGAACAATCATTCACGTGAAGGGCAAGCACCTC TGTCCGTCACCCTTGTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGT GGGTGGAGTCCTCGCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCT GGGTTAGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGAATATGACTCC

ACGCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCACCACCTAGAGA
TTTCGCTGCCTATCGGAGC

[0175] In some embodiments, the polynucleotide encoding a costimulatory domain comprises, consists essentially of, or consists of a nucleotide sequence at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the nucleotide sequence of SEQ ID NO: 240, wherein the costimulatory domain does not comprises amino acids 1 to 122 of SEQ ID NO: 1, amino acids 1 to 121 of SEQ ID NO: 1, amino acids 1 to 120 of SEQ ID NO: 1, amino acids 1 to 119 of SEQ ID NO: 1, amino acids 1 to 118 of SEQ ID NO: 1, or amino acids 1 to 118 of SEQ ID NO: 1.

[0176] The corresponding amino acid sequence of the costimulatory domain is set forth in SEQ ID NO. 241:
LDNEKSNGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVR
SKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS

[0177] In some embodiments, the costimulatory domain comprises, consists essentially of, or consists of a nucleotide sequence at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence of SEQ ID NO: 241, wherein the costimulatory domain does not comprises amino acids 1 to 122 of SEQ ID NO: 1, amino acids 1 to 121 of SEQ ID NO: 1, amino acids 1 to 120 of SEQ ID NO: 1, amino acids 1 to 119 of SEQ ID NO: 1, amino acids 1 to 118 of SEQ ID NO: 1, or amino acids 1 to 118 of SEQ ID NO: 1.

I.B. Activating Domain.

[0178] 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 one embodiment, the CD3 is CD3 zeta, the nucleotide sequence of which is set forth in SEQ ID NO. 8:
AGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAAC
CAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGAC
AAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCC
CCAGGAGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTC
TGAAATAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGT

ACCAGGGACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAG CCCTGCCACCTAGG

[0179] In some embodiments, the polynucleotide encoding an activating domain comprises a nucleotide sequence at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the nucleotide sequence of SEQ ID NO: 8.

[0180] The corresponding amino acid of intracellular CD3 zeta is set forth in SEQ ID NO. 9:

RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQ EGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALP PR

[0181] In some embodiments, the activating domain comprises a nucleotide sequence at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence of SEQ ID NO: 9.

[0182] In some embodiments, the activating domain comprises an amino acid sequence at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the amino acid sequence of:

RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQ EGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALP PR (SEQ ID NO: 251).

I.C. Antigen Binding Molecules

[0183] 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. In some embodiments, the antigen binding molecule is an antibody fragment thereof, e.g., 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 useful 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.

[0184] In some embodiments, the polynucleotide encodes a CAR or a TCR comprising a THD of the present invention and an antigen binding molecule that specifically binds to a target antigen. In some embodiments, the target antigen is a tumor antigen. In some embodiments, the antigen is selected from a tumor-associated surface antigen, such as 5T4, alphafetoprotein (AFP), B7-1 (CD80), B7-2 (CD86), BCMA, B-human chorionic gonadotropin, CA-125, carcinoembryonic antigen (CEA), carcinoembryonic antigen (CEA), CD123, CD133, CD138, CD19, CD20, CD22, CD23, CD24, CD25, CD30, CD33, CD34, CD4, CD40, CD44, CD56, CD8, CLL-1, c-Met, CMV-specific antigen, CSPG4, CTLA-4, disialoganglioside GD2, ductal-epithelial mucine, EBV-specific antigen, EGFR variant III (EGFRvIII), ELF2M, endoglin, ephrin B2, epidermal growth factor receptor (EGFR), epithelial cell adhesion molecule (EpCAM), epithelial tumor antigen, ErbB2 (HER2/neu), fibroblast associated protein (fap), FLT3, folate binding protein, GD2, GD3, glioma-associated antigen, glycosphingolipids, gp36, HBV- specific antigen, HCV-specific antigen, HER1-HER2, HER2-HER3 in combination, HERV-K, high molecular weight-melanoma associated antigen (HMW-MAA), HIV-1 envelope glycoprotein gp41, HPV-specific antigen, human telomerase reverse transcriptase, IGFI receptor, IGF-II, IL-11Ralpha, IL-13R-a2, Influenza Virus-specific antigen; CD38, insulin growth factor (IGFl)-l, intestinal carboxyl esterase, kappa chain, LAGA-la, lambda chain, Lassa Virus-specific antigen, lectin-reactive AFP, lineage-specific or tissue specific antigen such as CD3, MAGE, MAGE-A1, major histocompatibility complex (MHC) molecule, major histocompatibility complex (MHC) molecule presenting a tumor-specific peptide epitope, M-CSF, melanoma-associated antigen, mesothelin, mesothelin, MN-CA IX, MUC-1, mut hsp70-2, mutated p53, mutated p53, mutated ras, neutrophil elastase, NKG2D, Nkp30, NY-ESO-1, p53, PAP, prostase, prostase specific antigen (PSA), prostate-carcinoma tumor antigen-1 (PCTA-1), prostate-specific antigen, prostein, PSMA, RAGE-1, ROR1, RU1, RU2 (AS), surface adhesion molecule, surviving and telomerase, TAG-72, the extra domain A (EDA) and extra domain B (EDB) of fibronectin and the Al domain of tenascin-

C (TnC Al) , thyroglobulin, tumor stromal antigens, vascular endothelial growth factor receptor-2 (VEGFR2), virus-specific surface antigen such as an HIV-specific antigen (such as HIV gpl20), as well as any derivate or variant of these surface markers. In certain embodiments, the antigen binding molecule specifically binds to BCMA. In other embodiments, the antigen binding molecule specifically binds to CLL-1. In other embodiments, the antigen binding molecule specifically binds to FLT3.

[0185] In some embodiments, the antigen binding molecule specifically binds BCMA. In certain embodiments, the antigen binding molecule comprises (a) a VH CDR1 comprising an amino acid sequence selected from SEQ ID NOs: 13-20; (b) a VH CDR2 comprising an amino acid sequence selected from SEQ ID NOs: 21-28; (c) a VH CDR3 comprising an amino acid sequence selected from SEQ ID NOs: 29-36; (d) a VL CDR1 comprising an amino acid sequence selected from SEQ ID NOs: 37-44; (e) a VL CDR2 comprising an amino acid sequence selected from SEQ ID NOs: 45-52; and/or (f) a VL CDR3 comprising an amino acid sequence selected from SEQ ID NOs: 53-60.

[0186] In one embodiment, the antigen binding molecule comprises (a) a VH CDR1 comprising an amino acid of SEQ ID NO: 13; (b) a VH CDR2 comprising an amino acid sequence of SEQ ID NO: 21; (c) a VH CDR3 comprising an amino acid sequence of SEQ ID NO: 29; (d) a VL CDR1 comprising an amino acid sequence of SEQ ID NO: 37; (e) a VL CDR2 comprising an amino acid sequence of SEQ ID NO: 45; and/or (f) a VL CDR3 comprising an amino acid sequence of SEQ ID NO: 53.

[0187] In another embodiment, the antigen binding molecule comprises (a) a VH CDR1 comprising an amino acid of SEQ ID NO: 14; (b) a VH CDR2 comprising an amino acid sequence of SEQ ID NO: 22; (c) a VH CDR3 comprising an amino acid sequence of SEQ ID NO: 30; (d) a VL CDR1 comprising an amino acid sequence of SEQ ID NO: 38; (e) a VL CDR2 comprising an amino acid sequence of SEQ ID NO: 46; and/or (f) a VL CDR3 comprising an amino acid sequence of SEQ ID NO: 54.

[0188] In another embodiment, the antigen binding molecule comprises (a) a VH CDR1 comprising an amino acid of SEQ ID NO: 15; (b) a VH CDR2 comprising an amino acid sequence of SEQ ID NO: 23; (c) a VH CDR3 comprising an amino acid sequence of SEQ ID NO: 31; (d) a VL CDR1 comprising an amino acid sequence of SEQ ID NO: 39; (e) a VL CDR2 comprising an amino acid sequence of SEQ ID NO: 47; and/or (f) a VL CDR3 comprising an amino acid sequence of SEQ ID NO: 55.

[0189] In another embodiment, the antigen binding molecule comprises (a) a VH CDR1 comprising an amino acid of SEQ ID NO: 16; (b) a VH CDR2 comprising an amino acid sequence of SEQ ID NO: 24; (c) a VH CDR3 comprising an amino acid sequence of SEQ ID NO: 32; (d) a VL CDR1 comprising an amino acid sequence of SEQ ID NO: 40; (e) a VL CDR2 comprising an amino acid sequence of SEQ ID NO: 48; and/or (f) a VL CDR3 comprising an amino acid sequence of SEQ ID NO: 56.

[0190] In another embodiment, the antigen binding molecule comprises (a) a VH CDR1 comprising an amino acid of SEQ ID NO: 17; (b) a VH CDR2 comprising an amino acid sequence of SEQ ID NO: 25; (c) a VH CDR3 comprising an amino acid sequence of SEQ ID NO: 33; (d) a VL CDR1 comprising an amino acid sequence of SEQ ID NO: 41; (e) a VL CDR2 comprising an amino acid sequence of SEQ ID NO: 49; and/or (f) a VL CDR3 comprising an amino acid sequence of SEQ ID NO: 57.

[0191] In another embodiment, the antigen binding molecule comprises (a) a VH CDR1 comprising an amino acid of SEQ ID NO: 18; (b) a VH CDR2 comprising an amino acid sequence of SEQ ID NO: 26; (c) a VH CDR3 comprising an amino acid sequence of SEQ ID NO: 34; (d) a VL CDR1 comprising an amino acid sequence of SEQ ID NO: 42; (e) a VL CDR2 comprising an amino acid sequence of SEQ ID NO: 50; and/or (f) a VL CDR3 comprising an amino acid sequence of SEQ ID NO: 58.

[0192] In another embodiment, the antigen binding molecule comprises (a) a VH CDR1 comprising an amino acid of SEQ ID NO: 19; (b) a VH CDR2 comprising an amino acid sequence of SEQ ID NO: 27; (c) a VH CDR3 comprising an amino acid sequence of SEQ ID NO: 35; (d) a VL CDR1 comprising an amino acid sequence of SEQ ID NO: 43; (e) a VL CDR2 comprising an amino acid sequence of SEQ ID NO: 51; and/or (f) a VL CDR3 comprising an amino acid sequence of SEQ ID NO: 59.

[0193] In another embodiment, the antigen binding molecule comprises (a) a VH CDR1 comprising an amino acid of SEQ ID NO: 20; (b) a VH CDR2 comprising an amino acid sequence of SEQ ID NO: 28; (c) a VH CDR3 comprising an amino acid sequence of SEQ ID NO: 36; (d) a VL CDR1 comprising an amino acid sequence of SEQ ID NO: 44; (e) a VL CDR2 comprising an amino acid sequence of SEQ ID NO: 52; and/or (f) a VL CDR3 comprising an amino acid sequence of SEQ ID NO: 60.

[0194] In certain embodiments, the antigen binding molecule comprises a VH comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 77-84 and a VL comprising an amino acid sequence selected from the group consisting of SEQ ID

NOs: 85-92. In one embodiment, the antigen binding molecule comprises a VH comprising an amino acid sequence of SEQ ID NO: 77 and a VL comprising an amino acid sequence of SEQ ID NO: 85. In another embodiment, the antigen binding molecule comprises a VH comprising an amino acid sequence of SEQ ID NO: 78 and a VL comprising an amino acid sequence of SEQ ID NO: 86. In another embodiment, the antigen binding molecule comprises a VH comprising an amino acid sequence of SEQ ID NO: 79 and a VL comprising an amino acid sequence of SEQ ID NO: 87. In another embodiment, the antigen binding molecule comprises a VH comprising an amino acid sequence of SEQ ID NO: 80 and a VL comprising an amino acid sequence of SEQ ID NO: 88. In another embodiment, the antigen binding molecule comprises a VH comprising an amino acid sequence of SEQ ID NO: 81 and a VL comprising an amino acid sequence of SEQ ID NO: 89. In another embodiment, the antigen binding molecule comprises a VH comprising an amino acid sequence of SEQ ID NO: 82 and a VL comprising an amino acid sequence of SEQ ID NO: 90. In another embodiment, the antigen binding molecule comprises a VH comprising an amino acid sequence of SEQ ID NO: 83 and a VL comprising an amino acid sequence of SEQ ID NO: 91. In another embodiment, the antigen binding molecule comprises a VH comprising an amino acid sequence of SEQ ID NO: 84 and a VL comprising an amino acid sequence of SEQ ID NO: 92.

[0195] In one particular embodiment, the polynucleotide of the present invention comprises a nucleotide sequence at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to a nucleotide sequence selected form the group consisting of SEQ ID NOs: 61-68. In another embodiment, the polynucleotide of the present invention comprises a nucleotide sequence at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to a nucleotide sequence selected form the group consisting of SEQ ID NOs: 69-76.

[0196] Other known anti-BCMA antibodies or antigen binding molecules thereof can be used as antigen binding molecules of a CAR or TCR comprising a THD of the present invention. Non-limiting examples of such BCMA antibodies or antigen binding molecule thereof include antibodies or antigen binding molecules described in WO2015158671A1, published October 22, 2015 and WO2016014565A2, published January 28, 2016.

[0197] In some embodiments, the antigen binding molecule specifically binds CLL-1. In certain embodiments, the antigen binding molecule comprises (a) a VH CDR1 comprising

an amino acid sequence selected from SEQ ID NOs: 93-96; (b) a VH CDR2 comprising an amino acid sequence selected from SEQ ID NOs: 97-100; (c) a VH CDR3 comprising an amino acid sequence selected from SEQ ID NOs: 101-104; (d) a VL CDR1 comprising an amino acid sequence selected from SEQ ID NOs: 105-108; (e) a VL CDR2 comprising an amino acid sequence selected from SEQ ID NOs: 109-112; and/or (f) a VL CDR3 comprising an amino acid sequence selected from SEQ ID NOs: 113-116.

[0198] In one embodiment, the antigen binding molecule comprises (a) a VH CDR1 comprising an amino acid of SEQ ID NO: 93; (b) a VH CDR2 comprising an amino acid sequence of SEQ ID NO: 97; (c) a VH CDR3 comprising an amino acid sequence of SEQ ID NO: 101; (d) a VL CDR1 comprising an amino acid sequence of SEQ ID NO: 105; (e) a VL CDR2 comprising an amino acid sequence of SEQ ID NO: 109; and/or (f) a VL CDR3 comprising an amino acid sequence of SEQ ID NO: 113.

[0199] In one embodiment, the antigen binding molecule comprises (a) a VH CDR1 comprising an amino acid of SEQ ID NO: 94; (b) a VH CDR2 comprising an amino acid sequence of SEQ ID NO: 98; (c) a VH CDR3 comprising an amino acid sequence of SEQ ID NO: 102; (d) a VL CDR1 comprising an amino acid sequence of SEQ ID NO: 106; (e) a VL CDR2 comprising an amino acid sequence of SEQ ID NO: 110; and/or (f) a VL CDR3 comprising an amino acid sequence of SEQ ID NO: 114.

[0200] In one embodiment, the antigen binding molecule comprises (a) a VH CDR1 comprising an amino acid of SEQ ID NO: 95; (b) a VH CDR2 comprising an amino acid sequence of SEQ ID NO: 99; (c) a VH CDR3 comprising an amino acid sequence of SEQ ID NO: 103; (d) a VL CDR1 comprising an amino acid sequence of SEQ ID NO: 107; (e) a VL CDR2 comprising an amino acid sequence of SEQ ID NO: 111; and/or (f) a VL CDR3 comprising an amino acid sequence of SEQ ID NO: 115.

[0201] In one embodiment, the antigen binding molecule comprises (a) a VH CDR1 comprising an amino acid of SEQ ID NO: 96; (b) a VH CDR2 comprising an amino acid sequence of SEQ ID NO: 100; (c) a VH CDR3 comprising an amino acid sequence of SEQ ID NO: 104; (d) a VL CDR1 comprising an amino acid sequence of SEQ ID NO: 108; (e) a VL CDR2 comprising an amino acid sequence of SEQ ID NO: 112; and/or (f) a VL CDR3 comprising an amino acid sequence of SEQ ID NO: 116.

[0202] In certain embodiments, the antigen binding molecule comprises a VH comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 125-128 and a VL comprising an amino acid sequence selected from the group consisting of SEQ

ID NOs: 129-132. In one embodiment, the antigen binding molecule comprises a VH comprising an amino acid sequence of SEQ ID NO: 125 and a VL comprising an amino acid sequence of SEQ ID NO: 129. In another embodiment, the antigen binding molecule comprises a VH comprising an amino acid sequence of SEQ ID NO: 126 and a VL comprising an amino acid sequence of SEQ ID NO: 130. In another embodiment, the antigen binding molecule comprises a VH comprising an amino acid sequence of SEQ ID NO: 127 and a VL comprising an amino acid sequence of SEQ ID NO: 131. In another embodiment, the antigen binding molecule comprises a VH comprising an amino acid sequence of SEQ ID NO: 128 and a VL comprising an amino acid sequence of SEQ ID NO: 132.

[0203] In one particular embodiment, the polynucleotide of the present invention comprises a nucleotide sequence at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to a nucleotide sequence selected form the group consisting of SEQ ID NOs: 117-120. In another embodiment, the polynucleotide of the present invention comprises a nucleotide sequence at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to a nucleotide sequence selected form the group consisting of SEQ ID NOs: 121-124.

[0204] Other examples of anti-CLL-1 antibodies or antigen binding molecules thereof include antibodies or antigen binding molecules described in WO2016014535, published January 28, 2016, and US 2016/0051651 A1, published Feb. 25, 2016.

[0205] The antigen binding molecule encoded by the polynucleotide of the present invention can be single chained or double chained. In some embodiments, the antigen binding molecule is single chained. In certain embodiments, the antigen binding molecule is selected from the group consisting of an scFv, an Fab, an Fab', an Fv, an F(ab')2, a dAb, and any combination thereof. In one particular embodiment, the antigen binding molecule comprises an scFv.

[0206] In certain embodiments, the antigen binding molecule comprises a single chain, wherein the heavy chain variable region and the light chain variable region are connected by a linker. In some embodiments, the VH is located at the N terminus of the linker and the VL is located at the C terminus of the linker. In other embodiments, the VL is located at the N terminus of the linker and the VH is located at the C terminus of the linker. In some

embodiments, the linker comprises at least about 5, at least about 8, at least about 10, at least about 13, at least about 15, at least about 18, at least about 20, at least about 25, at least about 30, at least about 35, at least about 40, at least about 45, at least about 50, at least about 60, at least about 70, at least about 80, at least about 90, or at least about 100 amino acids. In some embodiments, the linker comprises at least about 18 amino acids. In certain embodiments, the linker comprises an amino acid sequence that is at least about 75%, at least about 85%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to the amino acid sequence GSTSGSGKPGSGEGSTKG (SEQ ID NO: 12) or the amino acid sequence GGGGSGGGGSGGGGS (SEQ ID NO: 237). In one embodiment, the linker is a Whitlow linker. In certain embodiments, the binding molecule comprises a single chain, wherein the heavy chain variable region and the light chain variable region are connected by a linker, wherein the linker comprises the amino acid sequence of SEQ ID NO: 12.

[0207] In some embodiments, the antigen binding molecule binds a target antigen (*e.g.*, human BCMA, human FLT3, or human CLL-1) with a K_D of less than 1 x 10^{-6} M, less than 1 x 10^{-7} M, less than 1 x 10^{-8} M, or less than 1 x 10^{-9} M. In one particular embodiment, the antigen binding molecule binds a target antigen (*e.g.*, human BCMA, human FLT3, or human CLL-1) with a K_D of less than 1 x 10^{-7} M. In another embodiment, the antigen binding molecule binds a target antigen (*e.g.*, human BCMA, human FLT3, or human CLL-1) with a K_D of less than 1 x 10^{-8} M. In some embodiments, the antigen binding molecule binds a target antigen (*e.g.*, human BCMA, human FLT3, or human CLL-1) with a K_D of about 1 x 10^{-7} M, about 2 x 10^{-7} M, about 3 x 10^{-7} M, about 4 x 10^{-7} M, about 5 x 10^{-7} M, about 6 x 10^{-7} M, about 7 x 10^{-7} M, about 8 x 10^{-7} M, about 9 x 10^{-7} M, about 1 x 10^{-8} M, about 2 x 10^{-8} M, about 3 x 10^{-8} M, about 4 x 10^{-8} M, about 5 x 10^{-8} M, about 6 x 10^{-8} M, about 7 x 10^{-8} M, about 8 x 10^{-8} M, about 9 x 10^{-8} M, about 1 x 10^{-9} M, about 2 x 10^{-9} M, about 3 x 10^{-9} M, about 4 x 10^{-9} M, about 5 x 10^{-9} M, about 6 x 10^{-9} M, about 7 x 10^{-9} M, about 8 x 10^{-9} M, about 9 x 10^{-9} M, about 1 x 10^{-10} M, or about 5 x 10^{-10} M. In certain embodiments, the K_D is calculated as the quotient of k_{off}/k_{on}, and the k_{on} and k_{off} are determined using a monovalent antibody, such as a Fab fragment, as measured by, *e.g.*, BIAcore® surface plasmon resonance technology. In other embodiments, the K_D is calculated as the quotient of k_{off}/k_{on}, and the k_{on} and k_{off} are determined using a bivalent antibody, such as a Fab fragment, as measured by, *e.g.*, BIAcore® surface plasmon resonance technology.

[0208] In some embodiments, the antigen binding molecule binds a target antigen (*e.g.*, human BCMA, human FLT3, or human CLL-1) with an association rate (k_{on}) of less than 1 x 10^{-4} M^{-1} s^{-1}, less than 2 x 10^{-4} M^{-1} s^{-1}, less than 3 x 10^{-4} M^{-1} s^{-1}, less than 4 x 10^{-4} M^{-1} s^{-1}, less than 5 x 10^{-4} M^{-1} s^{-1}, less than 6 x 10^{-4} M^{-1} s^{-1}, less than 7 x 10^{-4} M^{-1} s^{-1}, less than 8 x 10^{-4} M^{-1} s^{-1}, less than 9 x 10^{-4} M^{-1} s^{-1}, less than 1 x 10^{-5} M^{-1} s^{-1}, less than 2 x 10^{-5} M^{-1} s^{-1}, less than 3 x 10^{-5} M^{-1} s^{-1}, less than 4 x 10^{-5} M^{-1} s^{-1}, less than 5 x 10^{-5} M^{-1} s^{-1}, less than 6 x 10^{-5} M^{-1} s^{-1}, less than 7 x 10^{-5} M^{-1} s^{-1}, less than 8 x 10^{-5} M^{-1} s^{-1}, less than 9 x 10^{-5} M^{-1} s^{-1}, less than 1 x 10^{-6} M^{-1} s^{-1}, less than 2 x 10^{-6} M^{-1} s^{-1}, less than 3 x 10^{-6} M^{-1} s^{-1}, less than 4 x 10^{-6} M^{-1} s^{-1}, less than 5 x 10^{-6} M^{-1} s^{-1}, less than 6 x 10^{-6} M^{-1} s^{-1}, less than 7 x 10^{-6} M^{-1} s^{-1}, less than 8 x 10^{-6} M^{-1} s^{-1}, less than 9 x 10^{-6} M^{-1} s^{-1}, or less than 1 x 10^{-7} M^{-1} s^{-1}. In certain embodiments, the k_{on} is determined using a monovalent antibody, such as a Fab fragment, as measured by, *e.g.*, BIAcore® surface plasmon resonance technology. In other embodiments, the k_{on} is determined using a bivalent antibody as measured by, *e.g.*, BIAcore® surface plasmon resonance technology.

[0209] In some embodiments, the antigen binding molecule binds a target antigen (*e.g.*, human BCMA, human FLT3, or human CLL-1) with an dissociation rate (k_{off}) of less than 1 x 10^{-2} s^{-1}, less than 2 x 10^{-2} s^{-1}, less than 3 x 10^{-2} s^{-1}, less than 4 x 10^{-2} s^{-1}, less than 5 x 10^{-2} s^{-1}, less than 6 x 10^{-2} s^{-1}, less than 7 x 10^{-2} s^{-1}, less than 8 x 10^{-2} s^{-1}, less than 9 x 10^{-2} s^{-1}, less than 1 x 10^{-3} s^{-1}, less than 2 x 10^{-3} s^{-1}, less than 3 x 10^{-3} s^{-1}, less than 4 x 10^{-3} s^{-1}, less than 5 x 10^{-3} s^{-1}, less than 6 x 10^{-3} s^{-1}, less than 7 x 10^{-3} s^{-1}, less than 8 x 10^{-3} s^{-1}, less than 9 x 10^{-3} s^{-1}, less than 1 x 10^{-4} s^{-1}, less than 2 x 10^{-4} s^{-1}, less than 3 x 10^{-4} s^{-1}, less than 4 x 10^{-4} s^{-1}, less than 5 x 10^{-4} s^{-1}, less than 6 x 10^{-4} s^{-1}, less than 7 x 10^{-4} s^{-1}, less than 8 x 10^{-4} s^{-1}, less than 9 x 10^{-4} s^{-1}, less than 1 x 10^{-4} s^{-1}, or less than 5 x 10^{-4} s^{-1}. In certain embodiments, the k_{off} is determined using a monovalent antibody, such as a Fab fragment, as measured by, *e.g.*, BIAcore® surface plasmon resonance technology. In other embodiments, the k_{off} is determined using a bivalent antibody as measured by, *e.g.*, BIAcore® surface plasmon resonance technology.

[0210] In some embodiments, the polynucleotide encodes a TCR, wherein the TCR further comprises a fourth complementarity determining region (CDR4). In certain embodiments, the polynucleotide encodes a TCR, wherein the TCR further comprises a constant region. In some embodiments, the constant region is selected from a constant region of IgG1, IgG2, IgG3, IgG4, IgA, IgD, IgE, and IgM.

I.D. Switch Domain

[0211] 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.

[0212] In accordance with the invention, additional 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.

I.E. Leader Peptide

[0213] In some embodiments, the polynucleotide of the present invention encodes a CAR or a TCR can further comprises a leader peptide (also referred to herein as a "signal peptide"). In certain embodiments, the leader peptide comprises an amino acid sequence that is at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to the amino acid sequence MALPVTALLLPLALLLHAARP (SEQ ID NO: 11). In some embodiments, the leader peptide comprises the amino acid sequence of SEQ ID NO: 11.

[0214] In some embodiments, the polynucleotide of the present invention encodes a CAR or a TCR, wherein the CAR or the TCR comprises a leader peptide (P), an antigen binding molecule (B), a costimulatory protein's extracellular domain (E), a transmembrane domain (T), a costimulatory region (C), and an activation domain (A), wherein the CAR is configured according to the following: P-B-E-T-C-A. In some embodiments, the antigen binding molecule comprises a VH and a VL, wherein the CAR is configured according to the following: P-VH-VL-E-T-C-A or P-VL-VH-E-T-C-A. In some embodiments, the VH and the VL are connected by a linker (L), wherein the CAR is configured according to the following, from N-terminus to C-terminus: P-VH-L-VL-E-T-C-A or P-VH-L-VL-E-T-C-A.

[0215] In some embodiments, the polynucleotide of the present invention encodes a CAR, wherein the CAR comprises an amino acid sequence at least about 75%, at least about 85%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to an amino acid sequence selected from Table 2. In certain embodiments, the polynucleotide of the present invention encodes a CAR, wherein the CAR comprises an amino acid sequence selected from Table 2.

[0216] Table 2. Example CAR Sequences

CAR Construct	Nucleotide Sequence	SEQ ID NO:	Amino Acid Sequence	SEQ ID NO:
10E3_CHD	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTGACCCTCAAAGAGTCTGGA CCCGTGCTCGTAAAACCTACGGAGACCCT GACACTCACCTGCACAGTCTCCGGCTTCA GCCTCATCAATGCCAGGATGGGAGTTTCC TGGATCAGGCAACCGCCCGGAAAGGCCCT GGAATGGCTCGCACATATTTTCAGTAACG CTGAAAAAAGCTATCGGACTTCTCTGAAA AGTCGGCTCACGATTAGTAAGGACACATC CAAGAGCCAAGTGGTGCTTACGATGACTA ACATGGACCCTGTGGATACTGCAACCTAT TACTGTGCTCGAATCCCTGGTTATGGCGG AAATGGGGACTACCACTACTACGGTATGG ATGTCTGGGGCCAAGGGACCACGGTTACT GTTTCAAGCGGAGGGGGAGGGAGTGGGGG TGGCGGATCTGGCGGAGGAGGCAGCGATA TCCAGATGACGCAGTCCCCTAGTTCACTT TCCGCATCCCTGGGGGATCGGGTTACCAT TACATGCCGCGCGTCACAGGGTATCCGGA ATGATCTGGGATGGTACCAGCAGAAGCCG GGAAAGGCTCCTAAGCGCCTCATCTACGC CAGCTCCACCCTGCAGAGTGGAGTGCCCT CCCGGTTTTCAGGCAGTGGCTCCGGTACG GAGTTTACTCTTACAATTAGCAGCCTGCA GCCAGAAGATTTTGCAACTTACTACTGTT	242	MALPVTALLLPLALLL HAARPQVTLKESGPVL VKPTETLTLTCTVSGF SLINARMGVSWIRQPP GKALEWLAHIFSNAEK SYRTSLKSRLTISKDT SKSQVVLTMTNMDPVD TATYYCARIPGYGGNG DYHYYGMDVWGQGTTV TVSSGGGGSGGGGSGG GGSDIQMTQSPSSLSA SLGDRVTITCRASQGI RNDLGWYQQKPGKAPK RLIYASSTLQSGVPSR FSGSGSGTEFTLTISS LQPEDFATYYCLQHNN FPWTFGQGTKVEIKRA AAIEVMYPPPYLDNEK SNGTIIHVKGKHLCPS PLFPGPSKPFWVLVVV GGVLACYSLLVTVAFI IFWVRSKRSRLLHSDY MNMTPRRPGPTRKHYQ PYAPPRDFAAYRSRVK FSRSADAPAYQQGQNQ LYNELNLGRREEYDVL	243

	TGCAGCATAATAATTTCCCCTGGACCTTT GGTCAGGGCACCAAGGTGGAGATCAAAAG AGCAGCCGCCATCGAAGTAATGTATCCCC CCCCGTACCTTGACAATGAGAAGTCAAAT GGAACCATTATCCATGTTAAGGGCAAACA CCTCTGCCCTTCTCCACTGTTCCCTGGCC CTAGTAAGCCGTTTTGGGTGCTGGTGGTA GTCGGTGGGGTGCTGGCTTGTTACTCTCT TCTCGTGACCGTCGCCTTTATAATCTTTT GGGTCAGATCCAAAAGAAGCCGCCTGCTC CATAGCGATTACATGAATATGACTCCACG CCGCCCTGGCCCCACAAGGAAACACTACC AGCCTTACGCACCACCTAGAGATTTCGCT GCCTATCGGAGCCGAGTGAAATTTTCTAG ATCAGCTGATGCTCCCGCCTATCAGCAGG GACAGAATCAACTTTACAATGAGCTGAAC CTGGGTCGCAGAGAAGAGTACGACGTTTT GGACAAACGCCGGGGCCGAGATCCTGAGA TGGGGGGGAAGCCGAGAAGGAAGAATCCT CAAGAAGGCCTGTACAACGAGCTTCAAAA AGACAAAATGGCTGAGGCGTACTCTGAGA TCGGCATGAAGGGCGAGCGGAGACGAGGC AAGGGTCACGATGGCTTGTATCAGGGCCT GAGTACAGCCACAAAGGACACCTATGACG CCCTCCACATGCAGGCACTGCCCCCACGC TAG		DKRRGRDPEMGGKPRR KNPQEGLYNELQKDKM AEAYSEIGMKGERRRG KGHDGLYQGLSTATKD TYDALHMQALPPR	
10E3_THD	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAAGTTACTTTGAAGGAGTCTGGA CCTGTACTGGTGAAGCCAACCGAGACACT GACACTCACGTGTACAGTGAGTGGTTTTT CCTTGATCAACGCAAGGATGGGCGTCAGC TGGATCAGGCAACCCCCTGGCAAGGCTCT GGAATGGCTCGCTCACATATTCAGCAATG CCGAAAAAAGCTACCGGACAAGCCTGAAA TCCCGCCTGACTATTTCCAAGGACACTTC TAAGTCTCAGGTGGTGCTGACCATGACCA ACATGGACCCGGTGGACACCGCCACCTAT TACTGCGCAAGAATCCCTGGGTATGGTGG GAATGGTGACTACCATTATTATGGGATGG ATGTGTGGGGGCAAGGCACAACCGTAACG GTCTCAAGCGGTGGGGGAGGCTCAGGGGG CGGAGGCTCCGGAGGTGGCGGCTCCGACA TTCAGATGACCCAAAGCCCGTCCAGCCTG TCCGCCAGCCTGGGAGATAGAGTGACAAT CACGTGTAGAGCTTCCCAAGGGATAAGAA ATGATCTCGGGTGGTATCAGCAGAAGCCC GGCAAAGCCCCCAAAAGGCTTATATATGC TAGTAGTACACTGCAGTCTGGAGTTCCTT CCCGATTTTCAGGTAGCGGCTCCGGTACA GAGTTCACCCTCACGATAAGCTCACTCCA GCCTGAGGATTTCGCAACGTACTACTGCC TCCAGCACAACAATTTTCCCTGGACTTTC GGCCAGGGCACCAAGGTGGAGATCAAGAG GGCCGCTGCCCTTGATAATGAAAAGTCAA ACGGAACAATCATTCACGTGAAGGGCAAG CACCTCTGTCCGTCACCCTTGTTCCCTGG TCCATCCAAGCCATTCTGGGTGTTGGTCG TAGTGGGTGGAGTCCTCGCTTGTTACTCT	244	MALPVTALLLPLALLL HAARPQVTLKESGPVL VKPTETLTLTCTVSGF SLINARMGVSWIRQPP GKALEWLAHIFSNAEK SYRTSLKSRLTISKDT SKSQVVLTMTNMDPVD TATYYCARIPGYGGNG DYHYYGMDVWGQGTTV TVSSGGGGSGGGGSGG GGSDIQMTQSPSSLSA SLGDRVTITCRASQGI RNDLGWYQQKPGKAPK RLIYASSTLQSGVPSR FSGSGSGTEFTLTISS LQPEDFATYYCLQHNN FPWTFGQGTKVEIKRA AALDNEKSNGTIIHVK GKHLCPSPLFPGPSKP FWVLVVVGGVLACYSL LVTVAFIIFWVRSKRS RLLHSDYMNMTPRRPG PTRKHYQPYAPPRDFA AYRSRVKFSRSADAPA YQQGQNQLYNELNLGR REEYDVLDKRRGRDPE MGGKPRRKNPQEGLYN ELQKDKMAEAYSEIGM KGERRRGKGHDGLYQG LSTATKDTYDALHMQA LPPR	245

	CTGCTCGTCACCGTGGCTTTTATAATCTT CTGGGTTAGATCCAAAAGAAGCCGCCTGC TCCATAGCGATTACATGAATATGACTCCA CGCCGCCCTGGCCCCACAAGGAAACACTA CCAGCCTTACGCACCACCTAGAGATTTCG CTGCCTATCGGAGCCGAGTGAAATTTTCT AGATCAGCTGATGCTCCCGCCTATCAGCA GGGACAGAATCAACTTTACAATGAGCTGA ACCTGGGTCGCAGAGAAGAGTACGACGTT TTGGACAAACGCCGGGGCCGAGATCCTGA GATGGGGGGGAAGCCGAGAAGGAAGAATC CTCAAGAAGGCCTGTACAACGAGCTTCAA AAAGACAAAATGGCTGAGGCGTACTCTGA GATCGGCATGAAGGGCGAGCGGAGACGAG GCAAGGGTCACGATGGCTTGTATCAGGGC CTGAGTACAGCCACAAAGGACACCTATGA CGCCCTCCACATGCAGGCACTGCCCCCAC GCTAG			
8B5_CHD	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGATCCAGTTGGTGGAATCAGGG GGCGGTGTGGTGCAGCCGGGTAGGAGCCT GAGACTGTCATGCGTGGCGTCTGGCTTCA CATTCAAGAACTACGGCATGCACTGGGTG CGACAGGCCCCCGGAAAGGGTTTGGAGTG GGTCGCCGTGATCTGGTACGACGGATCTA ATGAGTATTACGGAGATCCTGTGAAGGGA AGGTTCACCATCTCCCGCGACAATAGCAA AAATATGCTCTACCTGCAAATGAACTCAC TCAGGGCGGATGATACGGCGGTCTACTAT TGCGCTCGCTCAGGGATTGCTGTGGCCGG CGCATTCGATTACTGGGGACAGGGTACCC TGGTGACAGTATCAAGCGGAGGCGGCGGC TCTGGCGGCGGCGGATCTGGCGGGGGGGG AAGTGAGATTGTGTTGACACAGTCTCCCG ATACCCTGTCACTGTCACCCGGCGAGAAG GCAACGCTGAGTTGCAGAGCAAGCCAGTC AGTCTCCTCTTCTTTTCTGGCCTGGTATC AGCAAAAACCAGGTCAGGCACCATCTCTC CTGATTTACGTTGCCAGCAGACGGGCGGC TGGCATTCCCGACAGGTTCTCTGGAAGCG GATCTGGGACCGATTTTACCCTGACAATT AGCCGCTTGGAGCCCGAAGACTTTGGTAT GTTTTACTGCCAGCACTACGGAAGGACAC CTTTCACATTTGGCCCGGGCACGAAAGTC GATATAAAACGCGCAGCCGCCATTGAAGT AATGTACCCACCACCTTATTTGGACAATG AAAAGTCCAATGGTACCATTATTCACGTC AAGGGAAAGCATCTCTGTCCAAGCCCTCT GTTCCCCGGCCCCTCCAAACCATTCTGGG TGCTGGTGGTCGTCGGCGGAGTTCTGGCC TGCTATTCTCTGCTCGTGACTGTTGCATT CATCATTTTCTGGGTGAGATCCAAAAGAA GCCGCCTGCTCCATAGCGATTACATGAAT ATGACTCCACGCCGCCCTGGCCCCACAAG GAAACACTACCAGCCTTACGCACCACCTA GAGATTTCGCTGCCTATCGGAGCCGAGTG AAATTTTCTAGATCAGCTGATGCTCCCGC CTATCAGCAGGGACAGAATCAACTTTACA	246	MALPVTALLLPLALLL HAARPQIQLVESGGGV VQPGRSLRLSCVASGF TFKNYGMHWVRQAPGK GLEWVAVIWYDGSNEY YGDPVKGRFTISRDNS KNMLYLQMNSLRADDT AVYYCARSGIAVAGAF DYWGQGTLVTVSSGGG GSGGGGSGGGGSEIVL TQSPDTLSLSPGEKAT LSCRASQSVSSSFLAW YQQKPGQAPSLLIYVA SRRAAGIPDRFSGSGS GTDFTLTISRLEPEDF GMFYCQHYGRTPFTFG PGTKVDIKRAAAIEVM YPPPYLDNEKSNGTII HVKGKHLCPSPLFPGP SKPFWVLVVVGGVLAC YSLLVTVAFIIFWVRS KRSRLLHSDYMNMTPR RPGPTRKHYQPYAPPR DFAAYRSRVKFSRSAD APAYQQGQNQLYNELN LGRREEYDVLDKRRGR DPEMGGKPRRKNPQEG LYNELQKDKMAEAYSE IGMKGERRRGKGHDGL YQGLSTATKDTYDALH MQALPPR	247

	ATGAGCTGAACCTGGGTCGCAGAGAAGAG TACGACGTTTTGGACAAACGCCGGGGCCG AGATCCTGAGATGGGGGGGAAGCCGAGAA GGAAGAATCCTCAAGAAGGCCTGTACAAC GAGCTTCAAAAAGACAAAATGGCTGAGGC GTACTCTGAGATCGGCATGAAGGGCGAGC GGAGACGAGGCAAGGGTCACGATGGCTTG TATCAGGGCCTGAGTACAGCCACAAAGGA CACCTATGACGCCCTCCACATGCAGGCAC TGCCCCCACGCTAG			
8B5_THD	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGATTCAGCTCGTGGAGTCAGGT GGTGGCGTGGTTCAGCCCGGACGGTCCCT GCGACTCTCTTGTGTGGCAAGCGGATTTA CCTTTAAGAACTATGGCATGCACTGGGTG AGGCAGGCCCCTGGAAAAGGACTGGAGTG GGTTGCTGTGATCTGGTACGACGGGTCCA ACGAATATTATGGCGATCCTGTGAAGGGA CGGTTTACAATCTCACGCGATAACTCAAA GAACATGCTGTACCTGCAAATGAACTCTC TGCGCGCTGATGACACTGCCGTGTATTAT TGCGCTCGGAGTGGTATCGCCGTCGCAGG AGCATTTGATTATTGGGGGCAAGGGACCC TCGTGACAGTGAGTTCCGGAGGGGGAGGT TCTGGTGGAGGCGGCTCTGGTGGGGGAGG CAGCGAGATCGTTCTGACCCAGTCTCCTG ACACACTGTCACTGTCCCCTGGTGAAAAG GCCACACTGTCTTGTAGAGCGTCCCAGAG CGTTTCCAGTTCCTTCCTTGCATGGTATC AACAAAAACCCGGGCAGGCTCCAAGCTTG CTGATCTACGTGGCCAGCCGCCGGGCCGC AGGCATCCCTGATAGGTTTAGCGGTTCTG GGAGCGGGACGGACTTCACCTTGACAATA TCACGGCTGGAACCCGAAGACTTCGGAAT GTTTTATTGCCAGCACTACGGAAGAACTC CATTCACCTTTGGCCCGGGAACGAAGGTA GACATCAAGAGAGCAGCAGCCCTCGACAA CGAGAAATCCAATGGAACCATTATCCATG TGAAGGGGAAACATCTCTGCCCTTCACCA TTGTTCCCTGGACCCAGCAAGCCTTTTTG GGTTCTGGTCGTGGTGGGGGGCGTCCTGG CTTGTTACTCCCTCCTCGTTACAGTCGCC TTCATAATCTTTTGGGTTAGATCCAAAAG AAGCCGCCTGCTCCATAGCGATTACATGA ATATGACTCCACGCCGCCCTGGCCCCACA AGGAAACACTACCAGCCTTACGCACCACC TAGAGATTTCGCTGCCTATCGGAGCCGAG TGAAATTTTCTAGATCAGCTGATGCTCCC GCCTATCAGCAGGGACAGAATCAACTTTA CAATGAGCTGAACCTGGGTCGCAGAGAAG AGTACGACGTTTTGGACAAACGCCGGGGC CGAGATCCTGAGATGGGGGGGAAGCCGAG AAGGAAGAATCCTCAAGAAGGCCTGTACA ACGAGCTTCAAAAAGACAAAATGGCTGAG GCGTACTCTGAGATCGGCATGAAGGGCGA GCGGAGACGAGGCAAGGGTCACGATGGCT TGTATCAGGGCCTGAGTACAGCCACAAAG	248	MALPVTALLLPLALLL HAARPQIQLVESGGGV VQPGRSLRLSCVASGF TFKNYGMHWVRQAPGK GLEWVAVIWYDGSNEY YGDPVKGRFTISRDNS KNMLYLQMNSLRADDT AVYYCARSGIAVAGAF DYWGQGTLVTVSSGGG GSGGGGSGGGGSEIVL TQSPDTLSLSPGEKAT LSCRASQSVSSSFLAW YQQKPGQAPSLLIYVA SRRAAGIPDRFSGSGS GTDFTLTISRLEPEDF GMFYCQHYGRTPFTFG PGTKVDIKRAAALDNE KSNGTIIHVKGKHLCP SPLFPGPSKPFWVLVV VGGVLACYSLLVTVAF IIFWVRSKRSRLLHSD YMNMTPRRPGPTRKHY QPYAPPRDFAAYRSRV KFSRSADAPAYQQGQN QLYNELNLGRREEYDV LDKRRGRDPEMGGKPR RKNPQEGLYNELQKDK MAEAYSEIGMKGERRR GKGHDGLYQGLSTATK DTYDALHMQALPPR	249

	GACACCTATGACGCCCTCCACATGCAGGC ACTGCCCCCACGCTAG			
FS- 21495CARHx L	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGGAGGTGCAGCTGTTGGAGTCTGGG GGAGGCTTGGTACAGCCTGGGGGGTCCCT GAGACTCTCCTGTGCAGCCTCTGGATTCA CCTTTAGCAGCTATGCCATGAGCTGGGTC CGCCAGGCTCCAGGGAAGGGGCTGGAGTG GGTCTCAGCTATTAGTGGTAGTGGTGGTA GCACATACTACGCAGACTCCGTGAAGGGC CGGTTCACCATCTCCAGAGACAATTCCAA GAACACGCTGTATCTGCAAATGAACAGCC TGAGAGCCGAGGACACGGCGGTGTACTAC TGCGCAAGAGCCGAGATGGGAGCCGTATT CGACATATGGGGTCAGGGTACAATGGTCA CCGTCTCCTCAGGGTCTACATCCGGCTCC GGGAAGCCCGGAAGTGGCGAAGGTAGTAC AAAGGGGGAAATTGTGTTGACACAGTCTC CAGCCACCCTGTCTTTGTCTCCAGGGGAA AGAGCCACCCTCTCCTGCAGGGCCAGTCA GAGTGTTAGCAGGTACTTAGCCTGGTACC AACAGAAACCTGGCCAGGCTCCCAGGCTC CTCATCTATGATGCATCCAACAGGGCCAC TGGCATCCCAGCCAGGTTCAGTGGCAGTG GGTCTGGGACAGACTTCACTCTCACCATC AGCAGCCTAGAGCCTGAAGATTTTGCAGT TTATTACTGTCAGCAGAGAATCTCCTGGC CTTTCACTTTTGGCGGAGGGACCAAGGTT GAGATCAAACGGGCCGCTGCCCTTGATAA TGAAAAGTCAAACGGAACAATCATTCACG TGAAGGGCAAGCACCTCTGTCCGTCACCC TTGTTCCCTGGTCCATCCAAGCCATTCTG GGTGTTGGTCGTAGTGGGTGGAGTCCTCG CTTGTTACTCTCTGCTCGTCACCGTGGCT TTTATAATCTTCTGGGTTAGATCCAAAAG AAGCCGCCTGCTCCATAGCGATTACATGA ATATGACTCCACGCCGCCCTGGCCCCACA AGGAAACACTACCAGCCTTACGCACCACC TAGAGATTTCGCTGCCTATCGGAGCAGGG TGAAGTTTTCCAGATCTGCAGATGCACCA GCGTATCAGCAGGGCCAGAACCAACTGTA TAACGAGCTCAACCTGGGACGCAGGGAAG AGTATGACGTTTTGGACAAGCGCAGAGGA CGGGACCCTGAGATGGGTGGCAAACCAAG ACGAAAAAACCCCCAGGAGGGTCTCTATA ATGAGCTGCAGAAGGATAAGATGGCTGAA GCCTATTCTGAAATAGGCATGAAAGGAGA GCGGAGAAGGGGAAAAGGGCACGACGGTT TGTACCAGGGACTCAGCACTGCTACGAAG GATACTTATGACGCTCTCCACATGCAAGC CCTGCCACCTAGGTAA	133	MALPVTALLLPLALLL HAARPEVQLLESGGGL VQPGGSLRLSCAASGF TFSSYAMSWVRQAPGK GLEWVSAISGSGGSTY YADSVKGRFTISRDNS KNTLYLQMNSLRAEDT AVYYCARAEMGAVFDI WGQGTMVTVSSGSTSG SGKPGSGEGSTKGEIV LTQSPATLSLSPGERA TLSCRASQSVSRYLAW YQQKPGQAPRLLIYDA SNRATGIPARFSGSGS GTDFTLTISSLEPEDF AVYYCQQRISWPFTFG GGTKVEIKRAAALDNE KSNGTIIHVKGKHLCP SPLFPGPSKPFWVLVV VGGVLACYSLLVTVAF IIFWVRSKRSRLLHSD YMNMTPRRPGPTRKHY QPYAPPRDFAAYRSRV KFSRSADAPAYQQGQN QLYNELNLGRREEYDV LDKRRGRDPEMGGKPR RKNPQEGLYNELQKDK MAEAYSEIGMKGERRR GKGHDGLYQGLSTATK DTYDALHMQALPPR	134
FS- 21495CARLx H	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGGAAATTGTGTTGACACAGTCTCCA GCCACCCTGTCTTTGTCTCCAGGGGAAAG AGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGGTACTTAGCCTGGTACCAA CAGAAACCTGGCCAGGCTCCCAGGCTCCT	135	MALPVTALLLPLALLL HAARPEIVLTQSPATL SLSPGERATLSCRASQ SVSRYLAWYQQKPGQA PRLLIYDASNRATGIP ARFSGSGSGTDFTLTI SSLEPEDFAVYYCQQR	136

	CATCTATGATGCATCCAACAGGGCCACTG GCATCCCAGCCAGGTTCAGTGGCAGTGGG TCTGGGACAGACTTCACTCTCACCATCAG CAGCCTAGAGCCTGAAGATTTTGCAGTTT ATTACTGTCAGCAGAGAATCTCCTGGCCT TTCACTTTTGGCGGAGGGACCAAGGTTGA GATCAAACGGGGGTCTACATCCGGCTCCG GGAAGCCCGGAAGTGGCGAAGGTAGTACA AAGGGGGAGGTGCAGCTGTTGGAGTCTGG GGGAGGCTTGGTACAGCCTGGGGGGTCCC TGAGACTCTCCTGTGCAGCCTCTGGATTC ACCTTTAGCAGCTATGCCATGAGCTGGGT CCGCCAGGCTCCAGGGAAGGGGCTGGAGT GGGTCTCAGCTATTAGTGGTAGTGGTGGT AGCACATACTACGCAGACTCCGTGAAGGG CCGGTTCACCATCTCCAGAGACAATTCCA AGAACACGCTGTATCTGCAAATGAACAGC CTGAGAGCCGAGGACACGGCGGTGTACTA CTGCGCAAGAGCCGAGATGGGAGCCGTAT TCGACATATGGGGTCAGGGTACAATGGTC ACCGTCTCCTCAGCCGCTGCCCTTGATAA TGAAAAGTCAAACGGAACAATCATTCACG TGAAGGGCAAGCACCTCTGTCCGTCACCC TTGTTCCCTGGTCCATCCAAGCCATTCTG GGTGTTGGTCGTAGTGGGTGGAGTCCTCG CTTGTTACTCTCTGCTCGTCACCGTGGCT TTTATAATCTTCTGGGTTAGATCCAAAAG AAGCCGCCTGCTCCATAGCGATTACATGA ATATGACTCCACGCCGCCCTGGCCCCACA AGGAAACACTACCAGCCTTACGCACCACC TAGAGATTTCGCTGCCTATCGGAGCAGGG TGAAGTTTTCCAGATCTGCAGATGCACCA GCGTATCAGCAGGGCCAGAACCAACTGTA TAACGAGCTCAACCTGGGACGCAGGGAAG AGTATGACGTTTTGGACAAGCGCAGAGGA CGGGACCCTGAGATGGGTGGCAAACCAAG ACGAAAAAACCCCCAGGAGGGTCTCTATA ATGAGCTGCAGAAGGATAAGATGGCTGAA GCCTATTCTGAAATAGGCATGAAAGGAGA GCGGAGAAGGGGAAAAGGGCACGACGGTT TGTACCAGGGACTCAGCACTGCTACGAAG GATACTTATGACGCTCTCCACATGCAAGC CCTGCCACCTAGGTAA		ISWPFTFGGGTKVEIK RGSTSGSGKPGSGEGS TKGEVQLLESGGGLVQ PGGSLRLSCAASGFTF SSYAMSWVRQAPGKGL EWVSAISGSGGSTYYA DSVKGRFTISRDNSKN TLYLQMNSLRAEDTAV YYCARAEMGAVFDIWG QGTMVTVSSAAALDNE KSNGTIIHVKGKHLCP SPLFPGPSKPFWVLVV VGGVLACYSLLVTVAF IIFWVRSKRSRLLHSD YMNMTPRRPGPTRKHY QPYAPPRDFAAYRSRV KFSRSADAPAYQQGQN QLYNELNLGRREEYDV LDKRRGRDPEMGGKPR RKNPQEGLYNELQKDK MAEAYSEIGMKGERRR GKGHDGLYQGLSTATK DTYDALHMQALPPR	
PC-21497CARHxL	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTGCAGCTGGTGGAGTCTGGG GGAGGCGTGGTCCAGCCTGGGAGGTCCCT GAGACTCTCCTGTGCAGCGTCTGGATTCA CCTTCAGTAGCTATGGCATGCACTGGGTC CGCCAGGCTCCAGGCAAGGGGCTGGAGTG GGTGGCAGTTATATCGTATGATGGAAGTA ATAAATACTATGCAGACTCCGTGAAGGGC CGATTCACCATCTCCAGAGACAATTCCAA GAACACGCTGTATCTGCAAATGAACAGCC TGAGAGCCGAGGACACGGCGGTGTACTAC TGCGCCAGAGACGGTACTTATCTAGGTGG TCTCTGGTACTTCGACTTATGGGGGAGAG GTACCTTGGTCACCGTCTCCTCAGGGTCT ACATCCGGCTCCGGGAAGCCCGGAAGTGG	137	MALPVTALLLPLALLL HAARPQVQLVESGGGV VQPGRSLRLSCAASGF TFSSYGMHWVRQAPGK GLEWVAVISYDGSNKY YADSVKGRFTISRDNS KNTLYLQMNSLRAEDT AVYYCARDGTYLGGLW YFDLWGRGTLVTVSSG STSGSGKPGSGEGSTK GDIVMTQSPLSLPVTP GEPASISCRSSQSLLH SNGYNYLDWYLQKPGQ SPQLLIYLGSNRASGV PDRFSGSGSGTDFTLK ISRVEAEDVGVYYCMQ	138

	CGAAGGTAGTACAAAGGGGGATATTGTGA TGACTCAGTCTCCACTCTCCCTGCCCGTC ACCCCTGGAGAGCCGGCCTCCATCTCCTG CAGGTCTAGTCAGAGCCTCCTGCATAGTA ATGGATACAACTATTTGGATTGGTACCTG CAGAAGCCAGGGCAGTCTCCACAGCTCCT GATCTATTTGGGTTCTAATCGGGCCTCCG GGGTCCCTGACAGGTTCAGTGGCAGTGGA TCAGGCACAGATTTTACACTGAAAATCAG CAGAGTGGAGGCTGAGGATGTTGGGGTTT ATTACTGCATGCAGGGACTCGGCCTCCCT CTCACTTTTGGCGGAGGGACCAAGGTTGA GATCAAACGGGCCGCTGCCCTTGATAATG AAAAGTCAAACGGAACAATCATTCACGTG AAGGGCAAGCACCTCTGTCCGTCACCCTT GTTCCCTGGTCCATCCAAGCCATTCTGGG TGTTGGTCGTAGTGGGTGGAGTCCTCGCT TGTTACTCTCTGCTCGTCACCGTGGCTTT TATAATCTTCTGGGTTAGATCCAAAAGAA GCCGCCTGCTCCATAGCGATTACATGAAT ATGACTCCACGCCGCCCTGGCCCCACAAG GAAACACTACCAGCCTTACGCACCACCTA GAGATTTCGCTGCCTATCGGAGCAGGGTG AAGTTTTCCAGATCTGCAGATGCACCAGC GTATCAGCAGGGCCAGAACCAACTGTATA ACGAGCTCAACCTGGGACGCAGGGAAGAG TATGACGTTTTGGACAAGCGCAGAGGACG GGACCCTGAGATGGGTGGCAAACCAAGAC GAAAAAACCCCCAGGAGGGTCTCTATAAT GAGCTGCAGAAGGATAAGATGGCTGAAGC CTATTCTGAAATAGGCATGAAAGGAGAGC GGAGAAGGGGAAAAGGGCACGACGGTTTG TACCAGGGACTCAGCACTGCTACGAAGGA TACTTATGACGCTCTCCACATGCAAGCCC TGCCACCTAGGTAA		GLGLPLTFGGGTKVEI KRAAALDNEKSNGTII HVKGKHLCPSPLFPGP SKPFWVLVVVGGVLAC YSLLVTVAFIIFWVRS KRSRLLHSDYMNMTPR RPGPTRKHYQPYAPPR DFAAYRSRVKFSRSAD APAYQQGQNQLYNELN LGRREEYDVLDKRRGR DPEMGGKPRRKNPQEG LYNELQKDKMAEAYSE IGMKGERRRGKGHDGL YQGLSTATKDTYDALH MQALPPR	
PC-21497CARHxL	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGGATATTGTGATGACTCAGTCTCCA CTCTCCCTGCCCGTCACCCCTGGAGAGCC GGCCTCCATCTCCTGCAGGTCTAGTCAGA GCCTCCTGCATAGTAATGGATACAACTAT TTGGATTGGTACCTGCAGAAGCCAGGGCA GTCTCCACAGCTCCTGATCTATTTGGGTT CTAATCGGGCCTCCGGGGTCCCTGACAGG TTCAGTGGCAGTGGATCAGGCACAGATTT TACACTGAAAATCAGCAGAGTGGAGGCTG AGGATGTTGGGGTTTATTACTGCATGCAG GGACTCGGCCTCCCTCTCACTTTTGGCGG AGGGACCAAGGTTGAGATCAAACGGGGGT CTACATCCGGCTCCGGGAAGCCCGGAAGT GGCGAAGGTAGTACAAAGGGGCAGGTGCA GCTGGTGGAGTCTGGGGGAGGCGTGGTCC AGCCTGGGAGGTCCCTGAGACTCTCCTGT GCAGCGTCTGGATTCACCTTCAGTAGCTA TGGCATGCACTGGGTCCGCCAGGCTCCAG GCAAGGGGCTGGAGTGGGTGGCAGTTATA TCGTATGATGGAAGTAATAAATACTATGC AGACTCCGTGAAGGGCCGATTCACCATCT CCAGAGACAATTCCAAGAACACGCTGTAT	139	MALPVTALLLPLALLL HAARPDIVMTQSPLSL PVTPGEPASISCRSSQ SLLHSNGYNYLDWYLQ KPGQSPQLLIYLGSNR ASGVPDRFSGSGSGTD FTLKISRVEAEDVGVY YCMQGLGLPLTFGGGT KVEIKRGSTSGSGKPG SGEGSTKGQVQLVESG GGVVQPGRSLRLSCAA SGFTFSSYGMHWVRQA PGKGLEWVAVISYDGS NKYYADSVKGRFTISR DNSKNTLYLQMNSLRA EDTAVYYCARDGTYLG GLWYFDLWGRGTLVTV SSAAALDNEKSNGTII HVKGKHLCPSPLFPGP SKPFWVLVVVGGVLAC YSLLVTVAFIIFWVRS KRSRLLHSDYMNMTPR RPGPTRKHYQPYAPPR DFAAYRSRVKFSRSAD	140

	CTGCAAATGAACAGCCTGAGAGCCGAGGA CACGGCGGTGTACTACTGCGCCAGAGACG GTACTTATCTAGGTGGTCTCTGGTACTTC GACTTATGGGGGAGAGGTACCTTGGTCAC CGTCTCCTCAGCCGCTGCCCTTGATAATG AAAAGTCAAACGGAACAATCATTCACGTG AAGGGCAAGCACCTCTGTCCGTCACCCTT GTTCCCTGGTCCATCCAAGCCATTCTGGG TGTTGGTCGTAGTGGGTGGAGTCCTCGCT TGTTACTCTCTGCTCGTCACCGTGGCTTT TATAATCTTCTGGGTTAGATCCAAAAGAA GCCGCCTGCTCCATAGCGATTACATGAAT ATGACTCCACGCCGCCCTGGCCCCACAAG GAAACACTACCAGCCTTACGCACCACCTA GAGATTTCGCTGCCTATCGGAGCAGGGTG AAGTTTTCCAGATCTGCAGATGCACCAGC GTATCAGCAGGGCCAGAACCAACTGTATA ACGAGCTCAACCTGGGACGCAGGGAAGAG TATGACGTTTTGGACAAGCGCAGAGGACG GGACCCTGAGATGGGTGGCAAACCAAGAC GAAAAAACCCCCAGGAGGGTCTCTATAAT GAGCTGCAGAAGGATAAGATGGCTGAAGC CTATTCTGAAATAGGCATGAAAGGAGAGC GGAGAAGGGGAAAAGGGCACGACGGTTTG TACCAGGGACTCAGCACTGCTACGAAGGA TACTTATGACGCTCTCCACATGCAAGCCC TGCCACCTAGGTAA		APAYQQGQNQLYNELN LGRREEYDVLDKRRGR DPEMGGKPRRKNPQEG LYNELQKDKMAEAYSE IGMKGERRRGKGHDGL YQGLSTATKDTYDALH MQALPPR	
AJ-21508CARHxL	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTGCAGCTGGTGCAGTCTGGG GCTGAGGTGAAGAAGCCTGGGGCCTCAGT GAAGGTTTCCTGCAAGGCATCTGGATACA CCTTCACCAGCTACTATATGCACTGGGTG CGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGAATAATCAACCCTGGTGGTGGTA GCACAAGCTACGCACAGAAGTTCCAGGGC AGAGTCACCATGACCAGGGACACGTCCAC GAGCACAGTCTACATGGAGCTGAGCAGCC TGAGATCTGAGGACACGGCGGTGTACTAC TGCGCCAGAGAGAGTTGGCCAATGGACGT ATGGGGCCAGGGAACAACTGTCACCGTCT CCTCAGGGTCTACATCCGGCTCCGGGAAG CCCGGAAGTGGCGAAGGTAGTACAAAGGG GGAAATAGTGATGACGCAGTCTCCAGCCA CCCTGTCTGTGTCTCCAGGGGAAAGAGCC ACCCTCTCCTGCAGGGCCAGTCAGAGTGT TAGCAGCAACTTAGCCTGGTACCAGCAGA AACCTGGCCAGGCTCCCAGGCTCCTCATC TATGGTGCATCCACCAGGGCCACTGGTAT CCCAGCCAGGTTCAGTGGCAGTGGGTCTG GGACAGAGTTCACTCTCACCATCAGCAGC CTGCAGTCTGAAGATTTTGCAGTTTATTA CTGTCAGCAGTACGCCGCCTACCCTACTT TTGGCGGAGGGACCAAGGTTGAGATCAAA CGGGCCGCTGCCCTTGATAATGAAAAGTC AAACGGAACAATCATTCACGTGAAGGGCA AGCACCTCTGTCCGTCACCCTTGTTCCCT GGTCCATCCAAGCCATTCTGGGTGTTGGT CGTAGTGGGTGGAGTCCTCGCTTGTTACT	141	MALPVTALLLPLALLL HAARPQVQLVQSGAEV KKPGASVKVSCKASGY TFTSYYMHWVRQAPGQ GLEWMGIINPGGGSTS YAQKFQGRVTMTRDTS TSTVYMELSSLRSEDT AVYYCARESWPMDVWG QGTTVTVSSGSTSGSG KPGSGEGSTKGEIVMT QSPATLSVSPGERATL SCRASQSVSSNLAWYQ QKPGQAPRLLIYGAST RATGIPARFSGSGSGT EFTLTISSLQSEDFAV YYCQQYAAYPTFGGGT KVEIKRAAALDNEKSN GTIIHVKGKHLCPSPL FPGPSKPFWVLVVVGG VLACYSLLVTVAFIIF WVRSKRSRLLHSDYMN MTPRRPGPTRKHYQPY APPRDFAAYRSRVKFS RSADAPAYQQGQNQLY NELNLGRREEYDVLDK RRGRDPEMGGKPRRKN PQEGLYNELQKDKMAE AYSEIGMKGERRRGKG HDGLYQGLSTATKDTY DALHMQALPPR	142

	CTCTGCTCGTCACCGTGGCTTTTATAATC TTCTGGGTTAGATCCAAAAGAAGCCGCCT GCTCCATAGCGATTACATGAATATGACTC CACGCCGCCCTGGCCCCACAAGGAAACAC TACCAGCCTTACGCACCACCTAGAGATTT CGCTGCCTATCGGAGCAGGGTGAAGTTTT CCAGATCTGCAGATGCACCAGCGTATCAG CAGGGCCAGAACCAACTGTATAACGAGCT CAACCTGGGACGCAGGGAAGAGTATGACG TTTTGGACAAGCGCAGAGGACGGGACCCT GAGATGGGTGGCAAACCAAGACGAAAAAA CCCCCAGGAGGGTCTCTATAATGAGCTGC AGAAGGATAAGATGGCTGAAGCCTATTCT GAAATAGGCATGAAAGGAGAGCGGAGAAG GGGAAAAGGGCACGACGGTTTGTACCAGG GACTCAGCACTGCTACGAAGGATACTTAT GACGCTCTCCACATGCAAGCCCTGCCACC TAGGTAA			
AJ- 21508CARLx H	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGGAAATAGTGATGACGCAGTCTCCA GCCACCCTGTCTGTGTCTCCAGGGGAAAG AGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGCAACTTAGCCTGGTACCAG CAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATGGTGCATCCACCAGGGCCACTG GTATCCCAGCCAGGTTCAGTGGCAGTGGG TCTGGGACAGAGTTCACTCTCACCATCAG CAGCCTGCAGTCTGAAGATTTTGCAGTTT ATTACTGTCAGCAGTACGCCGCCTACCCT ACTTTTGGCGGAGGGACCAAGGTTGAGAT CAAACGGGGGTCTACATCCGGCTCCGGGA AGCCCGGAAGTGGCGAAGGTAGTACAAAG GGGCAGGTGCAGCTGGTGCAGTCTGGGGC TGAGGTGAAGAAGCCTGGGGCCTCAGTGA AGGTTTCCTGCAAGGCATCTGGATACACC TTCACCAGCTACTATATGCACTGGGTGCG ACAGGCCCCTGGACAAGGGCTTGAGTGGA TGGGAATAATCAACCCTGGTGGTGGTAGC ACAAGCTACGCACAGAAGTTCCAGGGCAG AGTCACCATGACCAGGGACACGTCCACGA GCACAGTCTACATGGAGCTGAGCAGCCTG AGATCTGAGGACACGGCGGTGTACTACTG CGCCAGAGAGAGTTGGCCAATGGACGTAT GGGGCCAGGGAACAACTGTCACCGTCTCC TCAGCCGCTGCCCTTGATAATGAAAAGTC AAACGGAACAATCATTCACGTGAAGGGCA AGCACCTCTGTCCGTCACCCTTGTTCCCT GGTCCATCCAAGCCATTCTGGGTGTTGGT CGTAGTGGGTGGAGTCCTCGCTTGTTACT CTCTGCTCGTCACCGTGGCTTTTATAATC TTCTGGGTTAGATCCAAAAGAAGCCGCCT GCTCCATAGCGATTACATGAATATGACTC CACGCCGCCCTGGCCCCACAAGGAAACAC TACCAGCCTTACGCACCACCTAGAGATTT CGCTGCCTATCGGAGCAGGGTGAAGTTTT CCAGATCTGCAGATGCACCAGCGTATCAG CAGGGCCAGAACCAACTGTATAACGAGCT CAACCTGGGACGCAGGGAAGAGTATGACG	143	MALPVTALLLPLALLL HAARPEIVMTQSPATL SVSPGERATLSCRASQ SVSSNLAWYQQKPGQA PRLLIYGASTRATGIP ARFSGSGSGTEFTLTI SSLQSEDFAVYYCQQY AAYPTFGGGTKVEIKR GSTSGSGKPGSGEGST KGQVQLVQSGAEVKKP GASVKVSCKASGYTFT SYYMHWVRQAPGQGLE WMGIINPGGGSTSYAQ KFQGRVTMTRDTSTST VYMELSSLRSEDTAVY YCARESWPMDVWGQGT TVTVSSAAALDNEKSN GTIIHVKGKHLCPSPL FPGPSKPFWVLVVVGG VLACYSLLVTVAFIIF WVRSKRSRLLHSDYMN MTPRRPGPTRKHYQPY APPRDFAAYRSRVKFS RSADAPAYQQGQNQLY NELNLGRREEYDVLDK RRGRDPEMGGKPRRKN PQEGLYNELQKDKMAE AYSEIGMKGERRRGKG HDGLYQGLSTATKDTY DALHMQALPPR	144

	TTTTGGACAAGCGCAGAGGACGGGACCCT GAGATGGGTGGCAAACCAAGACGAAAAAA CCCCCAGGAGGGTCTCTATAATGAGCTGC AGAAGGATAAGATGGCTGAAGCCTATTCT GAAATAGGCATGAAAGGAGAGCGGAGAAG GGGAAAAGGGCACGACGGTTTGTACCAGG GACTCAGCACTGCTACGAAGGATACTTAT GACGCTCTCCACATGCAAGCCCTGCCACC TAGGTAA			
NM-21517CARHxL	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGCTGCAGCTGCAGGAGTCGGGC CCAGGACTGGTGAAGCCTTCGGAGACCCT GTCCCTCACCTGCACTGTCTCTGGTGGCT CCATCAGCAGTAGTAGTTACTACTGGGGC TGGATCCGCCAGCCCCCAGGGAAGGGGCT GGAGTGGATTGGGAGTATCTCCTATAGTG GGAGCACCTACTACAACCCGTCCCTCAAG AGTCGAGTCACCATATCCGTAGACACGTC CAAGAACCAGTTCTCCCTGAAGCTGAGTT CTGTGACCGCCGCAGACACGGCGGTGTAC TACTGCGCCAGAGGCAGGGGATATGCAAC CAGCTTAGCCTTCGATATCTGGGGTCAGG GTACAATGGTCACCGTCTCCTCAGGGTCT ACATCCGGCTCCGGGAAGCCCGGAAGTGG CGAAGGTAGTACAAAGGGGGAAATTGTGT TGACACAGTCTCCAGCCACCCTGTCTTTG TCTCCAGGGGAAAGAGCCACCCTCTCCTG CAGGGCCAGTCAGAGTGTTAGCAGCTACT TAGCCTGGTACCAACAGAAACCTGGCCAG GCTCCCAGGCTCCTCATCTATGATGCATC CAACAGGGCCACTGGCATCCCAGCCAGGT TCAGTGGCAGTGGGTCTGGGACAGACTTC ACTCTCACCATCAGCAGCCTAGAGCCTGA AGATTTTGCAGTTTATTACTGTCAGCAGA GACACGTCTGGCCTCCTACTTTTGGCGGA GGGACCAAGGTTGAGATCAAACGGGCCGC TGCCCTTGATAATGAAAAGTCAAACGGAA CAATCATTCACGTGAAGGGCAAGCACCTC TGTCCGTCACCCTTGTTCCCTGGTCCATC CAAGCCATTCTGGGTGTTGGTCGTAGTGG GTGGAGTCCTCGCTTGTTACTCTCTGCTC GTCACCGTGGCTTTTATAATCTTCTGGGT TAGATCCAAAAGAAGCCGCCTGCTCCATA GCGATTACATGAATATGACTCCACGCCGC CCTGGCCCCACAAGGAAACACTACCAGCC TTACGCACCACCTAGAGATTTCGCTGCCT ATCGGAGCAGGGTGAAGTTTTCCAGATCT GCAGATGCACCAGCGTATCAGCAGGGCCA GAACCAACTGTATAACGAGCTCAACCTGG GACGCAGGGAAGAGTATGACGTTTTGGAC AAGCGCAGAGGACGGGACCCTGAGATGGG TGGCAAACCAAGACGAAAAAACCCCCAGG AGGGTCTCTATAATGAGCTGCAGAAGGAT AAGATGGCTGAAGCCTATTCTGAAATAGG CATGAAAGGAGAGCGGAGAAGGGGAAAAG GGCACGACGGTTTGTACCAGGGACTCAGC ACTGCTACGAAGGATACTTATGACGCTCT CCACATGCAAGCCCTGCCACCTAGGTAA	145	MALPVTALLLPLALLL HAARPQLQLQESGPGL VKPSETLSLTCTVSGG SISSSSYYWGWIRQPP GKGLEWIGSISYSGST YYNPSLKSRVTISVDT SKNQFSLKLSSVTAAD TAVYYCARGRGYATSL AFDIWGQGTMVTVSSG STSGSGKPGSGEGSTK GEIVLTQSPATLSLSP GERATLSCRASQSVSS YLAWYQQKPGQAPRLL IYDASNRATGIPARFS GSGSGTDFTLTISSLE PEDFAVYYCQQRHVWP PTFGGGTKVEIKRAAA LDNEKSNGTIIHVKGK HLCPSPLFPGPSKPFW VLVVVGGVLACYSLLV TVAFIIFWVRSKRSRL LHSDYMNMTPRRPGPT RKHYQPYAPPRDFAAY RSRVKFSRSADAPAYQ QGQNQLYNELNLGRRE EYDVLDKRRGRDPEMG GKPRRKNPQEGLYNEL QKDKMAEAYSEIGMKG ERRRGKGHDGLYQGLS TATKDTYDALHMQALP PR	146

NM-21517CARLxH	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGGAAATTGTGTTGACACAGTCTCCA GCCACCCTGTCTTTGTCTCCAGGGGAAAG AGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGCTACTTAGCCTGGTACCAA CAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATGATGCATCCAACAGGGCCACTG GCATCCCAGCCAGGTTCAGTGGCAGTGGG TCTGGGACAGACTTCACTCTCACCATCAG CAGCCTAGAGCCTGAAGATTTTGCAGTTT ATTACTGTCAGCAGAGACACGTCTGGCCT CCTACTTTTGGCGGAGGGACCAAGGTTGA GATCAAACGGGGGTCTACATCCGGCTCCG GGAAGCCCGGAAGTGGCGAAGGTAGTACA AAGGGGCAGCTGCAGCTGCAGGAGTCGGG CCCAGGACTGGTGAAGCCTTCGGAGACCC TGTCCCTCACCTGCACTGTCTCTGGTGGC TCCATCAGCAGTAGTAGTTACTACTGGGG CTGGATCCGCCAGCCCCCAGGGAAGGGGC TGGAGTGGATTGGGAGTATCTCCTATAGT GGGAGCACCTACTACAACCCGTCCCTCAA GAGTCGAGTCACCATATCCGTAGACACGT CCAAGAACCAGTTCTCCCTGAAGCTGAGT TCTGTGACCGCCGCAGACACGGCGGTGTA CTACTGCGCCAGAGGCAGGGGATATGCAA CCAGCTTAGCCTTCGATATCTGGGGTCAG GGTACAATGGTCACCGTCTCCTCAGCCGC TGCCCTTGATAATGAAAAGTCAAACGGAA CAATCATTCACGTGAAGGGCAAGCACCTC TGTCCGTCACCCTTGTTCCCTGGTCCATC CAAGCCATTCTGGGTGTTGGTCGTAGTGG GTGGAGTCCTCGCTTGTTACTCTCTGCTC GTCACCGTGGCTTTTATAATCTTCTGGGT TAGATCCAAAAGAAGCCGCCTGCTCCATA GCGATTACATGAATATGACTCCACGCCGC CCTGGCCCCACAAGGAAACACTACCAGCC TTACGCACCACCTAGAGATTTCGCTGCCT ATCGGAGCAGGGTGAAGTTTTCCAGATCT GCAGATGCACCAGCGTATCAGCAGGGCCA GAACCAACTGTATAACGAGCTCAACCTGG GACGCAGGGAAGAGTATGACGTTTTGGAC AAGCGCAGAGGACGGGACCCTGAGATGGG TGGCAAACCAAGACGAAAAAACCCCCAGG AGGGTCTCTATAATGAGCTGCAGAAGGAT AAGATGGCTGAAGCCTATTCTGAAATAGG CATGAAAGGAGAGCGGAGAAGGGGAAAAG GGCACGACGGTTTGTACCAGGGACTCAGC ACTGCTACGAAGGATACTTATGACGCTCT CCACATGCAAGCCCTGCCACCTAGGTAA	147	MALPVTALLLPLALLL HAARPEIVLTQSPATL SLSPGERATLSCRASQ SVSSYLAWYQQKPGQA PRLLIYDASNRATGIP ARFSGSGSGTDFTLTI SSLEPEDFAVYYCQQR HVWPPTFGGGTKVEIK RGSTSGSGKPGSGEGS TKGQLQLQESGPGLVK PSETLSLTCTVSGGSI SSSSYYWGWIRQPPGK GLEWIGSISYSGSTYY NPSLKSRVTISVDTSK NQFSLKLSSVTAADTA VYYCARGRGYATSLAF DIWGQGTMVTVSSAAA LDNEKSNGTIIHVKGK HLCPSPLFPGPSKPFW VLVVVGGVLACYSLLV TVAFIIFWVRSKRSRL LHSDYMNMTPRRPGPT RKHYQPYAPPRDFAAY RSRVKFSRSADAPAYQ QGQNQLYNELNLGRRE EYDVLDKRRGRDPEMG GKPRRKNPQEGLYNEL QKDKMAEAYSEIGMKG ERRRGKGHDGLYQGLS TATKDTYDALHMQALP PR	148
TS-21522CARHxL	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGGAGGTGCAGCTGGTGGAGTCTGGG GGAGGCTTGGTACAGCCTGGGGGGTCCCT GAGACTCTCCTGTGCAGCCTCTGGATTCA CCTTCAGTAGCTATAGCATGAACTGGGTC CGCCAGGCTCCAGGGAAGGGGCTGGAGTG GGTTTCAACCATTAGTAGTAGTAGTAGTA CCATATACTACGCAGACTCTGTGAAGGGC	149	MALPVTALLLPLALLL HAARPEVQLVESGGGL VQPGGSLRLSCAASGF TFSSYSMNWVRQAPGK GLEWVSTISSSSSTIY YADSVKGRFTISRDNA KNSLYLQMNSLRAEDT AVYYCARGSQEHLIFD YWGQGTLVTVSSGSTS	150

	CGATTCACCATCTCCAGAGACAATGCCAA GAACTCACTGTATCTGCAAATGAACAGCC TGAGAGCTGAGGACACGGCGGTGTACTAC TGCGCCAGAGGTTCTCAGGAGCACCTGAT TTTCGATTATTGGGGACAGGGTACATTGG TCACCGTCTCCTCAGGGTCTACATCCGGC TCCGGGAAGCCCGGAAGTGGCGAAGGTAG TACAAAGGGGGAAATTGTGTTGACACAGT CTCCAGCCACCCTGTCTTTGTCTCCAGGG GAAAGAGCCACCCTCTCCTGCAGGGCCAG TCAGAGTGTTAGCAGGTACTTAGCCTGGT ACCAACAGAAACCTGGCCAGGCTCCCAGG CTCCTCATCTATGATGCATCCAACAGGGC CACTGGCATCCCAGCCAGGTTCAGTGGCA GTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGCCTAGAGCCTGAAGATTTTGC AGTTTATTACTGTCAGCAGAGATTCTACT ACCCTTGGACTTTTGGCGGAGGGACCAAG GTTGAGATCAAACGGGCCGCTGCCCTTGA TAATGAAAAGTCAAACGGAACAATCATTC ACGTGAAGGGCAAGCACCTCTGTCCGTCA CCCTTGTTCCCTGGTCCATCCAAGCCATT CTGGGTGTTGGTCGTAGTGGGTGGAGTCC TCGCTTGTTACTCTCTGCTCGTCACCGTG GCTTTTATAATCTTCTGGGTTAGATCCAA AAGAAGCCGCCTGCTCCATAGCGATTACA TGAATATGACTCCACGCCGCCCTGGCCCC ACAAGGAAACACTACCAGCCTTACGCACC ACCTAGAGATTTCGCTGCCTATCGGAGCA GGGTGAAGTTTTCCAGATCTGCAGATGCA CCAGCGTATCAGCAGGGCCAGAACCAACT GTATAACGAGCTCAACCTGGGACGCAGGG AAGAGTATGACGTTTTGGACAAGCGCAGA GGACGGGACCCTGAGATGGGTGGCAAACC AAGACGAAAAAACCCCCAGGAGGGTCTCT ATAATGAGCTGCAGAAGGATAAGATGGCT GAAGCCTATTCTGAAATAGGCATGAAAGG AGAGCGGAGAAGGGGAAAAGGGCACGACG GTTTGTACCAGGGACTCAGCACTGCTACG AAGGATACTTATGACGCTCTCCACATGCA AGCCCTGCCACCTAGGTAA		GSGKPGSGEGSTKGEI VLTQSPATLSLSPGER ATLSCRASQSVSRYLA WYQQKPGQAPRLLIYD ASNRATGIPARFSGSG SGTDFTLTISSLEPED FAVYYCQQRFYYPWTF GGGTKVEIKRAAALDN EKSNGTIIHVKGKHLC PSPLFPGPSKPFWVLV VVGGVLACYSLLVTVA FIIFWVRSKRSRLLHS DYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSR VKFSRSADAPAYQQGQ NQLYNELNLGRREEYD VLDKRRGRDPEMGGKP RRKNPQEGLYNELQKD KMAEAYSEIGMKGERR RGKGHDGLYQGLSTAT KDTYDALHMQALPPR	
TS-21522CARLxH	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGGAAATTGTGTTGACACAGTCTCCA GCCACCCTGTCTTTGTCTCCAGGGGAAAG AGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGGTACTTAGCCTGGTACCAA CAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATGATGCATCCAACAGGGCCACTG GCATCCCAGCCAGGTTCAGTGGCAGTGGG TCTGGGACAGACTTCACTCTCACCATCAG CAGCCTAGAGCCTGAAGATTTTGCAGTTT ATTACTGTCAGCAGAGATTCTACTACCCT TGGACTTTTGGCGGAGGGACCAAGGTTGA GATCAAACGGGGGTCTACATCCGGCTCCG GGAAGCCCGGAAGTGGCGAAGGTAGTACA AAGGGGGAGGTGCAGCTGGTGGAGTCTGG GGGAGGCTTGGTACAGCCTGGGGGGTCCC TGAGACTCTCCTGTGCAGCCTCTGGATTC	151	MALPVTALLLPLALLL HAARPEIVLTQSPATL SLSPGERATLSCRASQ SVSRYLAWYQQKPGQA PRLLIYDASNRATGIP ARFSGSGSGTDFTLTI SSLEPEDFAVYYCQQR FYYPWTFGGGTKVEIK RGSTSGSGKPGSGEGS TKGEVQLVESGGGLVQ PGGSLRLSCAASGFTF SSYSMNWVRQAPGKGL EWVSTISSSSSTIYYA DSVKGRFTISRDNAKN SLYLQMNSLRAEDTAV YYCARGSQEHLIFDYW GQGTLVTVSSAAALDN EKSNGTIIHVKGKHLC	152

	ACCTTCAGTAGCTATAGCATGAACTGGGT CCGCCAGGCTCCAGGGAAGGGGCTGGAGT GGGTTTCAACCATTAGTAGTAGTAGTAGT ACCATATACTACGCAGACTCTGTGAAGGG CCGATTCACCATCTCCAGAGACAATGCCA AGAACTCACTGTATCTGCAAATGAACAGC CTGAGAGCTGAGGACACGGCGGTGTACTA CTGCGCCAGAGGTTCTCAGGAGCACCTGA TTTTCGATTATTGGGGACAGGGTACATTG GTCACCGTCTCCTCAGCCGCTGCCCTTGA TAATGAAAAGTCAAACGGAACAATCATTC ACGTGAAGGGCAAGCACCTCTGTCCGTCA CCCTTGTTCCCTGGTCCATCCAAGCCATT CTGGGTGTTGGTCGTAGTGGGTGGAGTCC TCGCTTGTTACTCTCTGCTCGTCACCGTG GCTTTTATAATCTTCTGGGTTAGATCCAA AAGAAGCCGCCTGCTCCATAGCGATTACA TGAATATGACTCCACGCCGCCCTGGCCCC ACAAGGAAACACTACCAGCCTTACGCACC ACCTAGAGATTTCGCTGCCTATCGGAGCA GGGTGAAGTTTTCCAGATCTGCAGATGCA CCAGCGTATCAGCAGGGCCAGAACCAACT GTATAACGAGCTCAACCTGGGACGCAGGG AAGAGTATGACGTTTTGGACAAGCGCAGA GGACGGGACCCTGAGATGGGTGGCAAACC AAGACGAAAAAACCCCCAGGAGGGTCTCT ATAATGAGCTGCAGAAGGATAAGATGGCT GAAGCCTATTCTGAAATAGGCATGAAAGG AGAGCGGAGAAGGGGAAAAGGGCACGACG GTTTGTACCAGGGACTCAGCACTGCTACG AAGGATACTTATGACGCTCTCCACATGCA AGCCCTGCCACCTAGGTAA		PSPLFPGPSKPFWVLV VVGGVLACYSLLVTVA FIIFWVRSKRSRLLHS DYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSR VKFSRSADAPAYQQGQ NQLYNELNLGRREEYD VLDKRRGRDPEMGGKP RRKNPQEGLYNELQKD KMAEAYSEIGMKGERR RGKGHDGLYQGLSTAT KDTYDALHMQALPPR	
RY-21527CARHxL	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTGCAGCTGGTGGAGTCTGGG GGAGGCGTGGTCCAGCCTGGGAGGTCCCT GAGACTCTCCTGTGCAGCGTCTGGATTCA CCTTCAGTAGCTATGGCATGCACTGGGTC CGCCAGGCTCCAGGCAAGGGGCTGGAGTG GGTGGCAGTTATATCGTATGATGGAAGTA ATAAATACTATGCAGACTCCGTGAAGGGC CGATTCACCATCTCCAGAGACAATTCCAA GAACACGCTGTATCTGCAAATGAACAGCC TGAGAGCCGAGGACACGGCGGTGTACTAC TGCGCCAGAACTGACTTCTGGAGCGGATC CCCTCCAGGCTTAGATTACTGGGGACAGG GTACATTGGTCACCGTCTCCTCAGGGTCT ACATCCGGCTCCGGGAAGCCCGGAAGTGG CGAAGGTAGTACAAAGGGGGACATCCAGT TGACCCAGTCTCCATCTTCCGTGTCTGCA TCTGTAGGAGACAGAGTCACCATCACTTG TCGGGCGAGTCAGGGTATTAGCAGCTGGT TAGCCTGGTATCAGCAGAAACCAGGGAAA GCCCCTAAGCTCCTGATCTATGGTGCATC CAGTTTGCAAAGTGGGGTCCCATCAAGGT TCAGCGGCAGTGGATCTGGGACAGATTTC ACTCTCACCATCAGCAGCCTGCAGCCTGA AGATTTTGCAACTTATTACTGTCAGCAGA TATACACCTTCCCTTTCACTTTTGGCGGA	153	MALPVTALLLPLALLL HAARPQVQLVESGGGV VQPGRSLRLSCAASGF TFSSYGMHWVRQAPGK GLEWVAVISYDGSNKY YADSVKGRFTISRDNS KNTLYLQMNSLRAEDT AVYYCARTDFWSGSPP GLDYWGQGTLVTVSSG STSGSGKPGSGEGSTK GDIQLTQSPSSVSASV GDRVTITCRASQGISS WLAWYQQKPGKAPKLL IYGASSLQSGVPSRFS GSGSGTDFTLTISSLQ PEDFATYYCQQIYTFP FTFGGGTKVEIKRAAA LDNEKSNGTIIHVKGK HLCPSPLFPGPSKPFW VLVVVGGVLACYSLLV TVAFIIFWVRSKRSRL LHSDYMNMTPRRPGPT RKHYQPYAPPRDFAAY RSRVKFSRSADAPAYQ QGQNQLYNELNLGRRE EYDVLDKRRGRDPEMG GKPRRKNPQEGLYNEL	154

	GGGACCAAGGTTGAGATCAAACGGGCCGC TGCCCTTGATAATGAAAAGTCAAACGGAA CAATCATTCACGTGAAGGGCAAGCACCTC TGTCCGTCACCCTTGTTCCCTGGTCCATC CAAGCCATTCTGGGTGTTGGTCGTAGTGG GTGGAGTCCTCGCTTGTTACTCTCTGCTC GTCACCGTGGCTTTTATAATCTTCTGGGT TAGATCCAAAAGAAGCCGCCTGCTCCATA GCGATTACATGAATATGACTCCACGCCGC CCTGGCCCCACAAGGAAACACTACCAGCC TTACGCACCACCTAGAGATTTCGCTGCCT ATCGGAGCAGGGTGAAGTTTTCCAGATCT GCAGATGCACCAGCGTATCAGCAGGGCCA GAACCAACTGTATAACGAGCTCAACCTGG GACGCAGGGAAGAGTATGACGTTTTGGAC AAGCGCAGAGGACGGGACCCTGAGATGGG TGGCAAACCAAGACGAAAAAACCCCCAGG AGGGTCTCTATAATGAGCTGCAGAAGGAT AAGATGGCTGAAGCCTATTCTGAAATAGG CATGAAAGGAGAGCGGAGAAGGGGAAAAG GGCACGACGGTTTGTACCAGGGACTCAGC ACTGCTACGAAGGATACTTATGACGCTCT CCACATGCAAGCCCTGCCACCTAGGTAA		QKDKMAEAYSEIGMKG ERRRGKGHDGLYQGLS TATKDTYDALHMQALP PR	
RY-21527CARLxH	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGGACATCCAGTTGACCCAGTCTCCA TCTTCCGTGTCTGCATCTGTAGGAGACAG AGTCACCATCACTTGTCGGGCGAGTCAGG GTATTAGCAGCTGGTTAGCCTGGTATCAG CAGAAACCAGGGAAAGCCCCTAAGCTCCT GATCTATGGTGCATCCAGTTTGCAAAGTG GGGTCCCATCAAGGTTCAGCGGCAGTGGA TCTGGGACAGATTTCACTCTCACCATCAG CAGCCTGCAGCCTGAAGATTTTGCAACTT ATTACTGTCAGCAGATATACACCTTCCCT TTCACTTTTGGCGGAGGGACCAAGGTTGA GATCAAACGGGGGTCTACATCCGGCTCCG GGAAGCCCGGAAGTGGCGAAGGTAGTACA AAGGGGCAGGTGCAGCTGGTGGAGTCTGG GGGAGGCGTGGTCCAGCCTGGGAGGTCCC TGAGACTCTCCTGTGCAGCGTCTGGATTC ACCTTCAGTAGCTATGGCATGCACTGGGT CCGCCAGGCTCCAGGCAAGGGGCTGGAGT GGGTGGCAGTTATATCGTATGATGGAAGT AATAAATACTATGCAGACTCCGTGAAGGG CCGATTCACCATCTCCAGAGACAATTCCA AGAACACGCTGTATCTGCAAATGAACAGC CTGAGAGCCGAGGACACGGCGGTGTACTA CTGCGCCAGAACTGACTTCTGGAGCGGAT CCCCTCCAGGCTTAGATTACTGGGGACAG GGTACATTGGTCACCGTCTCCTCAGCCGC TGCCCTTGATAATGAAAAGTCAAACGGAA CAATCATTCACGTGAAGGGCAAGCACCTC TGTCCGTCACCCTTGTTCCCTGGTCCATC CAAGCCATTCTGGGTGTTGGTCGTAGTGG GTGGAGTCCTCGCTTGTTACTCTCTGCTC GTCACCGTGGCTTTTATAATCTTCTGGGT TAGATCCAAAAGAAGCCGCCTGCTCCATA GCGATTACATGAATATGACTCCACGCCGC	155	MALPVTALLLPLALLL HAARPDIQLTQSPSSV SASVGDRVTITCRASQ GISSWLAWYQQKPGKA PKLLIYGASSLQSGVP SRFSGSGSGTDFTLTI SSLQPEDFATYYCQQI YTFPFTFGGGTKVEIK RGSTSGSGKPGSGEGS TKGQVQLVESGGGVVQ PGRSLRLSCAASGFTF SSYGMHWVRQAPGKGL EWVAVISYDGSNKYYA DSVKGRFTISRDNSKN TLYLQMNSLRAEDTAV YYCARTDFWSGSPPGL DYWGQGTLVTVSSAAA LDNEKSNGTIIHVKGK HLCPSPLFPGPSKPFW VLVVVGGVLACYSLLV TVAFIIFWVRSKRSRL LHSDYMNMTPRRPGPT RKHYQPYAPPRDFAAY RSRVKFSRSADAPAYQ QGQNQLYNELNLGRRE EYDVLDKRRGRDPEMG GKPRRKNPQEGLYNEL QKDKMAEAYSEIGMKG ERRRGKGHDGLYQGLS TATKDTYDALHMQALP PR	156

	CCTGGCCCCACAAGGAAACACTACCAGCC TTACGCACCACCTAGAGATTTCGCTGCCT ATCGGAGCAGGGTGAAGTTTTCCAGATCT GCAGATGCACCAGCGTATCAGCAGGGCCA GAACCAACTGTATAACGAGCTCAACCTGG GACGCAGGGAAGAGTATGACGTTTTGGAC AAGCGCAGAGGACGGGACCCTGAGATGGG TGGCAAACCAAGACGAAAAAACCCCCAGG AGGGTCTCTATAATGAGCTGCAGAAGGAT AAGATGGCTGAAGCCTATTCTGAAATAGG CATGAAAGGAGAGCGGAGAAGGGGAAAAG GGCACGACGGTTTGTACCAGGGACTCAGC ACTGCTACGAAGGATACTTATGACGCTCT CCACATGCAAGCCCTGCCACCTAGGTAA			
PP- 21528CARHx L	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTGCAGCTGGTGCAGTCTGGGG GCTGAGGTGAAGAAGCCTGGGTCCTCGGT GAAGGTCTCCTGCAAGGCTTCTGGAGGCA CCTTCAGCAGCTATGCTATCAGCTGGGTG CGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGAGGGATCATCCCTATCTTTGGTA CAGCAAACTACGCACAGAAGTTCCAGGGC AGAGTCACGATTACCGCGGACGAATCCAC GAGCACAGCCTACATGGAGCTGAGCAGCC TGAGATCTGAGGACACGGCGGTGTACTAC TGCGCCAGAACTCCTGAATACTCCTCCAG CATATGGCACTATTACTACGGCATGGACG TATGGGGCCAGGGAACAACTGTCACCGTC TCCTCAGGGTCTACATCCGGCTCCGGGAA GCCCGGAAGTGGCGAAGGTAGTACAAAGG GGGACATCGTGATGACCCAGTCTCCAGAC TCCCTGGCTGTGTCTCTGGGCGAGAGGGC CACCATCAACTGCAAGTCCAGCCAGAGTG TTTTATACAGCTCCAACAATAAGAACTAC TTAGCTTGGTACCAGCAGAAACCAGGACA GCCTCCTAAGCTGCTCATTTACTGGGCAT CTACCCGGGAATCCGGGGTCCCTGACCGA TTCAGTGGCAGCGGGTCTGGGACAGATTT CACTCTCACCATCAGCAGCCTGCAGGCTG AAGATGTGGCAGTTTATTACTGTCAGCAG TTCGCCCACACTCCTTTCACTTTTGGCGG AGGGACCAAGGTTGAGATCAAACGGGCCG CTGCCCTTGATAATGAAAAGTCAAACGGA ACAATCATTCACGTGAAGGGCAAGCACCT CTGTCCGTCACCCTTGTTCCCTGGTCCAT CCAAGCCATTCTGGGTGTTGGTCGTAGTG GGTGGAGTCCTCGCTTGTTACTCTCTGCT CGTCACCGTGGCTTTTATAATCTTCTGGG TTAGATCCAAAAGAAGCCGCCTGCTCCAT AGCGATTACATGAATATGACTCCACGCCG CCCTGGCCCCACAAGGAAACACTACCAGC CTTACGCACCACCTAGAGATTTCGCTGCC TATCGGAGCAGGGTGAAGTTTTCCAGATC TGCAGATGCACCAGCGTATCAGCAGGGCC AGAACCAACTGTATAACGAGCTCAACCTG GGACGCAGGGAAGAGTATGACGTTTTGGA CAAGCGCAGAGGACGGGACCCTGAGATGG GTGGCAAACCAAGACGAAAAAACCCCCAG	157	MALPVTALLLPLALLL HAARPQVQLVQSGAEV KKPGSSVKVSCKASGG TFSSYAISWVRQAPGQ GLEWMGGIIPIFGTAN YAQKFQGRVTITADES TSTAYMELSSLRSEDT AVYYCARTPEYSSSIW HYYYGMDVWGQGTTVT VSSGSTSGSGKPGSGE GSTKGDIVMTQSPDSL AVSLGERATINCKSSQ SVLYSSNNKNYLAWYQ QKPGQPPKLLIYWAST RESGVPDRFSGSGSGT DFTLTISSLQAEDVAV YYCQQFAHTPFTFGGG TKVEIKRAAALDNEKS NGTIIHVKGKHLCPSP LFPGPSKPFWVLVVVG GVLACYSLLVTVAFII FWVRSKRSRLLHSDYM NMTPRRPGPTRKHYQP YAPPRDFAAYRSRVKF SRSADAPAYQQGQNQL YNELNLGRREEYDVLD KRRGRDPEMGGKPRRK NPQEGLYNELQKDKMA EAYSEIGMKGERRRGK GHDGLYQGLSTATKDT YDALHMQALPPR	158

	GAGGGTCTCTATAATGAGCTGCAGAAGGA TAAGATGGCTGAAGCCTATTCTGAAATAG GCATGAAAGGAGAGCGGAGAAGGGGAAAA GGGCACGACGGTTTGTACCAGGGACTCAG CACTGCTACGAAGGATACTTATGACGCTC TCCACATGCAAGCCCTGCCACCTAGGTAA			
PP-21528CARLxH	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGGACATCGTGATGACCCAGTCTCCA GACTCCCTGGCTGTGTCTCTGGGCGAGAG GGCCACCATCAACTGCAAGTCCAGCCAGA GTGTTTTATACAGCTCCAACAATAAGAAC TACTTAGCTTGGTACCAGCAGAAACCAGG ACAGCCTCCTAAGCTGCTCATTTACTGGG CATCTACCCGGGAATCCGGGGTCCCTGAC CGATTCAGTGGCAGCGGGTCTGGGACAGA TTTCACTCTCACCATCAGCAGCCTGCAGG CTGAAGATGTGGCAGTTTATTACTGTCAG CAGTTCGCCCACACTCCTTTCACTTTTGG CGGAGGGACCAAGGTTGAGATCAAACGGG GGTCTACATCCGGCTCCGGGAAGCCCGGA AGTGGCGAAGGTAGTACAAAGGGGCAGGT GCAGCTGGTGCAGTCTGGGGCTGAGGTGA AGAAGCCTGGGTCCTCGGTGAAGGTCTCC TGCAAGGCTTCTGGAGGCACCTTCAGCAG CTATGCTATCAGCTGGGTGCGACAGGCCC CTGGACAAGGGCTTGAGTGGATGGGAGGG ATCATCCCTATCTTTGGTACAGCAAACTA CGCACAGAAGTTCCAGGGCAGAGTCACGA TTACCGCGGACGAATCCACGAGCACAGCC TACATGGAGCTGAGCAGCCTGAGATCTGA GGACACGGCGGTGTACTACTGCGCCAGAA CTCCTGAATACTCCTCCAGCATATGGCAC TATTACTACGGCATGGACGTATGGGGCCA GGGAACAACTGTCACCGTCTCCTCAGCCG CTGCCCTTGATAATGAAAAGTCAAACGGA ACAATCATTCACGTGAAGGGCAAGCACCT CTGTCCGTCACCCTTGTTCCCTGGTCCAT CCAAGCCATTCTGGGTGTTGGTCGTAGTG GGTGGAGTCCTCGCTTGTTACTCTCTGCT CGTCACCGTGGCTTTTATAATCTTCTGGG TTAGATCCAAAAGAAGCCGCCTGCTCCAT AGCGATTACATGAATATGACTCCACGCCG CCCTGGCCCCACAAGGAAACACTACCAGC CTTACGCACCACCTAGAGATTTCGCTGCC TATCGGAGCAGGGTGAAGTTTTCCAGATC TGCAGATGCACCAGCGTATCAGCAGGGCC AGAACCAACTGTATAACGAGCTCAACCTG GGACGCAGGGAAGAGTATGACGTTTTGGA CAAGCGCAGAGGACGGGACCCTGAGATGG GTGGCAAACCAAGACGAAAAAACCCCCAG GAGGGTCTCTATAATGAGCTGCAGAAGGA TAAGATGGCTGAAGCCTATTCTGAAATAG GCATGAAAGGAGAGCGGAGAAGGGGAAAA GGGCACGACGGTTTGTACCAGGGACTCAG CACTGCTACGAAGGATACTTATGACGCTC TCCACATGCAAGCCCTGCCACCTAGGTAA	159	MALPVTALLLPLALLL HAARPDIVMTQSPDSL AVSLGERATINCKSSQ SVLYSSNNKNYLAWYQ QKPGQPPKLLIYWAST RESGVPDRFSGSGSGT DFTLTISSLQAEDVAV YYCQQFAHTPFTFGGG TKVEIKRGSTSGSGKP GSGEGSTKGQVQLVQS GAEVKKPGSSVKVSCK ASGGTFSSYAISWVRQ APGQGLEWMGGIIPIF GTANYAQKFQGRVTIT ADESTSTAYMELSSLR SEDTAVYYCARTPEYS SSIWHYYYGMDVWGQG TTVTVSSAAALDNEKS NGTIIHVKGKHLCPSP LFPGPSKPFWVLVVVG GVLACYSLLVTVAFII FWVRSKRSRLLHSDYM NMTPRRPGPTRKHYQP YAPPRDFAAYRSRVKF SRSADAPAYQQGQNQL YNELNLGRREEYDVLD KRRGRDPEMGGKPRRK NPQEGLYNELQKDKMA EAYSEIGMKGERRRGK GHDGLYQGLSTATKDT YDALHMQALPPR	160

RD-21530CARHxL	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTGCAGCTGGTGGAGTCTGGG GGAGGCGTGGTCCAGCCTGGGAGGTCCCT GAGACTCTCCTGTGCAGCGTCTGGATTCA CCTTCAGTAGCTATGGCATGCACTGGGTC CGCCAGGCTCCAGGCAAGGGGCTGGAGTG GGTGGCAGTTATATCGTATGATGGAAGTA ATAAATACTATGCAGACTCCGTGAAGGGC CGATTCACCATCTCCAGAGACAATTCCAA GAACACGCTGTATCTGCAAATGAACAGCC TGAGAGCCGAGGACACGGCGGTGTACTAC TGCGTCAAGGGGCCGTTGCAGGAGCCGCC ATACGATTATGGAATGGACGTATGGGGCC AGGGAACAACTGTCACCGTCTCCTCAGGG TCTACATCCGGCTCCGGGAAGCCCGGAAG TGGCGAAGGTAGTACAAAGGGGGAAATAG TGATGACGCAGTCTCCAGCCACCCTGTCT GTGTCTCCAGGGGAAAGAGCCACCCTCTC CTGCAGGGCCAGTCAGAGTGTTAGCAGCA ACTTAGCCTGGTACCAGCAGAAACCTGGC CAGGCTCCCAGGCTCCTCATCTATAGCGC ATCCACCAGGGCCACTGGTATCCCAGCCA GGTTCAGTGGCAGTGGGTCTGGGACAGAG TTCACTCTCACCATCAGCAGCCTGCAGTC TGAAGATTTTGCAGTTTATTACTGTCAGC AGCACCACGTCTGGCCTCTCACTTTTGGC GGAGGGACCAAGGTTGAGATCAAACGGGC CGCTGCCCTTGATAATGAAAAGTCAAACG GAACAATCATTCACGTGAAGGGCAAGCAC CTCTGTCCGTCACCCTTGTTCCCTGGTCC ATCCAAGCCATTCTGGGTGTTGGTCGTAG TGGGTGGAGTCCTCGCTTGTTACTCTCTG CTCGTCACCGTGGCTTTTATAATCTTCTG GGTTAGATCCAAAAGAAGCCGCCTGCTCC ATAGCGATTACATGAATATGACTCCACGC CGCCCTGGCCCCACAAGGAAACACTACCA GCCTTACGCACCACCTAGAGATTTCGCTG CCTATCGGAGCAGGGTGAAGTTTTCCAGA TCTGCAGATGCACCAGCGTATCAGCAGGG CCAGAACCAACTGTATAACGAGCTCAACC TGGGACGCAGGGAAGAGTATGACGTTTTG GACAAGCGCAGAGGACGGGACCCTGAGAT GGGTGGCAAACCAAGACGAAAAAACCCCC AGGAGGGTCTCTATAATGAGCTGCAGAAG GATAAGATGGCTGAAGCCTATTCTGAAAT AGGCATGAAAGGAGAGCGGAGAAGGGGAA AAGGGCACGACGGTTTGTACCAGGGACTC AGCACTGCTACGAAGGATACTTATGACGC TCTCCACATGCAAGCCCTGCCACCTAGGT AA	161	MALPVTALLLPLALLL HAARPQVQLVESGGGV VQPGRSLRLSCAASGF TFSSYGMHWVRQAPGK GLEWVAVISYDGSNKY YADSVKGRFTISRDNS KNTLYLQMNSLRAEDT AVYYCVKGPLQEPPYD YGMDVWGQGTTVTVSS GSTSGSGKPGSGEGST KGEIVMTQSPATLSVS PGERATLSCRASQSVS SNLAWYQQKPGQAPRL LIYSASTRATGIPARF SGSGSGTEFTLTISSL QSEDFAVYYCQQHHVW PLTFGGGTKVEIKRAA ALDNEKSNGTIIHVKG KHLCPSPLFPGPSKPF WVLVVVGGVLACYSLL VTVAFIIFWVRSKRSR LLHSDYMNMTPRRPGP TRKHYQPYAPPRDFAA YRSRVKFSRSADAPAY QQGQNQLYNELNLGRR EEYDVLDKRRGRDPEM GGKPRRKNPQEGLYNE LQKDKMAEAYSEIGMK GERRRGKGHDGLYQGL STATKDTYDALHMQAL PPR	162
RD-21530CARLxH	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGGAAATAGTGATGACGCAGTCTCCA GCCACCCTGTCTGTGTCTCCAGGGGAAAG AGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGCAACTTAGCCTGGTACCAG CAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATAGCGCATCCACCAGGGCCACTG	163	MALPVTALLLPLALLL HAARPEIVMTQSPATL SVSPGERATLSCRASQ SVSSNLAWYQQKPGQA PRLLIYSASTRATGIP ARFSGSGSGTEFTLTI SSLQSEDFAVYYCQQH HVWPLTFGGGTKVEIK	164

	GTATCCCAGCCAGGTTCAGTGGCAGTGGG TCTGGGACAGAGTTCACTCTCACCATCAG CAGCCTGCAGTCTGAAGATTTTGCAGTTT ATTACTGTCAGCAGCACCACGTCTGGCCT CTCACTTTTGGCGGAGGGACCAAGGTTGA GATCAAACGGGGGTCTACATCCGGCTCCG GGAAGCCCGGAAGTGGCGAAGGTAGTACA AAGGGGCAGGTGCAGCTGGTGGAGTCTGG GGGAGGCGTGGTCCAGCCTGGGAGGTCCC TGAGACTCTCCTGTGCAGCGTCTGGATTC ACCTTCAGTAGCTATGGCATGCACTGGGT CCGCCAGGCTCCAGGCAAGGGGCTGGAGT GGGTGGCAGTTATATCGTATGATGGAAGT AATAAATACTATGCAGACTCCGTGAAGGG CCGATTCACCATCTCCAGAGACAATTCCA AGAACACGCTGTATCTGCAAATGAACAGC CTGAGAGCCGAGGACACGGCGGTGTACTA CTGCGTCAAGGGGCCGTTGCAGGAGCCGC CATACGATTATGGAATGGACGTATGGGGC CAGGGAACAACTGTCACCGTCTCCTCAGC CGCTGCCCTTGATAATGAAAAGTCAAACG GAACAATCATTCACGTGAAGGGCAAGCAC CTCTGTCCGTCACCCTTGTTCCCTGGTCC ATCCAAGCCATTCTGGGTGTTGGTCGTAG TGGGTGGAGTCCTCGCTTGTTACTCTCTG CTCGTCACCGTGGCTTTTATAATCTTCTG GGTTAGATCCAAAAGAAGCCGCCTGCTCC ATAGCGATTACATGAATATGACTCCACGC CGCCCTGGCCCCACAAGGAAACACTACCA GCCTTACGCACCACCTAGAGATTTCGCTG CCTATCGGAGCAGGGTGAAGTTTTCCAGA TCTGCAGATGCACCAGCGTATCAGCAGGG CCAGAACCAACTGTATAACGAGCTCAACC TGGGACGCAGGGAAGAGTATGACGTTTTG GACAAGCGCAGAGGACGGGACCCTGAGAT GGGTGGCAAACCAAGACGAAAAAACCCCC AGGAGGGTCTCTATAATGAGCTGCAGAAG GATAAGATGGCTGAAGCCTATTCTGAAAT AGGCATGAAAGGAGAGCGGAGAAGGGGAA AAGGGCACGACGGTTTGTACCAGGGACTC AGCACTGCTACGAAGGATACTTATGACGC TCTCCACATGCAAGCCCTGCCACCTAGGT AA		RGSTSGSGKPGSGEGS TKGQVQLVESGGGVVQ PGRSLRLSCAASGFTF SSYGMHWVRQAPGKGL EWVAVISYDGSNKYYA DSVKGRFTISRDNSKN TLYLQMNSLRAEDTAV YYCVKGPLQEPPYDYG MDVWGQGTTVTVSSAA ALDNEKSNGTIIHVKG KHLCPSPLFPGPSKPF WVLVVVGGVLACYSLL VTVAFIIFWVRSKRSR LLHSDYMNMTPRRPGP TRKHYQPYAPPRDFAA YRSRVKFSRSADAPAY QQGQNQLYNELNLGRR EEYDVLDKRRGRDPEM GGKPRRKNPQEGLYNE LQKDKMAEAYSEIGMK GERRRGKGHDGLYQGL STATKDTYDALHMQAL PPR	
Clone 24C1 THD CAR DNA HxL	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTCCAACTGCAAGAAAGCGGA CCCGGACTGGTGAAGCCTTCTGAGACACT TAGTCTGACGTGCACGGTCAGTGGCGGCT CCATCTCCTCCTATTATTGGTCATGGATA CGACAACCCCCAGGTAAGGGCCTGGAATG GATTGGCTATATCTACTATTCAGGAAGCA CGAACTACAATCCCAGCCTGAAGTCCCGA GTGACAATTTCAGTAGATACCAGTAAAAA CCAGTTCAGTCTTAAACTGTCAAGCGTGA CAGCTGCCGACACCGCTGTGTATTACTGC GTCTCACTGGTGTATTGTGGAGGGGATTG TTATAGCGGGTTCGATTATTGGGGACAGG GAACCCTGGTGACTGTATCTTCCGGCGGC GGCGGCTCAGGGGGTGGCGGTAGTGGCGG	165	MALPVTALLLPLALLL HAARPQVQLQESGPGL VKPSETLSLTCTVSGG SISSYYWSWIRQPPGK GLEWIGYIYYSGSTNY NPSLKSRVTISVDTSK NQFSLKLSSVTAADTA VYYCVSLVYCGGDCYS GFDYWGQGTLVTVSSG GGGSGGGGSGGGGSDI QLTQSPSSLSASVGDR VSFTCQASQDINNFLN WYQQKPGKAPKLLIYD ASNLETGVPSRFSGSG SGTDFTFTISSLQPED IATYYCQQYGNLPFTF	166

	TGGGGGTTCCGATATTCAACTGACACAAT CCCCCAGCTCACTCAGCGCCAGCGTGGGG GACAGGGTTAGCTTTACCTGTCAAGCCTC TCAGGATATAAATAACTTTCTGAACTGGT ATCAACAGAAGCCTGGGAAGGCGCCCAAA CTCCTGATCTATGATGCGTCCAACCTGGA AACTGGCGTGCCTTCACGCTTTAGCGGCT CTGGCAGTGGTACAGACTTCACTTTTACC ATCTCTTCACTTCAGCCGGAGGACATCGC CACATATTACTGTCAACAGTACGGAAACT TGCCCTTTACTTTTGGAGGCGGCACCAAA GTTGAAATCAAAAGGGCCGCTGCCCTGGA TAACGAAAAGAGCAATGGGACTATAATAC ATGTTAAAGGAAAACACCTGTGTCCATCT CCCCTGTTCCCTGGACCGTCAAAGCCATT TTGGGTGCTCGTGGTTGTCGGTGGCGTTC TCGCCTGTTATAGCTTGCTGGTGACAGTA GCCTTCATTATCTTTTGGGTGAGATCCAA AAGAAGCCGCCTGCTCCATAGCGATTACA TGAATATGACTCCACGCCGCCCTGGCCCC ACAAGGAAACACTACCAGCCTTACGCACC ACCTAGAGATTTCGCTGCCTATCGGAGCA GGGTGAAGTTTTCCAGATCTGCAGATGCA CCAGCGTATCAGCAGGGCCAGAACCAACT GTATAACGAGCTCAACCTGGGACGCAGGG AAGAGTATGACGTTTTGGACAAGCGCAGA GGACGGGACCCTGAGATGGGTGGCAAACC AAGACGAAAAAACCCCCAGGAGGGTCTCT ATAATGAGCTGCAGAAGGATAAGATGGCT GAAGCCTATTCTGAAATAGGCATGAAAGG AGAGCGGAGAAGGGGAAAAGGGCACGACG GTTTGTACCAGGGACTCAGCACTGCTACG AAGGATACTTATGACGCTCTCCACATGCA AGCCCTGCCACCTAGGTAA		GGGTKVEIKRAAALDN EKSNGTIIHVKGKHLC PSPLFPGPSKPFWVLV VVGGVLACYSLLVTVA FIIFWVRSKRSRLLHS DYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSR VKFSRSADAPAYQQGQ NQLYNELNLGRREEYD VLDKRRGRDPEMGGKP RRKNPQEGLYNELQKD KMAEAYSEIGMKGERR RGKGHDGLYQGLSTAT KDTYDALHMQALPPR	
(CAR1.1) Clone 24C1 THD CAR DNA HxL	CAGGTCCAACTGCAAGAAAGCGGACCCGG ACTGGTGAAGCCTTCTGAGACACTTAGTC TGACGTGCACGGTCAGTGGCGGCTCCATC TCCTCCTATTATTGGTCATGGATACGACA ACCCCCAGGTAAGGGCCTGGAATGGATTG GCTATATCTACTATTCAGGAAGCACGAAC TACAATCCCAGCCTGAAGTCCCGAGTGAC AATTTCAGTAGATACCAGTAAAAACCAGT TCAGTCTTAAACTGTCAAGCGTGACAGCT GCCGACACCGCTGTGTATTACTGCGTCTC ACTGGTGTATTGTGGAGGGGATTGTTATA GCGGGTTCGATTATTGGGGACAGGGAACC CTGGTGACTGTATCTTCCGGCGGCGGCGG CTCAGGGGGTGGCGGTAGTGGCGGTGGGG GTTCCGATATTCAACTGACACAATCCCCC AGCTCACTCAGCGCCAGCGTGGGGGACAG GGTTAGCTTTACCTGTCAAGCCTCTCAGG ATATAAATAACTTTCTGAACTGGTATCAA CAGAAGCCTGGGAAGGCGCCCAAACTCCT GATCTATGATGCGTCCAACCTGGAAACTG GCGTGCCTTCACGCTTTAGCGGCTCTGGC AGTGGTACAGACTTCACTTTTACCATCTC TTCACTTCAGCCGGAGGACATCGCCACAT ATTACTGTCAACAGTACGGAAACTTGCCC TTTACTTTTGGAGGCGGCACCAAAGTTGA	167	QVQLQESGPGLVKPSE TLSLTCTVSGGSISSY YWSWIRQPPGKGLEWI GYIYYSGSTNYNPSLK SRVTISVDTSKNQFSL KLSSVTAADTAVYYCV SLVYCGGDCYSGFDYW GQGTLVTVSSGGGGSG GGGSGGGGSDIQLTQS PSSLSASVGDRVSFTC QASQDINNFLNWYQQK PGKAPKLLIYDASNLE TGVPSRFSGSGSGTDF TFTISSLQPEDIATYY CQQYGNLPFTFGGGTK VEIKRAAALDNEKSNG TIIHVKGKHLCPSPLF PGPSKPFWVLVVVGGV LACYSLLVTVAFIIFW VRSKRSRLLHSDYMNM TPRRPGPTRKHYQPYA PPRDFAAYRSRVKFSR SADAPAYQQGQNQLYN ELNLGRREEYDVLDKR RGRDPEMGGKPRRKNP	168

	AATCAAAAGGGCCGCTGCCCTGGATAACG AAAAGAGCAATGGGACTATAATACATGTT AAAGGAAAACACCTGTGTCCATCTCCCCT GTTCCCTGGACCGTCAAAGCCATTTTGGG TGCTCGTGGTTGTCGGTGGCGTTCTCGCC TGTTATAGCTTGCTGGTGACAGTAGCCTT CATTATCTTTTGGGTGAGATCCAAAAGAA GCCGCCTGCTCCATAGCGATTACATGAAT ATGACTCCACGCCGCCCTGGCCCCACAAG GAAACACTACCAGCCTTACGCACCACCTA GAGATTTCGCTGCCTATCGGAGCAGGGTG AAGTTTTCCAGATCTGCAGATGCACCAGC GTATCAGCAGGGCCAGAACCAACTGTATA ACGAGCTCAACCTGGGACGCAGGGAAGAG TATGACGTTTTGGACAAGCGCAGAGGACG GGACCCTGAGATGGGTGGCAAACCAAGAC GAAAAAACCCCCAGGAGGGTCTCTATAAT GAGCTGCAGAAGGATAAGATGGCTGAAGC CTATTCTGAAATAGGCATGAAAGGAGAGC GGAGAAGGGGAAAAGGGCACGACGGTTTG TACCAGGGACTCAGCACTGCTACGAAGGA TACTTATGACGCTCTCCACATGCAAGCCC TGCCACCTAGG		QEGLYNELQKDKMAEA YSEIGMKGERRRGKGH DGLYQGLSTATKDTYD ALHMQALPPR	
(CAR1.2) Clone 24C1 CHD CAR DNA HxL	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTGCAGCTGCAGGAATCCGGA CCGGGGCTGGTGAAGCCCAGCGAGACTCT GAGTCTCACGTGTACAGTTTCTGGAGGTA GCATTAGCTCCTACTATTGGTCATGGATA AGGCAGCCCCCCGGGAAGGGATTGGAATG GATCGGCTATATTTACTACAGTGGGAGCA CCAATTACAACCCCTCACTGAAGTCTAGA GTTACAATCAGCGTTGACACCTCAAAGAA TCAGTTCAGTTTGAAATTGTCTAGCGTCA CAGCAGCTGATACAGCCGTCTATTATTGT GTTTCTCTGGTCTATTGCGGTGGGGATTG TTACAGTGGCTTTGACTATTGGGGGCAGG GTACTCTGGTTACAGTTTCTTCCGGGGGG GGAGGCTCTGGGGGCGGAGGCTCAGGTGG TGGAGGCAGCGACATCCAGTTGACACAGA GCCCGAGTTCCTTGTCCGCCTCCGTCGGG GATAGAGTGTCATTTACCTGTCAGGCCTC TCAGGATATTAATAACTTTCTGAATTGGT ATCAGCAAAAGCCCGGAAAGGCACCCAAG CTGTTGATTTACGACGCCAGTAACCTGGA GACAGGCGTGCCCTCCCGGTTTAGTGGTA GCGGAAGCGGTACGGATTTTACCTTTACT ATCAGCTCTCTCCAACCCGAAGACATTGC AACCTACTATTGTCAACAATATGGAAACC TGCCTTTTACATTTGGCGGCGGCACCAAG GTGGAGATTAAGCGGGCGGCAGCTATTGA GGTGATGTATCCACCGCCTTACCTGGATA ACGAAAAGAGTAACGGTACCATCATTCAC GTGAAAGGTAAACACCTGTGTCCTTCTCC CCTCTTCCCCGGGCCATCAAAGCCCTTCT GGGTTCTTGTGGTCGTGGGAGGCGTGCTT GCTTGTTATTCTCTGCTCGTTACCGTGGC GTTTATCATTTTTTGGGTTAGATCCAAAA GAAGCCGCCTGCTCCATAGCGATTACATG	169	MALPVTALLLPLALLL HAARPQVQLQESGPGL VKPSETLSLTCTVSGG SISSYYWSWIRQPPGK GLEWIGYIYYSGSTNY NPSLKSRVTISVDTSK NQFSLKLSSVTAADTA VYYCVSLVYCGGDCYS GFDYWGQGTLVTVSSG GGGSGGGGSGGGGSDI QLTQSPSSLSASVGDR VSFTCQASQDINNFLN WYQQKPGKAPKLLIYD ASNLETGVPSRFSGSG SGTDFTFTISSLQPED IATYYCQQYGNLPFTF GGGTKVEIKRAAAIEV MYPPPYLDNEKSNGTI IHVKGKHLCPSPLFPG PSKPFWVLVVVGGVLA CYSLLVTVAFIIFWVR SKRSRLLHSDYMNMTP RRPGPTRKHYQPYAPP RDFAAYRSRVKFSRSA DAPAYQQGQNQLYNEL NLGRREEYDVLDKRRG RDPEMGGKPRRKNPQE GLYNELQKDKMAEAYS EIGMKGERRRGKGHDG LYQGLSTATKDTYDAL HMQALPPR	170

	AATATGACTCCACGCCGCCCTGGCCCCAC AAGGAAACACTACCAGCCTTACGCACCAC CTAGAGATTTCGCTGCCTATCGGAGCAGG GTGAAGTTTTCCAGATCTGCAGATGCACC AGCGTATCAGCAGGGCCAGAACCAACTGT ATAACGAGCTCAACCTGGGACGCAGGGAA GAGTATGACGTTTTGGACAAGCGCAGAGG ACGGGACCCTGAGATGGGTGGCAAACCAA GACGAAAAAACCCCCAGGAGGGTCTCTAT AATGAGCTGCAGAAGGATAAGATGGCTGA AGCCTATTCTGAAATAGGCATGAAAGGAG AGCGGAGAAGGGGAAAAGGGCACGACGGT TTGTACCAGGGACTCAGCACTGCTACGAA GGATACTTATGACGCTCTCCACATGCAAG CCCTGCCACCTAGGTAA			
(CAR1.2) Clone 24C1 CHD CAR DNA HxL	CAGGTGCAGCTGCAGGAATCCGGACCGGG GCTGGTGAAGCCCAGCGAGACTCTGAGTC TCACGTGTACAGTTTCTGGAGGTAGCATT AGCTCCTACTATTGGTCATGGATAAGGCA GCCCCCCGGGAAGGGATTGGAATGGATCG GCTATATTTACTACAGTGGGAGCACCAAT TACAACCCCTCACTGAAGTCTAGAGTTAC AATCAGCGTTGACACCTCAAAGAATCAGT TCAGTTTGAAATTGTCTAGCGTCACAGCA GCTGATACAGCCGTCTATTATTGTGTTTC TCTGGTCTATTGCGGTGGGGATTGTTACA GTGGCTTTGACTATTGGGGGCAGGGTACT CTGGTTACAGTTTCTTCCGGGGGGGGAGG CTCTGGGGGCGGAGGCTCAGGTGGTGGAG GCAGCGACATCCAGTTGACACAGAGCCCG AGTTCCTTGTCCGCCTCCGTCGGGGATAG AGTGTCATTTACCTGTCAGGCCTCTCAGG ATATTAATAACTTTCTGAATTGGTATCAG CAAAAGCCCGGAAAGGCACCCAAGCTGTT GATTTACGACGCCAGTAACCTGGAGACAG GCGTGCCCTCCCGGTTTAGTGGTAGCGGA AGCGGTACGGATTTTACCTTTACTATCAG CTCTCTCCAACCCGAAGACATTGCAACCT ACTATTGTCAACAATATGGAAACCTGCCT TTTACATTTGGCGGCGGCACCAAGGTGGA GATTAAGCGGGCGGCAGCTATTGAGGTGA TGTATCCACCGCCTTACCTGGATAACGAA AAGAGTAACGGTACCATCATTCACGTGAA AGGTAAACACCTGTGTCCTTCTCCCCTCT TCCCCGGGCCATCAAAGCCCTTCTGGGTT CTTGTGGTCGTGGGAGGCGTGCTTGCTTG TTATTCTCTGCTCGTTACCGTGGCGTTTA TCATTTTTTGGGTTAGATCCAAAAGAAGC CGCCTGCTCCATAGCGATTACATGAATAT GACTCCACGCCGCCCTGGCCCCACAAGGA AACACTACCAGCCTTACGCACCACCTAGA GATTTCGCTGCCTATCGGAGCAGGGTGAA GTTTTCCAGATCTGCAGATGCACCAGCGT ATCAGCAGGGCCAGAACCAACTGTATAAC GAGCTCAACCTGGGACGCAGGGAAGAGTA TGACGTTTTGGACAAGCGCAGAGGACGGG ACCCTGAGATGGGTGGCAAACCAAGACGA AAAAACCCCCAGGAGGGTCTCTATAATGA GCTGCAGAAGGATAAGATGGCTGAAGCCT	171	QVQLQESGPGLVKPSE TLSLTCTVSGGSISSY YWSWIRQPPGKGLEWI GYIYYSGSTNYNPSLK SRVTISVDTSKNQFSL KLSSVTAADTAVYYCV SLVYCGGDCYSGFDYW GQGTLVTVSSGGGGSG GGGSGGGGSDIQLTQS PSSLSASVGDRVSFTC QASQDINNFLNWYQQK PGKAPKLLIYDASNLE TGVPSRFSGSGSGTDF TFTISSLQPEDIATYY CQQYGNLPFTFGGGTK VEIKRAAAIEVMYPPP YLDNEKSNGTIIHVKG KHLCPSPLFPGPSKPF WVLVVVGGVLACYSLL VTVAFIIFWVRSKRSR LLHSDYMNMTPRRPGP TRKHYQPYAPPRDFAA YRSRVKFSRSADAPAY QQGQNQLYNELNLGRR EEYDVLDKRRGRDPEM GGKPRRKNPQEGLYNE LQKDKMAEAYSEIGMK GERRRGKGHDGLYQGL STATKDTYDALHMQAL PPR	172

	ATTCTGAAATAGGCATGAAAGGAGAGCGG AGAAGGGGAAAAGGGCACGACGGTTTGTA CCAGGGACTCAGCACTGCTACGAAGGATA CTTATGACGCTCTCCACATGCAAGCCCTG CCACCTAGG			
(CAR1.3) Clone 24C1 CD8 CAR DNA HxL	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTGCAATTGCAAGAGTCCGGC CCCGGACTCGTTAAACCCAGTGAGACGCT TAGCCTGACCTGTACCGTCTCAGGGGGCA GCATCTCCTCTTATTACTGGAGCTGGATC AGGCAGCCTCCAGGAAAAGGCCTTGAATG GATTGGGTACATCTACTACTCTGGCTCAA CAAATTATAATCCATCCCTGAAGTCCCGC GTGACTATCTCTGTGGACACCAGCAAGAA TCAGTTTTCACTGAAGTTGTCTAGTGTTA CCGCGGCCGACACCGCCGTATACTACTGT GTGTCTCTTGTGTACTGTGGCGGCGACTG CTATTCCGGGTTCGACTACTGGGGCCAAG GGACTCTGGTAACCGTGTCCTCAGGCGGC GGCGGGTCAGGAGGAGGCGGCAGTGGAGG TGGCGGCTCCGACATCCAGCTGACACAAT CACCATCTTCCCTTTCAGCTTCAGTCGGG GACAGAGTGTCCTTCACATGCCAGGCCAG CCAGGATATCAATAACTTCCTGAACTGGT ACCAACAGAAACCCGGAAAGGCTCCAAAG CTCCTGATCTATGATGCTTCCAACCTGGA GACCGGCGTGCCCTCCAGGTTCAGTGGTT CAGGATCAGGCACTGACTTTACGTTCACC ATATCCAGTCTTCAGCCCGAAGACATTGC AACCTATTACTGCCAACAATACGGGAACC TTCCCTTTACATTCGGAGGCGGCACCAAG GTGGAAATCAAAAGGGCTGCAGCATTGAG CAACTCAATAATGTATTTTAGTCACTTTG TACCAGTGTTCTTGCCGGCTAAGCCTACT ACCACACCCGCTCCACGGCCACCTACCCC AGCTCCTACCATCGCTTCACAGCCTCTGT CCCTGCGCCCAGAGGCTTGCCGACCGGCC GCAGGGGGCGCTGTTCATACCAGAGGACT GGATTTCGCCTGCGATATCTATATCTGGG CACCCCTGGCCGGAACCTGCGGCGTACTC CTGCTGTCCCTGGTCATCACGCTCTATTG TAATCACAGGAACAGATCCAAAAGAAGCC GCCTGCTCCATAGCGATTACATGAATATG ACTCCACGCCGCCCTGGCCCCACAAGGAA ACACTACCAGCCTTACGCACCACCTAGAG ATTTCGCTGCCTATCGGAGCAGGGTGAAG TTTTCCAGATCTGCAGATGCACCAGCGTA TCAGCAGGGCCAGAACCAACTGTATAACG AGCTCAACCTGGGACGCAGGGAAGAGTAT GACGTTTTGGACAAGCGCAGAGGACGGGA CCCTGAGATGGGTGGCAAACCAAGACGAA AAAACCCCCAGGAGGGTCTCTATAATGAG CTGCAGAAGGATAAGATGGCTGAAGCCTA TTCTGAAATAGGCATGAAAGGAGAGCGGA GAAGGGGAAAAGGGCACGACGGTTTGTAC CAGGGACTCAGCACTGCTACGAAGGATAC TTATGACGCTCTCCACATGCAAGCCCTGC CACCTAGGTAA	173	MALPVTALLLPLALLL HAARPQVQLQESGPGL VKPSETLSLTCTVSGG SISSYYWSWIRQPPGK GLEWIGYIYYSGSTNY NPSLKSRVTISVDTSK NQFSLKLSSVTAADTA VYYCVSLVYCGGDCYS GFDYWGQGTLVTVSSG GGGSGGGGSGGGGSDI QLTQSPSSLSASVGDR VSFTCQASQDINNFLN WYQQKPGKAPKLLIYD ASNLETGVPSRFSGSG SGTDFTFTISSLQPED IATYYCQQYGNLPFTF GGGTKVEIKRAAALSN SIMYFSHFVPVFLPAK PTTTPAPRPPTPAPTI ASQPLSLRPEACRPAA GGAVHTRGLDFACDIY IWAPLAGTCGVLLLSL VITLYCNHRNRSKRSR LLHSDYMNMTPRRPGP TRKHYQPYAPPRDFAA YRSRVKFSRSADAPAY QQGQNQLYNELNLGRR EEYDVLDKRRGRDPEM GGKPRRKNPQEGLYNE LQKDKMAEAYSEIGMK GERRRGKGHDGLYQGL STATKDTYDALHMQAL PPR	174

(CAR1.3) Clone 24C1 CD8 CAR DNA HxL	CAGGTGCAATTGCAAGAGTCCGGCCCCGG ACTCGTTAAACCCAGTGAGACGCTTAGCC TGACCTGTACCGTCTCAGGGGGCAGCATC TCCTCTTATTACTGGAGCTGGATCAGGCA GCCTCCAGGAAAAGGCCTTGAATGGATTG GGTACATCTACTACTCTGGCTCAACAAAT TATAATCCATCCCTGAAGTCCCGCGTGAC TATCTCTGTGGACACCAGCAAGAATCAGT TTTCACTGAAGTTGTCTAGTGTTACCGCG GCCGACACCGCCGTATACTACTGTGTGTC TCTTGTGTACTGTGGCGGCGACTGCTATT CCGGGTTCGACTACTGGGGCCAAGGGACT CTGGTAACCGTGTCCTCAGGCGGCGGCGG GTCAGGAGGAGGCGGCAGTGGAGGTGGCG GCTCCGACATCCAGCTGACACAATCACCA TCTTCCCTTTCAGCTTCAGTCGGGGACAG AGTGTCCTTCACATGCCAGGCCAGCCAGG ATATCAATAACTTCCTGAACTGGTACCAA CAGAAACCCGGAAAGGCTCCAAAGCTCCT GATCTATGATGCTTCCAACCTGGAGACCG GCGTGCCCTCCAGGTTCAGTGGTTCAGGA TCAGGCACTGACTTTACGTTCACCATATC CAGTCTTCAGCCCGAAGACATTGCAACCT ATTACTGCCAACAATACGGGAACCTTCCC TTTACATTCGGAGGCGGCACCAAGGTGGA AATCAAAAGGGCTGCAGCATTGAGCAACT CAATAATGTATTTTAGTCACTTTGTACCA GTGTTCTTGCCGGCTAAGCCTACTACCAC ACCCGCTCCACGGCCACCTACCCCAGCTC CTACCATCGCTTCACAGCCTCTGTCCCTG CGCCCAGAGGCTTGCCGACCGGCCGCAGG GGGCGCTGTTCATACCAGAGGACTGGATT TCGCCTGCGATATCTATATCTGGGCACCC CTGGCCGGAACCTGCGGCGTACTCCTGCT GTCCCTGGTCATCACGCTCTATTGTAATC ACAGGAACAGATCCAAAAGAAGCCGCCTG CTCCATAGCGATTACATGAATATGACTCC ACGCCGCCCTGGCCCCACAAGGAAACACT ACCAGCCTTACGCACCACCTAGAGATTTC GCTGCCTATCGGAGCAGGGTGAAGTTTTC CAGATCTGCAGATGCACCAGCGTATCAGC AGGGCCAGAACCAACTGTATAACGAGCTC AACCTGGGACGCAGGGAAGAGTATGACGT TTTGGACAAGCGCAGAGGACGGGACCCTG AGATGGGTGGCAAACCAAGACGAAAAAAC CCCCAGGAGGGTCTCTATAATGAGCTGCA GAAGGATAAGATGGCTGAAGCCTATTCTG AAATAGGCATGAAAGGAGAGCGGAGAAGG GGAAAAGGGCACGACGGTTTGTACCAGGG ACTCAGCACTGCTACGAAGGATACTTATG ACGCTCTCCACATGCAAGCCCTGCCACCT AGG	175	QVQLQESGPGLVKPSE TLSLTCTVSGGSISSY YWSWIRQPPGKGLEWI GYIYYSGSTNYNPSLK SRVTISVDTSKNQFSL KLSSVTAADTAVYYCV SLVYCGGDCYSGFDYW GQGTLVTVSSGGGGSG GGGSGGGGSDIQLTQS PSSLSASVGDRVSFTC QASQDINNFLNWYQQK PGKAPKLLIYDASNLE TGVPSRFSGSGSGTDF TFTISSLQPEDIATYY CQQYGNLPFTFGGGTK VEIKRAAALSNSIMYF SHFVPVFLPAKPTTTP APRPPTPAPTIASQPL SLRPEACRPAAGGAVH TRGLDFACDIYIWAPL AGTCGVLLLSLVITLY CNHRNRSKRSRLLHSD YMNMTPRRPGPTRKHY QPYAPPRDFAAYRSRV KFSRSADAPAYQQGQN QLYNELNLGRREEYDV LDKRRGRDPEMGGKPR RKNPQEGLYNELQKDK MAEAYSEIGMKGERRR GKGHDGLYQGLSTATK DTYDALHMQALPPR	176
(CAR1.4) Clone 24C1 THD CAR DNA LxH	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGGATATCCAGCTCACGCAATCCCCC TCAAGCTTGAGTGCCTCCGTGGGCGACCG GGTGTCCTTCACATGTCAGGCAAGCCAAG ACATAAATAATTTCCTGAATTGGTACCAA CAAAAACCCGGCAAGGCTCCCAAACTCCT	177	MALPVTALLLPLALLL HAARPDIQLTQSPSSL SASVGDRVSFTCQASQ DINNFLNWYQQKPGKA PKLLIYDASNLETGVP SRFSGSGSGTDFTFTI SSLQPEDIATYYCQQY	178

	GATTTATGATGCCTCCAATCTGGAGACCG GGGTCCCTTCTAGATTCAGCGGAAGTGGC AGCGGCACAGACTTTACATTTACTATCTC TTCTCTGCAACCAGAGGACATCGCCACAT ACTATTGCCAGCAATACGGCAATCTGCCC TTCACCTTCGGAGGCGGAACCAAGGTAGA AATTAAAAGGGGCGGTGGAGGCTCCGGAG GGGGGGGCTCTGGCGGAGGGGGCTCCCAA GTACAATTGCAGGAGTCAGGGCCTGGACT CGTGAAGCCTTCAGAAACTTTGTCACTGA CATGTACAGTGTCCGGCGGAAGCATTTCC AGTTACTATTGGTCCTGGATTAGACAGCC ACCCGGCAAAGGACTGGAATGGATTGGAT ATATCTACTACTCTGGATCTACAAACTAT AATCCCAGCCTCAAATCCAGGGTCACTAT TAGTGTGGATACATCAAAGAATCAGTTCT CCTTGAAGCTGAGCTCAGTCACTGCTGCC GACACCGCAGTGTACTATTGTGTGAGCCT GGTCTACTGCGGCGGAGATTGCTACAGCG GTTTCGATTACTGGGGCCAGGGCACCCTG GTTACCGTTAGTTCCGCGGCTGCTCTTGA TAACGAGAAGTCCAACGGTACGATTATCC ACGTTAAGGGTAAGCACCTTTGCCCTAGC CCGCTGTTCCCAGGCCCCAGTAAGCCCTT TTGGGTCCTCGTTGTGGTAGGTGGGGTAC TCGCCTGCTACTCCCTGCTCGTCACTGTC GCATTCATCATCTTCTGGGTCAGATCCAA AAGAAGCCGCCTGCTCCATAGCGATTACA TGAATATGACTCCACGCCGCCCTGGCCCC ACAAGGAAACACTACCAGCCTTACGCACC ACCTAGAGATTTCGCTGCCTATCGGAGCA GGGTGAAGTTTTCCAGATCTGCAGATGCA CCAGCGTATCAGCAGGGCCAGAACCAACT GTATAACGAGCTCAACCTGGGACGCAGGG AAGAGTATGACGTTTTGGACAAGCGCAGA GGACGGGACCCTGAGATGGGTGGCAAACC AAGACGAAAAAACCCCCAGGAGGGTCTCT ATAATGAGCTGCAGAAGGATAAGATGGCT GAAGCCTATTCTGAAATAGGCATGAAAGG AGAGCGGAGAAGGGGAAAAGGGCACGACG GTTTGTACCAGGGACTCAGCACTGCTACG AAGGATACTTATGACGCTCTCCACATGCA AGCCCTGCCACCTAGGTAA		GNLPFTFGGGTKVEIK RGGGGSGGGGSGGGGS QVQLQESGPGLVKPSE TLSLTCTVSGGSISSY YWSWIRQPPGKGLEWI GYIYYSGSTNYNPSLK SRVTISVDTSKNQFSL KLSSVTAADTAVYYCV SLVYCGGDCYSGFDYW GQGTLVTVSSAAALDN EKSNGTIIHVKGKHLC PSPLFPGPSKPFWVLV VVGGVLACYSLLVTVA FIIFWVRSKRSRLLHS DYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSR VKFSRSADAPAYQQGQ NQLYNELNLGRREEYD VLDKRRGRDPEMGGKP RRKNPQEGLYNELQKD KMAEAYSEIGMKGERR RGKGHDGLYQGLSTAT KDTYDALHMQALPPR	
(CAR1.4) Clone 24C1 THD CAR DNA LxH	GATATCCAGCTCACGCAATCCCCCTCAAG CTTGAGTGCCTCCGTGGGCGACCGGGTGT CCTTCACATGTCAGGCAAGCCAAGACATA AATAATTTCCTGAATTGGTACCAACAAAA ACCCGGCAAGGCTCCCAAACTCCTGATTT ATGATGCCTCCAATCTGGAGACCGGGGTC CCTTCTAGATTCAGCGGAAGTGGCAGCGG CACAGACTTTACATTTACTATCTCTTCTC TGCAACCAGAGGACATCGCCACATACTAT TGCCAGCAATACGGCAATCTGCCCTTCAC CTTCGGAGGCGGAACCAAGGTAGAAATTA AAAGGGGCGGTGGAGGCTCCGGAGGGGGG GGCTCTGGCGGAGGGGGCTCCCAAGTACA ATTGCAGGAGTCAGGGCCTGGACTCGTGA AGCCTTCAGAAACTTTGTCACTGACATGT ACAGTGTCCGGCGGAAGCATTTCCAGTTA	179	DIQLTQSPSSLSASVG DRVSFTCQASQDINNF LNWYQQKPGKAPKLLI YDASNLETGVPSRFSG SGSGTDFTFTISSLQP EDIATYYCQQYGNLPF TFGGGTKVEIKRGGGG SGGGGSGGGGSQVQLQ ESGPGLVKPSETLSLT CTVSGGSISSYYWSWI RQPPGKGLEWIGYIYY SGSTNYNPSLKSRVTI SVDTSKNQFSLKLSSV TAADTAVYYCVSLVYC GGDCYSGFDYWGQGTL VTVSSAAALDNEKSNG	180

	CTATTGGTCCTGGATTAGACAGCCACCCG GCAAAGGACTGGAATGGATTGGATATATC TACTACTCTGGATCTACAAACTATAATCC CAGCCTCAAATCCAGGGTCACTATTAGTG TGGATACATCAAAGAATCAGTTCTCCTTG AAGCTGAGCTCAGTCACTGCTGCCGACAC CGCAGTGTACTATTGTGTGAGCCTGGTCT ACTGCGGCGGAGATTGCTACAGCGGTTTC GATTACTGGGGCCAGGGCACCCTGGTTAC CGTTAGTTCCGCGGCTGCTCTTGATAACG AGAAGTCCAACGGTACGATTATCCACGTT AAGGGTAAGCACCTTTGCCCTAGCCCGCT GTTCCCAGGCCCCAGTAAGCCCTTTTGGG TCCTCGTTGTGGTAGGTGGGGTACTCGCC TGCTACTCCCTGCTCGTCACTGTCGCATT CATCATCTTCTGGGTCAGATCCAAAAGAA GCCGCCTGCTCCATAGCGATTACATGAAT ATGACTCCACGCCGCCCTGGCCCCACAAG GAAACACTACCAGCCTTACGCACCACCTA GAGATTTCGCTGCCTATCGGAGCAGGGTG AAGTTTTCCAGATCTGCAGATGCACCAGC GTATCAGCAGGGCCAGAACCAACTGTATA ACGAGCTCAACCTGGGACGCAGGGAAGAG TATGACGTTTTGGACAAGCGCAGAGGACG GGACCCTGAGATGGGTGGCAAACCAAGAC GAAAAAACCCCCAGGAGGGTCTCTATAAT GAGCTGCAGAAGGATAAGATGGCTGAAGC CTATTCTGAAATAGGCATGAAAGGAGAGC GGAGAAGGGGAAAAGGGCACGACGGTTTG TACCAGGGACTCAGCACTGCTACGAAGGA TACTTATGACGCTCTCCACATGCAAGCCC TGCCACCTAGG		TIIHVKGKHLCPSPLF PGPSKPFWVLVVVGGV LACYSLLVTVAFIIFW VRSKRSRLLHSDYMNM TPRRPGPTRKHYQPYA PPRDFAAYRSRVKFSR SADAPAYQQGQNQLYN ELNLGRREEYDVLDKR RGRDPEMGGKPRRKNP QEGLYNELQKDKMAEA YSEIGMKGERRRGKGH DGLYQGLSTATKDTYD ALHMQALPPR	
(CAR1.5) Clone 24C1 CHD CAR DNA LxH	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGGATATCCAGCTGACCCAGTCTCCA TCCTCTTTGAGTGCCTCCGTGGGTGACCG CGTCTCTTTCACTTGCCAAGCCAGCCAAG ACATCAACAACTTTCTGAATTGGTACCAG CAGAAACCAGGCAAAGCACCAAAGCTCCT CATCTACGACGCCTCCAACCTGGAAACCG GGGTGCCCAGCAGGTTTAGCGGGAGCGGT TCTGGCACGGATTTTACGTTCACCATCTC CTCTCTGCAGCCCGAGGATATAGCTACTT ATTACTGTCAGCAGTACGGGAATCTGCCA TTTACTTTTGGGGGTGGAACTAAGGTGGA AATCAAAAGGGGCGGCGGGGGAAGCGGGG GCGGGGGCTCAGGTGGCGGAGGGAGCCAG GTGCAACTCCAGGAAAGTGGCCCAGGATT GGTGAAGCCCAGCGAGACCCTTTCCCTTA CTTGTACTGTTAGCGGAGGCAGCATAAGC AGCTACTATTGGTCCTGGATCAGACAGCC ACCAGGGAAAGGGCTTGAATGGATTGGCT ACATTTACTATTCCGGGTCCACCAACTAC AACCCATCCCTCAAGTCCCGCGTGACAAT TTCCGTCGACACAAGCAAGAACCAGTTCT CCCTGAAACTTAGTAGCGTCACTGCTGCA GATACAGCAGTGTACTATTGTGTCAGCCT TGTCTACTGTGGCGGCGACTGCTACAGTG GCTTTGATTACTGGGGACAGGGCACGCTC	181	MALPVTALLLPLALLL HAARPDIQLTQSPSSL SASVGDRVSFTCQASQ DINNFLNWYQQKPGKA PKLLIYDASNLETGVP SRFSGSGSGTDFTFTI SSLQPEDIATYYCQQY GNLPFTFGGGTKVEIK RGGGGSGGGGSGGGGS QVQLQESGPGLVKPSE TLSLTCTVSGGSISSY YWSWIRQPPGKGLEWI GYIYYSGSTNYNPSLK SRVTISVDTSKNQFSL KLSSVTAADTAVYYCV SLVYCGGDCYSGFDYW GQGTLVTVSSAAAIEV MYPPPYLDNEKSNGTI IHVKGKHLCPSPLFPG PSKPFWVLVVVGGVLA CYSLLVTVAFIIFWVR SKRSRLLHSDYMNMTP RRPGPTRKHYQPYAPP RDFAAYRSRVKFSRSA DAPAYQQGQNQLYNEL NLGRREEYDVLDKRRG RDPEMGGKPRRKNPQE	182

	GTGACAGTGTCCAGCGCTGCGGCTATCGA GGTAATGTATCCGCCACCGTATCTGGACA ACGAGAAGTCTAATGGGACAATCATTCAC GTGAAGGGGAAGCACCTGTGTCCATCCCC CCTGTTTCCGGGTCCCAGTAAACCCTTCT GGGTGCTTGTTGTCGTTGGCGGGGTGCTG GCCTGCTATTCCCTGCTGGTGACCGTCGC GTTTATTATTTTCTGGGTTAGATCCAAAA GAAGCCGCCTGCTCCATAGCGATTACATG AATATGACTCCACGCCGCCCTGGCCCCAC AAGGAAACACTACCAGCCTTACGCACCAC CTAGAGATTTCGCTGCCTATCGGAGCAGG GTGAAGTTTTCCAGATCTGCAGATGCACC AGCGTATCAGCAGGGCCAGAACCAACTGT ATAACGAGCTCAACCTGGGACGCAGGGAA GAGTATGACGTTTTGGACAAGCGCAGAGG ACGGGACCCTGAGATGGGTGGCAAACCAA GACGAAAAAACCCCCAGGAGGGTCTCTAT AATGAGCTGCAGAAGGATAAGATGGCTGA AGCCTATTCTGAAATAGGCATGAAAGGAG AGCGGAGAAGGGGAAAAGGGCACGACGGT TTGTACCAGGGACTCAGCACTGCTACGAA GGATACTTATGACGCTCTCCACATGCAAG CCCTGCCACCTAGGTAA		GLYNELQKDKMAEAYS EIGMKGERRRGKGHDG LYQGLSTATKDTYDAL HMQALPPR	
(CAR1.5) Clone 24C1 CHD CAR DNA LxH	GATATCCAGCTGACCCAGTCTCCATCCTC TTTGAGTGCCTCCGTGGGTGACCGCGTCT CTTTCACTTGCCAAGCCAGCCAAGACATC AACAACTTTCTGAATTGGTACCAGCAGAA ACCAGGCAAAGCACCAAAGCTCCTCATCT ACGACGCCTCCAACCTGGAAACCGGGGTG CCCAGCAGGTTTAGCGGGAGCGGTTCTGG CACGGATTTTACGTTCACCATCTCCTCTC TGCAGCCCGAGGATATAGCTACTTATTAC TGTCAGCAGTACGGGAATCTGCCATTTAC TTTTGGGGGTGGAACTAAGGTGGAAATCA AAAGGGGCGGCGGGGGAAGCGGGGGCGGG GGCTCAGGTGGCGGAGGGAGCCAGGTGCA ACTCCAGGAAAGTGGCCCAGGATTGGTGA AGCCCAGCGAGACCCTTTCCCTTACTTGT ACTGTTAGCGGAGGCAGCATAAGCAGCTA CTATTGGTCCTGGATCAGACAGCCACCAG GGAAAGGGCTTGAATGGATTGGCTACATT TACTATTCCGGGTCCACCAACTACAACCC ATCCCTCAAGTCCCGCGTGACAATTTCCG TCGACACAAGCAAGAACCAGTTCTCCCTG AAACTTAGTAGCGTCACTGCTGCAGATAC AGCAGTGTACTATTGTGTCAGCCTTGTCT ACTGTGGCGGCGACTGCTACAGTGGCTTT GATTACTGGGGACAGGGCACGCTCGTGAC AGTGTCCAGCGCTGCGGCTATCGAGGTAA TGTATCCGCCACCGTATCTGGACAACGAG AAGTCTAATGGGACAATCATTCACGTGAA GGGGAAGCACCTGTGTCCATCCCCCCTGT TTCCGGGTCCCAGTAAACCCTTCTGGGTG CTTGTTGTCGTTGGCGGGGTGCTGGCCTG CTATTCCCTGCTGGTGACCGTCGCGTTTA TTATTTTCTGGGTTAGATCCAAAAGAAGC CGCCTGCTCCATAGCGATTACATGAATAT GACTCCACGCCGCCCTGGCCCCACAAGGA	183	DIQLTQSPSSLSASVG DRVSFTCQASQDINNF LNWYQQKPGKAPKLLI YDASNLETGVPSRFSG SGSGTDFTFTISSLQP EDIATYYCQQYGNLPF TFGGGTKVEIKRGGGG SGGGGSGGGGSQVQLQ ESGPGLVKPSETLSLT CTVSGGSISSYYWSWI RQPPGKGLEWIGYIYY SGSTNYNPSLKSRVTI SVDTSKNQFSLKLSSV TAADTAVYYCVSLVYC GGDCYSGFDYWGQGTL VTVSSAAAIEVMYPPP YLDNEKSNGTIIHVKG KHLCPSPLFPGPSKPF WVLVVVGGVLACYSLL VTVAFIIFWVRSKRSR LLHSDYMNMTPRRPGP TRKHYQPYAPPRDFAA YRSRVKFSRSADAPAY QQGQNQLYNELNLGRR EEYDVLDKRRGRDPEM GGKPRRKNPQEGLYNE LQKDKMAEAYSEIGMK GERRRGKGHDGLYQGL STATKDTYDALHMQAL PPR	184

	AACACTACCAGCCTTACGCACCACCTAGA GATTTCGCTGCCTATCGGAGCAGGGTGAA GTTTTCCAGATCTGCAGATGCACCAGCGT ATCAGCAGGGCCAGAACCAACTGTATAAC GAGCTCAACCTGGGACGCAGGGAAGAGTA TGACGTTTTGGACAAGCGCAGAGGACGGG ACCCTGAGATGGGTGGCAAACCAAGACGA AAAAACCCCCAGGAGGGTCTCTATAATGA GCTGCAGAAGGATAAGATGGCTGAAGCCT ATTCTGAAATAGGCATGAAAGGAGAGCGG AGAAGGGGAAAAGGGCACGACGGTTTGTA CCAGGGACTCAGCACTGCTACGAAGGATA CTTATGACGCTCTCCACATGCAAGCCCTG CCACCTAGG			
(CAR1.6) Clone 24C1 CD8 CAR DNA LxH	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGGACATTCAATTGACCCAGTCCCCT AGCAGTCTCTCAGCAAGTGTGGGAGATAG GGTGTCATTCACCTGTCAGGCTTCACAGG ACATCAACAACTTCCTCAATTGGTATCAG CAGAAGCCAGGGAAGGCACCAAAGCTGCT CATATATGACGCTTCAAACCTTGAAACCG GAGTACCTAGCCGCTTCAGCGGAAGCGGA TCAGGGACTGACTTCACTTTTACCATCTC TTCACTGCAGCCCGAAGACATCGCCACAT ACTACTGCCAGCAGTACGGAAACTTGCCT TTTACATTTGGGGGCGGCACCAAAGTGGA GATTAAGCGAGGGGGAGGCGGCTCAGGAG GCGGTGGCTCCGGAGGCGGGGGTTCCCAG GTCCAGCTCCAGGAATCCGGCCCAGGTCT GGTTAAGCCCAGTGAAACTTTGTCCCTCA CGTGTACTGTGAGCGGTGGTTCAATCTCC TCATACTATTGGTCTTGGATACGGCAACC TCCTGGAAAGGGCCTCGAGTGGATCGGCT ATATCTACTATAGTGGCTCCACTAATTAC AACCCTTCCCTCAAGTCCAGAGTCACCAT TTCCGTGGACACATCTAAGAACCAGTTCA GTCTGAAGTTGTCCAGCGTTACAGCCGCA GACACAGCCGTTTATTACTGTGTGTCTCT TGTTTACTGCGGGGGAGACTGTTATAGCG GCTTCGATTACTGGGGCCAGGGCACCTTG GTCACAGTCTCTTCCGCGGCCGCCCTCTC TAACAGTATTATGTACTTTTCTCATTTTG TACCCGTGTTCCTTCCCGCTAAGCCAACT ACTACCCCGGCCCCACGGCCGCCTACCCC TGCACCCACAATAGCCAGTCAGCCTTTGA GCCTGAGACCTGAGGCTTGTCGGCCGGCT GCTGGGGGTGCAGTGCACACACGAGGTCT TGATTTTGCTTGCGACATATACATCTGGG CCCCTCTGGCCGGGACCTGTGGGGTGCTG CTTCTGAGCTTGGTCATCACGCTCTATTG CAACCATCGCAACAGATCCAAAAGAAGCC GCCTGCTCCATAGCGATTACATGAATATG ACTCCACGCCGCCCTGGCCCCACAAGGAA ACACTACCAGCCTTACGCACCACCTAGAG ATTTCGCTGCCTATCGGAGCAGGGTGAAG TTTTCCAGATCTGCAGATGCACCAGCGTA TCAGCAGGGCCAGAACCAACTGTATAACG AGCTCAACCTGGGACGCAGGGAAGAGTAT	185	MALPVTALLLPLALLL HAARPDIQLTQSPSSL SASVGDRVSFTCQASQ DINNFLNWYQQKPGKA PKLLIYDASNLETGVP SRFSGSGSGTDFTFTI SSLQPEDIATYYCQQY GNLPFTFGGGTKVEIK RGGGGSGGGGSGGGGS QVQLQESGPGLVKPSE TLSLTCTVSGGSISSY YWSWIRQPPGKGLEWI GYIYYSGSTNYNPSLK SRVTISVDTSKNQFSL KLSSVTAADTAVYYCV SLVYCGGDCYSGFDYW GQGTLVTVSSAAALSN SIMYFSHFVPVFLPAK PTTTPAPRPPTPAPTI ASQPLSLRPEACRPAA GGAVHTRGLDFACDIY IWAPLAGTCGVLLLSL VITLYCNHRNRSKRSR LLHSDYMNMTPRRPGP TRKHYQPYAPPRDFAA YRSRVKFSRSADAPAY QQGQNQLYNELNLGRR EEYDVLDKRRGRDPEM GGKPRRKNPQEGLYNE LQKDKMAEAYSEIGMK GERRRGKGHDGLYQGL STATKDTYDALHMQAL PPR	186

	GACGTTTTGGACAAGCGCAGAGGACGGGA CCCTGAGATGGGTGGCAAACCAAGACGAA AAAACCCCCAGGAGGGTCTCTATAATGAG CTGCAGAAGGATAAGATGGCTGAAGCCTA TTCTGAAATAGGCATGAAAGGAGAGCGGA GAAGGGGAAAAGGGCACGACGGTTTGTAC CAGGGACTCAGCACTGCTACGAAGGATAC TTATGACGCTCTCCACATGCAAGCCCTGC CACCTAGGTAA			
(CAR1.6) Clone 24C1 CD8 CAR DNA LxH	GACATTCAATTGACCCAGTCCCCTAGCAG TCTCTCAGCAAGTGTGGGAGATAGGGTGT CATTCACCTGTCAGGCTTCACAGGACATC AACAACTTCCTCAATTGGTATCAGCAGAA GCCAGGGAAGGCACCAAAGCTGCTCATAT ATGACGCTTCAAACCTTGAAACCGGAGTA CCTAGCCGCTTCAGCGGAAGCGGATCAGG GACTGACTTCACTTTTACCATCTCTTCAC TGCAGCCCGAAGACATCGCCACATACTAC TGCCAGCAGTACGGAAACTTGCCTTTTAC ATTTGGGGGCGGCACCAAAGTGGAGATTA AGCGAGGGGGAGGCGGCTCAGGAGGCGGT GGCTCCGGAGGCGGGGGTTCCCAGGTCCA GCTCCAGGAATCCGGCCCAGGTCTGGTTA AGCCCAGTGAAACTTTGTCCCTCACGTGT ACTGTGAGCGGTGGTTCAATCTCCTCATA CTATTGGTCTTGGATACGGCAACCTCCTG GAAAGGGCCTCGAGTGGATCGGCTATATC TACTATAGTGGCTCCACTAATTACAACCC TTCCCTCAAGTCCAGAGTCACCATTTCCG TGGACACATCTAAGAACCAGTTCAGTCTG AAGTTGTCCAGCGTTACAGCCGCAGACAC AGCCGTTTATTACTGTGTGTCTCTTGTTT ACTGCGGGGGAGACTGTTATAGCGGCTTC GATTACTGGGGCCAGGGCACCTTGGTCAC AGTCTCTTCCGCGGCCGCCCTCTCTAACA GTATTATGTACTTTTCTCATTTTGTACCC GTGTTCCTTCCCGCTAAGCCAACTACTAC CCCGGCCCCACGGCCGCCTACCCCTGCAC CCACAATAGCCAGTCAGCCTTTGAGCCTG AGACCTGAGGCTTGTCGGCCGGCTGCTGG GGGTGCAGTGCACACACGAGGTCTTGATT TTGCTTGCGACATATACATCTGGGCCCCT CTGGCCGGGACCTGTGGGGTGCTGCTTCT GAGCTTGGTCATCACGCTCTATTGCAACC ATCGCAACAGATCCAAAAGAAGCCGCCTG CTCCATAGCGATTACATGAATATGACTCC ACGCCGCCCTGGCCCCACAAGGAAACACT ACCAGCCTTACGCACCACCTAGAGATTTC GCTGCCTATCGGAGCAGGGTGAAGTTTTC CAGATCTGCAGATGCACCAGCGTATCAGC AGGGCCAGAACCAACTGTATAACGAGCTC AACCTGGGACGCAGGGAAGAGTATGACGT TTTGGACAAGCGCAGAGGACGGGACCCTG AGATGGGTGGCAAACCAAGACGAAAAAAC CCCCAGGAGGGTCTCTATAATGAGCTGCA GAAGGATAAGATGGCTGAAGCCTATTCTG AAATAGGCATGAAAGGAGAGCGGAGAAGG GGAAAAGGGCACGACGGTTTGTACCAGGG ACTCAGCACTGCTACGAAGGATACTTATG	187	DIQLTQSPSSLSASVG DRVSFTCQASQDINNF LNWYQQKPGKAPKLLI YDASNLETGVPSRFSG SGSGTDFTFTISSLQP EDIATYYCQQYGNLPF TFGGGTKVEIKRGGGG SGGGGSGGGGSQVQLQ ESGPGLVKPSETLSLT CTVSGGSISSYYWSWI RQPPGKGLEWIGYIYY SGSTNYNPSLKSRVTI SVDTSKNQFSLKLSSV TAADTAVYYCVSLVYC GGDCYSGFDYWGQGTL VTVSSAAALSNSIMYF SHFVPVFLPAKPTTTP APRPPTPAPTIASQPL SLRPEACRPAAGGAVH TRGLDFACDIYIWAPL AGTCGVLLLSLVITLY CNHRNRSKRSRLLHSD YMNMTPRRPGPTRKHY QPYAPPRDFAAYRSRV KFSRSADAPAYQQGQN QLYNELNLGRREEYDV LDKRRGRDPEMGGKPR RKNPQEGLYNELQKDK MAEAYSEIGMKGERRR GKGHDGLYQGLSTATK DTYDALHMQALPPR	188

	ACGCTCTCCACATGCAAGCCCTGCCACCT AGG			
(CAR2.1) Clone 24C8 THD CAR DNA HxL	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTACAGCTGCAGGAATCTGGG CCCGGACTTGTCAAGCCAAGTCAGACACT TTCTCTTACATGTACCGTGAGCGGCGGAA GTATAAGCAGTGGAGGCTTTTACTGGTCT TGGATACGGCAGCACCCAGGCAAAGGCTT GGAGTGGATTGGATACATTCATCATTCAG GATCTACACACTATAATCCATCCCTTAAG TCCCGGGTCACCATTAGCATTGATACGTC TAAGAATCTGTTCAGTCTCAGGCTGTCCT CCGTCACTGCTGCCGACACAGCCGTGTAC TACTGCGCCTCCTTGGTTTACTGCGGAGG CGACTGTTATAGCGGCTTTGATTATTGGG GGCAGGGGACCCTCGTAACCGTGAGCTCT GGAGGGGGTGGGAGCGGGGGAGGAGGTTC AGGGGGGGGCGGCTCCGATATCCAGCTCA CTCAAAGCCCCTCTAGTCTCTCTGCCTCA GTGGGGGATCGGGTCAGTTTTACTTGTCA AGCTTCACAGGATATCAACAACTTCCTTA ATTGGTATCAGCAGAAGCCAGGAAAAGCA CCCAAGCTGCTCATCTATGATGCCTCAAA TTTGGAGACGGGTGTTCCCAGTCGATTCT CTGGGTCAGGGTCCGGGACCGACTTTACG TTTACGATCTCCTCTCTGCAGCCCGAAGA CATCGCCACATACTATTGTCAACAGTACG GCAACTTGCCTTTCACATTTGGGGGCGGG ACTAAGGTTGAAATCAAGAGGGCCGCTGC ACTGGACAATGAGAAGTCCAACGGCACCA TCATCCACGTGAAGGGCAAGCACCTGTGC CCTAGTCCTCTGTTCCCAGGCCCATCCAA ACCTTTTTGGGTTCTTGTTGTGGTCGGGG GGGTGCTGGCCTGCTATTCTCTGCTGGTC ACGGTGGCCTTCATAATTTTCTGGGTTAG ATCCAAAAGAAGCCGCCTGCTCCATAGCG ATTACATGAATATGACTCCACGCCGCCCT GGCCCCACAAGGAAACACTACCAGCCTTA CGCACCACCTAGAGATTTCGCTGCCTATC GGAGCAGGGTGAAGTTTTCCAGATCTGCA GATGCACCAGCGTATCAGCAGGGCCAGAA CCAACTGTATAACGAGCTCAACCTGGGAC GCAGGGAAGAGTATGACGTTTTGGACAAG CGCAGAGGACGGGACCCTGAGATGGGTGG CAAACCAAGACGAAAAAACCCCCAGGAGG GTCTCTATAATGAGCTGCAGAAGGATAAG ATGGCTGAAGCCTATTCTGAAATAGGCAT GAAAGGAGAGCGGAGAAGGGGAAAAGGGC ACGACGGTTTGTACCAGGGACTCAGCACT GCTACGAAGGATACTTATGACGCTCTCCA CATGCAAGCCCTGCCACCTAGGTAA	189	MALPVTALLLPLALLL HAARPQVQLQESGPGL VKPSQTLSLTCTVSGG SISSGGFYWSWIRQHP GKGLEWIGYIHHSGST HYNPSLKSRVTISIDT SKNLFSLRLSSVTAAD TAVYYCASLVYCGGDC YSGFDYWGQGTLVTVS SGGGGSGGGGSGGGGS DIQLTQSPSSLSASVG DRVSFTCQASQDINNF LNWYQQKPGKAPKLLI YDASNLETGVPSRFSG SGSGTDFTFTISSLQP EDIATYYCQQYGNLPF TFGGGTKVEIKRAAAL DNEKSNGTIIHVKGKH LCPSPLFPGPSKPFWV LVVVGGVLACYSLLVT VAFIIFWVRSKRSRLL HSDYMNMTPRRPGPTR KHYQPYAPPRDFAAYR SRVKFSRSADAPAYQQ GQNQLYNELNLGRREE YDVLDKRRGRDPEMGG KPRRKNPQEGLYNELQ KDKMAEAYSEIGMKGE RRRGKGHDGLYQGLST ATKDTYDALHMQALPP R	190
(CAR2.1) Clone 24C8 THD CAR DNA HxL	CAGGTACAGCTGCAGGAATCTGGGCCCGG ACTTGTCAAGCCAAGTCAGACACTTTCTC TTACATGTACCGTGAGCGGCGGAAGTATA AGCAGTGGAGGCTTTTACTGGTCTTGGAT ACGGCAGCACCCAGGCAAAGGCTTGGAGT GGATTGGATACATTCATCATTCAGGATCT ACACACTATAATCCATCCCTTAAGTCCCG	191	QVQLQESGPGLVKPSQ TLSLTCTVSGGSISSG GFYWSWIRQHPGKGLE WIGYIHHSGSTHYNPS LKSRVTISIDTSKNLF SLRLSSVTAADTAVYY CASLVYCGGDCYSGFD	192

	GGTCACCATTAGCATTGATACGTCTAAGA ATCTGTTCAGTCTCAGGCTGTCCTCCGTC ACTGCTGCCGACACAGCCGTGTACTACTG CGCCTCCTTGGTTTACTGCGGAGGCGACT GTTATAGCGGCTTTGATTATTGGGGGCAG GGGACCCTCGTAACCGTGAGCTCTGGAGG GGGTGGGAGCGGGGGAGGAGGTTCAGGGG GGGGCGGCTCCGATATCCAGCTCACTCAA AGCCCCTCTAGTCTCTCTGCCTCAGTGGG GGATCGGGTCAGTTTTACTTGTCAAGCTT CACAGGATATCAACAACTTCCTTAATTGG TATCAGCAGAAGCCAGGAAAAGCACCCAA GCTGCTCATCTATGATGCCTCAAATTTGG AGACGGGTGTTCCCAGTCGATTCTCTGGG TCAGGGTCCGGGACCGACTTTACGTTTAC GATCTCCTCTCTGCAGCCCGAAGACATCG CCACATACTATTGTCAACAGTACGGCAAC TTGCCTTTCACATTTGGGGGCGGGACTAA GGTTGAAATCAAGAGGGCCGCTGCACTGG ACAATGAGAAGTCCAACGGCACCATCATC CACGTGAAGGGCAAGCACCTGTGCCCTAG TCCTCTGTTCCCAGGCCCATCCAAACCTT TTTGGGTTCTTGTTGTGGTCGGGGGGGTG CTGGCCTGCTATTCTCTGCTGGTCACGGT GGCCTTCATAATTTTCTGGGTTAGATCCA AAAGAAGCCGCCTGCTCCATAGCGATTAC ATGAATATGACTCCACGCCGCCCTGGCCC CACAAGGAAACACTACCAGCCTTACGCAC CACCTAGAGATTTCGCTGCCTATCGGAGC AGGGTGAAGTTTTCCAGATCTGCAGATGC ACCAGCGTATCAGCAGGGCCAGAACCAAC TGTATAACGAGCTCAACCTGGGACGCAGG GAAGAGTATGACGTTTTGGACAAGCGCAG AGGACGGGACCCTGAGATGGGTGGCAAAC CAAGACGAAAAAACCCCCAGGAGGGTCTC TATAATGAGCTGCAGAAGGATAAGATGGC TGAAGCCTATTCTGAAATAGGCATGAAAG GAGAGCGGAGAAGGGGAAAAGGGCACGAC GGTTTGTACCAGGGACTCAGCACTGCTAC GAAGGATACTTATGACGCTCTCCACATGC AAGCCCTGCCACCTAGG		YWGQGTLVTVSSGGGG SGGGGSGGGGSDIQLT QSPSSLSASVGDRVSF TCQASQDINNFLNWYQ QKPGKAPKLLIYDASN LETGVPSRFSGSGSGT DFTFTISSLQPEDIAT YYCQQYGNLPFTFGGG TKVEIKRAAALDNEKS NGTIIHVKGKHLCPSP LFPGPSKPFWVLVVVG GVLACYSLLVTVAFII FWVRSKRSRLLHSDYM NMTPRRPGPTRKHYQP YAPPRDFAAYRSRVKF SRSADAPAYQQGQNQL YNELNLGRREEYDVLD KRRGRDPEMGGKPRRK NPQEGLYNELQKDKMA EAYSEIGMKGERRRGK GHDGLYQGLSTATKDT YDALHMQALPPR	
(CAR2.2) Clone 24C8 CHD CAR DNA HxL	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTGCAGCTGCAGGAAAGCGGT CCGGGACTTGTCAAGCCGTCCCAAACGCT GAGTCTGACGTGTACTGTCTCTGGTGGCT CTATTTCTTCCGGGGGCTTTTATTGGTCT TGGATCAGACAACACCCTGGCAAAGGGCT GGAGTGGATAGGGTATATTCACCACTCTG GGTCCACTCACTACAACCCATCATTGAAA TCCAGAGTGACTATCTCAATCGACACATC CAAGAACCTTTTCAGCCTGAGGTTGTCAT CAGTTACCGCCGCTGACACCGCGGTGTAT TATTGCGCCTCTCTCGTGTACTGCGGTGG CGATTGTTATAGTGGCTTTGACTACTGGG GGCAGGGGACATTGGTTACCGTTTCAAGT GGAGGCGGTGGGTCTGGCGGGGGCGGTAG CGGAGGTGGGGGGAGCGACATACAGCTTA CGCAGAGCCCCTCCAGCCTTTCAGCCTCC	193	MALPVTALLLPLALLL HAARPQVQLQESGPGL VKPSQTLSLTCTVSGG SISSGGFYWSWIRQHP GKGLEWIGYIHHSGST HYNPSLKSRVTISIDT SKNLFSLRLSSVTAAD TAVYYCASLVYCGGDC YSGFDYWGQGTLVTVS SGGGGSGGGGSGGGGS DIQLTQSPSSLSASVG DRVSFTCQASQDINNF LNWYQQKPGKAPKLLI YDASNLETGVPSRFSG SGSGTDFTFTISSLQP EDIATYYCQQYGNLPF TFGGGTKVEIKRAAAI EVMYPPPYLDNEKSNG	194

	GTGGGGGATAGGGTGTCCTTTACCTGCCA GGCTTCCCAGGACATAAACAACTTCCTCA ATTGGTATCAGCAAAAGCCCGGGAAAGCA CCAAAGCTGCTCATCTACGATGCCAGCAA CCTGGAAACCGGAGTGCCGTCTCGCTTCT CTGGAAGTGGCAGTGGGACCGATTTCACT TTTACAATCTCAAGTTTGCAGCCAGAAGA CATTGCAACATACTACTGTCAACAGTACG GCAATCTCCCCTTTACATTTGGGGGGGGA ACTAAAGTGGAGATTAAGCGCGCTGCAGC CATTGAAGTTATGTATCCGCCCCCGTATC TGGATAACGAGAAATCTAATGGTACCATA ATACATGTGAAGGGGAAGCACCTCTGTCC ATCACCGCTGTTCCCCGGCCCTTCAAAAC CTTTCTGGGTACTCGTTGTCGTGGGTGGA GTTCTGGCCTGCTATAGTCTGCTGGTGAC CGTGGCGTTTATCATCTTCTGGGTAAGAT CCAAAAGAAGCCGCCTGCTCCATAGCGAT TACATGAATATGACTCCACGCCGCCCTGG CCCCACAAGGAAACACTACCAGCCTTACG CACCACCTAGAGATTTCGCTGCCTATCGG AGCAGGGTGAAGTTTTCCAGATCTGCAGA TGCACCAGCGTATCAGCAGGGCCAGAACC AACTGTATAACGAGCTCAACCTGGGACGC AGGGAAGAGTATGACGTTTTGGACAAGCG CAGAGGACGGGACCCTGAGATGGGTGGCA AACCAAGACGAAAAAACCCCCAGGAGGGT CTCTATAATGAGCTGCAGAAGGATAAGAT GGCTGAAGCCTATTCTGAAATAGGCATGA AAGGAGAGCGGAGAAGGGGAAAAGGGCAC GACGGTTTGTACCAGGGACTCAGCACTGC TACGAAGGATACTTATGACGCTCTCCACA TGCAAGCCCTGCCACCTAGGTAA		TIIHVKGKHLCPSPLF PGPSKPFWVLVVVGGV LACYSLLVTVAFIIFW VRSKRSRLLHSDYMNM TPRRPGPTRKHYQPYA PPRDFAAYRSRVKFSR SADAPAYQQGQNQLYN ELNLGRREEYDVLDKR RGRDPEMGGKPRRKNP QEGLYNELQKDKMAEA YSEIGMKGERRRGKGH DGLYQGLSTATKDTYD ALHMQALPPR	
(CAR2.2) Clone 24C8 CHD CAR DNA HxL	CAGGTGCAGCTGCAGGAAAGCGGTCCGGG ACTTGTCAAGCCGTCCCAAACGCTGAGTC TGACGTGTACTGTCTCTGGTGGCTCTATT TCTTCCGGGGGCTTTTATTGGTCTTGGAT CAGACAACACCCTGGCAAAGGGCTGGAGT GGATAGGGTATATTCACCACTCTGGGTCC ACTCACTACAACCCATCATTGAAATCCAG AGTGACTATCTCAATCGACACATCCAAGA ACCTTTTCAGCCTGAGGTTGTCATCAGTT ACCGCCGCTGACACCGCGGTGTATTATTG CGCCTCTCTCGTGTACTGCGGTGGCGATT GTTATAGTGGCTTTGACTACTGGGGGCAG GGGACATTGGTTACCGTTTCAAGTGGAGG CGGTGGGTCTGGCGGGGGCGGTAGCGGAG GTGGGGGGAGCGACATACAGCTTACGCAG AGCCCCTCCAGCCTTTCAGCCTCCGTGGG GGATAGGGTGTCCTTTACCTGCCAGGCTT CCCAGGACATAAACAACTTCCTCAATTGG TATCAGCAAAAGCCCGGGAAAGCACCAAA GCTGCTCATCTACGATGCCAGCAACCTGG AAACCGGAGTGCCGTCTCGCTTCTCTGGA AGTGGCAGTGGGACCGATTTCACTTTTAC AATCTCAAGTTTGCAGCCAGAAGACATTG CAACATACTACTGTCAACAGTACGGCAAT CTCCCCTTTACATTTGGGGGGGGAACTAA AGTGGAGATTAAGCGCGCTGCAGCCATTG	195	QVQLQESGPGLVKPSQ TLSLTCTVSGGSISSG GFYWSWIRQHPGKGLE WIGYIHHSGSTHYNPS LKSRVTISIDTSKNLF SLRLSSVTAADTAVYY CASLVYCGGDCYSGFD YWGQGTLVTVSSGGGG SGGGGSGGGGSDIQLT QSPSSLSASVGDRVSF TCQASQDINNFLNWYQ QKPGKAPKLLIYDASN LETGVPSRFSGSGSGT DFTFTISSLQPEDIAT YYCQQYGNLPFTFGGG TKVEIKRAAAIEVMYP PPYLDNEKSNGTIIHV KGKHLCPSPLFPGPSK PFWVLVVVGGVLACYS LLVTVAFIIFWVRSKR SRLLHSDYMNMTPRRP GPTRKHYQPYAPPRDF AAYRSRVKFSRSADAP AYQQGQNQLYNELNLG RREEYDVLDKRRGRDP EMGGKPRRKNPQEGLY	196

	AAGTTATGTATCCGCCCCCGTATCTGGAT AACGAGAAATCTAATGGTACCATAATACA TGTGAAGGGGAAGCACCTCTGTCCATCAC CGCTGTTCCCCGGCCCTTCAAAACCTTTC TGGGTACTCGTTGTCGTGGGTGGAGTTCT GGCCTGCTATAGTCTGCTGGTGACCGTGG CGTTTATCATCTTCTGGGTAAGATCCAAA AGAAGCCGCCTGCTCCATAGCGATTACAT GAATATGACTCCACGCCGCCCTGGCCCCA CAAGGAAACACTACCAGCCTTACGCACCA CCTAGAGATTTCGCTGCCTATCGGAGCAG GGTGAAGTTTTCCAGATCTGCAGATGCAC CAGCGTATCAGCAGGGCCAGAACCAACTG TATAACGAGCTCAACCTGGGACGCAGGGA AGAGTATGACGTTTTGGACAAGCGCAGAG GACGGGACCCTGAGATGGGTGGCAAACCA AGACGAAAAAACCCCCAGGAGGGTCTCTA TAATGAGCTGCAGAAGGATAAGATGGCTG AAGCCTATTCTGAAATAGGCATGAAAGGA GAGCGGAGAAGGGGAAAAGGGCACGACGG TTTGTACCAGGGACTCAGCACTGCTACGA AGGATACTTATGACGCTCTCCACATGCAA GCCCTGCCACCTAGG		NELQKDKMAEAYSEIG MKGERRRGKGHDGLYQ GLSTATKDTYDALHMQ ALPPR	
(CAR2.3) Clone 24C8 CD8 CAR DNA HxL	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTGCAGTTGCAGGAAAGCGGG CCTGGCCTTGTGAAACCAAGCCAGACACT GAGCCTGACATGCACTGTGTCCGGCGGGT CCATATCTTCCGGGGGTTTTTATTGGTCC TGGATACGCCAGCATCCCGGGAAAGGACT TGAATGGATTGGATATATCCACCATTCCG GAAGCACCCACTACAATCCAAGCCTTAAA TCCCGGGTGACAATCTCCATCGACACCTC AAAGAATCTTTTTTCCCTGCGGTTGTCTT CAGTAACTGCCGCCGATACCGCTGTGTAC TACTGTGCCAGCCTCGTCTATTGCGGCGG AGATTGTTATTCTGGGTTCGATTATTGGG GTCAAGGCACACTGGTAACTGTCAGCAGC GGAGGCGGCGGTTCCGGGGGCGGGGGCAG TGGAGGGGGCGGATCTGACATTCAGCTTA CGCAGTCCCCATCTTCACTTAGCGCCAGC GTTGGCGATCGGGTCAGCTTCACGTGTCA AGCAAGTCAGGATATCAACAACTTTCTTA ACTGGTACCAGCAGAAGCCAGGCAAGGCA CCCAAGTTGCTGATTTACGATGCTTCTAA CCTCGAGACGGGAGTGCCTAGCCGCTTCT CCGGGAGCGGCAGCGGCACAGACTTTACC TTTACGATTTCCAGTCTGCAGCCAGAGGA TATAGCAACTTATTACTGTCAGCAGTATG GCAACCTCCCTTTTACCTTCGGTGGTGGC ACAAAGGTCGAGATTAAAAGAGCCGCAGC GTTGTCCAACTCCATAATGTATTTTTCTC ATTTTGTGCCCGTCTTTCTGCCTGCCAAA CCTACCACCACCCCCGCCCCACGACCACC TACTCCAGCCCCCACCATCGCCTCCCAGC CCCTCAGCCTGAGGCCAGAGGCTTGTCGC CCTGCTGCGGGGGGCGCTGTCCATACCAG AGGACTCGACTTCGCCTGCGATATTTATA TATGGGCCCCCCTCGCCGGCACCTGCGGA	197	MALPVTALLLPLALLL HAARPQVQLQESGPGL VKPSQTLSLTCTVSGG SISSGGFYWSWIRQHP GKGLEWIGYIHHSGST HYNPSLKSRVTISIDT SKNLFSLRLSSVTAAD TAVYYCASLVYCGGDC YSGFDYWGQGTLVTVS SGGGGSGGGGSGGGGS DIQLTQSPSSLSASVG DRVSFTCQASQDINNF LNWYQQKPGKAPKLLI YDASNLETGVPSRFSG SGSGTDFTFTISSLQP EDIATYYCQQYGNLPF TFGGGTKVEIKRAAAL SNSIMYFSHFVPVFLP AKPTTTPAPRPPTPAP TIASQPLSLRPEACRP AAGGAVHTRGLDFACD IYIWAPLAGTCGVLLL SLVITLYCNHRNRSKR SRLLHSDYMNMTPRRP GPTRKHYQPYAPPRDF AAYRSRVKFSRSADAP AYQQGQNQLYNELNLG RREEYDVLDKRRGRDP EMGGKPRRKNPQEGLY NELQKDKMAEAYSEIG MKGERRRGKGHDGLYQ GLSTATKDTYDALHMQ ALPPR	198

	GTCTTGCTCCTGAGCCTTGTGATCACGCT TTATTGTAACCATCGGAATAGATCCAAAA GAAGCCGCCTGCTCCATAGCGATTACATG AATATGACTCCACGCCGCCCTGGCCCCAC AAGGAAACACTACCAGCCTTACGCACCAC CTAGAGATTTCGCTGCCTATCGGAGCAGG GTGAAGTTTTCCAGATCTGCAGATGCACC AGCGTATCAGCAGGGCCAGAACCAACTGT ATAACGAGCTCAACCTGGGACGCAGGGAA GAGTATGACGTTTTGGACAAGCGCAGAGG ACGGGACCCTGAGATGGGTGGCAAACCAA GACGAAAAAACCCCCAGGAGGGTCTCTAT AATGAGCTGCAGAAGGATAAGATGGCTGA AGCCTATTCTGAAATAGGCATGAAAGGAG AGCGGAGAAGGGGAAAAGGGCACGACGGT TTGTACCAGGGACTCAGCACTGCTACGAA GGATACTTATGACGCTCTCCACATGCAAG CCCTGCCACCTAGGTAA			
(CAR2.3) Clone 24C8 CD8 CAR DNA HxL	CAGGTGCAGTTGCAGGAAAGCGGGCCTGG CCTTGTGAAACCAAGCCAGACACTGAGCC TGACATGCACTGTGTCCGGCGGGTCCATA TCTTCCGGGGGTTTTTATTGGTCCTGGAT ACGCCAGCATCCCGGGAAAGGACTTGAAT GGATTGGATATATCCACCATTCCGGAAGC ACCCACTACAATCCAAGCCTTAAATCCCG GGTGACAATCTCCATCGACACCTCAAAGA ATCTTTTTTCCCTGCGGTTGTCTTCAGTA ACTGCCGCCGATACCGCTGTGTACTACTG TGCCAGCCTCGTCTATTGCGGCGGAGATT GTTATTCTGGGTTCGATTATTGGGGTCAA GGCACACTGGTAACTGTCAGCAGCGGAGG CGGCGGTTCCGGGGGCGGGGGCAGTGGAG GGGGCGGATCTGACATTCAGCTTACGCAG TCCCCATCTTCACTTAGCGCCAGCGTTGG CGATCGGGTCAGCTTCACGTGTCAAGCAA GTCAGGATATCAACAACTTTCTTAACTGG TACCAGCAGAAGCCAGGCAAGGCACCCAA GTTGCTGATTTACGATGCTTCTAACCTCG AGACGGGAGTGCCTAGCCGCTTCTCCGGG AGCGGCAGCGGCACAGACTTTACCTTTAC GATTTCCAGTCTGCAGCCAGAGGATATAG CAACTTATTACTGTCAGCAGTATGGCAAC CTCCCTTTTACCTTCGGTGGTGGCACAAA GGTCGAGATTAAAAGAGCCGCAGCGTTGT CCAACTCCATAATGTATTTTTCTCATTTT GTGCCCGTCTTTCTGCCTGCCAAACCTAC CACCACCCCCGCCCCACGACCACCTACTC CAGCCCCCACCATCGCCTCCCAGCCCCTC AGCCTGAGGCCAGAGGCTTGTCGCCCTGC TGCGGGGGGCGCTGTCCATACCAGAGGAC TCGACTTCGCCTGCGATATTTATATATGG GCCCCCCTCGCCGGCACCTGCGGAGTCTT GCTCCTGAGCCTTGTGATCACGCTTTATT GTAACCATCGGAATAGATCCAAAAGAAGC CGCCTGCTCCATAGCGATTACATGAATAT GACTCCACGCCGCCCTGGCCCCACAAGGA AACACTACCAGCCTTACGCACCACCTAGA GATTTCGCTGCCTATCGGAGCAGGGTGAA GTTTTCCAGATCTGCAGATGCACCAGCGT	199	QVQLQESGPGLVKPSQ TLSLTCTVSGGSISSG GFYWSWIRQHPGKGLE WIGYIHHSGSTHYNPS LKSRVTISIDTSKNLF SLRLSSVTAADTAVYY CASLVYCGGDCYSGFD YWGQGTLVTVSSGGGG SGGGGSGGGGSDIQLT QSPSSLSASVGDRVSF TCQASQDINNFLNWYQ QKPGKAPKLLIYDASN LETGVPSRFSGSGSGT DFTFTISSLQPEDIAT YYCQQYGNLPFTFGGG TKVEIKRAAALSNSIM YFSHFVPVFLPAKPTT TPAPRPPTPAPTIASQ PLSLRPEACRPAAGGA VHTRGLDFACDIYIWA PLAGTCGVLLLSLVIT LYCNHRNRSKRSRLLH SDYMNMTPRRPGPTRK HYQPYAPPRDFAAYRS RVKFSRSADAPAYQQG QNQLYNELNLGRREEY DVLDKRRGRDPEMGGK PRRKNPQEGLYNELQK DKMAEAYSEIGMKGER RRGKGHDGLYQGLSTA TKDTYDALHMQALPPR	200

	ATCAGCAGGGCCAGAACCAACTGTATAAC GAGCTCAACCTGGGACGCAGGGAAGAGTA TGACGTTTTGGACAAGCGCAGAGGACGGG ACCCTGAGATGGGTGGCAAACCAAGACGA AAAAACCCCCAGGAGGGTCTCTATAATGA GCTGCAGAAGGATAAGATGGCTGAAGCCT ATTCTGAAATAGGCATGAAAGGAGAGCGG AGAAGGGGAAAAGGGCACGACGGTTTGTA CCAGGGACTCAGCACTGCTACGAAGGATA CTTATGACGCTCTCCACATGCAAGCCCTG CCACCTAGG			
(CAR3.1) Clone 20C5.1 THD CAR DNA HxL	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTCCAACTGGTGCAGTCCGGA GCCGAAGTCAAGAAACCAGGTGCCTCCGT TAAAGTGAGTTGCAAAGTCTCTGGATACA CTCTGACCGAGCTCTCTATGCACTGGGTC CGGCAGGCCCCCGGCAAGGGATTGGAATG GATGGGCGGGTTCGATCCTGAGGACGGAG AGACTATCTACGCTCAAAAATTCCAGGGA CGAGTGACTGTGACCGAAGACACTAGTAC CGACACTGCCTACATGGAACTTTCCTCTC TGCGATCAGAAGATACCGCAGTGTACTAC TGTGCTACTGAATCTAGGGGCATTGGATG GCCCTACTTCGATTACTGGGGTCAGGGAA CTCTGGTGACTGTCTCCAGCGGTGGAGGT GGCAGCGGTGGTGGCGGAAGCGGGGGGGG CGGCTCTGATATTCAGATGACTCAATCTC CTTCTTCTCTGTCCGCTTCCGTGGGCGAT AGAGTGACCATTACTTGTAGGGCGTCCCA GTCAATCTCCAGTTATTTGAATTGGTATC AGCAGAAGCCCGGGAAAGCACCTAAGCTG TTGATCAGCGGGGCTTCTAGCCTGAAGAG TGGGGTACCTTCACGGTTCAGCGGAAGCG GAAGCGGAACCGATTTCACCCTGACTATC AGCAGCCTGCCACCTGAGGACTTTGCAAC TTACTACTGCCAACAGTCATACAGCACTC CGATCACTTTCGGCCAGGGCACCCGGCTC GAAATCAAGCGCGCTGCTGCTTTGGACAA TGAGAAGTCAAACGGCACCATCATACATG TTAAAGGTAAACATCTGTGTCCCTCCCCG CTGTTCCCCGGCCCTTCCAAACCGTTCTG GGTTCTGGTGGTGGTCGGAGGCGTACTCG CTTGCTATAGTCTGCTGGTAACTGTCGCC TTCATCATCTTTTGGGTGAGATCCAAAAG AAGCCGCCTGCTCCATAGCGATTACATGA ATATGACTCCACGCCGCCCTGGCCCCACA AGGAAACACTACCAGCCTTACGCACCACC TAGAGATTTCGCTGCCTATCGGAGCAGGG TGAAGTTTTCCAGATCTGCAGATGCACCA GCGTATCAGCAGGGCCAGAACCAACTGTA TAACGAGCTCAACCTGGGACGCAGGGAAG AGTATGACGTTTTGGACAAGCGCAGAGGA CGGGACCCTGAGATGGGTGGCAAACCAAG ACGAAAAAACCCCCAGGAGGGTCTCTATA ATGAGCTGCAGAAGGATAAGATGGCTGAA GCCTATTCTGAAATAGGCATGAAAGGAGA GCGGAGAAGGGGAAAAGGGCACGACGGTT TGTACCAGGGACTCAGCACTGCTACGAAG	201	MALPVTALLLPLALLL HAARPQVQLVQSGAEV KKPGASVKVSCKVSGY TLTELSMHWVRQAPGK GLEWMGGFDPEDGETI YAQKFQGRVTVTEDTS TDTAYMELSSLRSEDT AVYYCATESRGIGWPY FDYWGQGTLVTVSSGG GGSGGGGSGGGGSDIQ MTQSPSSLSASVGDRV TITCRASQSISSYLNW YQQKPGKAPKLLISGA SSLKSGVPSRFSGSGS GTDFTLTISSLPPEDF ATYYCQQSYSTPITFG QGTRLEIKRAAALDNE KSNGTIIHVKGKHLCP SPLFPGPSKPFWVLVV VGGVLACYSLLVTVAF IIFWVRSKRSRLLHSD YMNMTPRRPGPTRKHY QPYAPPRDFAAYRSRV KFSRSADAPAYQQGQN QLYNELNLGRREEYDV LDKRRGRDPEMGGKPR RKNPQEGLYNELQKDK MAEAYSEIGMKGERRR GKGHDGLYQGLSTATK DTYDALHMQALPPR	202

	GATACTTATGACGCTCTCCACATGCAAGC CCTGCCACCTAGGTAA			
(CAR3.1) Clone 20C5.1 THD CAR DNA HxL	CAGGTCCAACTGGTGCAGTCCGGAGCCGA AGTCAAGAAACCAGGTGCCTCCGTTAAAG TGAGTTGCAAAGTCTCTGGATACACTCTG ACCGAGCTCTCTATGCACTGGGTCCGGCA GGCCCCCGGCAAGGGATTGGAATGGATGG GCGGGTTCGATCCTGAGGACGGAGAGACT ATCTACGCTCAAAAATTCCAGGGACGAGT GACTGTGACCGAAGACACTAGTACCGACA CTGCCTACATGGAACTTTCCTCTCTGCGA TCAGAAGATACCGCAGTGTACTACTGTGC TACTGAATCTAGGGGCATTGGATGGCCCT ACTTCGATTACTGGGGTCAGGGAACTCTG GTGACTGTCTCCAGCGGTGGAGGTGGCAG CGGTGGTGGCGGAAGCGGGGGGGGCGGCT CTGATATTCAGATGACTCAATCTCCTTCT TCTCTGTCCGCTTCCGTGGGCGATAGAGT GACCATTACTTGTAGGGCGTCCCAGTCAA TCTCCAGTTATTTGAATTGGTATCAGCAG AAGCCCGGGAAAGCACCTAAGCTGTTGAT CAGCGGGGCTTCTAGCCTGAAGAGTGGGG TACCTTCACGGTTCAGCGGAAGCGGAAGC GGAACCGATTTCACCCTGACTATCAGCAG CCTGCCACCTGAGGACTTTGCAACTTACT ACTGCCAACAGTCATACAGCACTCCGATC ACTTTCGGCCAGGGCACCCGGCTCGAAAT CAAGCGCGCTGCTGCTTTGGACAATGAGA AGTCAAACGGCACCATCATACATGTTAAA GGTAAACATCTGTGTCCCTCCCCGCTGTT CCCCGGCCCTTCCAAACCGTTCTGGGTTC TGGTGGTGGTCGGAGGCGTACTCGCTTGC TATAGTCTGCTGGTAACTGTCGCCTTCAT CATCTTTTGGGTGAGATCCAAAAGAAGCC GCCTGCTCCATAGCGATTACATGAATATG ACTCCACGCCGCCCTGGCCCCACAAGGAA ACACTACCAGCCTTACGCACCACCTAGAG ATTTCGCTGCCTATCGGAGCAGGGTGAAG TTTTCCAGATCTGCAGATGCACCAGCGTA TCAGCAGGGCCAGAACCAACTGTATAACG AGCTCAACCTGGGACGCAGGGAAGAGTAT GACGTTTTGGACAAGCGCAGAGGACGGGA CCCTGAGATGGGTGGCAAACCAAGACGAA AAAACCCCCAGGAGGGTCTCTATAATGAG CTGCAGAAGGATAAGATGGCTGAAGCCTA TTCTGAAATAGGCATGAAAGGAGAGCGGA GAAGGGGAAAAGGGCACGACGGTTTGTAC CAGGGACTCAGCACTGCTACGAAGGATAC TTATGACGCTCTCCACATGCAAGCCCTGC CACCTAGG	203	QVQLVQSGAEVKKPGA SVKVSCKVSGYTLTEL SMHWVRQAPGKGLEWM GGFDPEDGETIYAQKF QGRVTVTEDTSTDTAY MELSSLRSEDTAVYYC ATESRGIGWPYFDYWG QGTLVTVSSGGGGSGG GGSGGGGSDIQMTQSP SSLSASVGDRVTITCR ASQSISSYLNWYQQKP GKAPKLLISGASSLKS GVPSRFSGSGSGTDFT LTISSLPPEDFATYYC QQSYSTPITFGQGTRL EIKRAAALDNEKSNGT IIHVKGKHLCPSPLFP GPSKPFWVLVVVGGVL ACYSLLVTVAFIIFWV RSKRSRLLHSDYMNMT PRRPGPTRKHYQPYAP PRDFAAYRSRVKFSRS ADAPAYQQGQNQLYNE LNLGRREEYDVLDKRR GRDPEMGGKPRRKNPQ EGLYNELQKDKMAEAY SEIGMKGERRRGKGHD GLYQGLSTATKDTYDA LHMQALPPR	204
(CAR3.2) Clone 20C5.1 CHD CAR DNA HxL	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTGCAGCTTGTGCAGAGCGGG GCCGAGGTGAAGAAGCCCGGGGCCAGCGT CAAAGTGTCCTGTAAGGTCAGCGGTTACA CCCTCACCGAGCTGAGCATGCACTGGGTA CGGCAGGCTCCCGGCAAAGGTCTTGAGTG GATGGGTGGATTTGATCCAGAAGATGGAG AGACTATCTACGCCCAGAAGTTCCAGGGC	205	MALPVTALLLPLALLL HAARPQVQLVQSGAEV KKPGASVKVSCKVSGY TLTELSMHWVRQAPGK GLEWMGGFDPEDGETI YAQKFQGRVTVTEDTS TDTAYMELSSLRSEDT AVYYCATESRGIGWPY FDYWGQGTLVTVSSGG	206

	CGGGTCACCGTAACAGAAGACACCTCAAC TGACACCGCTTACATGGAGCTGAGTTCAC TGCGGTCCGAGGACACGGCCGTGTATTAT TGTGCCACCGAGAGCCGCGGAATCGGATG GCCTTACTTCGACTACTGGGGACAGGGTA CACTTGTTACAGTATCATCCGGGGGTGGC GGCTCTGGTGGGGGCGGCTCCGGAGGGGG TGGATCAGATATCCAAATGACTCAAAGTC CAAGTTCCCTGTCTGCCTCAGTCGGAGAT AGAGTCACCATAACCTGCAGGGCAAGTCA GTCCATCTCCTCCTATCTGAACTGGTACC AACAGAAACCTGGAAAGGCGCCTAAGCTC CTGATCTCCGGAGCCTCATCTTTGAAATC CGGTGTCCCATCTCGCTTCAGTGGCTCTG GAAGCGGTACAGATTTTACTTTGACCATT AGCAGCCTCCCACCGGAAGACTTTGCTAC ATATTACTGCCAGCAGTCTTACTCAACCC CAATCACCTTCGGGCAAGGCACCAGACTC GAAATAAAAAGAGCAGCTGCTATCGAGGT TATGTACCCACCGCCGTACTTGGATAACG AAAAAAGCAATGGGACCATCATTCATGTG AAGGGTAAGCACCTTTGCCCTAGCCCACT GTTTCCTGGCCCGAGTAAACCCTTTTGGG TACTTGTGGTCGTCGGCGGCGTGCTGGCC TGCTACTCACTCCTGGTTACCGTCGCATT CATCATCTTTTGGGTGAGATCCAAAAGAA GCCGCCTGCTCCATAGCGATTACATGAAT ATGACTCCACGCCGCCCTGGCCCCACAAG GAAACACTACCAGCCTTACGCACCACCTA GAGATTTCGCTGCCTATCGGAGCAGGGTG AAGTTTTCCAGATCTGCAGATGCACCAGC GTATCAGCAGGGCCAGAACCAACTGTATA ACGAGCTCAACCTGGGACGCAGGGAAGAG TATGACGTTTTGGACAAGCGCAGAGGACG GGACCCTGAGATGGGTGGCAAACCAAGAC GAAAAAACCCCCAGGAGGGTCTCTATAAT GAGCTGCAGAAGGATAAGATGGCTGAAGC CTATTCTGAAATAGGCATGAAAGGAGAGC GGAGAAGGGGAAAAGGGCACGACGGTTTG TACCAGGGACTCAGCACTGCTACGAAGGA TACTTATGACGCTCTCCACATGCAAGCCC TGCCACCTAGGTAA		GGSGGGGSGGGGSDIQ MTQSPSSLSASVGDRV TITCRASQSISSYLNW YQQKPGKAPKLLISGA SSLKSGVPSRFSGSGS GTDFTLTISSLPPEDF ATYYCQQSYSTPITFG QGTRLEIKRAAAIEVM YPPPYLDNEKSNGTII HVKGKHLCPSPLFPGP SKPFWVLVVVGGVLAC YSLLVTVAFIIFWVRS KRSRLLHSDYMNMTPR RPGPTRKHYQPYAPPR DFAAYRSRVKFSRSAD APAYQQGQNQLYNELN LGRREEYDVLDKRRGR DPEMGGKPRRKNPQEG LYNELQKDKMAEAYSE IGMKGERRRGKGHDGL YQGLSTATKDTYDALH MQALPPR	
(CAR3.2) Clone 20C5.1 CHD CAR DNA HxL	CAGGTGCAGCTTGTGCAGAGCGGGGCCGA GGTGAAGAAGCCCGGGGCCAGCGTCAAAG TGTCCTGTAAGGTCAGCGGTTACACCCTC ACCGAGCTGAGCATGCACTGGGTACGGCA GGCTCCCGGCAAAGGTCTTGAGTGGATGG GTGGATTTGATCCAGAAGATGGAGAGACT ATCTACGCCCAGAAGTTCCAGGGCCGGGT CACCGTAACAGAAGACACCTCAACTGACA CCGCTTACATGGAGCTGAGTTCACTGCGG TCCGAGGACACGGCCGTGTATTATTGTGC CACCGAGAGCCGCGGAATCGGATGGCCTT ACTTCGACTACTGGGGACAGGGTACACTT GTTACAGTATCATCCGGGGGTGGCGGCTC TGGTGGGGGCGGCTCCGGAGGGGGTGGAT CAGATATCCAAATGACTCAAAGTCCAAGT TCCCTGTCTGCCTCAGTCGGAGATAGAGT CACCATAACCTGCAGGGCAAGTCAGTCCA	207	QVQLVQSGAEVKKPGA SVKVSCKVSGYTLTEL SMHWVRQAPGKGLEWM GGFDPEDGETIYAQKF QGRVTVTEDTSTDTAY MELSSLRSEDTAVYYC ATESRGIGWPYFDYWG QGTLVTVSSGGGGSGG GGSGGGGSDIQMTQSP SSLSASVGDRVTITCR ASQSISSYLNWYQQKP GKAPKLLISGASSLKS GVPSRFSGSGSGTDFT LTISSLPPEDFATYYC QQSYSTPITFGQGTRL EIKRAAAIEVMYPPPY LDNEKSNGTIIHVKGK	208

	TCTCCTCCTATCTGAACTGGTACCAACAG AAACCTGGAAAGGCGCCTAAGCTCCTGAT CTCCGGAGCCTCATCTTTGAAATCCGGTG TCCCATCTCGCTTCAGTGGCTCTGGAAGC GGTACAGATTTTACTTTGACCATTAGCAG CCTCCCACCGGAAGACTTTGCTACATATT ACTGCCAGCAGTCTTACTCAACCCCAATC ACCTTCGGGCAAGGCACCAGACTCGAAAT AAAAAGAGCAGCTGCTATCGAGGTTATGT ACCCACCGCCGTACTTGGATAACGAAAAA AGCAATGGGACCATCATTCATGTGAAGGG TAAGCACCTTTGCCCTAGCCCACTGTTTC CTGGCCCGAGTAAACCCTTTTGGGTACTT GTGGTCGTCGGCGGCGTGCTGGCCTGCTA CTCACTCCTGGTTACCGTCGCATTCATCA TCTTTTGGGTGAGATCCAAAAGAAGCCGC CTGCTCCATAGCGATTACATGAATATGAC TCCACGCCGCCCTGGCCCCACAAGGAAAC ACTACCAGCCTTACGCACCACCTAGAGAT TTCGCTGCCTATCGGAGCAGGGTGAAGTT TTCCAGATCTGCAGATGCACCAGCGTATC AGCAGGGCCAGAACCAACTGTATAACGAG CTCAACCTGGGACGCAGGGAAGAGTATGA CGTTTTGGACAAGCGCAGAGGACGGGACC CTGAGATGGGTGGCAAACCAAGACGAAAA AACCCCCAGGAGGGTCTCTATAATGAGCT GCAGAAGGATAAGATGGCTGAAGCCTATT CTGAAATAGGCATGAAAGGAGAGCGGAGA AGGGGAAAAGGGCACGACGGTTTGTACCA GGGACTCAGCACTGCTACGAAGGATACTT ATGACGCTCTCCACATGCAAGCCCTGCCA CCTAGG		HLCPSPLFPGPSKPFW VLVVVGGVLACYSLLV TVAFIIFWVRSKRSRL LHSDYMNMTPRRPGPT RKHYQPYAPPRDFAAY RSRVKFSRSADAPAYQ QGQNQLYNELNLGRRE EYDVLDKRRGRDPEMG GKPRRKNPQEGLYNEL QKDKMAEAYSEIGMKG ERRRGKGHDGLYQGLS TATKDTYDALHMQALP PR	
(CAR3.3) Clone 20C5.1 CD8 CAR DNA HxL	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTGCAGTTGGTGCAAAGCGGC GCAGAAGTTAAGAAACCTGGGGCGTCAGT TAAGGTGTCTTGCAAAGTATCTGGCTATA CCCTCACTGAGCTGTCCATGCATTGGGTA AGGCAGGCTCCTGGAAAGGGGCTCGAATG GATGGGAGGATTTGACCCTGAAGACGGAG AGACCATCTACGCCCAGAAATTCCAGGGT AGAGTAACAGTGACTGAGGACACTAGCAC TGACACAGCGTACATGGAGCTGAGTTCTC TGAGAAGTGAGGACACAGCCGTTTACTAC TGCGCTACCGAGTCCAGAGGTATTGGCTG GCCATACTTCGACTATTGGGGTCAGGGCA CCCTGGTTACAGTGAGTTCAGGAGGCGGG GGCTCTGGGGGGGGCGGTTCCGGAGGGGG GGGCTCAGATATACAGATGACGCAGAGTC CATCAAGTCTCTCAGCCAGCGTGGGAGAT CGCGTGACTATTACTTGCCGCGCCAGCCA GAGTATTAGCTCCTATCTGAATTGGTACC AGCAAAAGCCCGGGAAGGCCCCTAAGCTT CTGATTTCTGGCGCCTCCTCTTTGAAGTC AGGTGTGCCAAGCAGATTTAGCGGGTCTG GAAGTGGCACTGACTTTACACTTACTATC TCCAGCCTGCCCCCAGAGGATTTTGCCAC ATATTACTGTCAGCAAAGCTACTCTACTC CAATCACTTTCGGCCAGGGCACAAGATTG	209	MALPVTALLLPLALLL HAARPQVQLVQSGAEV KKPGASVKVSCKVSGY TLTELSMHWVRQAPGK GLEWMGGFDPEDGETI YAQKFQGRVTVTEDTS TDTAYMELSSLRSEDT AVYYCATESRGIGWPY FDYWGQGTLVTVSSGG GGSGGGGSGGGGSDIQ MTQSPSSLSASVGDRV TITCRASQSISSYLNW YQQKPGKAPKLLISGA SSLKSGVPSRFSGSGS GTDFTLTISSLPPEDF ATYYCQQSYSTPITFG QGTRLEIKRAAALSNS IMYFSHFVPVFLPAKP TTTPAPRPPTPAPTIA SQPLSLRPEACRPAAG GAVHTRGLDFACDIYI WAPLAGTCGVLLLSLV ITLYCNHRNRSKRSRL LHSDYMNMTPRRPGPT RKHYQPYAPPRDFAAY RSRVKFSRSADAPAYQ QGQNQLYNELNLGRRE	210

	GAGATTAAGAGGGCTGCCGCACTTTCAAA TTCCATCATGTATTTCAGCCATTTTGTGC CTGTTTTTCTTCCGGCCAAACCTACAACC ACTCCCGCCCCACGCCCACCTACTCCCGC CCCTACCATTGCCTCCCAGCCTCTGTCTC TTAGACCTGAGGCTTGTAGACCTGCTGCC GGCGGAGCCGTGCACACTCGCGGTCTGGA CTTCGCCTGCGACATCTATATCTGGGCCC CTCTGGCCGGCACCTGCGGCGTTCTCCTT CTCTCACTCGTAATCACACTCTATTGCAA TCACAGGAACAGATCCAAAAGAAGCCGCC TGCTCCATAGCGATTACATGAATATGACT CCACGCCGCCCTGGCCCCACAAGGAAACA CTACCAGCCTTACGCACCACCTAGAGATT TCGCTGCCTATCGGAGCAGGGTGAAGTTT TCCAGATCTGCAGATGCACCAGCGTATCA GCAGGGCCAGAACCAACTGTATAACGAGC TCAACCTGGGACGCAGGGAAGAGTATGAC GTTTTGGACAAGCGCAGAGGACGGGACCC TGAGATGGGTGGCAAACCAAGACGAAAAA ACCCCCAGGAGGGTCTCTATAATGAGCTG CAGAAGGATAAGATGGCTGAAGCCTATTC TGAAATAGGCATGAAAGGAGAGCGGAGAA GGGGAAAAGGGCACGACGGTTTGTACCAG GGACTCAGCACTGCTACGAAGGATACTTA TGACGCTCTCCACATGCAAGCCCTGCCAC CTAGGTAA		EYDVLDKRRGRDPEMG GKPRRKNPQEGLYNEL QKDKMAEAYSEIGMKG ERRRGKGHDGLYQGLS TATKDTYDALHMQALP PR	
(CAR3.3) Clone 20C5.1 CD8 CAR DNA HxL	CAGGTGCAGTTGGTGCAAAGCGGCGCAGA AGTTAAGAAACCTGGGGCGTCAGTTAAGG TGTCTTGCAAAGTATCTGGCTATACCCTC ACTGAGCTGTCCATGCATTGGGTAAGGCA GGCTCCTGGAAAGGGGCTCGAATGGATGG GAGGATTTGACCCTGAAGACGGAGAGACC ATCTACGCCCAGAAATTCCAGGGTAGAGT AACAGTGACTGAGGACACTAGCACTGACA CAGCGTACATGGAGCTGAGTTCTCTGAGA AGTGAGGACACAGCCGTTTACTACTGCGC TACCGAGTCCAGAGGTATTGGCTGGCCAT ACTTCGACTATTGGGGTCAGGGCACCCTG GTTACAGTGAGTTCAGGAGGCGGGGGCTC TGGGGGGGGCGGTTCCGGAGGGGGGGCT CAGATATACAGATGACGCAGAGTCCATCA AGTCTCTCAGCCAGCGTGGGAGATCGCGT GACTATTACTTGCCGCGCCAGCCAGAGTA TTAGCTCCTATCTGAATTGGTACCAGCAA AAGCCCGGGAAGGCCCCTAAGCTTCTGAT TTCTGGCGCCTCCTCTTTGAAGTCAGGTG TGCCAAGCAGATTTAGCGGGTCTGGAAGT GGCACTGACTTTACACTTACTATCTCCAG CCTGCCCCCAGAGGATTTTGCCACATATT ACTGTCAGCAAAGCTACTCTACTCCAATC ACTTTCGGCCAGGGCACAAGATTGGAGAT TAAGAGGGCTGCCGCACTTTCAAATTCCA TCATGTATTTCAGCCATTTTGTGCCTGTT TTTCTTCCGGCCAAACCTACAACCACTCC CGCCCCACGCCCACCTACTCCCGCCCCTA CCATTGCCTCCCAGCCTCTGTCTCTTAGA CCTGAGGCTTGTAGACCTGCTGCCGGCGG AGCCGTGCACACTCGCGGTCTGGACTTCG	211	QVQLVQSGAEVKKPGA SVKVSCKVSGYTLTEL SMHWVRQAPGKGLEWM GGFDPEDGETIYAQKF QGRVTVTEDTSTDTAY MELSSLRSEDTAVYYC ATESRGIGWPYFDYWG QGTLVTVSSGGGGSGG GGSGGGGSDIQMTQSP SSLSASVGDRVTITCR ASQSISSYLNWYQQKP GKAPKLLISGASSLKS GVPSRFSGSGSGTDFT LTISSLPPEDFATYYC QQSYSTPITFGQGTRL EIKRAAALSNSIMYFS HFVPVFLPAKPTTTPA PRPPTPAPTIASQPLS LRPEACRPAAGGAVHT RGLDFACDIYIWAPLA GTCGVLLLSLVITLYC NHRNRSKRSRLLHSDY MNMTPRRPGPTRKHYQ PYAPPRDFAAYRSRVK FSRSADAPAYQQGQNQ LYNELNLGRREEYDVL DKRRGRDPEMGGKPRR KNPQEGLYNELQKDKM AEAYSEIGMKGERRRG KGHDGLYQGLSTATKD TYDALHMQALPPR	212

	CCTGCGACATCTATATCTGGGCCCCTCTG GCCGGCACCTGCGGCGTTCTCCTTCTCTC ACTCGTAATCACACTCTATTGCAATCACA GGAACAGATCCAAAAGAAGCCGCCTGCTC CATAGCGATTACATGAATATGACTCCACG CCGCCCTGGCCCCACAAGGAAACACTACC AGCCTTACGCACCACCTAGAGATTTCGCT GCCTATCGGAGCAGGGTGAAGTTTTCCAG ATCTGCAGATGCACCAGCGTATCAGCAGG GCCAGAACCAACTGTATAACGAGCTCAAC CTGGGACGCAGGGAAGAGTATGACGTTTT GGACAAGCGCAGAGGACGGGACCCTGAGA TGGGTGGCAAACCAAGACGAAAAAACCCC CAGGAGGGTCTCTATAATGAGCTGCAGAA GGATAAGATGGCTGAAGCCTATTCTGAAA TAGGCATGAAAGGAGAGCGGAGAAGGGGA AAAGGGCACGACGGTTTGTACCAGGGACT CAGCACTGCTACGAAGGATACTTATGACG CTCTCCACATGCAAGCCCTGCCACCTAGG			
(CAR4.1) Clone 20C5.2 THD CAR DNA HxL	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTCCAGTTGGTCGAAAGTGGC GGTGGTGTAGTGCAGCCGGGCCGCAGTTT GAGGCTTTCCTGTGCGGCTTCAGGCTTTA CTTTTTCCAGCTATGGAATGCACTGGGTG CGGCAGGCCCCCGGCAAAGGACTTGAGTG GGTGGCCGTCATTTCTTATGACGGATCAG ATAAGTACTACGTGGACAGCGTCAAGGGC AGATTCACCATCTCTAGGGACAACAGTAA AAATAGACTCTACCTCCAGATGAATAGCC TCAGAGCTGAAGACACGGCCGTCTACTAT TGTGCTCGGGAGCGGTATAGTGGCAGAGA CTACTGGGGGCAGGGCACACTCGTTACAG TGAGTAGCGGCGGAGGAGGGAGTGGGGGC GGTGGCTCCGGTGGAGGAGGTTCTGAGAT TGTTATGACCCAGAGTCCTGCGACCCTCT CAGTCAGCCCCGGGGAGCGCGCAACTTTG TCTTGCAGAGCTAGTCAGTCCGTGTCCTC TCTTCTGACATGGTACCAGCAAAAGCCCG GGCAGGCTCCGCGCCTTTTGATCTTTGGG GCTTCAACAAGAGCCACTGGGATTCCCGC ACGATTCTCTGGCTCCGGGAGCGGTACTG GTTTCACCCTGACGATTAGCAGTCTCCAG AGCGAGGACTTCGCCGTATACTACTGCCA GCAGTACGATACGTGGCCATTCACTTTTG GACCAGGGACTAAAGTGGATTTTAAGCGC GCCGCCGCTCTCGATAACGAAAAGTCAAA TGGCACCATAATCCACGTCAAAGGCAAGC ACCTGTGCCCTTCCCCGCTCTTCCCCGGA CCCAGTAAACCATTTTGGGTGCTGGTTGT TGTGGGGGGCGTGCTGGCCTGCTATAGCC TTTTGGTCACTGTAGCCTTCATTATTTTT TGGGTCAGATCCAAAAGAAGCCGCCTGCT CCATAGCGATTACATGAATATGACTCCAC GCCGCCCTGGCCCCACAAGGAAACACTAC CAGCCTTACGCACCACCTAGAGATTTCGC TGCCTATCGGAGCAGGGTGAAGTTTTCCA GATCTGCAGATGCACCAGCGTATCAGCAG GGCCAGAACCAACTGTATAACGAGCTCAA	213	MALPVTALLLPLALLL HAARPQVQLVESGGGV VQPGRSLRLSCAASGF TFSSYGMHWVRQAPGK GLEWVAVISYDGSDKY YVDSVKGRFTISRDNS KNRLYLQMNSLRAEDT AVYYCARERYSGRDYW GQGTLVTVSSGGGGSG GGGSGGGGSEIVMTQS PATLSVSPGERATLSC RASQSVSSLLTWYQQK PGQAPRLLIFGASTRA TGIPARFSGSGSGTGF TLTISSLQSEDFAVYY CQQYDTWPFTFGPGTK VDFKRAAALDNEKSNG TIIHVKGKHLCPSPLF PGPSKPFWVLVVVGGV LACYSLLVTVAFIIFW VRSKRSRLLHSDYMNM TPRRPGPTRKHYQPYA PPRDFAAYRSRVKFSR SADAPAYQQGQNQLYN ELNLGRREEYDVLDKR RGRDPEMGGKPRRKNP QEGLYNELQKDKMAEA YSEIGMKGERRRGKGH DGLYQGLSTATKDTYD ALHMQALPPR	214

	CCTGGGACGCAGGGAAGAGTATGACGTTT TGGACAAGCGCAGAGGACGGGACCCTGAG ATGGGTGGCAAACCAAGACGAAAAAACCC CCAGGAGGGTCTCTATAATGAGCTGCAGA AGGATAAGATGGCTGAAGCCTATTCTGAA ATAGGCATGAAAGGAGAGCGGAGAAGGGG AAAAGGGCACGACGGTTTGTACCAGGGAC TCAGCACTGCTACGAAGGATACTTATGAC GCTCTCCACATGCAAGCCCTGCCACCTAG GTAA			
(CAR4.1) Clone 20C5.2 THD CAR DNA HxL	CAGGTCCAGTTGGTCGAAAGTGGCGGTGG TGTAGTGCAGCCGGGCCGCAGTTTGAGGC TTTCCTGTGCGGCTTCAGGCTTTACTTTT TCCAGCTATGGAATGCACTGGGTGCGGCA GGCCCCCGGCAAAGGACTTGAGTGGGTGG CCGTCATTTCTTATGACGGATCAGATAAG TACTACGTGGACAGCGTCAAGGGCAGATT CACCATCTCTAGGGACAACAGTAAAAATA GACTCTACCTCCAGATGAATAGCCTCAGA GCTGAAGACACGGCCGTCTACTATTGTGC TCGGGAGCGGTATAGTGGCAGAGACTACT GGGGGCAGGGCACACTCGTTACAGTGAGT AGCGGCGGAGGAGGGAGTGGGGGCGGTGG CTCCGGTGGAGGAGGTTCTGAGATTGTTA TGACCCAGAGTCCTGCGACCCTCTCAGTC AGCCCCGGGGAGCGCGCAACTTTGTCTTG CAGAGCTAGTCAGTCCGTGTCCTCTCTTC TGACATGGTACCAGCAAAAGCCCGGGCAG GCTCCGCGCCTTTTGATCTTTGGGGCTTC AACAAGAGCCACTGGGATTCCCGCACGAT TCTCTGGCTCCGGGAGCGGTACTGGTTTC ACCCTGACGATTAGCAGTCTCCAGAGCGA GGACTTCGCCGTATACTACTGCCAGCAGT ACGATACGTGGCCATTCACTTTTGGACCA GGGACTAAAGTGGATTTTAAGCGCGCCGC CGCTCTCGATAACGAAAAGTCAAATGGCA CCATAATCCACGTCAAAGGCAAGCACCTG TGCCCTTCCCCGCTCTTCCCCGGACCCAG TAAACCATTTTGGGTGCTGGTTGTTGTGG GGGGCGTGCTGGCCTGCTATAGCCTTTTG GTCACTGTAGCCTTCATTATTTTTTGGGT CAGATCCAAAAGAAGCCGCCTGCTCCATA GCGATTACATGAATATGACTCCACGCCGC CCTGGCCCCACAAGGAAACACTACCAGCC TTACGCACCACCTAGAGATTTCGCTGCCT ATCGGAGCAGGGTGAAGTTTTCCAGATCT GCAGATGCACCAGCGTATCAGCAGGGCCA GAACCAACTGTATAACGAGCTCAACCTGG GACGCAGGGAAGAGTATGACGTTTTGGAC AAGCGCAGAGGACGGGACCCTGAGATGGG TGGCAAACCAAGACGAAAAAACCCCCAGG AGGGTCTCTATAATGAGCTGCAGAAGGAT AAGATGGCTGAAGCCTATTCTGAAATAGG CATGAAAGGAGAGCGGAGAAGGGGAAAAG GGCACGACGGTTTGTACCAGGGACTCAGC ACTGCTACGAAGGATACTTATGACGCTCT CCACATGCAAGCCCTGCCACCTAGG	215	QVQLVESGGGVVQPGR SLRLSCAASGFTFSSY GMHWVRQAPGKGLEWV AVISYDGSDKYYVDSV KGRFTISRDNSKNRLY LQMNSLRAEDTAVYYC ARERYSGRDYWGQGTL VTVSSGGGGSGGGGSG GGGSEIVMTQSPATLS VSPGERATLSCRASQS VSSLLTWYQQKPGQAP RLLIFGASTRATGIPA RFSGSGSGTGFTLTIS SLQSEDFAVYYCQQYD TWPFTFGPGTKVDFKR AAALDNEKSNGTIIHV KGKHLCPSPLFPGPSK PFWVLVVVGGVLACYS LLVTVAFIIFWVRSKR SRLLHSDYMNMTPRRP GPTRKHYQPYAPPRDF AAYRSRVKFSRSADAP AYQQGQNQLYNELNLG RREEYDVLDKRRGRDP EMGGKPRRKNPQEGLY NELQKDKMAEAYSEIG MKGERRRGKGHDGLYQ GLSTATKDTYDALHMQ ALPPR	216
(CAR4.2) Clone	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC	217	MALPVTALLLPLALLL HAARPQVQLVESGGGV	218

20C5.2 CHD CAR DNA HxL	GCCCGCAGGTGCAGCTCGTGGAGTCTGGC GGCGGCGTGGTCCAGCCCGGCCGGTCCCT GCGCCTGTCCTGCGCCGCCAGCGGGTTTA CTTTTTCCTCCTACGGCATGCACTGGGTG CGCCAGGCTCCCGGCAAGGGCCTCGAGTG GGTCGCCGTGATCTCATACGATGGGTCAG ACAAATACTATGTCGATTCTGTTAAAGGG CGGTTTACCATTTCAAGAGATAACTCTAA GAATAGGCTGTATTTGCAGATGAACAGCC TGAGGGCTGAAGATACCGCAGTGTACTAT TGCGCTAGGGAGCGGTATAGTGGCCGCGA TTACTGGGGACAGGGTACACTGGTGACCG TGAGCTCTGGGGGTGGCGGAAGCGGGGGT GGCGGAAGCGGCGGAGGGGGTAGTGAAAT TGTGATGACCCAGTCTCCGGCTACACTTT CAGTCTCCCCTGGGGAGAGAGCTACACTG TCATGCAGAGCGTCCCAGTCCGTCTCTTC TCTCCTTACCTGGTATCAGCAGAAGCCCG GCCAGGCTCCTCGACTGCTGATCTTCGGT GCCTCCACAAGGGCGACCGGGATTCCAGC CCGCTTCTCAGGTTCTGGGAGCGGAACTG GTTTCACTTTGACAATCAGTTCACTGCAG TCAGAGGATTTCGCCGTGTACTACTGCCA GCAATACGACACATGGCCATTCACTTTCG GACCCGGTACCAAAGTCGATTTCAAGAGA GCCGCGGCCATCGAGGTTATGTACCCACC ACCATATCTGGACAATGAAAAAAGCAATG GAACCATTATCCATGTGAAGGGTAAACAC CTCTGCCCTAGCCCACTTTTCCCTGGCCC ATCAAAGCCCTTCTGGGTCTTGGTGGTCG TGGGGGGTGTGCTGGCCTGTTACAGCCTT CTGGTGACGGTTGCTTTCATTATCTTCTG GGTTAGATCCAAAAGAAGCCGCCTGCTCC ATAGCGATTACATGAATATGACTCCACGC CGCCCTGGCCCCACAAGGAAACACTACCA GCCTTACGCACCACCTAGAGATTTCGCTG CCTATCGGAGCAGGGTGAAGTTTTCCAGA TCTGCAGATGCACCAGCGTATCAGCAGGG CCAGAACCAACTGTATAACGAGCTCAACC TGGGACGCAGGGAAGAGTATGACGTTTTG GACAAGCGCAGAGGACGGGACCCTGAGAT GGGTGGCAAACCAAGACGAAAAAACCCCC AGGAGGGTCTCTATAATGAGCTGCAGAAG GATAAGATGGCTGAAGCCTATTCTGAAAT AGGCATGAAAGGAGAGCGGAGAAGGGGAA AAGGGCACGACGGTTTGTACCAGGGACTC AGCACTGCTACGAAGGATACTTATGACGC TCTCCACATGCAAGCCCTGCCACCTAGGT AA		VQPGRSLRLSCAASGF TFSSYGMHWVRQAPGK GLEWVAVISYDGSDKY YVDSVKGRFTISRDNS KNRLYLQMNSLRAEDT AVYYCARERYSGRDYW GQGTLVTVSSGGGGSG GGGSGGGGSEIVMTQS PATLSVSPGERATLSC RASQSVSSLLTWYQQK PGQAPRLLIFGASTRA TGIPARFSGSGSGTGF TLTISSLQSEDFAVYY CQQYDTWPFTFGPGTK VDFKRAAAIEVMYPPP YLDNEKSNGTIIHVKG KHLCPSPLFPGPSKPF WVLVVVGGVLACYSLL VTVAFIIFWVRSKRSR LLHSDYMNMTPRRPGP TRKHYQPYAPPRDFAA YRSRVKFSRSADAPAY QQGQNQLYNELNLGRR EEYDVLDKRRGRDPEM GGKPRRKNPQEGLYNE LQKDKMAEAYSEIGMK GERRRGKGHDGLYQGL STATKDTYDALHMQAL PPR	
(CAR4.2) Clone 20C5.2 CHD CAR DNA HxL	CAGGTGCAGCTCGTGGAGTCTGGCGGCGG CGTGGTCCAGCCCGGCCGGTCCCTGCGCC TGTCCTGCGCCGCCAGCGGGTTTACTTTT TCCTCCTACGGCATGCACTGGGTGCGCCA GGCTCCCGGCAAGGGCCTCGAGTGGGTCG CCGTGATCTCATACGATGGGTCAGACAAA TACTATGTCGATTCTGTTAAAGGGCGGTT TACCATTTCAAGAGATAACTCTAAGAATA GGCTGTATTTGCAGATGAACAGCCTGAGG GCTGAAGATACCGCAGTGTACTATTGCGC	219	QVQLVESGGGVVQPGR SLRLSCAASGFTFSSY GMHWVRQAPGKGLEWV AVISYDGSDKYYVDSV KGRFTISRDNSKNRLY LQMNSLRAEDTAVYYC ARERYSGRDYWGQGTL VTVSSGGGGSGGGGSG GGGSEIVMTQSPATLS VSPGERATLSCRASQS	220

	TAGGGAGCGGTATAGTGGCCGCGATTACT GGGGACAGGGTACACTGGTGACCGTGAGC TCTGGGGGTGGCGGAAGCGGGGGTGGCGG AAGCGGCGGAGGGGGTAGTGAAATTGTGA TGACCCAGTCTCCGGCTACACTTTCAGTC TCCCCTGGGGAGAGAGCTACACTGTCATG CAGAGCGTCCCAGTCCGTCTCTTCTCTCC TTACCTGGTATCAGCAGAAGCCCGGCCAG GCTCCTCGACTGCTGATCTTCGGTGCCTC CACAAGGGCGACCGGGATTCCAGCCCGCT TCTCAGGTTCTGGGAGCGGAACTGGTTTC ACTTTGACAATCAGTTCACTGCAGTCAGA GGATTTCGCCGTGTACTACTGCCAGCAAT ACGACACATGGCCATTCACTTTCGGACCC GGTACCAAAGTCGATTTCAAGAGAGCCGC GGCCATCGAGGTTATGTACCCACCACCAT ATCTGGACAATGAAAAAAGCAATGGAACC ATTATCCATGTGAAGGGTAAACACCTCTG CCCTAGCCCACTTTTCCCTGGCCCATCAA AGCCCTTCTGGGTCTTGGTGGTCGTGGGG GGTGTGCTGGCCTGTTACAGCCTTCTGGT GACGGTTGCTTTCATTATCTTCTGGGTTA GATCCAAAAGAAGCCGCCTGCTCCATAGC GATTACATGAATATGACTCCACGCCGCCC TGGCCCCACAAGGAAACACTACCAGCCTT ACGCACCACCTAGAGATTTCGCTGCCTAT CGGAGCAGGGTGAAGTTTTCCAGATCTGC AGATGCACCAGCGTATCAGCAGGGCCAGA ACCAACTGTATAACGAGCTCAACCTGGGA CGCAGGGAAGAGTATGACGTTTTGGACAA GCGCAGAGGACGGGACCCTGAGATGGGTG GCAAACCAAGACGAAAAAACCCCCAGGAG GGTCTCTATAATGAGCTGCAGAAGGATAA GATGGCTGAAGCCTATTCTGAAATAGGCA TGAAAGGAGAGCGGAGAAGGGGAAAAGGG CACGACGGTTTGTACCAGGGACTCAGCAC TGCTACGAAGGATACTTATGACGCTCTCC ACATGCAAGCCCTGCCACCTAGG		VSSLLTWYQQKPGQAP RLLIFGASTRATGIPA RFSGSGSGTGFTLTIS SLQSEDFAVYYCQQYD TWPFTFGPGTKVDFKR AAAIEVMYPPPYLDNE KSNGTIIHVKGKHLCP SPLFPGPSKPFWVLVV VGGVLACYSLLVTVAF IIFWVRSKRSRLLHSD YMNMTPRRPGPTRKHY QPYAPPRDFAAYRSRV KFSRSADAPAYQQGQN QLYNELNLGRREEYDV LDKRRGRDPEMGGKPR RKNPQEGLYNELQKDK MAEAYSEIGMKGERRR GKGHDGLYQGLSTATK DTYDALHMQALPPR	
(CAR4.3) Clone 20C5.2 CD8 CAR DNA HxL	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTGCAGTTGGTTGAATCAGGA GGGGGTGTGGTGCAACCCGGTCGGTCACT GCGCCTCAGTTGTGCTGCTTCCGGGTTTA CTTTCAGCTCATATGGGATGCACTGGGTA CGGCAGGCTCCAGGTAAAGGCTTGGAATG GGTGGCGGTGATCAGCTATGACGGCTCTG ACAAATATTATGTGGACTCCGTGAAAGGC AGATTCACCATCAGTCGAGACAACTCAAA GAATAGACTCTACTTGCAGATGAATAGCC TCCGGGCCGAAGATACTGCAGTCTATTAT TGCGCCCGGGAGCGCTACAGTGGAAGAGA CTATTGGGGGCAAGGAACTCTTGTCACAG TCTCATCTGGCGGCGGCGGCAGCGGTGGG GGCGGATCTGGCGGGGGCGGCAGCGAAAT CGTTATGACTCAGAGTCCTGCCACACTGA GCGTTAGCCCTGGTGAGAGAGCAACACTT AGCTGCAGAGCTAGTCAGAGTGTTTCCAG TCTTTTGACATGGTACCAACAGAAGCCCG GTCAAGCTCCACGACTGCTCATCTTCGGT	221	MALPVTALLLPLALLL HAARPQVQLVESGGGV VQPGRSLRLSCAASGF TFSSYGMHWVRQAPGK GLEWVAVISYDGSDKY YVDSVKGRFTISRDNS KNRLYLQMNSLRAEDT AVYYCARERYSGRDYW GQGTLVTVSSGGGGSG GGGSGGGGSEIVMTQS PATLSVSPGERATLSC RASQSVSSLLTWYQQK PGQAPRLLIFGASTRA TGIPARFSGSGSGTGF TLTISSLQSEDFAVYY CQQYDTWPFTFGPGTK VDFKRAAALSNSIMYF SHFVPVFLPAKPTTTP APRPPTPAPTIASQPL SLRPEACRPAAGGAVH TRGLDFACDIYIWAPL	222

	GCATCCACCCGCGCAACCGGGATACCCGC CCGGTTTTCCGGTTCTGGAAGTGGCACAG GATTCACGCTCACCATTTCTTCTCTGCAG TCTGAAGACTTTGCCGTGTATTACTGCCA GCAGTACGATACCTGGCCCTTTACCTTTG GCCCAGGTACTAAAGTGGATTTTAAACGA GCTGCTGCACTTTCCAATAGTATTATGTA CTTTTCACATTTTGTGCCCGTGTTCCTGC CTGCGAAGCCTACGACAACCCCAGCCCCT AGGCCGCCCACACCGGCCCCAACTATTGC CTCCCAGCCATTGTCTCTGAGACCCGAAG CTTGCAGACCTGCTGCTGGAGGCGCCGTT CACACCCGAGGATTGGATTTCGCATGTGA CATTTACATCTGGGCCCCTTTGGCCGGAA CCTGCGGTGTGCTGCTGCTGTCACTCGTG ATTACACTTTACTGCAACCACCGAAACAG ATCCAAAAGAAGCCGCCTGCTCCATAGCG ATTACATGAATATGACTCCACGCCGCCCT GGCCCCACAAGGAAACACTACCAGCCTTA CGCACCACCTAGAGATTTCGCTGCCTATC GGAGCAGGGTGAAGTTTTCCAGATCTGCA GATGCACCAGCGTATCAGCAGGGCCAGAA CCAACTGTATAACGAGCTCAACCTGGGAC GCAGGGAAGAGTATGACGTTTTGGACAAG CGCAGAGGACGGGACCCTGAGATGGGTGG CAAACCAAGACGAAAAAACCCCCAGGAGG GTCTCTATAATGAGCTGCAGAAGGATAAG ATGGCTGAAGCCTATTCTGAAATAGGCAT GAAAGGAGAGCGGAGAAGGGGAAAAGGGC ACGACGGTTTGTACCAGGGACTCAGCACT GCTACGAAGGATACTTATGACGCTCTCCA CATGCAAGCCCTGCCACCTAGGTAA		AGTCGVLLLSLVITLY CNHRNRSKRSRLLHSD YMNMTPRRPGPTRKHY QPYAPPRDFAAYRSRV KFSRSADAPAYQQGQN QLYNELNLGRREEYDV LDKRRGRDPEMGGKPR RKNPQEGLYNELQKDK MAEAYSEIGMKGERRR GKGHDGLYQGLSTATK DTYDALHMQALPPR	
(CAR4.3) Clone 20C5.2 CD8 CAR DNA HxL	CAGGTGCAGTTGGTTGAATCAGGAGGGGG TGTGGTGCAACCCGGTCGGTCACTGCGCC TCAGTTGTGCTGCTTCCGGGTTTACTTTC AGCTCATATGGGATGCACTGGGTACGGCA GGCTCCAGGTAAAGGCTTGGAATGGGTGG CGGTGATCAGCTATGACGGCTCTGACAAA TATTATGTGGACTCCGTGAAAGGCAGATT CACCATCAGTCGAGACAACTCAAAGAATA GACTCTACTTGCAGATGAATAGCCTCCGG GCCGAAGATACTGCAGTCTATTATTGCGC CCGGGAGCGCTACAGTGGAAGAGACTATT GGGGGCAAGGAACTCTTGTCACAGTCTCA TCTGGCGGCGGCGGCAGCGGTGGGGGCGG ATCTGGCGGGGGCGGCAGCGAAATCGTTA TGACTCAGAGTCCTGCCACACTGAGCGTT AGCCCTGGTGAGAGAGCAACACTTAGCTG CAGAGCTAGTCAGAGTGTTTCCAGTCTTT TGACATGGTACCAACAGAAGCCCGGTCAA GCTCCACGACTGCTCATCTTCGGTGCATC CACCCGCGCAACCGGGATACCCGCCCGGT TTTCCGGTTCTGGAAGTGGCACAGGATTC ACGCTCACCATTTCTTCTCTGCAGTCTGA AGACTTTGCCGTGTATTACTGCCAGCAGT ACGATACCTGGCCCTTTACCTTTGGCCCA GGTACTAAAGTGGATTTTAAACGAGCTGC TGCACTTTCCAATAGTATTATGTACTTTT CACATTTTGTGCCCGTGTTCCTGCCTGCG	223	QVQLVESGGGVVQPGR SLRLSCAASGFTFSSY GMHWVRQAPGKGLEWV AVISYDGSDKYYVDSV KGRFTISRDNSKNRLY LQMNSLRAEDTAVYYC ARERYSGRDYWGQGTL VTVSSGGGGSGGGGSG GGGSEIVMTQSPATLS VSPGERATLSCRASQS VSSLLTWYQQKPGQAP RLLIFGASTRATGIPA RFSGSGSGTGFTLTIS SLQSEDFAVYYCQQYD TWPFTFGPGTKVDFKR AAALSNSIMYFSHFVP VFLPAKPTTTPAPRPP TPAPTIASQPLSLRPE ACRPAAGGAVHTRGLD FACDIYIWAPLAGTCG VLLLSLVITLYCNHRN RSKRSRLLHSDYMNMT PRRPGPTRKHYQPYAP PRDFAAYRSRVKFSRS ADAPAYQQGQNQLYNE LNLGRREEYDVLDKRR GRDPEMGGKPRRKNPQ	224

	AAGCCTACGACAACCCCAGCCCCTAGGCC GCCCACACCGGCCCCAACTATTGCCTCCC AGCCATTGTCTCTGAGACCCGAAGCTTGC AGACCTGCTGCTGGAGGCGCCGTTCACAC CCGAGGATTGGATTTCGCATGTGACATTT ACATCTGGGCCCCTTTGGCCGGAACCTGC GGTGTGCTGCTGCTGTCACTCGTGATTAC ACTTTACTGCAACCACCGAAACAGATCCA AAAGAAGCCGCCTGCTCCATAGCGATTAC ATGAATATGACTCCACGCCGCCCTGGCCC CACAAGGAAACACTACCAGCCTTACGCAC CACCTAGAGATTTCGCTGCCTATCGGAGC AGGGTGAAGTTTTCCAGATCTGCAGATGC ACCAGCGTATCAGCAGGGCCAGAACCAAC TGTATAACGAGCTCAACCTGGGACGCAGG GAAGAGTATGACGTTTTGGACAAGCGCAG AGGACGGGACCCTGAGATGGGTGGCAAAC CAAGACGAAAAAACCCCCAGGAGGGTCTC TATAATGAGCTGCAGAAGGATAAGATGGC TGAAGCCTATTCTGAAATAGGCATGAAAG GAGAGCGGAGAAGGGGAAAAGGGCACGAC GGTTTGTACCAGGGACTCAGCACTGCTAC GAAGGATACTTATGACGCTCTCCACATGC AAGCCCTGCCACCTAGG		EGLYNELQKDKMAEAY SEIGMKGERRRGKGHD GLYQGLSTATKDTYDA LHMQALPPR	
(CAR4.4) Clone 20C5.2 THD CAR DNA LxH	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGGAGATTGTGATGACCCAGTCCCCT GCTACCCTGTCCGTCAGTCCGGGCGAGAG AGCCACCTTGTCATGCCGGGCCAGCCAGT CCGTCAGCAGTCTCCTGACTTGGTATCAG CAAAAACCAGGGCAGGCACCGCGGCTTTT GATTTTTGGTGCAAGCACACGCGCCACTG GCATTCCAGCTAGGTTTTCTGGAAGTGGA TCTGGGACAGGCTTCACTCTGACAATCAG TAGCCTGCAGAGTGAGGACTTTGCTGTTT ACTACTGTCAACAGTACGACACCTGGCCA TTCACATTCGGGCCCGGCACCAAGGTCGA CTTCAAGAGGGGCGGTGGAGGTTCAGGTG GTGGCGGGTCAGGCGGCGGTGGGTCTCAG GTTCAACTGGTGGAATCAGGTGGCGGCGT TGTCCAACCGGGGCGATCACTTCGACTTT CCTGTGCTGCCTCAGGCTTTACTTTTTCA TCCTATGGGATGCACTGGGTTCGGCAGGC TCCCGGAAAAGGACTCGAGTGGGTTGCAG TGATCTCTTACGATGGCTCAGACAAGTAT TATGTGGACTCAGTCAAGGGGAGATTCAC AATAAGCCGAGACAACTCCAAAAACCGGC TTTATCTCCAGATGAACAGCCTTAGAGCG GAAGATACCGCGGTATACTACTGTGCCCG CGAGAGGTATTCCGGCAGAGACTACTGGG GACAGGGCACACTGGTCACCGTGAGTTCT GCCGCAGCGCTCGATAACGAAAAGAGCAA CGGAACCATTATCCACGTTAAGGGCAAGC ACCTGTGCCCCAGTCCCCTCTTCCCAGGA CCATCTAAACCCTTCTGGGTTCTGGTAGT AGTTGGAGGGGTCCTTGCATGTTACTCCC TTTTGGTCACCGTCGCCTTCATTATTTTC TGGGTGAGATCCAAAAGAAGCCGCCTGCT CCATAGCGATTACATGAATATGACTCCAC	225	MALPVTALLLPLALLL HAARPEIVMTQSPATL SVSPGERATLSCRASQ SVSSLLTWYQQKPGQA PRLLIFGASTRATGIP ARFSGSGSGTGFTLTI SSLQSEDFAVYYCQQY DTWPFTFGPGTKVDFK RGGGGSGGGGSGGGGS QVQLVESGGGVVQPGR SLRLSCAASGFTFSSY GMHWVRQAPGKGLEWV AVISYDGSDKYYVDSV KGRFTISRDNSKNRLY LQMNSLRAEDTAVYYC ARERYSGRDYWGQGTL VTVSSAAALDNEKSNG TIIHVKGKHLCPSPLF PGPSKPFWVLVVVGGV LACYSLLVTVAFIIFW VRSKRSRLLHSDYMNM TPRRPGPTRKHYQPYA PPRDFAAYRSRVKFSR SADAPAYQQGQNQLYN ELNLGRREEYDVLDKR RGRDPEMGGKPRRKNP QEGLYNELQKDKMAEA YSEIGMKGERRRGKGH DGLYQGLSTATKDTYD ALHMQALPPR	226

	GCCGCCCTGGCCCCACAAGGAAACACTAC CAGCCTTACGCACCACCTAGAGATTTCGC TGCCTATCGGAGCAGGGTGAAGTTTTCCA GATCTGCAGATGCACCAGCGTATCAGCAG GGCCAGAACCAACTGTATAACGAGCTCAA CCTGGGACGCAGGGAAGAGTATGACGTTT TGGACAAGCGCAGAGGACGGGACCCTGAG ATGGGTGGCAAACCAAGACGAAAAAACCC CCAGGAGGGTCTCTATAATGAGCTGCAGA AGGATAAGATGGCTGAAGCCTATTCTGAA ATAGGCATGAAAGGAGAGCGGAGAAGGGG AAAAGGGCACGACGGTTTGTACCAGGGAC TCAGCACTGCTACGAAGGATACTTATGAC GCTCTCCACATGCAAGCCCTGCCACCTAG GTAA			
(CAR4.4) Clone 20C5.2 THD CAR DNA LxH	GAGATTGTGATGACCCAGTCCCCTGCTAC CCTGTCCGTCAGTCCGGGCGAGAGAGCCA CCTTGTCATGCCGGGCCAGCCAGTCCGTC AGCAGTCTCCTGACTTGGTATCAGCAAAA ACCAGGGCAGGCACCGCGGCTTTTGATTT TTGGTGCAAGCACACGCGCCACTGGCATT CCAGCTAGGTTTTCTGGAAGTGGATCTGG GACAGGCTTCACTCTGACAATCAGTAGCC TGCAGAGTGAGGACTTTGCTGTTTACTAC TGTCAACAGTACGACACCTGGCCATTCAC ATTCGGGCCCGGCACCAAGGTCGACTTCA AGAGGGGCGGTGGAGGTTCAGGTGGTGGC GGGTCAGGCGGCGGTGGGTCTCAGGTTCA ACTGGTGGAATCAGGTGGCGGCGTTGTCC AACCGGGGCGATCACTTCGACTTTCCTGT GCTGCCTCAGGCTTTACTTTTTCATCCTA TGGGATGCACTGGGTTCGGCAGGCTCCCG GAAAAGGACTCGAGTGGGTTGCAGTGATC TCTTACGATGGCTCAGACAAGTATTATGT GGACTCAGTCAAGGGGAGATTCACAATAA GCCGAGACAACTCCAAAAACCGGCTTTAT CTCCAGATGAACAGCCTTAGAGCGGAAGA TACCGCGGTATACTACTGTGCCCGCGAGA GGTATTCCGGCAGAGACTACTGGGGACAG GGCACACTGGTCACCGTGAGTTCTGCCGC AGCGCTCGATAACGAAAAGAGCAACGGAA CCATTATCCACGTTAAGGGCAAGCACCTG TGCCCCAGTCCCCTCTTCCCAGGACCATC TAAACCCTTCTGGGTTCTGGTAGTAGTTG GAGGGGTCCTTGCATGTTACTCCCTTTTG GTCACCGTCGCCTTCATTATTTTCTGGGT GAGATCCAAAAGAAGCCGCCTGCTCCATA GCGATTACATGAATATGACTCCACGCCGC CCTGGCCCCACAAGGAAACACTACCAGCC TTACGCACCACCTAGAGATTTCGCTGCCT ATCGGAGCAGGGTGAAGTTTTCCAGATCT GCAGATGCACCAGCGTATCAGCAGGGCCA GAACCAACTGTATAACGAGCTCAACCTGG GACGCAGGGAAGAGTATGACGTTTTGGAC AAGCGCAGAGGACGGGACCCTGAGATGGG TGGCAAACCAAGACGAAAAAACCCCCAGG AGGGTCTCTATAATGAGCTGCAGAAGGAT AAGATGGCTGAAGCCTATTCTGAAATAGG CATGAAAGGAGAGCGGAGAAGGGGAAAAG	227	EIVMTQSPATLSVSPG ERATLSCRASQSVSSL LTWYQQKPGQAPRLLI FGASTRATGIPARFSG SGSGTGFTLTISSLQS EDFAVYYCQQYDTWPF TFGPGTKVDFKRGGGG SGGGGSGGGGSQVQLV ESGGGVVQPGRSLRLS CAASGFTFSSYGMHWV RQAPGKGLEWVAVISY DGSDKYYVDSVKGRFT ISRDNSKNRLYLQMNS LRAEDTAVYYCARERY SGRDYWGQGTLVTVSS AAALDNEKSNGTIIHV KGKHLCPSPLFPGPSK PFWVLVVVGGVLACYS LLVTVAFIIFWVRSKR SRLLHSDYMNMTPRRP GPTRKHYQPYAPPRDF AAYRSRVKFSRSADAP AYQQGQNQLYNELNLG RREEYDVLDKRRGRDP EMGGKPRRKNPQEGLY NELQKDKMAEAYSEIG MKGERRRGKGHDGLYQ GLSTATKDTYDALHMQ ALPPR	228

	GGCACGACGGTTTGTACCAGGGACTCAGC ACTGCTACGAAGGATACTTATGACGCTCT CCACATGCAAGCCCTGCCACCTAGG			
(CAR4.5) Clone 20C5.2 CHD CAR DNA LxH	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGGAGATCGTCATGACACAGAGTCCA GCTACCCTGAGCGTGTCCCCTGGAGAGAG AGCCACCCTGTCCTGTAGGGCTAGTCAGA GTGTGTCCAGCCTCCTCACCTGGTATCAA CAGAAGCCTGGTCAAGCTCCCCGGCTGCT TATCTTCGGGGCCAGCACGCGAGCCACAG GCATCCCGGCCAGATTCTCTGGCTCTGGC AGTGGCACCGGGTTCACTCTCACGATCTC ATCCCTGCAGTCAGAGGATTTCGCTGTGT ATTACTGTCAGCAGTACGATACATGGCCC TTCACCTTCGGCCCGGGCACAAAAGTAGA TTTCAAGCGCGGCGGCGGGGGTAGTGGGG GCGGGGGATCAGGAGGAGGGGGCTCCCAA GTACAGCTGGTTGAGAGCGGCGGCGGGGT GGTTCAGCCCGGGCGCAGCCTCAGGCTGA GTTGCGCAGCATCAGGATTCACATTCAGT TCTTATGGAATGCATTGGGTCAGACAGGC TCCCGGGAAGGGCCTTGAATGGGTGGCAG TCATTAGCTACGACGGAAGCGATAAGTAC TATGTGGACTCAGTTAAAGGGAGATTTAC TATCAGCCGCGACAATTCCAAAAACAGAT TGTATTTGCAGATGAACTCCCTCAGGGCG GAGGACACTGCTGTATATTACTGCGCACG AGAGAGATACTCCGGCCGAGACTATTGGG GCCAAGGAACATTGGTAACTGTGAGCTCC GCCGCAGCTATTGAGGTCATGTACCCCCC ACCTTATCTCGATAATGAGAAGAGTAATG GGACTATAATTCACGTAAAGGGCAAACAC CTGTGCCCTTCCCCGCTGTTTCCAGGTCC AAGTAAGCCGTTCTGGGTCCTGGTTGTGG TGGGAGGGGTGCTGGCCTGCTATTCTCTG TTGGTTACCGTGGCCTTTATCATTTTCTG GGTGAGATCCAAAAGAAGCCGCCTGCTCC ATAGCGATTACATGAATATGACTCCACGC CGCCCTGGCCCCACAAGGAAACACTACCA GCCTTACGCACCACCTAGAGATTTCGCTG CCTATCGGAGCAGGGTGAAGTTTTCCAGA TCTGCAGATGCACCAGCGTATCAGCAGGG CCAGAACCAACTGTATAACGAGCTCAACC TGGGACGCAGGGAAGAGTATGACGTTTTG GACAAGCGCAGAGGACGGGACCCTGAGAT GGGTGGCAAACCAAGACGAAAAAACCCCC AGGAGGGTCTCTATAATGAGCTGCAGAAG GATAAGATGGCTGAAGCCTATTCTGAAAT AGGCATGAAAGGAGAGCGGAGAAGGGGAA AAGGGCACGACGGTTTGTACCAGGGACTC AGCACTGCTACGAAGGATACTTATGACGC TCTCCACATGCAAGCCCTGCCACCTAGGT AA	229	MALPVTALLLPLALLL HAARPEIVMTQSPATL SVSPGERATLSCRASQ SVSSLLTWYQQKPGQA PRLLIFGASTRATGIP ARFSGSGSGTGFTLTI SSLQSEDFAVYYCQQY DTWPFTFGPGTKVDFK RGGGGSGGGGSGGGGS QVQLVESGGGVVQPGR SLRLSCAASGFTFSSY GMHWVRQAPGKGLEWV AVISYDGSDKYYVDSV KGRFTISRDNSKNRLY LQMNSLRAEDTAVYYC ARERYSGRDYWGQGTL VTVSSAAAIEVMYPPP YLDNEKSNGTIIHVKG KHLCPSPLFPGPSKPF WVLVVVGGVLACYSLL VTVAFIIFWVRSKRSR LLHSDYMNMTPRRPGP TRKHYQPYAPPRDFAA YRSRVKFSRSADAPAY QQGQNQLYNELNLGRR EEYDVLDKRRGRDPEM GGKPRRKNPQEGLYNE LQKDKMAEAYSEIGMK GERRRGKGHDGLYQGL STATKDTYDALHMQAL PPR	230
(CAR4.5) Clone 20C5.2 CHD CAR DNA LxH	GAGATCGTCATGACACAGAGTCCAGCTAC CCTGAGCGTGTCCCCTGGAGAGAGAGCCA CCCTGTCCTGTAGGGCTAGTCAGAGTGTG TCCAGCCTCCTCACCTGGTATCAACAGAA GCCTGGTCAAGCTCCCCGGCTGCTTATCT	231	EIVMTQSPATLSVSPG ERATLSCRASQSVSSL LTWYQQKPGQAPRLLI FGASTRATGIPARFSG SGSGTGFTLTISSLQS	232

	TCGGGGCCAGCACGCGAGCCACAGGCATC CCGGCCAGATTCTCTGGCTCTGGCAGTGG CACCGGGTTCACTCTCACGATCTCATCCC TGCAGTCAGAGGATTTCGCTGTGTATTAC TGTCAGCAGTACGATACATGGCCCTTCAC CTTCGGCCCGGGCACAAAAGTAGATTTCA AGCGCGGCGGCGGGGGTAGTGGGGGCGGG GGATCAGGAGGAGGGGGCTCCCAAGTACA GCTGGTTGAGAGCGGCGGCGGGGTGGTTC AGCCCGGGCGCAGCCTCAGGCTGAGTTGC GCAGCATCAGGATTCACATTCAGTTCTTA TGGAATGCATTGGGTCAGACAGGCTCCCG GGAAGGGCCTTGAATGGGTGGCAGTCATT AGCTACGACGGAAGCGATAAGTACTATGT GGACTCAGTTAAAGGGAGATTTACTATCA GCCGCGACAATTCCAAAAACAGATTGTAT TTGCAGATGAACTCCCTCAGGGCGGAGGA CACTGCTGTATATTACTGCGCACGAGAGA GATACTCCGGCCGAGACTATTGGGGCCAA GGAACATTGGTAACTGTGAGCTCCGCCGC AGCTATTGAGGTCATGTACCCCCCACCTT ATCTCGATAATGAGAAGAGTAATGGGACT ATAATTCACGTAAAGGGCAAACACCTGTG CCCTTCCCCGCTGTTTCCAGGTCCAAGTA AGCCGTTCTGGGTCCTGGTTGTGGTGGGA GGGGTGCTGGCCTGCTATTCTCTGTTGGT TACCGTGGCCTTTATCATTTTCTGGGTGA GATCCAAAAGAAGCCGCCTGCTCCATAGC GATTACATGAATATGACTCCACGCCGCCC TGGCCCCACAAGGAAACACTACCAGCCTT ACGCACCACCTAGAGATTTCGCTGCCTAT CGGAGCAGGGTGAAGTTTTCCAGATCTGC AGATGCACCAGCGTATCAGCAGGGCCAGA ACCAACTGTATAACGAGCTCAACCTGGGA CGCAGGGAAGAGTATGACGTTTTGGACAA GCGCAGAGGACGGGACCCTGAGATGGGTG GCAAACCAAGACGAAAAAACCCCCAGGAG GGTCTCTATAATGAGCTGCAGAAGGATAA GATGGCTGAAGCCTATTCTGAAATAGGCA TGAAAGGAGAGCGGAGAAGGGGAAAAGGG CACGACGGTTTGTACCAGGGACTCAGCAC TGCTACGAAGGATACTTATGACGCTCTCC ACATGCAAGCCCTGCCACCTAGG		EDFAVYYCQQYDTWPF TFGPGTKVDFKRGGGG SGGGGSGGGGSQVQLV ESGGGVVQPGRSLRLS CAASGFTFSSYGMHWV RQAPGKGLEWVAVISY DGSDKYYVDSVKGRFT ISRDNSKNRLYLQMNS LRAEDTAVYYCARERY SGRDYWGQGTLVTVSS AAAIEVMYPPPYLDNE KSNGTIIHVKGKHLCP SPLFPGPSKPFWVLVV VGGVLACYSLLVTVAF IIFWVRSKRSRLLHSD YMNMTPRRPGPTRKHY QPYAPPRDFAAYRSRV KFSRSADAPAYQQGQN QLYNELNLGRREEYDV LDKRRGRDPEMGGKPR RKNPQEGLYNELQKDK MAEAYSEIGMKGERRR GKGHDGLYQGLSTATK DTYDALHMQALPPR	
(CAR4.6) Clone 20C5.2 CD8 CAR DNA LxH	ATGGCACTCCCCGTAACTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGGAAATAGTGATGACTCAGTCCCCG GCCACCCTCAGCGTGTCCCCCGGGGAGCG AGCGACCCTGTCATGCAGGGCTTCCCAGA GTGTCAGCTCCCTGCTCACTTGGTATCAG CAAAAGCCGGGGCAGGCTCCCCGCCTCCT CATCTTCGGGGCATCAACTAGGGCCACCG GCATTCCTGCAAGATTTTCCGGGTCTGGC AGCGGCACCGGCTTCACCCTTACCATTAG CTCTCTGCAGTCTGAGGACTTCGCCGTTT ACTATTGTCAGCAGTATGATACTTGGCCC TTTACCTTCGGTCCCGGAACTAAGGTGGA CTTCAAGCGCGGGGGGGGTGGATCTGGAG GTGGTGGCTCCGGGGGCGGTGGAAGCCAG GTCCAGTTGGTTGAGAGCGGCGGCGGAGT	233	MALPVTALLLPLALLL HAARPEIVMTQSPATL SVSPGERATLSCRASQ SVSSLLTWYQQKPGQA PRLLIFGASTRATGIP ARFSGSGSGTGFTLTI SSLQSEDFAVYYCQQY DTWPFTFGPGTKVDFK RGGGGSGGGGSGGGGS QVQLVESGGGVVQPGR SLRLSCAASGFTFSSY GMHWVRQAPGKGLEWV AVISYDGSDKYYVDSV KGRFTISRDNSKNRLY LQMNSLRAEDTAVYYC ARERYSGRDYWGQGTL	234

	GGTGCAGCCCGGGAGGTCCTTGCGGCTGA GCTGTGCAGCCTCCGGTTTTACTTTTTCT AGCTATGGAATGCATTGGGTAAGACAGGC TCCCGGAAAAGGCCTCGAGTGGGTGGCGG TCATTAGCTATGATGGATCTGATAAATAC TATGTGGACTCAGTTAAGGGGCGCTTCAC AATCTCAAGAGACAATAGCAAAAATAGAC TGTACCTGCAGATGAATAGTCTGCGCGCC GAGGACACTGCCGTGTACTACTGCGCCCG CGAGAGATACAGCGGACGGGATTACTGGG GCCAGGGTACCCTCGTAACGGTGTCCTCC GCTGCCGCCCTTAGCAACAGCATTATGTA CTTTTCTCATTTCGTGCCAGTCTTTCTCC CAGCAAAGCCCACCACTACCCCGGCCCCC AGGCCGCCTACTCCTGCCCCCACTATCGC GTCTCAGCCTCTCTCCTTGCGGCCCGAGG CCTGCCGGCCAGCCGCAGGGGGCGCCGTA CATACTCGGGGTTTGGATTTCGCTTGCGA CATATATATTTGGGCCCCCCTCGCCGGCA CATGTGGAGTGCTGCTCCTGAGTCTCGTT ATAACCCTCTATTGCAACCATAGAAACAG ATCCAAAAGAAGCCGCCTGCTCCATAGCG ATTACATGAATATGACTCCACGCCGCCCT GGCCCCACAAGGAAACACTACCAGCCTTA CGCACCACCTAGAGATTTCGCTGCCTATC GGAGCAGGGTGAAGTTTTCCAGATCTGCA GATGCACCAGCGTATCAGCAGGGCCAGAA CCAACTGTATAACGAGCTCAACCTGGGAC GCAGGGAAGAGTATGACGTTTTGGACAAG CGCAGAGGACGGGACCCTGAGATGGGTGG CAAACCAAGACGAAAAAACCCCCAGGAGG GTCTCTATAATGAGCTGCAGAAGGATAAG ATGGCTGAAGCCTATTCTGAAATAGGCAT GAAAGGAGAGCGGAGAAGGGGAAAAGGGC ACGACGGTTTGTACCAGGGACTCAGCACT GCTACGAAGGATACTTATGACGCTCTCCA CATGCAAGCCCTGCCACCTAGGTAA		VTVSSAAALSNSIMYF SHFVPVFLPAKPTTTP APRPPTPAPTIASQPL SLRPEACRPAAGGAVH TRGLDFACDIYIWAPL AGTCGVLLLSLVITLY CNHRNRSKRSRLLHSD YMNMTPRRPGPTRKHY QPYAPPRDFAAYRSRV KFSRSADAPAYQQGQN QLYNELNLGRREEYDV LDKRRGRDPEMGGKPR RKNPQEGLYNELQKDK MAEAYSEIGMKGERRR GKGHDGLYQGLSTATK DTYDALHMQALPPR	
(CAR4.6) Clone 20C5.2 CD8 CAR DNA LxH	GAAATAGTGATGACTCAGTCCCCGGCCAC CCTCAGCGTGTCCCCCGGGGAGCGAGCGA CCCTGTCATGCAGGGCTTCCCAGAGTGTC AGCTCCCTGCTCACTTGGTATCAGCAAAA GCCGGGGCAGGCTCCCCGCCTCCTCATCT TCGGGGCATCAACTAGGGCCACCGGCATT CCTGCAAGATTTTCCGGGTCTGGCAGCGG CACCGGCTTCACCCTTACCATTAGCTCTC TGCAGTCTGAGGACTTCGCCGTTTACTAT TGTCAGCAGTATGATACTTGGCCCTTTAC CTTCGGTCCCGGAACTAAGGTGGACTTCA AGCGCGGGGGGGGTGGATCTGGAGGTGGT GGCTCCGGGGGCGGTGGAAGCCAGGTCCA GTTGGTTGAGAGCGGCGGCGGAGTGGTGC AGCCCGGGAGGTCCTTGCGGCTGAGCTGT GCAGCCTCCGGTTTTACTTTTTCTAGCTA TGGAATGCATTGGGTAAGACAGGCTCCCG GAAAAGGCCTCGAGTGGGTGGCGGTCATT AGCTATGATGGATCTGATAAATACTATGT GGACTCAGTTAAGGGGCGCTTCACAATCT CAAGAGACAATAGCAAAAATAGACTGTAC CTGCAGATGAATAGTCTGCGCGCCGAGGA	235	EIVMTQSPATLSVSPG ERATLSCRASQSVSSL LTWYQQKPGQAPRLLI FGASTRATGIPARFSG SGSGTGFTLTISSLQS EDFAVYYCQQYDTWPF TFGPGTKVDFKRGGGG SGGGGSGGGGSQVQLV ESGGGVVQPGRSLRLS CAASGFTFSSYGMHWV RQAPGKGLEWVAVISY DGSDKYYVDSVKGRFT ISRDNSKNRLYLQMNS LRAEDTAVYYCARERY SGRDYWGQGTLVTVSS AAALSNSIMYFSHFVP VFLPAKPTTTPAPRPP TPAPTIASQPLSLRPE ACRPAAGGAVHTRGLD FACDIYIWAPLAGTCG VLLLSLVITLYCNHRN RSKRSRLLHSDYMNMT	236

	CACTGCCGTGTACTACTGCGCCCGCGAGA GATACAGCGGACGGGATTACTGGGGCCAG GGTACCCTCGTAACGGTGTCCTCCGCTGC CGCCCTTAGCAACAGCATTATGTACTTTT CTCATTTCGTGCCAGTCTTTCTCCCAGCA AAGCCCACCACTACCCCGGCCCCCAGGCC GCCTACTCCTGCCCCCACTATCGCGTCTC AGCCTCTCTCCTTGCGGCCCGAGGCCTGC CGGCCAGCCGCAGGGGGCGCCGTACATAC TCGGGGTTTGGATTTCGCTTGCGACATAT ATATTTGGGCCCCCCTCGCCGGCACATGT GGAGTGCTGCTCCTGAGTCTCGTTATAAC CCTCTATTGCAACCATAGAAACAGATCCA AAAGAAGCCGCCTGCTCCATAGCGATTAC ATGAATATGACTCCACGCCGCCCTGGCCC CACAAGGAAACACTACCAGCCTTACGCAC CACCTAGAGATTTCGCTGCCTATCGGAGC AGGGTGAAGTTTTCCAGATCTGCAGATGC ACCAGCGTATCAGCAGGGCCAGAACCAAC TGTATAACGAGCTCAACCTGGGACGCAGG GAAGAGTATGACGTTTTGGACAAGCGCAG AGGACGGGACCCTGAGATGGGTGGCAAAC CAAGACGAAAAAACCCCCAGGAGGGTCTC TATAATGAGCTGCAGAAGGATAAGATGGC TGAAGCCTATTCTGAAATAGGCATGAAAG GAGAGCGGAGAAGGGGAAAAGGGCACGAC GGTTTGTACCAGGGACTCAGCACTGCTAC GAAGGATACTTATGACGCTCTCCACATGC AAGCCCTGCCACCTAGG		PRRPGPTRKHYQPYAP PRDFAAYRSRVKFSRS ADAPAYQQGQNQLYNE LNLGRREEYDVLDKRR GRDPEMGGKPRRKNPQ EGLYNELQKDKMAEAY SEIGMKGERRRGKGHD GLYQGLSTATKDTYDA LHMQALPPR	

[0217] In some embodiments, the polynucleotide of the present invention encodes a CAR, wherein the CAR comprises an amino acid sequence at least about 75%, at least about 85%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 178, 180, 190, 192, 202, 204, 214, 216, 226, and 228. In certain embodiments, the CAR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 178, 180, 190, 192, 202, 204, 214, 216, 226, and 228.

[0218] In some embodiments, the polynucleotide of the present invention comprises an nucleotide sequence at least about 50%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 85%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 167, 177, 179, 189, 191, 201, 203, 213, 215, 225, and 227. In certain embodiments, the polynucleotide

comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 167, 177, 179, 189, 191, 201, 203, 213, 215, 225, and 227.

II. Vectors, Cells, and Pharmaceutical Compositions

[0219] In certain aspects, provided herein are vectors comprising a polynucleotide of the present invention. In some embodiments, the present invention is directed to a vector or a set of vectors comprising a polynucleotide encoding a CAR or a TCR comprising the truncated hinge domain ("THD") domain, as described above.

[0220] 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, 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, or any combination thereof.

[0221] In an embodiment, a vector that can be employed in the context of the present invention is pGAR and has the coding sequence:

CTGACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCA
GCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTCGCTTTCTTCCCT
TCCTTTCTCGCCACGTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCC
TTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAAACTTGATTAG
GGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTCGCCCTTTGA
CGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACT
CAACCCTATCTCGGTCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTCGGCCT
ATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAAT
ATTAACGCTTACAATTTGCCATTCGCCATTCAGGCTGCGCAACTGTTGGGAAGGG
CGATCGGTGCGGGCCTCTTCGCTATTACGCCAGCTGGCGAAAGGGGGATGTGCTG
CAAGGCGATTAAGTTGGGTAACGCCAGGGTTTTCCCAGTCACGACGTTGTAAAAC
GACGGCCAGTGAATTGTAATACGACTCACTATAGGGCGACCCGGGGATGGCGCG
CCAGTAATCAATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTT
ACATAACTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCCCAT
TGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTG
ACGTCAATGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGTG
TATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGCCT
GGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATCTA
CGTATTAGTCATCGCTATTACCATGCTGATGCGGTTTTGGCAGTACATCAATGGG
CGTGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGACGTCA
ATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCGTAACAA
CTCCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGTCTATAT
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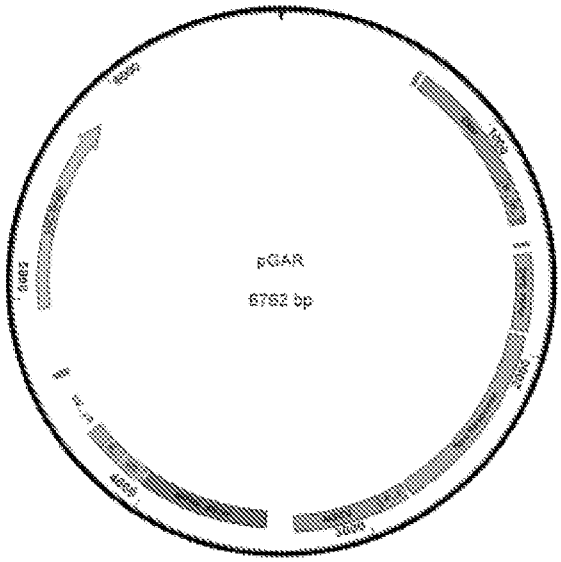
[0222] The pGAR vector map is set forth below:



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.

[0223] In other aspects, provided herein are cells comprising a polynucleotide or a vector of the present invention. In some embodiments, the present invention is directed to cells, *e.g.*, in vitro cells, comprising a polynucleotide encoding a CAR or a TCR comprising a TCD described herein. In other embodiments, the present invention is directed to cells, *e.g.*, in vitro cells, comprising a polypeptide encoded by a CAR or a TCR comprising a TCD described herein.

[0224] Any cell may be used as a host cell for the polynucleotides, the vectors, or the polypeptides of the present invention. In some embodiments, the cell can be a prokaryotic cell, fungal cell, yeast cell, or higher eukaryotic cells such as a mammalian cell. Suitable prokaryotic cells 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*; *Bacilli* such as *B. subtilis* and *B. licheniformis*; *Pseudomonas* such as *P. aeruginosa*; and *Streptomyces*. In some embodiments, the cell is a human cell. In some embodiments, the cell is an immune cell. In some embodiments, the immune cell is selected from the group consisting of a T cell, a B cell, a tumor infiltrating lymphocyte (TIL), a TCR expressing cell, a natural killer (NK) cell, a dendritic cell, a granulocyte, an innate lymphoid cell, a megakaryocyte, a monocyte, a macrophage, a platelet, a thymocyte, and a myeloid cell. In one embodiment, the immune cell is a T cell. In another embodiment, the immune cell is an NK cell. In certain embodiments, the T cell is a tumor-infiltrating lymphocyte (TIL), autologous T cell, engineered autologous T cell (eACT™), an allogeneic T cell, a heterologous T cell, or any combination thereof.

[0225] The cell of the present invention may be obtained through any source known in the art. For example, T cells can be differentiated in vitro from a hematopoietic stem cell population, or T cells can be obtained from a subject. T cells can be obtained from, *e.g.*, peripheral blood mononuclear cells, bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion, spleen tissue, and tumors. In addition, the T cells can be derived from one or more T cell lines available in the art. T cells can also be obtained from a unit of blood collected from a subject using any number of techniques known to the skilled artisan, such as FICOLL™ separation and/or apheresis. In certain embodiments, the cells collected by apheresis are washed to remove the plasma fraction, and placed in an appropriate buffer or media for subsequent processing. In some embodiments, the cells are washed with PBS. As will be appreciated, a washing step can be used, such as by using a semiautomated flowthrough centrifuge, *e.g.*, the Cobe™ 2991 cell processor, the Baxter CytoMate™, or the like. In some embodiments, the washed cells are resuspended in one or more biocompatible buffers, or other saline solution with or without buffer. In certain embodiments, the undesired components of the apheresis sample are removed. Additional methods of isolating T cells for a T cell therapy are disclosed in U.S. Patent Publication No. 2013/0287748, which is herein incorporated by references in its entirety.

[0226] In certain embodiments, T cells are isolated from PBMCs by lysing the red blood cells and depleting the monocytes, *e.g.*, by using centrifugation through a PERCOLL™ gradient. In some embodiments, a specific subpopulation of T cells, such as $CD4^+$, $CD8^+$, $CD28^+$, $CD45RA^+$, and $CD45RO^+$ T cells is 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. In some embodiments, 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 can be used. For example, to enrich for $CD4^+$ cells by negative selection, a monoclonal antibody cocktail typically includes antibodies to CD8, CD11b, CD14, CD16, CD20, and HLA-DR. In certain embodiments, flow cytometry and cell sorting are used to isolate cell populations of interest for use in the present invention.

[0227] In some embodiments, PBMCs are 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 are further isolated, and both cytotoxic and helper T lymphocytes are sorted into naive, memory, and effector T cell subpopulations either before or after genetic modification and/or expansion.

[0228] 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 includes CCR7, CD3, CD28, CD45RO, CD62L, and CD127 and are negative for granzyme B. In some embodiments, central memory T cells are $CD8^+$, $CD45RO^+$, and $CD62L^+$ T cells. In some embodiments, effector T cells are negative for CCR7, CD28, CD62L, 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.

[0229] In some embodiments, the immune cells, *e.g.*, T cells, are genetically modified following isolation using known methods, or the immune cells are activated and expanded (or differentiated in the case of progenitors) in vitro prior to being genetically modified. In another embodiment, the immune cells, *e.g.*, 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, *e.g.*, in U.S. Patent Nos. 6,905,874; 6,867,041; and 6,797,514; and PCT Publication No. WO 2012/079000, 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. In other embodiments, the T cells are activated and stimulated to proliferate with feeder cells and appropriate antibodies and cytokines using methods such as those described in U.S. Patent Nos. 6,040,177 and 5,827,642 and PCT Publication No. WO 2012/129514, the contents of which are hereby incorporated by reference in their entirety.

[0230] In certain embodiments, the T cells are obtained from a donor subject. In some embodiments, the donor subject is human patient afflicted with a cancer or a tumor. In other embodiments, the donor subject is a human patient not afflicted with a cancer or a tumor.

[0231] Other aspects of the present invention are directed to compositions comprising a polynucleotide described herein, a vector described herein, a polypeptide described herein, or an in vitro cell described herein. In some embodiments, the composition comprises a pharmaceutically acceptable carrier, diluent, solubilizer, emulsifier, preservative and/or adjuvant. In some embodiments, the composition comprises an excipient. In one embodiment, the composition comprises a polynucleotide encoding a CAR or a TCR comprising a truncated hinge domain ("THD") described herein. In another embodiment, the composition comprises a CAR or a TCR comprising a TCD encoded by a polynucleotide of the present invention. In another embodiment, the composition comprises a T cell comprising a CAR or a TCR comprising a TCD described herein.

[0232] In other embodiments, the composition is 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, the composition is in the form of a pyrogen-free, parenterally acceptable aqueous solution comprising a composition described herein, with or without additional therapeutic agents, in a pharmaceutically acceptable vehicle. In certain embodiments, the vehicle for parenteral injection is sterile distilled water in which composition described herein, with or without at least one additional therapeutic agent, is formulated as a sterile, isotonic solution, properly preserved. In certain embodiments, the preparation involves the formulation of the desired molecule with polymeric

compounds (such as polylactic acid or polyglycolic acid), beads or liposomes, that provide for the controlled or sustained release of the product, which are then be delivered via a depot injection. In certain embodiments, implantable drug delivery devices are used to introduce the desired molecule.

III. Methods of the Invention

[0233] Another aspect of the invention is directed to a method of making a cell expressing a CAR or a TCR comprising transducing a cell with a polynucleotide disclosed herein under suitable conditions. In some embodiments, the method comprises transducing a cell with a polynucleotide encoding a CAR or a TCR, as disclosed herein. In some embodiments, the method comprises transducing a cell with a vector comprising the polynucleotide encoding a CAR or a TCR.

[0234] Another aspect of the present invention is directed to a method of inducing an immunity against a tumor comprising administering to a subject an effective amount of a cell comprising a polynucleotide described herein, a vector described herein, or a CAR or a TCR described herein. In one embodiment, the method comprises administering to a subject an effective amount of a cell comprising a polynucleotide encoding a CAR or a TCR disclosed herein. In another embodiment, the method comprises administering to a subject an effective amount of a cell comprising a vector comprising a polynucleotide encoding a CAR or a TCR disclosed herein. In another embodiment, the method comprises administering to a subject an effective amount of a cell comprising a CAR or a TCR encoded by a polynucleotide disclosed herein.

[0235] Another aspect of the present invention is directed to a method of inducing an immune response in a subject comprising administering an effective amount of the engineered immune cells of the present application. In some embodiments, the immune response is a T cell-mediated immune response. In some embodiments, the T cell-mediated immune response is directed against one or more target cells. In some embodiments, the engineered immune cell comprises a CAR or a TCR, wherein the CAR or the TCR comprises a THD described in the present disclosure. In some embodiments, the target cell is a tumor cell.

[0236] Another aspect of the present invention is directed to 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 CAR or TCR, and wherein the CAR or the TCR comprises a THD described herein.

[0237] Another aspect of the present invention is directed to a method of treating a cancer in a subject in need thereof comprising administering to the subject a polynucleotide, a vector, a CAR or a TCR, a cell, or a composition disclosed herein. In one embodiment, the method comprises administering a polynucleotide encoding a CAR or a TCR. In another embodiment, the method comprises administering a vector comprising a polynucleotide encoding a CAR or a TCR. In another embodiment, the method comprises administering a CAR or a TCR encoded by a polynucleotide disclosed herein. In another embodiment, the method comprises administering a cell comprising the polynucleotide, or a vector comprising the polynucleotide, encoding a CAR or a TCR.

[0238] In some embodiments, the methods of treating a cancer in a subject in need thereof comprise a T cell therapy. In one embodiment, the T cell therapy of the present invention is engineered Autologous Cell Therapy (eACT™). According to this embodiment, the method can include collecting blood cells from the patient. The isolated blood cells (*e.g.,* T cells) can then be engineered to express a CAR or a TCR of the present invention. In a particular embodiment, the CAR T cells or the TCR T cells are administered to the patient. In some embodiments, the CAR T cells or the TCR T cells treat a tumor or a cancer in the patient. In one embodiment the CAR T cells or the TCR T cells reduce the size of a tumor or a cancer.

[0239] In some embodiments, the donor T cells for use in the T cell therapy are obtained from the patient (*e.g.*, for an autologous T cell therapy). In other embodiments, the donor T cells for use in the T cell therapy are obtained from a subject that is not the patient.

[0240] The T cells can be administered at a therapeutically effective amount. For example, a therapeutically effective amount of the T cells can be at least about 10^4 cells, at least about 10^5 cells, at least about 10^6 cells, at least about 10^7 cells, at least about 10^8 cells, at least about 10^9, or at least about 10^{10}. In another embodiment, the therapeutically effective amount of the T cells is about 10^4 cells, about 10^5 cells, about 10^6 cells, about 10^7 cells, or about 10^8 cells. In one particular embodiment, the therapeutically effective amount of the CAR T cells or the TCR T cells is about 2 X 10^6 cells/kg, about 3 X 10^6 cells/kg, about 4 X 10^6 cells/kg, about 5 X 10^6 cells/kg, about 6 X 10^6 cells/kg, about 7 X 10^6 cells/kg, about 8 X 10^6 cells/kg, about 9 X 10^6 cells/kg, about 1 X 10^7 cells/kg, about 2 X 10^7 cells/kg, about 3 X 10^7 cells/kg, about 4 X 10^7 cells/kg, about 5 X 10^7 cells/kg, about 6 X 10^7 cells/kg, about 7 X 10^7 cells/kg, about 8 X 10^7 cells/kg, or about 9 X 10^7 cells/kg.

IV. Cancer Treatment

[0241] The methods of the invention can be used to treat a cancer in a subject, reduce the size of a tumor, kill tumor cells, prevent tumor cell proliferation, prevent growth of a tumor, eliminate a tumor from a patient, prevent relapse of a tumor, prevent tumor metastasis, induce remission in a patient, or any combination thereof. In certain embodiments, the methods induce a complete response. In other embodiments, the methods induce a partial response.

[0242] Cancers that may be treated include tumors that are not vascularized, not yet substantially vascularized, or vascularized. The cancer may also include solid or non-solid tumors. In some embodiments, the cancer is a hematologic cancer. In some embodiments, the cancer is of the white blood cells. In other embodiments, the cancer is of the plasma cells. In some embodiments, the cancer is leukemia, lymphoma, or myeloma. In certain embodiments, the cancer is acute lymphoblastic leukemia (ALL) (including non T cell ALL), acute lymphoid leukemia (ALL), and hemophagocytic lymphohistocytosis (HLH)), B cell prolymphocytic leukemia, B-cell acute lymphoid leukemia ("BALL"), blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myeloid leukemia (CML), chronic or acute granulomatous disease, chronic or acute leukemia, diffuse large B cell lymphoma, diffuse large B cell lymphoma (DLBCL), follicular lymphoma, follicular lymphoma (FL), hairy cell leukemia, hemophagocytic syndrome (Macrophage Activating Syndrome (MAS), Hodgkin's Disease, large cell granuloma, leukocyte adhesion deficiency, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, monoclonal gammapathy of undetermined significance (MGUS), multiple myeloma, myelodysplasia and myelodysplastic syndrome (MDS), myeloid diseases including but not limited to acute myeloid leukemia (AML), non-Hodgkin's lymphoma (NHL), plasma cell proliferative disorders (e.g., asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, plasmacytomas (e.g., plasma cell dyscrasia; solitary myeloma; solitary plasmacytoma; extramedullary plasmacytoma; and multiple plasmacytoma), POEMS syndrome (Crow-Fukase syndrome; Takatsuki disease; PEP syndrome), primary mediastinal large B cell lymphoma (PMBC), small cell- or a large cell-follicular lymphoma, splenic marginal zone lymphoma (SMZL), systemic amyloid light chain amyloidosis, T-cell acute lymphoid leukemia ("TALL"), T-cell lymphoma, transformed follicular lymphoma, Waldenstrom macroglobulinemia, or a combination thereof.

[0243] In one embodiment, the cancer is a myeloma. In one particular embodiment, the cancer is multiple myeloma. In another embodiment, the cancer is a leukemia. In one embodiment, the cancer is acute myeloid leukemia.

[0244] In some embodiments, the methods further comprise administering a chemotherapeutic. In certain embodiments, the chemotherapeutic selected 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). One such 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.

[0245] 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.

[0246] In certain embodiments, compositions comprising CAR- and/or TCR-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. In some embodiments, compositions comprising CAR- and/or TCR-expressing immune effector cells disclosed herein may be administered in conjunction with an anti-hormonal agent that acts 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.

[0247] 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 some 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.

[0248] 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 (CureTech), and atezolizumab (Roche).

[0249] Additional therapeutic agents suitable for use in combination with the invention include, but are not limited to, ibrutinib (IMBRUVICA®), ofatumumab (ARZERRA®), rituximab (RITUXAN®), bevacizumab (AVASTIN®), trastuzumab (HERCEPTIN®), trastuzumab emtansine (KADCYLA®), imatinib (GLEEVEC®), cetuximab (ERBITUX®), panitumumab (VECTIBIX®), catumaxomab, ibritumomab, ofatumumab, tositumomab, brentuximab, alemtuzumab, gemtuzumab, erlotinib, gefitinib, vandetanib, afatinib, lapatinib, neratinib, axitinib, masitinib, pazopanib, sunitinib, sorafenib, toceranib, lestaurtinib, axitinib, cediranib, lenvatinib, nintedanib, pazopanib, regorafenib, semaxanib, sorafenib, sunitinib, tivozanib, toceranib, vandetanib, entrectinib, cabozantinib, imatinib, dasatinib, nilotinib, ponatinib, radotinib, bosutinib, lestaurtinib, ruxolitinib, pacritinib, cobimetinib, selumetinib, trametinib, binimetinib, alectinib, ceritinib, crizotinib, aflibercept,adipotide, denileukin diftitox, mTOR inhibitors such as Everolimus and Temsirolimus, hedgehog inhibitors such as sonidegib and vismodegib, CDK inhibitors such as CDK inhibitor (palbociclib).

[0250] In additional embodiments, the composition comprising CAR- and/or TCR-containing immune are administered with an anti-inflammatory agent. Anti-inflammatory agents or drugs can 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.

[0251] 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.

[0252] 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.

[0253] The present invention is further illustrated by the following examples which should not be construed as further limiting. The contents of all references cited throughout this application are expressly incorporated herein by reference.

EXAMPLES

EXAMPLE 1

[0254] Plasmids encoding a T7 promoter, CAR construct and a beta globin stabilizing sequence were linearized by overnight digestion of 10 μg DNA 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 assessed 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 FLT-=3-HIS (Sino

Biological Inc.) 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-HIS-PE (Miltenyi Biotec) 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 FLT3 CARs in electroporated T cells is shown in FIG. 3.

[0255] T cells were electroporated with plasmids encoding an anti-FLT3 CAR comprising a 10E3, 2E7, 8B5, 4E9, or 11F11 anti-FLT3 binding molecule and a hinge region selected from the full length hinge domain (a complete hinge domain or "CHD") or a truncated hinge domain ("THD"). The electroporated anti-FLT3 CAR T cells were then co-cultured with Namalwa (FLT3 negative), EoL1 (FLT3 positive), HL60 (FLT3 positive), or MV4;11 (FLT3 positive) target cells at a 1:1 E:T ratio in R10 medium. Sixteen hours post-co-culture, supernatants from Namalwa (FIGs. 4A-4F), EoL1 (FIGs. 4G-4L), HL60 (FIGs. 4M-4R, and MV4;11 (4S-4X) were analyzed by Luminex (EMD Millipore) for production of IFNγ (FIGs. 4A, 4B, 4G, 4H, 4M, 4N, 4S, and 4T), IL-2 (FIGs. 4C, 4D, 4I, 4J, 4O, 4P, 4U, and 4V), and TNFα (FIGs. 4E, 4F, 4K, 4L, 4Q, 4R, 4W, and 4X).

[0256] Target cell viability was assessed by flow cytometric analysis of propidium iodide (PI) uptake by CD3-negative cells. The electroporated anti-FLT3 CAR T cells were co-cultured with Namalwa (FIGs. 5A-5B), EoL1 (FIGs. 5C-5D), HL60 (FIGs. 5E-5F, and MV4;11 (5G-5H) target cells at 16 hours post-co-culture.

EXAMPLE 2

[0257] A third generation lentiviral transfer vector containing the different CAR constructs was used along with the ViraPower Lentiviral Packaging Mix (Life Technologies) to generate the lentiviral supernatants. Briefly, a transfection mix was generated by mixing 15 µg of DNA and 22.5 µl of polyethileneimine (Polysciences, 1 mg/ml) in 600 µl of OptiMEM medium. The mix was incubated for 5 minutes at room temperature. Simultaneously, 293T cells (ATCC) were trypsinized, counted and a total of $10x10^6$ total cells were plated in a T75 flask along the transfection mix. Three days after the transfection, supernatants were collected and filtered through a 0.45 µm filter and stored at -80°C until used. 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). Forty eight hours post-stimulation, cells were transduced using lentivirus at an

MOI = 10. Cells were maintained at 0.5-2.0 x 10^6 cells/ml prior to use in activity assays. To examine CAR expression, T cells were stained with FLT-3-HIS (Sino Biological Inc.) 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-HIS-PE (Miltenyi Biotec) 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 FLT3 CARs in T cells from two healthy donors is shown in FIG. 6A-6B.

[0258] T cells from two healthy donors were transduced with lentiviral vectors encoding anti-FLT3 CAR T cells comprising a 10E3, 8B5, or 11F11 binding molecule and a hinge region selected from the complete hinge domain ("CHD"), a truncated hinge domain ("THD"), and the CD8 hinge region. Transduced T cells were co-cultured with target cells at a 1:1 E:T ratio in R10 medium. Sixteen hours post-co-culture, supernatants were analyzed by Luminex (EMD Millipore) for production of IFNγ (FIGs. 7A-7B), TNFα (FIGs. 7C-7D), and IL-2 (FIGs. 7E-7F).

[0259] Target cell viability was assessed by flow cytometric analysis of propidium iodide (PI) uptake by CD3-negative cells. Average cytolytic activity of lentivirus-transduced CAR T cells (from two healthy donors) co-cultured with Namalwa (FIG. 8A), EoL1 (FIG. 8B), MV4;11 (FIG. 8C), and HL60 (FIG. 8D) target cells was measured.

[0260] To assess CAR T cell proliferation in response to FLT3 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 FLT3 CAR T cells is shown in FIGs. 9A-9B.

EXAMPLE 3

[0261] To examine in vivo anti-leukemic activity, FLT3 CAR T cells were generated for use in a xenogeneic model of human AML. CAR expression of the various effector lines used in the xenogeneic model of human AML are shown in FIGs. 10A-10D. Luciferase-labeled MV4;11 cells (2 x 10^6 cells/animal) were injected intravenously into 5 to 6 week-old female NSG mice. After 6 days, 6 x 10^6 T cells (~50% CAR+) in 200 µl PBS were injected intravenously, and the tumor burden of the animals was measured weekly using bioluminescence imaging (FIGs. 10E-10G). Survival analysis was performed by injection of controls (mock) or 10E3-CHD (FIG. 10H), 10E3-THD (FIG. 10I), or 8B5-THD (FIG. 10J) expressing CAR T cells.

EXAMPLE 4

[0262] T cells were electroporated with plasmids encoding the anti-CLL-1 CAR constructs 24C8_HL-CHD CAR (comprising a complete hinge domain of the costimulatory protein) and 24C8_HL-THD CAR (comprising a truncated hinge domain of the costimulatory protein). Anti-CLL-1 expression by electroporated T cells is shown in FIGs. 11A-11D. The anti-CLL-1 CAR T cells were then cultured with the target Namalwa (ATCC; CLL-1 negative), U937 (ATCC; CLL-1 positive), HL-60 (ATCC; CLL-1 positive), EoL-1 (Sigma; CLL-1 positive), KG1a (ATCC; CLL-1 positive) and MV4;11 (ATCC; CLL-1 positive) cells at a 1:1 E:T ratio in R10 media 6 hours after mRNA electroporation. Sixteen hours post-co-culture, supernatants were analyzed by Luminex (EMD Millipore), according to the manufacturer's instructions, for production of IL-2 (FIG. 12A), IFNγ (FIG. 12B), and TNFα (FIG. 12C).

[0263] Target cell viability was assessed by flow cytometric analysis of propidium iodide (PI) uptake. The electroporated anti-CLL-1 CAR T cells were co-cultured with Namalwa (FIG. 13A), MV4;11 (FIG. 13B), EoL-1 (FIG. 13C), HL-60 (FIG. 13D), or U937 (FIG. 13E) target cells for 16 hours. As expected, Namalwa cells co-cultured with the anti-CLL-1 CAR T cells showed little change in target cell viability, relative to controls (FIG. 13A). However, increased cytolytic activity was observed in MV;411 cells co-cultured with 24C8_HL-CHD and 24C8_HL-THD T cells, relative to controls, with a greater target cell cytolytic activity observed in the 24C8_HL-THD T cell co-culture (FIG. 13B). In addition, increased cytolytic activity was observed in EoL-1 cells co-cultured with 24C8_HL-CHD and 24C8_HL-THD T cells, relative to controls (FIG. 13C). Increased cytolytic activity was observed in HL-60 cells co-cultured with 24C8_HL-CHD and 24C8_HL-THD T cells, relative to controls (FIG. 13D). Increased cytolytic activity was observed in U937 cells co-cultured with 24C8_HL-CHD and 24C8_HL-THD T cells, relative to controls, with a greater target cell cytolytic activity observed in the 24C8_HL-THD T cell co-culture (FIG. 13E).

EXAMPLE 5

[0264] T cells transduced with lentiviral vectors comprising an anti-CLL-1 CAR construct with a truncated hinge domain ("THD") of the costimulatory protein, 10E3_THD or 24C1_LH_THD, were co-cultured with Namalwa, U937, HL-60, EoL-1, KG1a and MV4;11 target cells at a 1:1 E:T ratio in R10 media 12 days after T cell stimulation. Sixteen hours post-co-culture, supernatants were analyzed by Luminex (EMD Millipore), according to the manufacturer's instructions, for production of the cytokines IFNγ (FIG. 14A), IL-2 (FIG. 14B),

and TNFα (FIG. 14C) in co-cultures of effector 10E3_THD CAR T cells and 24C1_LH_THD CAR T cells with target Namalwa, HL-60, or MVA;11 cells, as indicated.

[0265] Target cell viability was assessed by flow cytometric analysis of propidium iodide (PI) uptake. Transduced effector 24C1_LH_THD CAR T cells were co-cultured with Namalwa, U937, HL-60, EoL-1, KG1a, or MV4;11 target cells for 16 hours or 40 hours. Co-culture of Namalwa target cells with transduced C1_24C1_LH_THD CAR T cells had no effect on the percent of viable Namalwa target cells at 16 hours and 40 hours, as compared to mock controls (FIG. 15A). However, C1_24C1_LH_THD CAR T cells co-cultured with either MV4;11 (FIG. 15B) or HL-60 (FIG. 15C) target cells resulted in a lower percent of viable target cells at both 16 hours and 40 hours, as compared to mock controls.

EXAMPLE 6

[0266] CAR T cells transduced with anti-BCMA CAR constructs comprising a truncated hinge domain ("THD") of the costimulatory protein were cultured with target cells at a 1:1 effector cell to target cell (E:T) ratio in R10 media 12 days after T cell stimulation. Cell lines tested included EoL-1 (Sigma; BCMA negative), NCI-H929 (Molecular Imaging; BCMA positive), and MM1S (Molecular Imaging; BCMA positive). Sixteen hours post-co-culture, supernatants were analyzed by Luminex (EMD Millipore), according to the manufacturer's instructions, for production of the cytokines IFNγ (FIGs. 16A-16B), TNFα (FIGs. 16C-16D), and IL-2 (FIGs. 16E-16F). IFNγ (FIGs. 16A-16B), TNFα (FIGs. 16C-16D), and IL-2 (FIGs. 16E-16F) were observed in the supernatant of NCI-H929 and MM1S target cell co-cultures for each anti-BCMA CAR T cell tested in both donors (FIGs. 16A-16B); however, IFNγ (FIGs. 16A-16B), TNFα (FIGs. 16C-16D), and IL-2 (FIGs. 16E-16F) were only observed in the supernatant of EoL-1 target cell co-cultures above background for the IR negative control T cells (FIG. 16A).

[0267] Target cell viability was assessed by flow cytometric analysis of propidium iodide (PI) uptake of CD3 negative cells. The anti-BCMA CAR T cells were co-cultured with EoL1 (FIGs. 17A-17B), NCI-H929 (FIGs. 17C-17D), or MM1S (FIGs. 17E-17F) target cells for 16 hours, 40 hours, 64 hours, 88 hours, or 112 hours. Little cytolytic activity was observed in the EoL-1 co-cultures at any time period for the anti-BCMA CAR T cells (FIG. 17A-17B). However, co-culture of the anti-BCMA CAR T cells and the NCI-H929 or MM1S target cells resulted in a decrease in the percentage of viable target cells at each time point measured for each of the anti-BCMA CAR T cells.

[0268] To examine proliferation, anti-BCMA CAR T cells were labeled with carboxyfluorescein succinimidyl ester (CFSE) prior to co-culture with EoL-1, NCI-H929, or MM1S target cells at a 1:1 E:T ratio in R10 media. Five days later, T cell proliferation was assessed by flow cytometric analysis of CFSE dilution (FIGs. 18A-18B).

EXAMPLE 7

[0269] Enhanced stability is a desired property of proteins. This is often assessed by determining the melting temperature of a protein under various conditions. Proteins with a higher melting temperature are generally stable for longer times. When a CAR is more thermostable, it may be functionally active for longer periods of time on the surface of a cell.

[0270] Thermal stability of the CAR extracellular domain (ECD) with the longer hinge domain, i.e., the complete hinge domain ("CHD") and the thermal stability of the CAR ECD with a truncated hinge domain ("THD") was measured using a Bio-Rad C1000 thermal cycler, CFx96 Real-Time system. Unfolding of the proteins was monitored using the fluorescent dye SYPRO Orange (Invitrogen) which binds to hydrophobic amino acids that become solvent exposed as the protein unfolds. A temperature gradient was set up from 25 °C to 95 °C with 1 °C / 1 minute increments. Each sample contained 10 μM recombinant CAR ECD protein and 5X SYPRO Orange (Molecular Probes™ SYPRO™ Orange Protein Gel Stain (5,000X Concentrate in DMSO)). The assay was performed in PBS with or without 50 mM NaCl.

[0271] As shown in FIG. 19A and FIG. 19B, a CAR's ECD which has a THD shows enhanced thermostability compared to a CAR's ECD which has a CHD, e.g., including the IEVMYPPPY (SEQ ID NO: 250) motif. These method described in this example is a useful method for testing stability of mRNA encoding a CAR and the CAR itself, because once a T cell has been transduced with the mRNA encoding a CAR, the transduced T cell will express the CAR and the stability of an individual mRNA or protein cannot be readily assessed.

CLAIMS

What is claimed is:

1. An isolated polynucleotide encoding a chimeric antigen receptor (CAR) or a T cell receptor (TCR), which comprises (i) an antigen binding molecule, (ii) a costimulatory domain, and (iii) an activating domain, wherein the costimulatory domain comprises an extracellular domain, a transmembrane domain, and an intracellular domain, wherein the extracellular domain comprises a truncated hinge domain consisting essentially of or consisting of (i) an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to amino acids 123 to 152 of SEQ ID NO: 1 and, optionally, (ii) one to six amino acids.

2. The polynucleotide of claim 1, wherein the one to six amino acids are heterologous amino acids.

3. The polynucleotide of claim 1 or 2, wherein the truncated hinge domain consists essentially of or consists of an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to amino acids 123 to 152 of SEQ ID NO: 1.

4. The polynucleotide of claim 1 or 2, wherein the amino acid sequence is encoded by a nucleotide sequence at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 2.

5. The polynucleotide of claim 1 or 2, wherein the transmembrane domain is a transmembrane domain of 4-1BB/CD137, an alpha chain of a T cell receptor, a beta chain of a T cell receptor, CD3 epsilon, CD4, CD5, CD8 alpha, CD9, CD16, CD19, CD22, CD33, CD37, CD45, CD64, CD80, CD86, CD134, CD137, CD154, or a zeta chain of a T cell receptor, or any combination thereof.

6. The polynucleotide of claim 1 or 2, wherein the transmembrane domain comprises an amino acid sequence at least about 80%, at least about 85%, at least about 90%,

at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 5.

7. The polynucleotide of claim 6, wherein the transmembrane domain is encoded by a nucleotide sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 4.

8. The polynucleotide of claim 1 or 2, wherein the intracellular domain comprises a signaling region of 4-1BB/CD137, activating NK cell receptors, B7-H3, BAFFR, BLAME (SLAMF8), BTLA, CD100 (SEMA4D), CD103, CD160 (BY55), CD18, CD19, CD19a, CD2, CD247, CD27, CD276 (B7-H3), CD29, CD3 delta, CD3 epsilon, CD3 gamma, CD30, CD4, CD40, CD49a, CD49D, CD49f, CD69, CD7, CD84, CD8alpha, CD8beta, CD96 (Tactile), CDl la, CDl lb, CDl lc, CDl ld, CDS, CEACAM1, CRT AM, cytokine receptors, DAP-10, DNAM1 (CD226), Fc gamma receptor, GADS, GITR, HVEM (LIGHTR), IA4, ICAM-1, ICAM-1, Ig alpha (CD79a), IL2R beta, IL2R gamma, IL7R alpha, Immunoglobulin-like proteins, inducible T cell costimulator (ICOS), integrins, ITGA4, ITGA4, ITGA6, ITGAD, ITGAE, ITGAL, ITGAM, ITGAX, ITGB2, ITGB7, ITGBl, KIRDS2, LAT, LFA-1, LFA-1, a ligand that specifically binds with CD83, LIGHT, LIGHT (tumor necrosis factor superfamily member 14; TNFSF14), LTBR, Ly9 (CD229), lymphocyte function-associated antigen-1 (LFA-1 (CDl la/CD18), MHC class I molecule, NKG2C, NKG2D, NKp30, NKp44, NKp46, NKp80 (KLRF1), OX-40, PAG/Cbp, programmed death-1 (PD-1), PSGL1, SELPLG (CD162), signaling lymphocytic activation molecules (SLAM proteins), SLAM (SLAMF1; CD150; IPO-3), SLAMF4 (CD244; 2B4), SLAMF6 (NTB-A; Lyl08), SLAMF7, SLP-76, TNF receptor proteins, TNFR2, a Toll ligand receptor, TRANCE/RANKL, VLA1, or VLA-6, or a combination thereof.

9. The polynucleotide of claim 1 or 2, wherein the intracellular domain comprises a 4-1BB/CD137 signaling region.

10. The polynucleotide of claim 1 or 2, wherein the intracellular domain comprises an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 7.

11. The polynucleotide of claim 1 or 2, wherein the intracellular domain comprises an amino acid sequence encoded by a nucleotide sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 6.

12. The polynucleotide of claim 1 or 2, wherein the antigen binding molecule comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises 3 complementarity determining regions (CDRs) and the VL comprises 3 CDRs.

13. The polynucleotide of claim 1 or 2, wherein the antigen binding molecule specifically binds an antigen selected from the group consisting of 5T4, alphafetoprotein, B cell maturation antigen (BCMA), CA-125, carcinoembryonic antigen, CD19, CD20, CD22, CD23, CD30 , CD33, CD56, CD123, CD138, c-Met, CSPG4, C-type lectin-like molecule 1 (CLL-1), EGFRvIII, epithelial tumor antigen, ERBB2, FLT3, folate binding protein, GD2, GD3, HER1-HER2 in combination, HER2-HER3 in combination, HER2/Neu, HERV-K, HIV-1 envelope glycoprotein gp41, HIV-1 envelope glycoprotein gpl20, IL-llRalpha, kappa chain, lambda chain, melanoma-associated antigen, mesothelin, MUC-1, mutated p53, mutated ras, prostate-specific antigen, ROR1, or VEGFR2, or a combination thereof.

14. The polynucleotide of claim 1 or 2, wherein the antigen binding molecule specifically binds BCMA, CLL-1, or FLT3.

15. The polynucleotide of claim 1 or 2, wherein the activation domain comprises an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 9 or SEQ ID NO: 251.

16. The polynucleotide of claim 1 or 2, wherein the activation domain is encoded by a nucleotide sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 8.

17. The polynucleotide of any one of claims 1 to 16, wherein the CAR or TCR further comprises a leader peptide.

18. The polynucleotide of claim 17, wherein the leader peptide comprises an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 11.

19. The polynucleotide of claim 17, wherein the leader peptide is encoded by a nucleotide sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 10.

20. A vector comprising the polynucleotide of any one of claims 1 to 19.

21. The vector of claim 20, wherein the vector is an adenoviral vector, an adenovirus-associated vector, a DNA vector, a lentiviral vector, a plasmid, a retroviral vector, or an RNA vector, or any combination thereof.

22. A polypeptide encoded by the polynucleotide of any one of claims 1 to 19 or the vector of claim 20 or 21.

23. A cell comprising the polynucleotide of any one of claims 1 to 19, the vector of claim 20 or 21, the polypeptide of claim 22, or any combination thereof.

24. The cell of claim 23, wherein the cell is a T cell.

25. The cell of claim 24, wherein the T cell is an allogeneic T cell, an autologous T cell, an engineered autologous T cell (eACT), or a tumor-infiltrating lymphocyte (TIL).

26. The cell of claim 24 or 25, wherein the T cell is a CD4+ T cell.

27. The cell of claim 24 or 25, wherein the T cell is a CD8+ T cell.

28. The cell of claim 24 or 25, wherein the T cell is an *in vitro* cell.

29. The cell of claim 24 or 25, wherein the T cell is an autologous T cell.

30. A composition comprising the polynucleotide of any one of claims 1 to 19, the vector of claim 20 or 21, the polypeptide of claim 22, or the cell of any one of claims 23 to 29.

31. The composition of claim 30, which is formulated to be delivered to a subject, optionally, comprising at least one pharmaceutically-acceptable excipient.

32. A method of making a cell expressing a CAR or TCR comprising transducing a cell with the polynucleotide of any one of claims 1 to 19 under suitable conditions.

33. The method of claim 32, further comprising isolating the cell.

34. A method of inducing an immunity against a tumor comprising administering to a subject an effective amount of a cell comprising the polynucleotide of any one of claims 1 to 19, the vector of claim 20 or 21, the polypeptide of claim 22, or any combination thereof.

35. Use of the polynucleotide of any one of claims 1 to 19, the vector of claim 20 or 21, the polypeptide of claim 22, the cell of any one of claims 23 to 29, or the composition of claim 30 or 31 for the manufacture of a medicament for treating a cancer in a subject in need thereof.

36. The use of claim 35, wherein the cancer is a hematologic cancer.

37. The use of claim 35, wherein the cancer is of the white blood cells.

38. The use of claim 35, wherein the cancer is of the plasma cells.

39. The use of any one of claims 35 to 38, wherein the cancer is leukemia, lymphoma, or myeloma.

40. The use of any one of claims 35 to 38, wherein the cancer is acute lymphoblastic leukemia (ALL) (including non T cell ALL), acute myeloid leukemia, B cell prolymphocytic leukemia, B-cell acute lymphoid leukemia ("BALL"), blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myeloid leukemia, chronic or acute leukemia, diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), hairy cell leukemia, Hodgkin's Disease, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, monoclonal gammapathy of undetermined significance (MGUS), multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma (NHL), plasma cell proliferative disorder (including asymptomatic myeloma (smoldering

multiple myeloma or indolent myeloma), plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, plasmacytomas (including plasma cell dyscrasia; solitary myeloma; solitary plasmacytoma; extramedullary plasmacytoma; and multiple plasmacytoma), POEMS syndrome (also known as Crow-Fukase syndrome; Takatsuki disease; and PEP syndrome), primary mediastinal large B cell lymphoma (PMBC), small cell- or a large cell-follicular lymphoma, splenic marginal zone lymphoma (SMZL), systemic amyloid light chain amyloidosis, T-cell acute lymphoid leukemia ("TALL"), T-cell lymphoma, transformed follicular lymphoma, or Waldenstrom macroglobulinemia, or a combination thereof.

FIG. 1A – (SEQ ID NO: 1)

MLRLLLALNLFPSIQVTGNKILVKQSPMLVAYDNAVNLSCKYSYNLFSREFRASLH

KGLDSAVEVCVVYGNYSQQLQVYSKTGFNCDGKLGNESVTFYLQNLYVNQTDIYFC

KIEVMYPPPY**LDNEKSNGTIIHVKGKHLCPSPLFPGPSKP**FWVLVVVGGVLACYSL

Hinge Domain *Transmembrane*

LVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS

Domain *Signaling Domain*

FIG. 1B

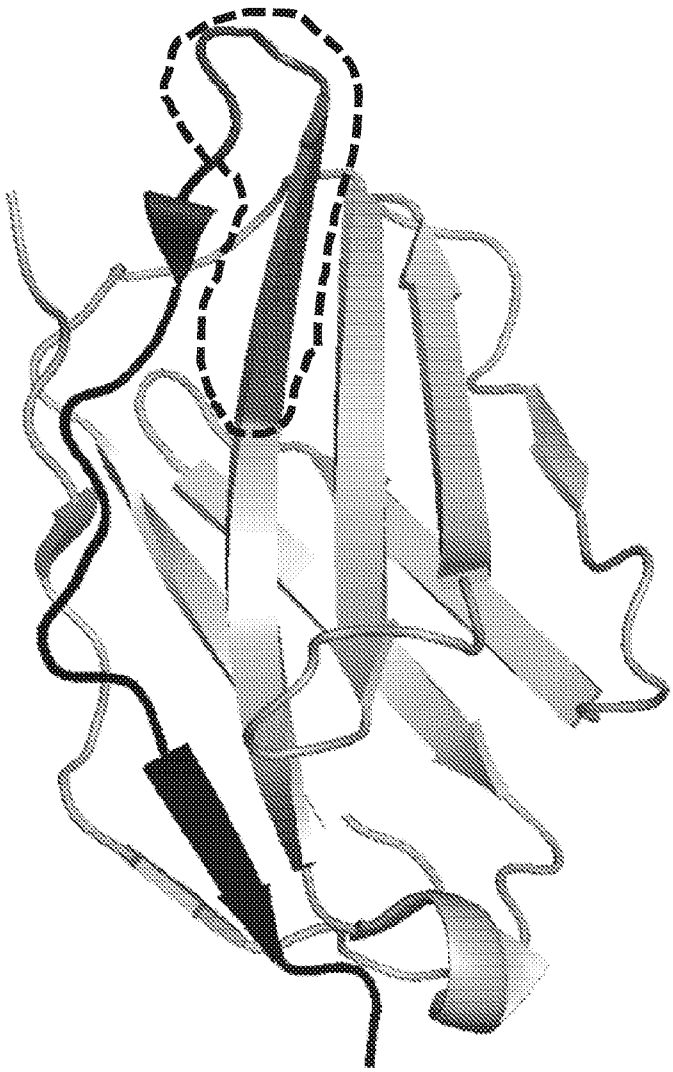


FIG. 1C

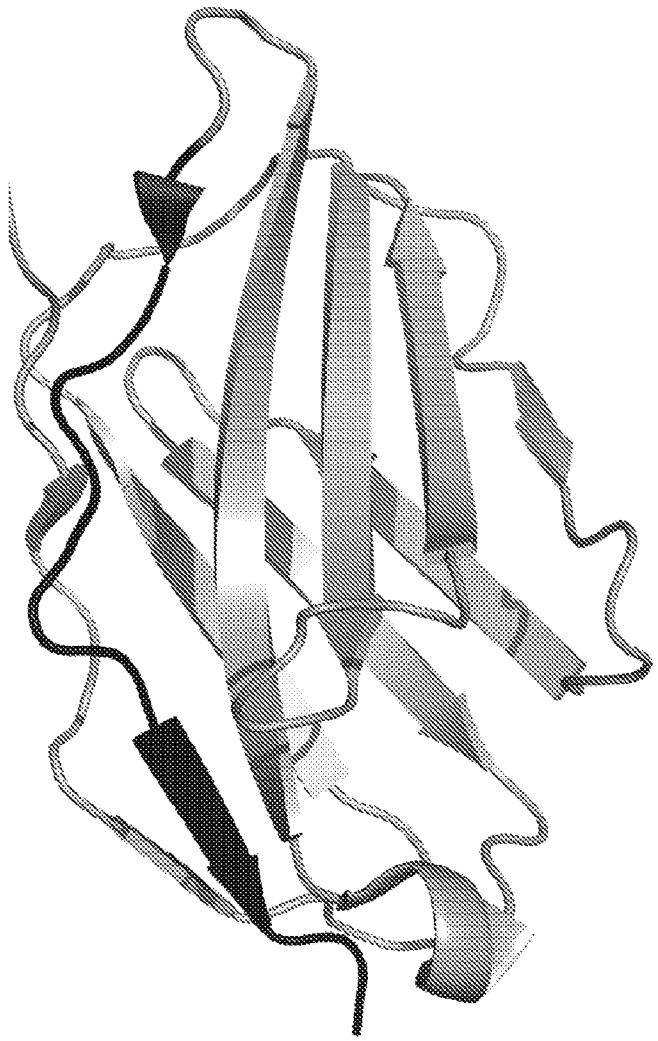


FIG. 2A – Anti-CLL-1 Binding Molecules

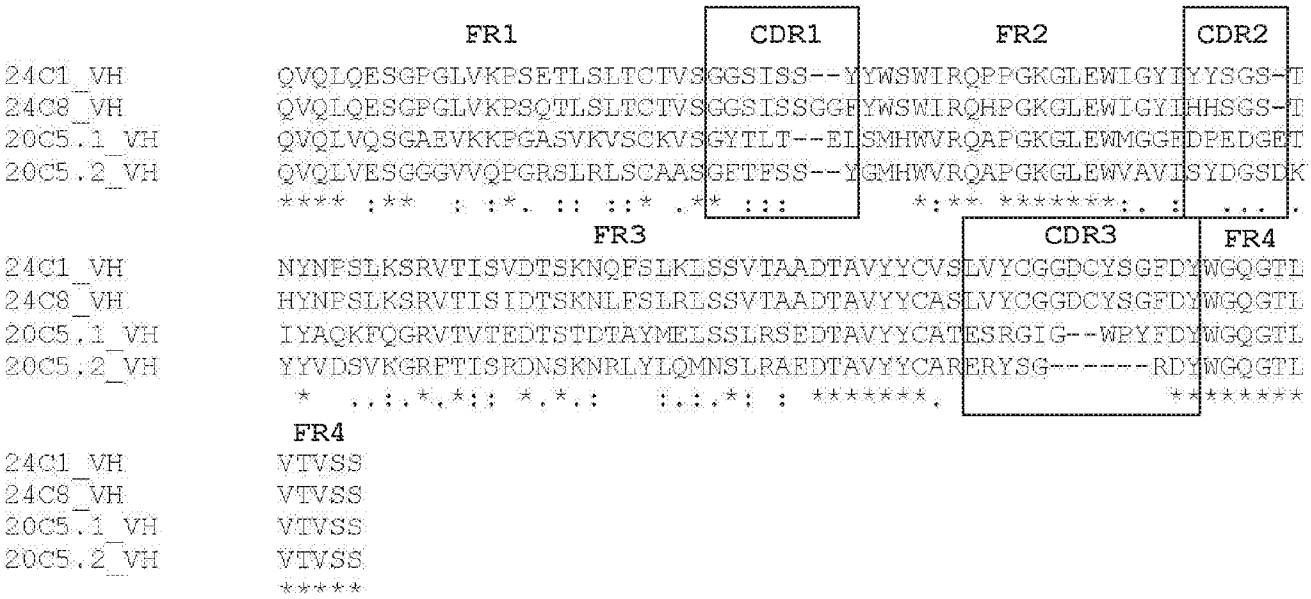


FIG. 2B	SEQ ID NO:			
	VH	CDR1	CDR2	CDR3
24C1_VH	125	93	97	101
24C8_VH	126	94	98	102
20C5.1_VH	127	95	99	103
20C5.2_VH	128	96	100	104

FIG. 2C – Anti-CLL-1 Binding Molecules

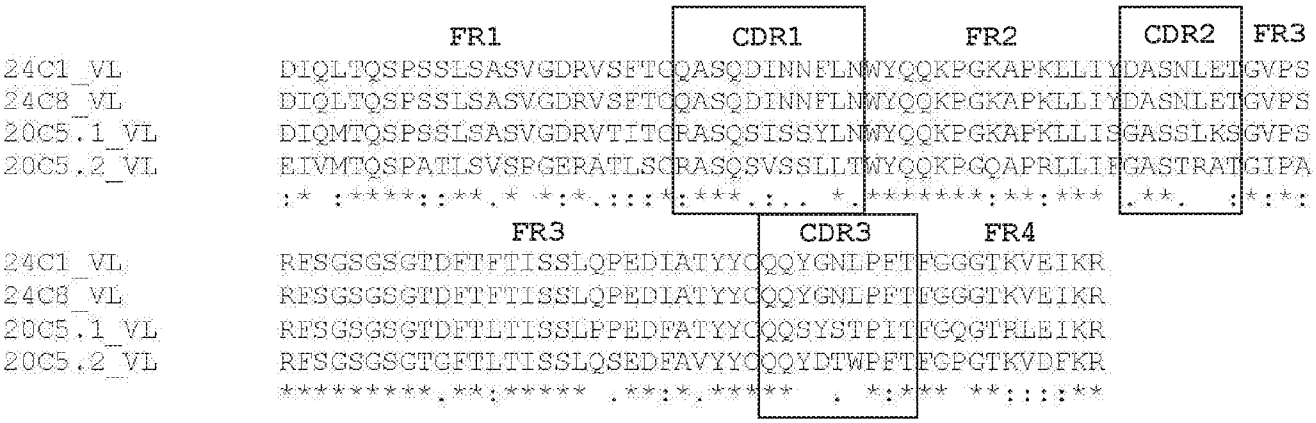


FIG. 2D	SEQ ID NO:			
	VL	CDR1	CDR2	CDR3
24C1_VL	125	93	97	101
24C8_VL	126	94	98	102
20C5.1_VL	127	95	99	103
20C5.2_VL	128	96	100	104

FIG. 2E – Anti-BCMA Binding Molecules

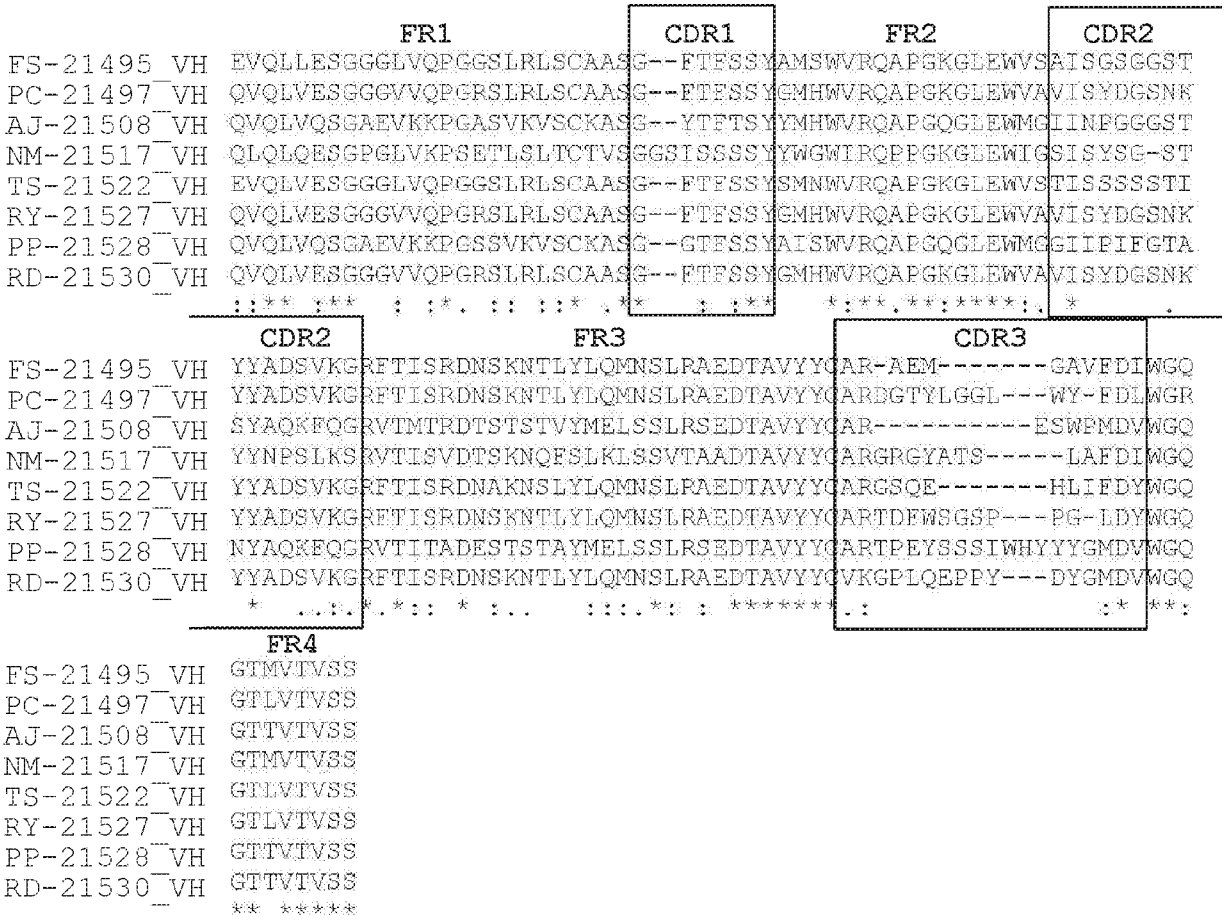


FIG. 2F	SEQ ID NO:			
	VH	CDR1	CDR2	CDR3
FS-21495_VH	77	13	21	29
PC-21497_VH	78	14	22	30
AJ-21508_VH	79	15	23	31
NM-21517_VH	80	16	24	32
TS-21522_VH	81	17	25	33
RY-21527_VH	82	18	26	34
PP-21528_VH	83	19	27	35
RD-21530_VH	84	20	28	36

FIG. 2G – Anti-BCMA Binding Molecules

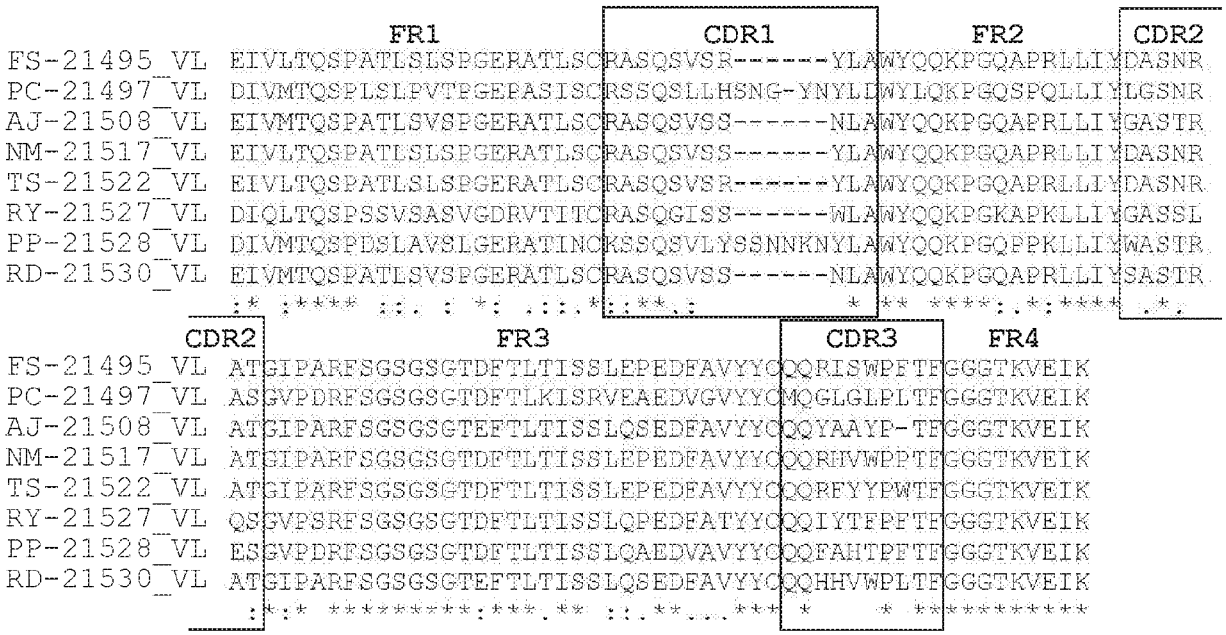


FIG. 2H	SEQ ID NO:			
	VL	CDR1	CDR2	CDR3
FS-21495_VL	85	37	45	53
PC-21497_VL	86	38	46	54
AJ-21508_VL	87	39	47	55
NM-21517_VL	88	40	48	56
TS-21522_VL	89	41	49	57
RY-21527_VL	90	42	50	58
PP-21528_VL	91	43	51	59
RD-21530_VL	92	44	52	60

FIG. 3

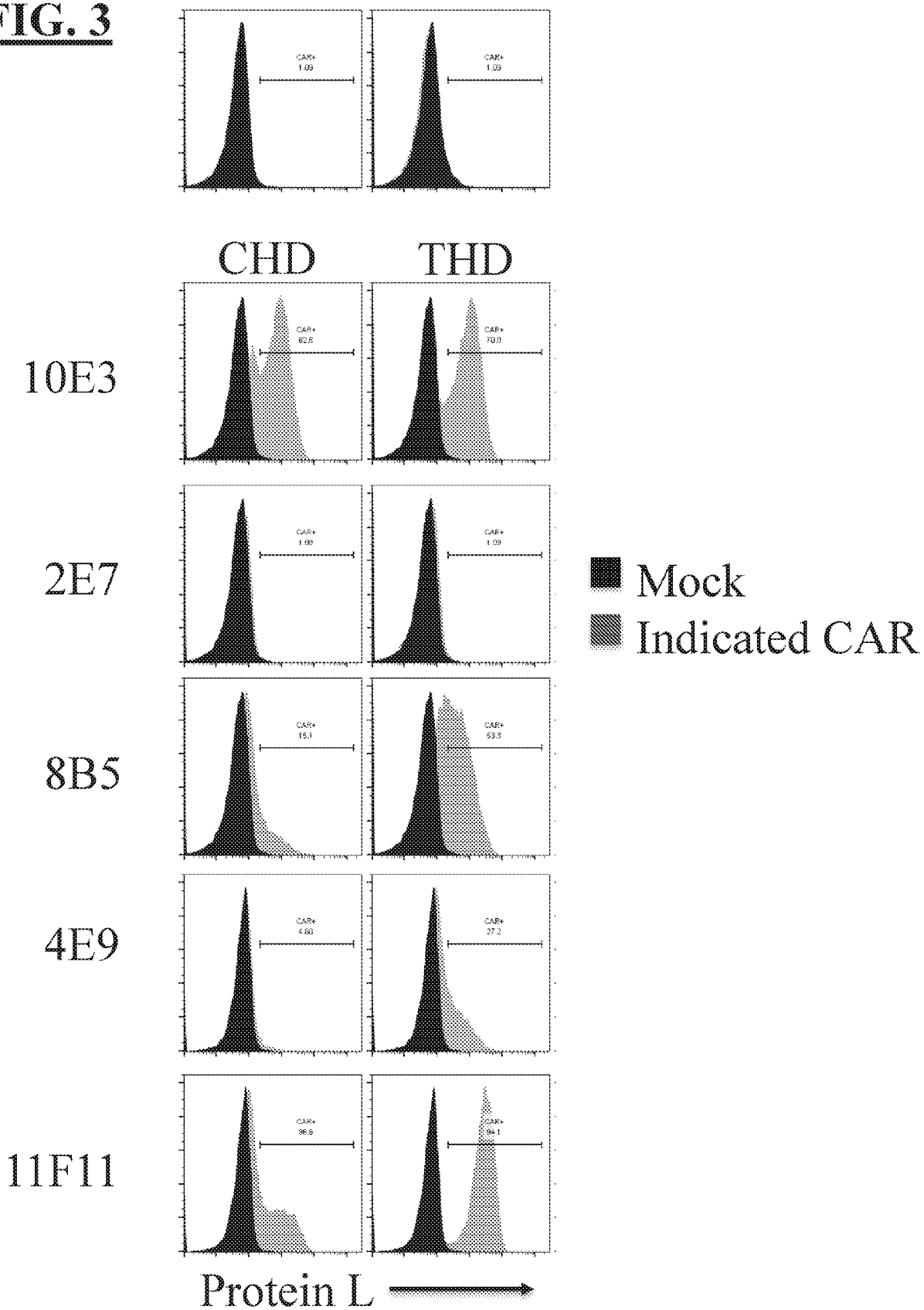

GFP
CD19 CAR
CHD
THD
10E3
2E7
8B5
4E9
11F11
Mock
Indicated CAR
Protein L

FIG. 4A

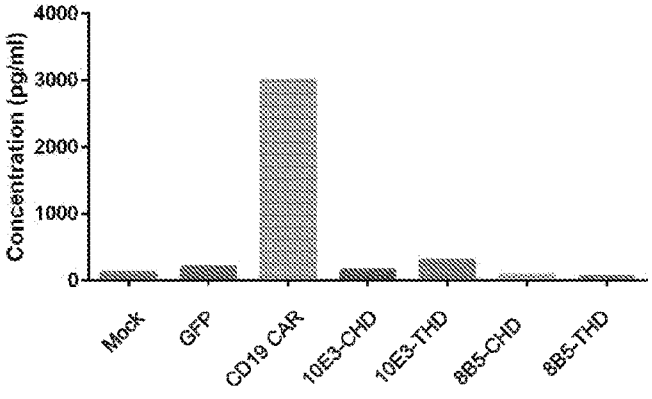


FIG. 4B

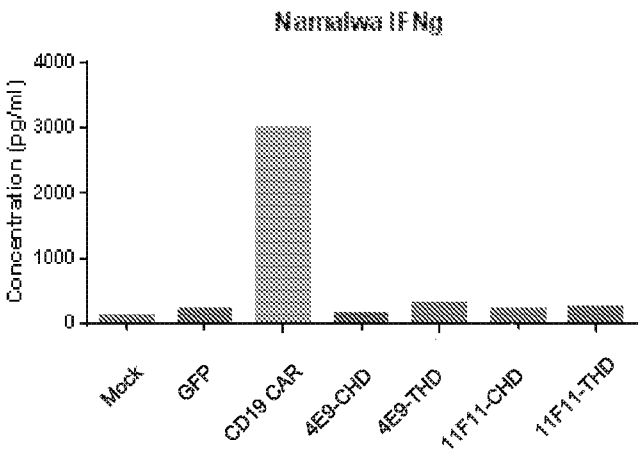


FIG. 4C

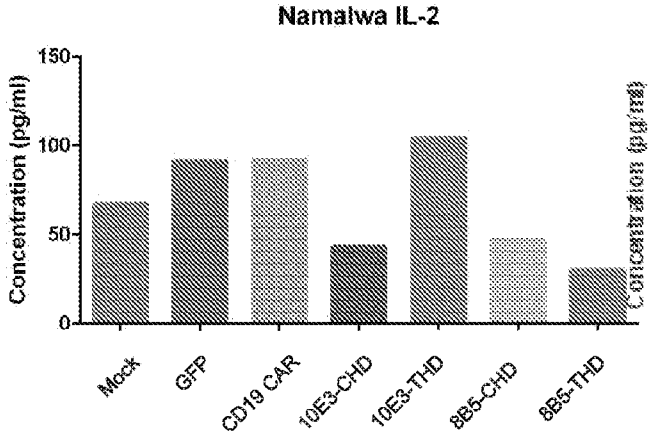


FIG. 4D

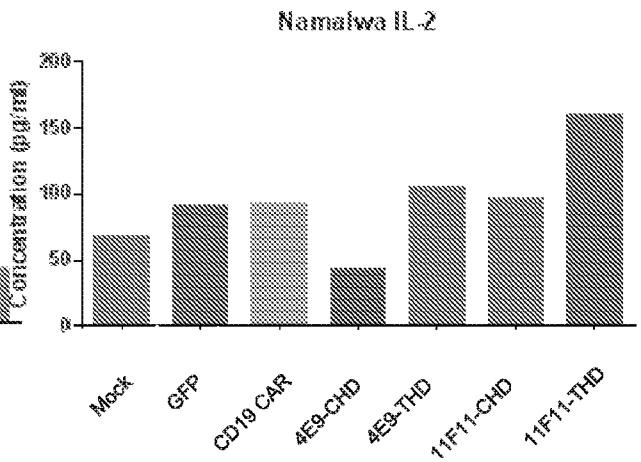


FIG. 4E

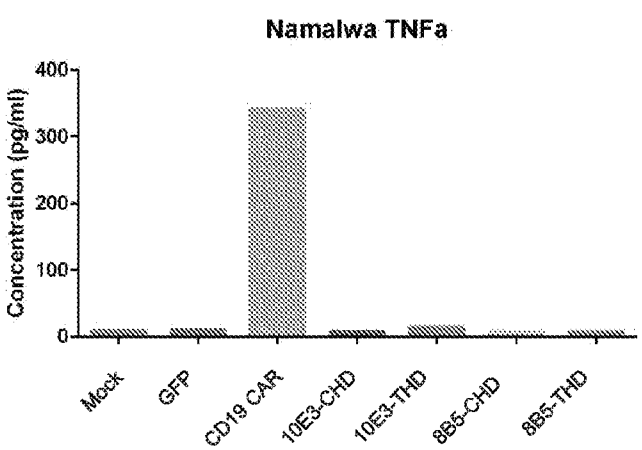


FIG. 4F

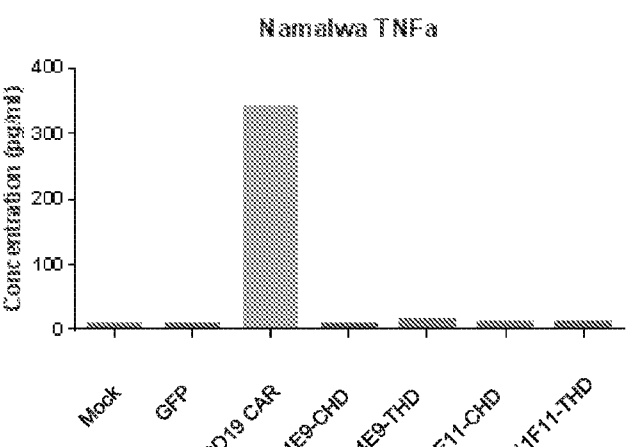


FIG. 4G

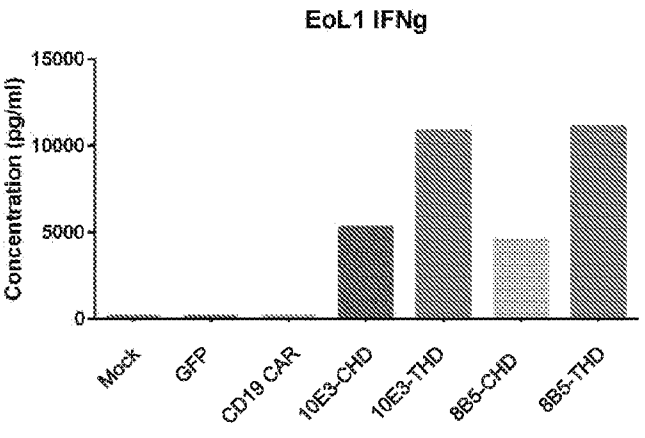


FIG. 4H

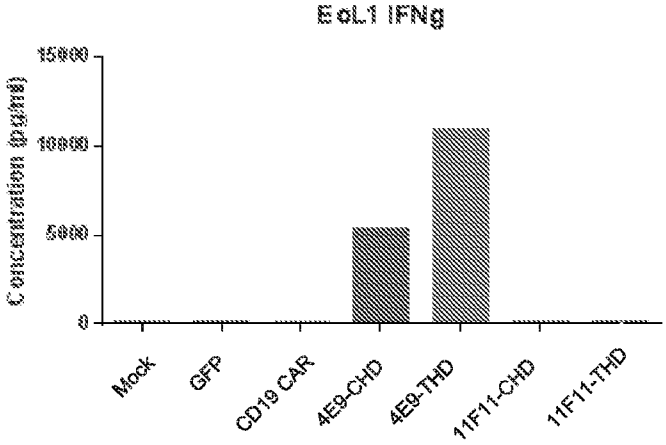


FIG. 4I

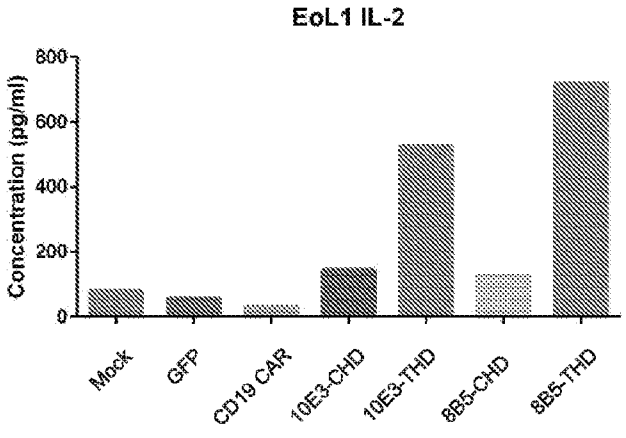


FIG. 4J

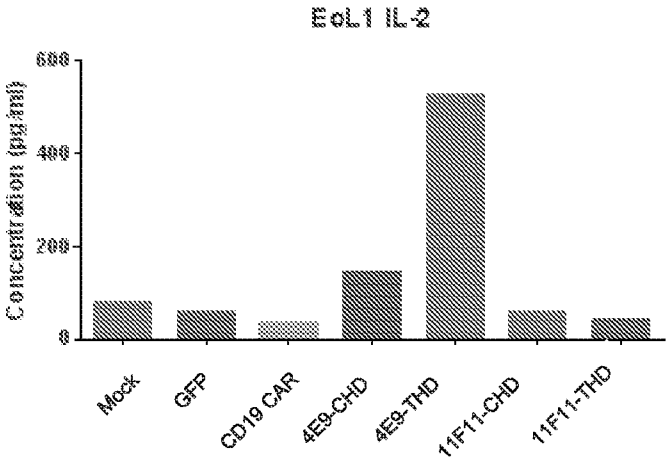


FIG. 4K

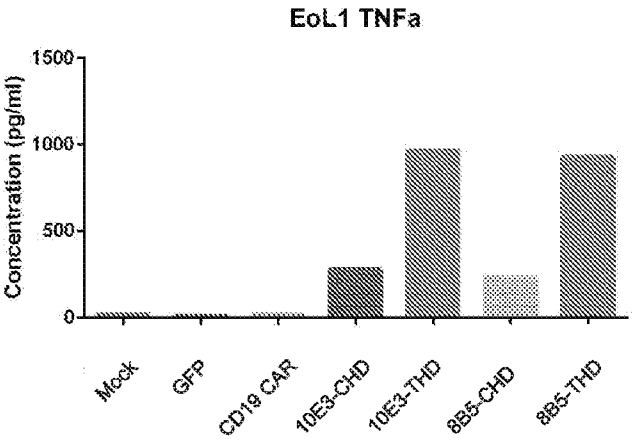


FIG. 4L

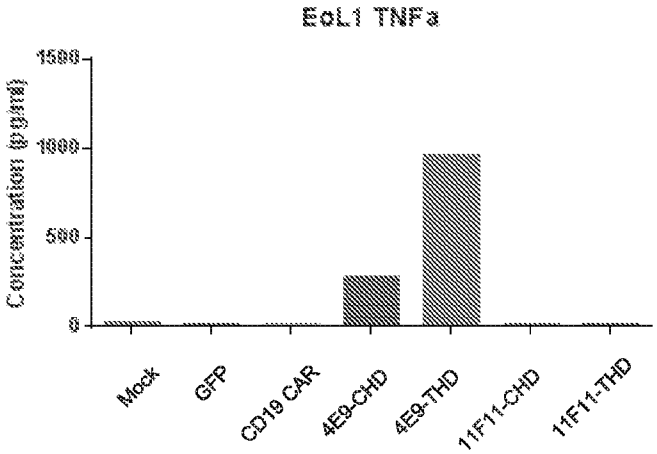


FIG. 4M

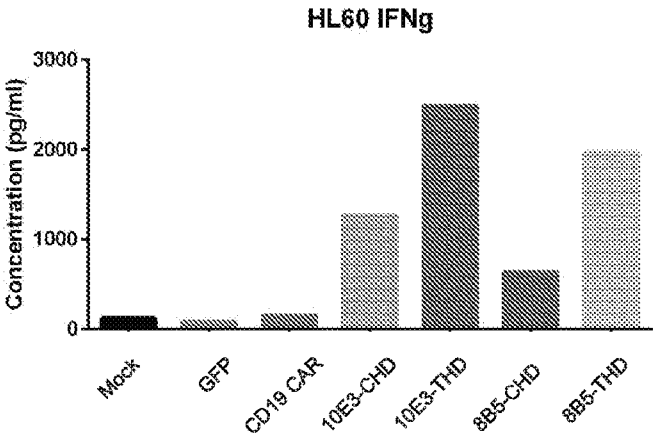


FIG. 4N

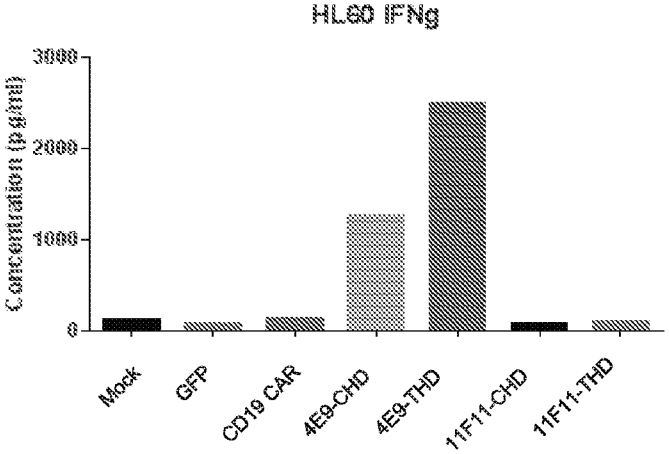


FIG. 4O

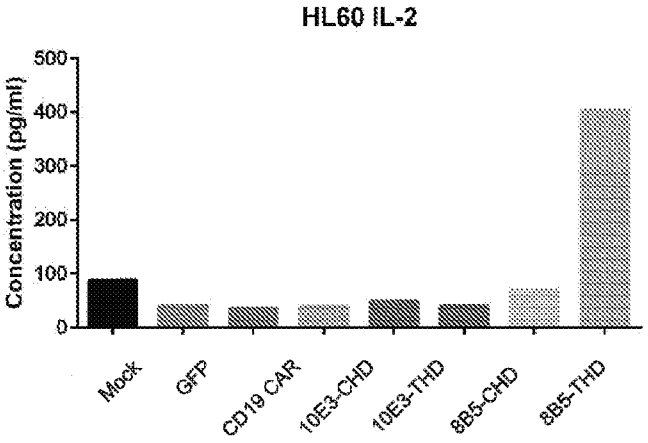


FIG. 4P

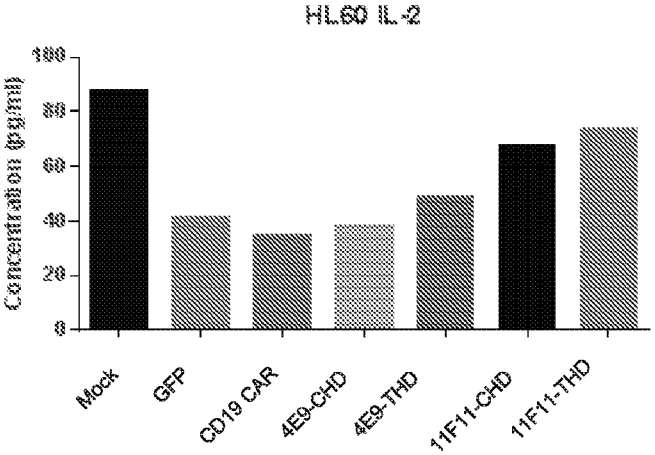


FIG. 4Q

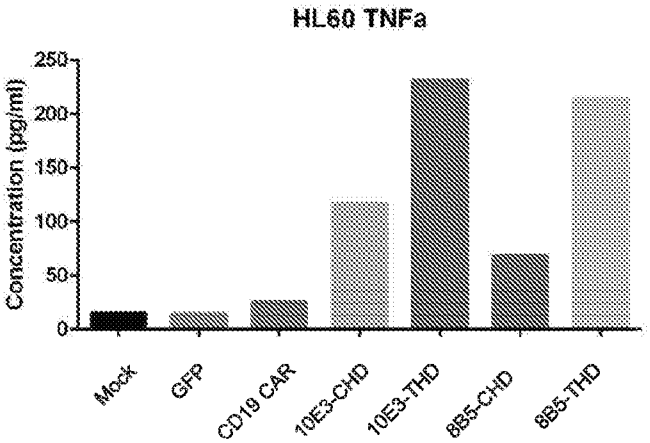


FIG. 4R

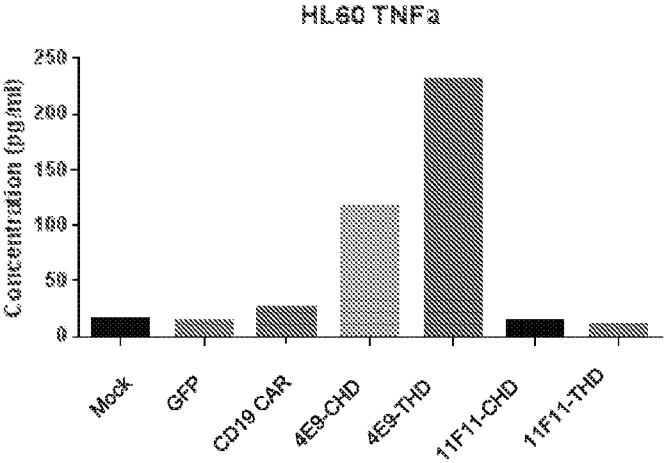


FIG. 4S

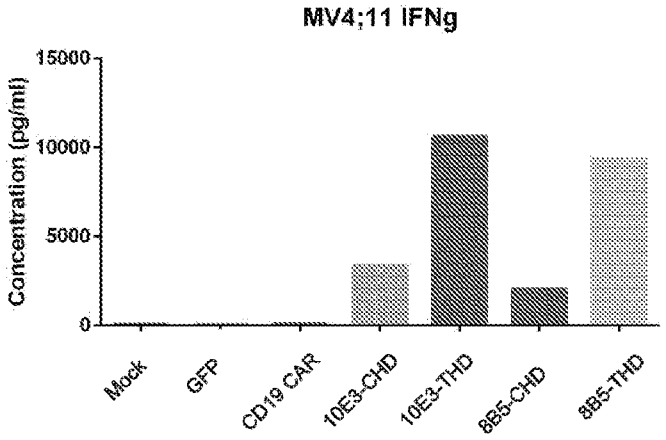


FIG. 4T

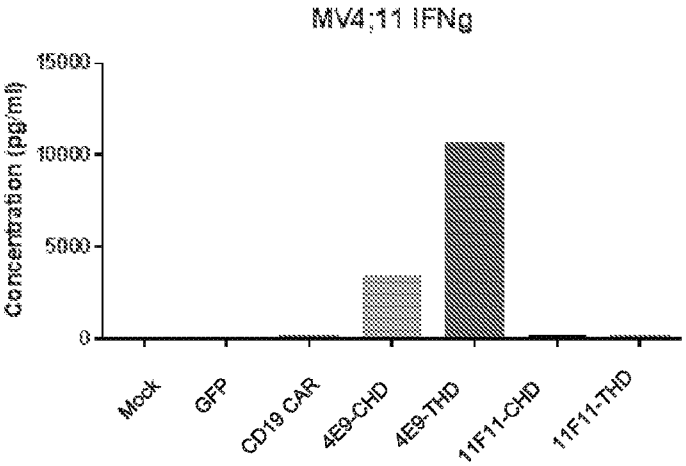


FIG. 4U

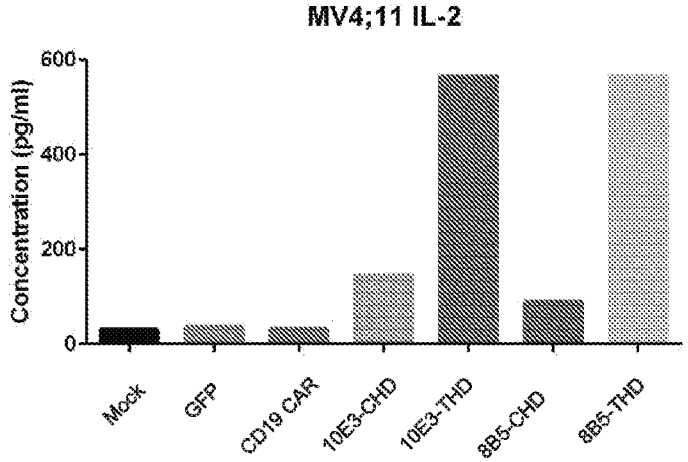


FIG. 4V

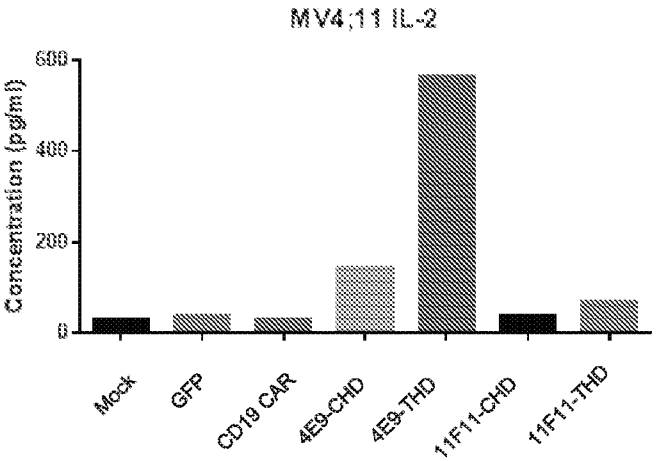


FIG. 4W

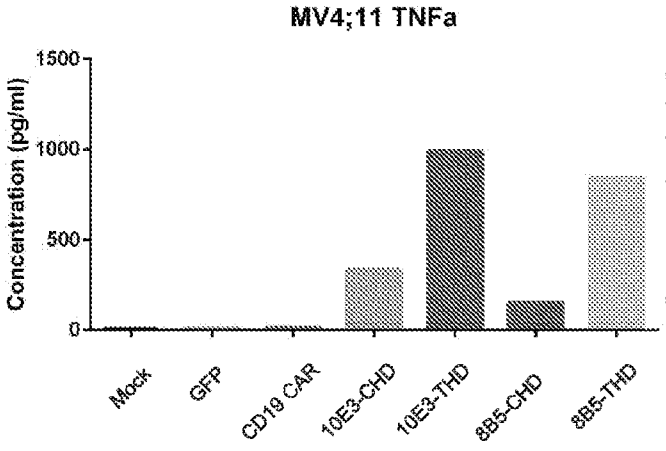
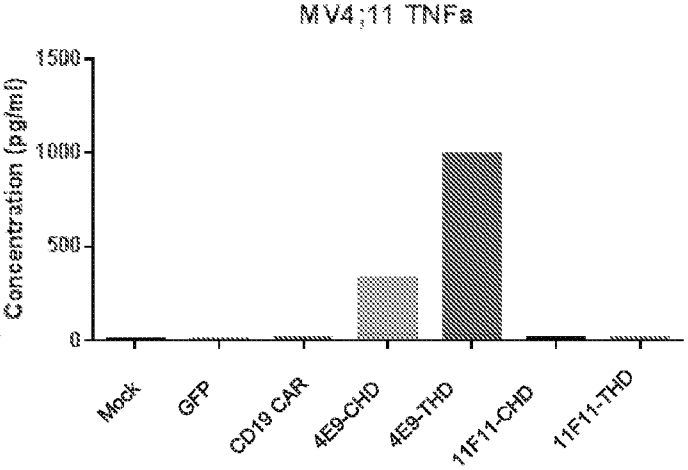


FIG. 4X



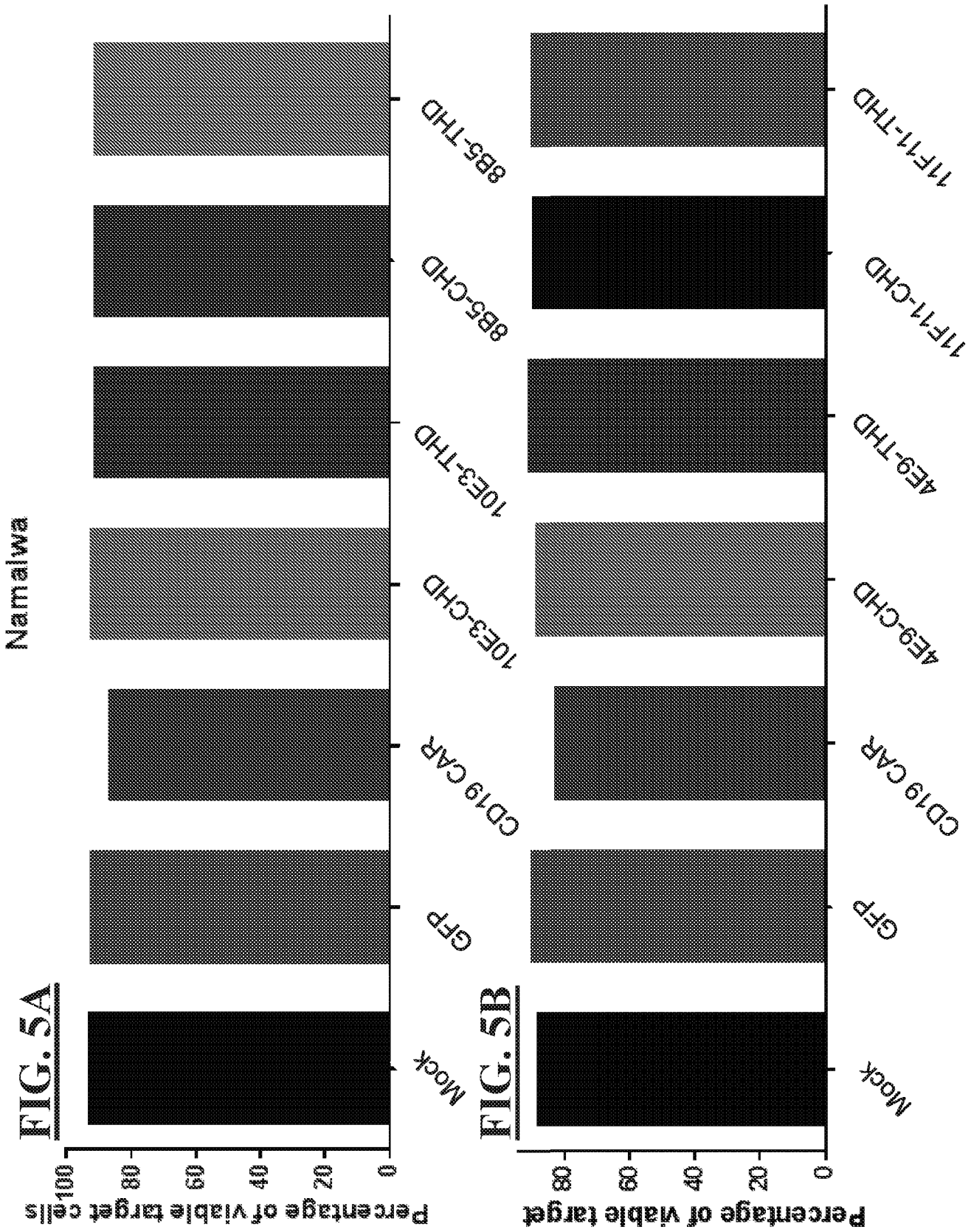


FIG. 5A
Namalwa
Percentage of viable target cells
0
20
40
60
80
100
Mock
GFP
CD19 CAR
10E3-CHD
10E3-THD
8B5-CHD
8B5-THD
FIG. 5B
Percentage of viable target
0
20
40
60
80
Mock
GFP
CD19 CAR
4E9-CHD
4E9-THD
11F11-CHD
11F11-THD

FIG. 5C

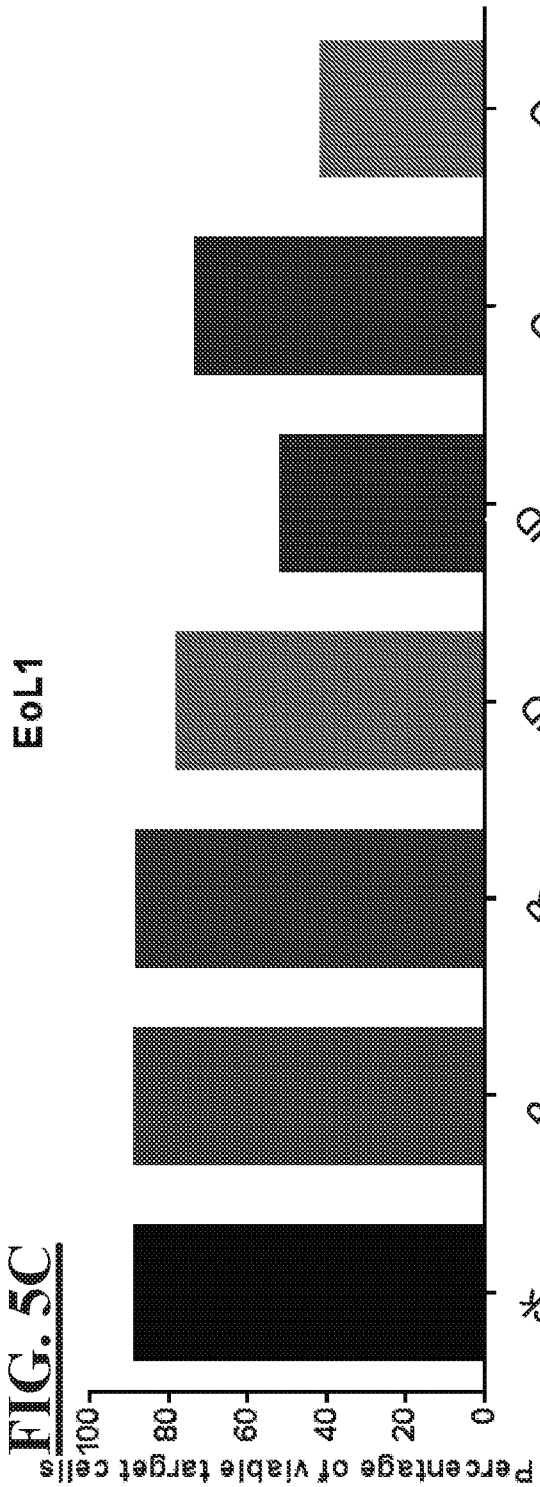

EoL1
Percentage of viable target cells
0
20
40
60
80
100
Mock
GFP
CD19 CAR
10E3-CHD
10E3-THD
8B6-CHD
8B6-THD

FIG. 5D

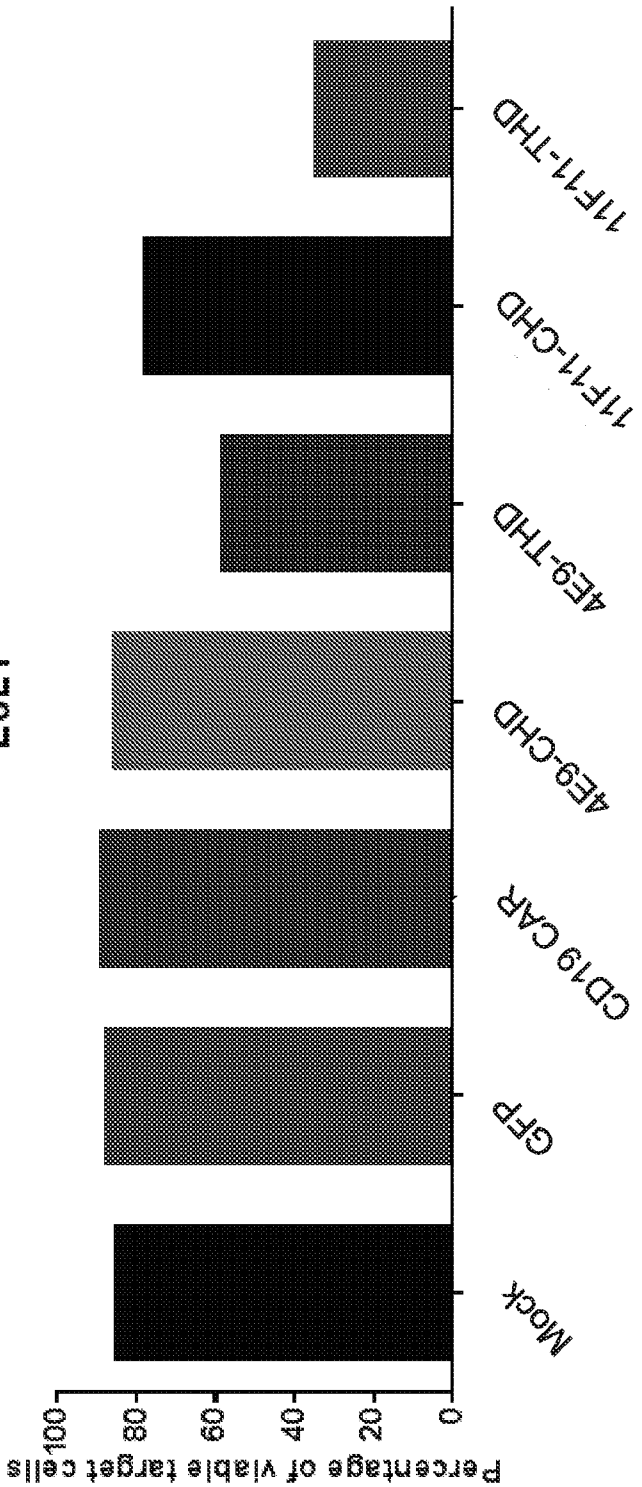

EoL1
Percentage of viable target cells
0
20
40
60
80
100
Mock
GFP
CD19 CAR
4E9-CHD
4E9-THD
11F11-CHD
11F11-THD

FIG. 5E

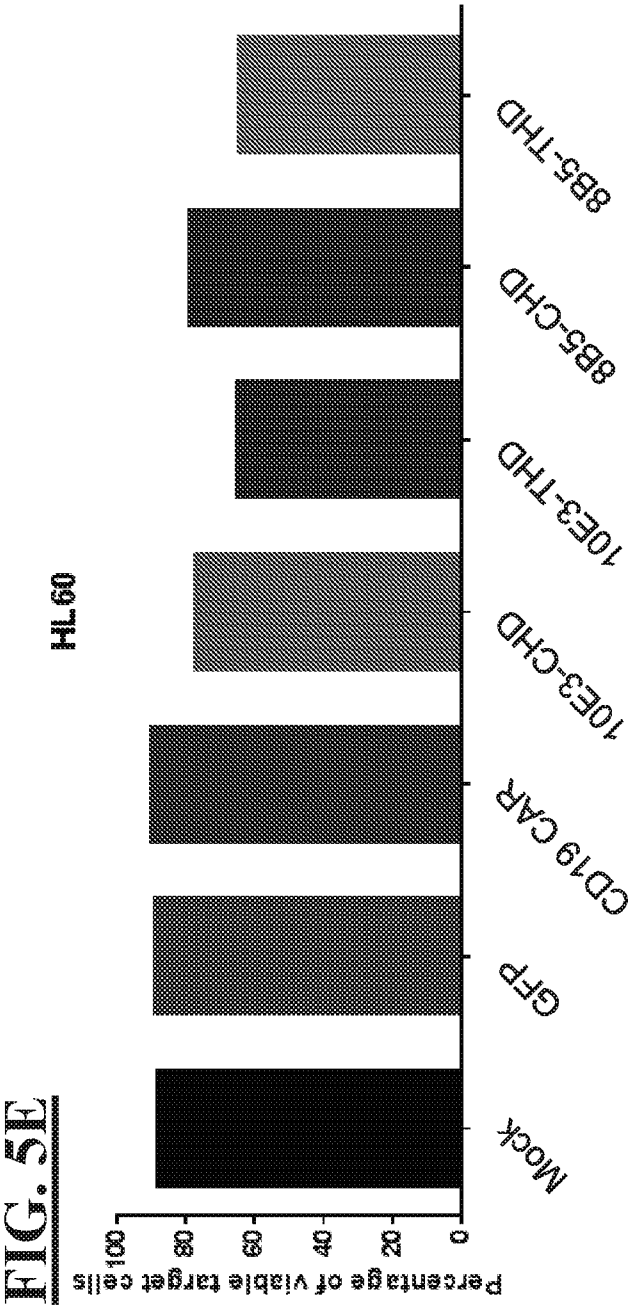
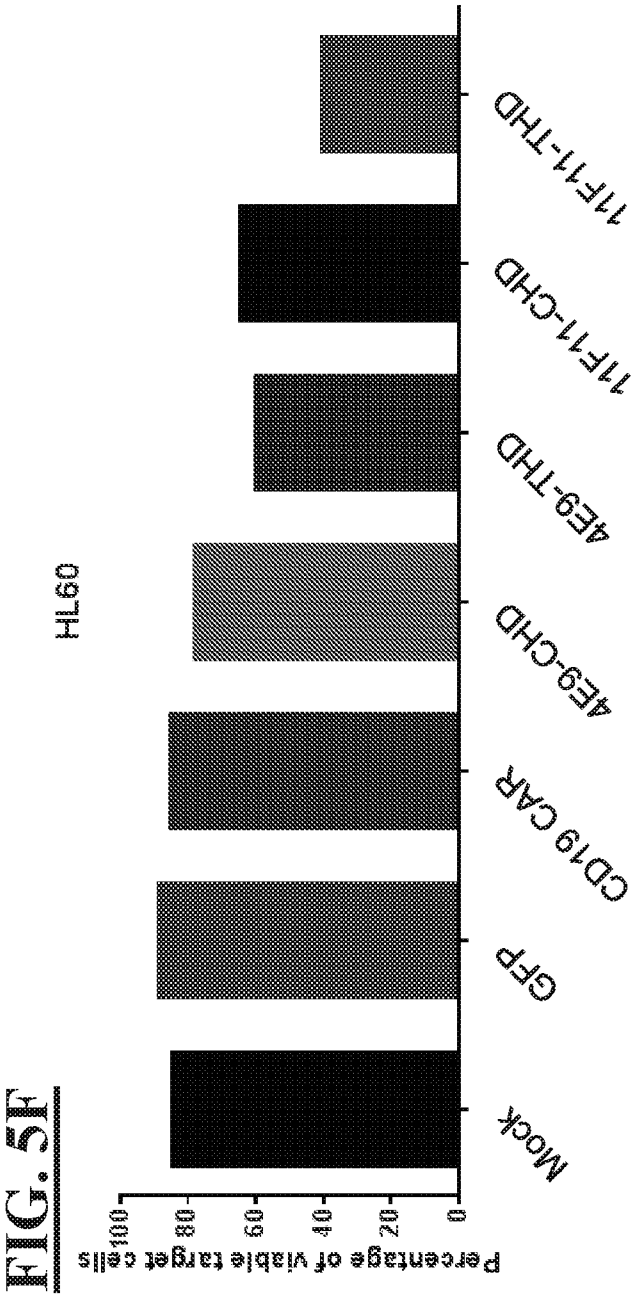

HL60
Percentage of viable target cells
0
20
40
60
80
100
Mock
GFP
CD19 CAR
10E3-CHD
10E3-THD
8B5-CHD
8B5-THD

FIG. 5F


HL60
Percentage of viable target cells
0
20
40
60
80
100
Mock
GFP
CD19 CAR
4E9-CHD
4E9-THD
11F1-CHD
11F1-THD

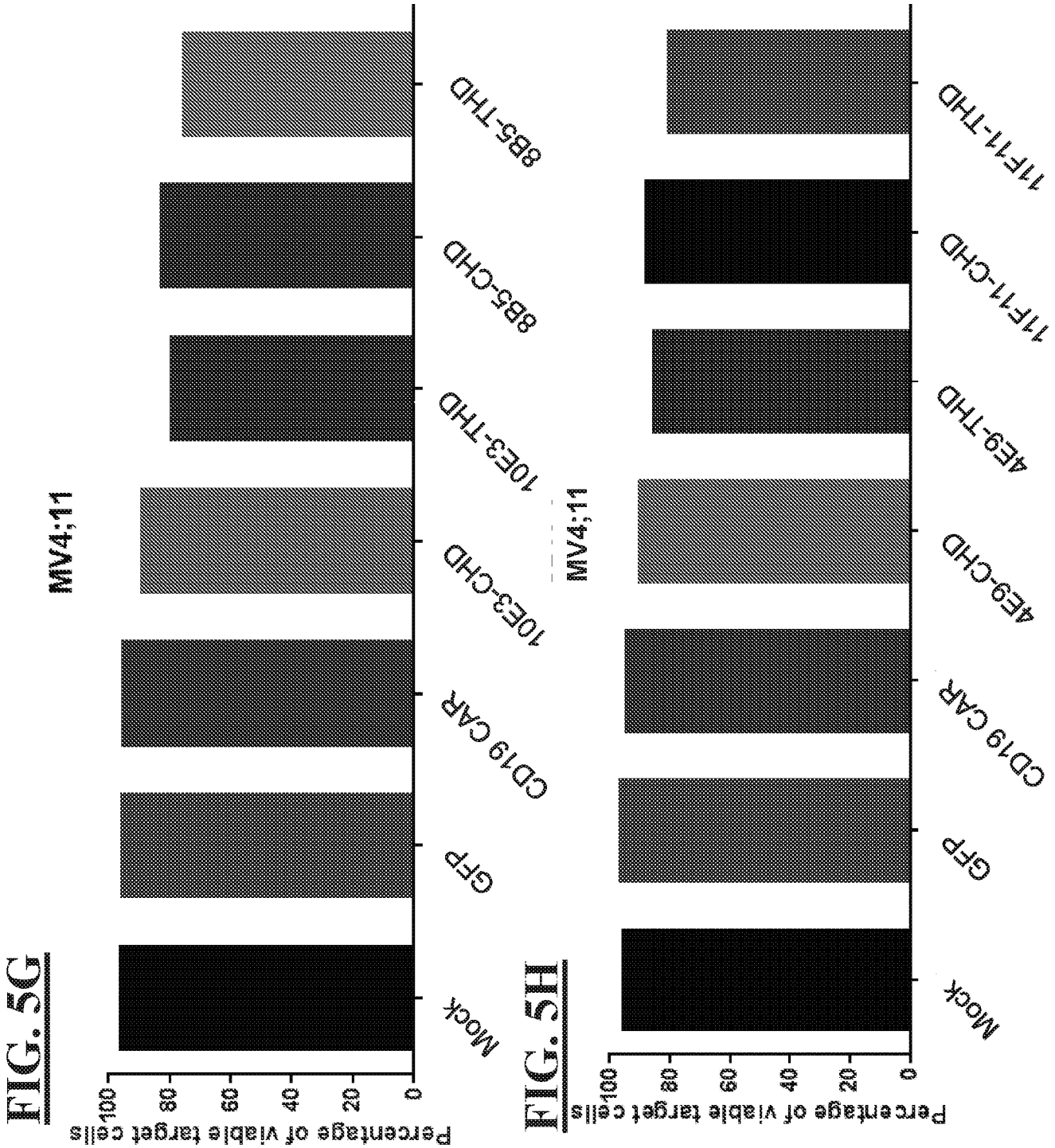


FIG. 5G
MV4;11
Percentage of viable target cells
0
20
40
60
80
100
Mock
GFP
CD19 CAR
10E3-CHD
10E3-THD
8B5-CHD
8B5-THD
FIG. 5H
MV4;11
Percentage of viable target cells
0
20
40
60
80
100
Mock
GFP
CD19 CAR
4E9-CHD
4E9-THD
11F11-CHD
11F11-THD

FIG. 6A

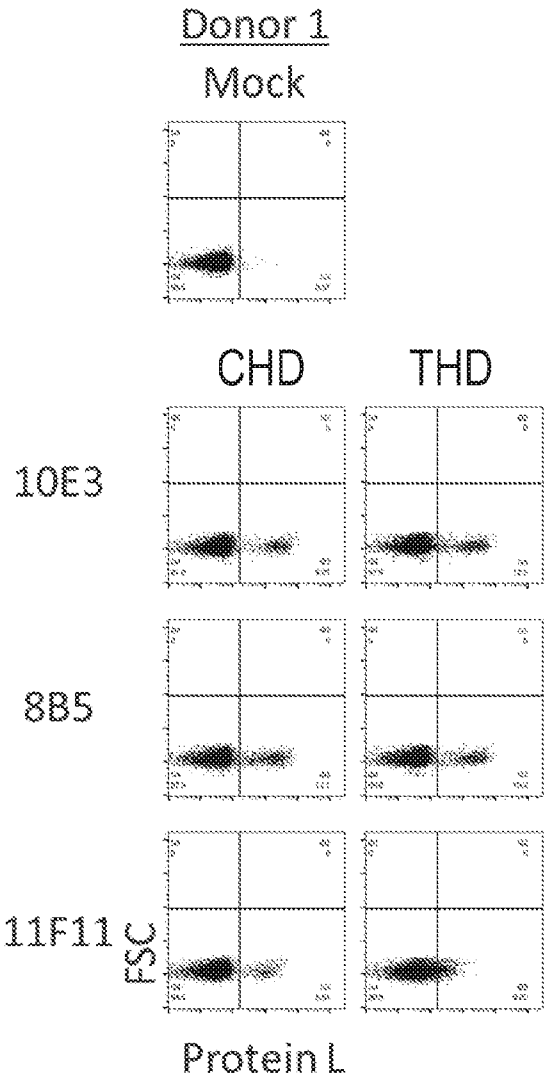
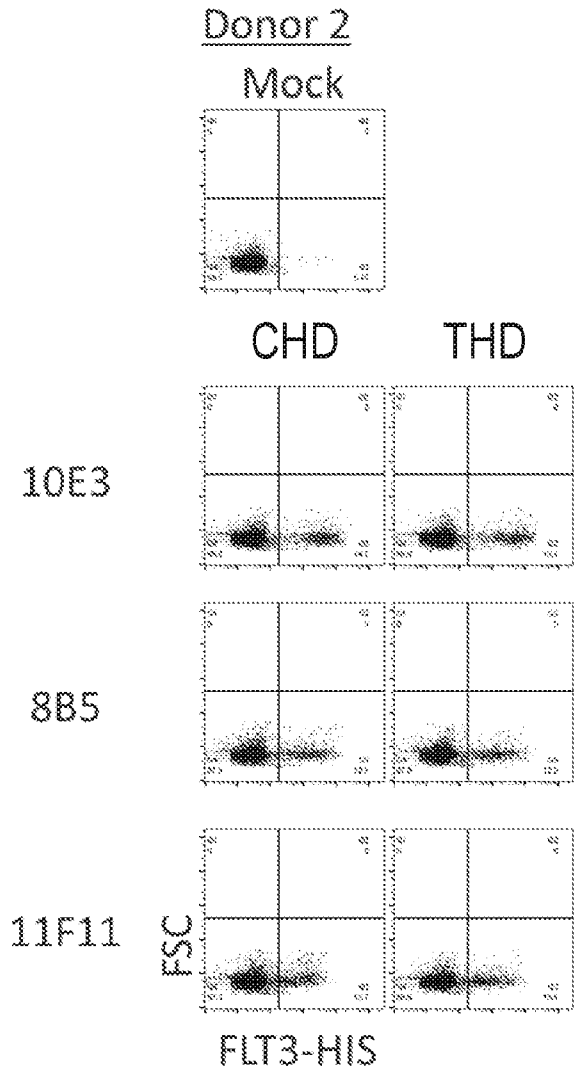

Donor 1
Mock
CHD
THD
10E3
8B5
11F11
FSC
Protein L

FIG. 6B


Donor 2
Mock
CHD
THD
10E3
8B5
11F11
FSC
FLT3-HIS

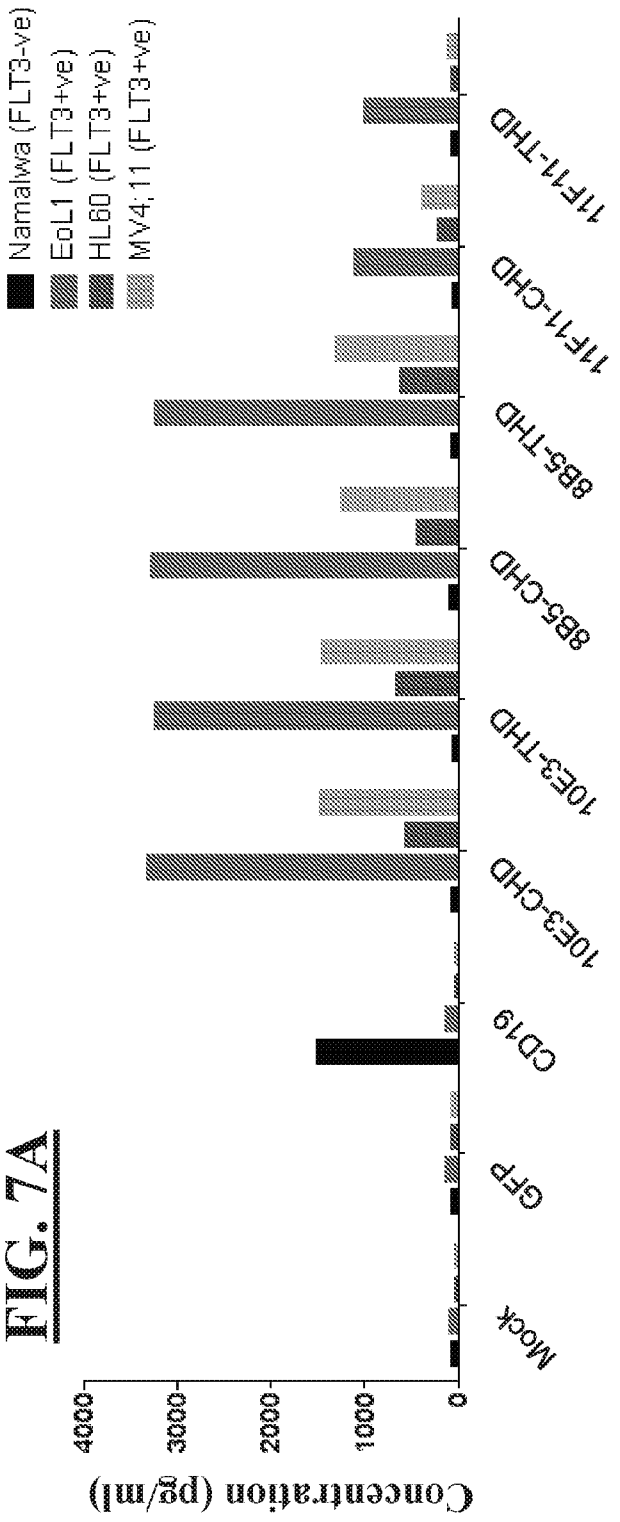

Namalwa (FLT3-ve)
EoL1 (FLT3+ve)
HL60 (FLT3+ve)
MV4;11 (FLT3+ve)
Concentration (pg/ml)
4000
3000
2000
1000
0
Mock
GFP
CD19
10E3-CHD
10E3-THD
8B5-CHD
8B5-THD
11F11-CHD
11F11-THD

FIG. 7A

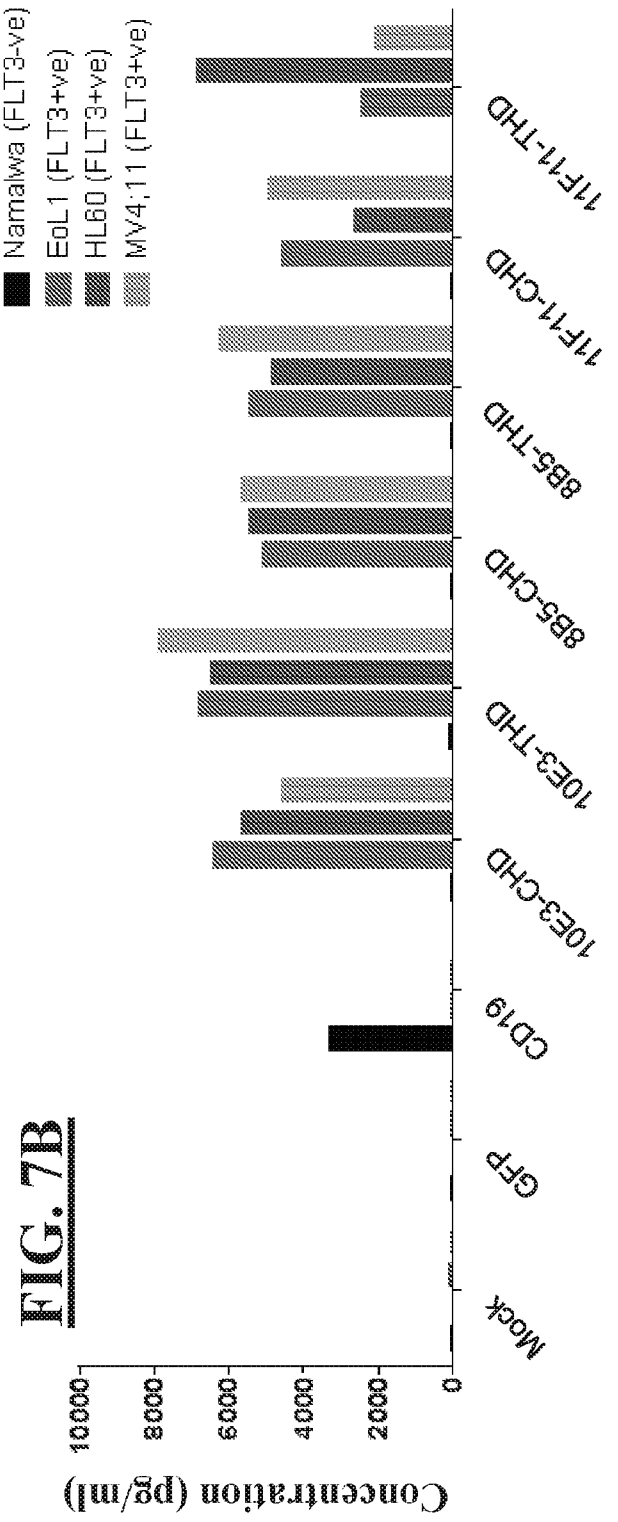

Namalwa (FLT3-ve)
EoL1 (FLT3+ve)
HL60 (FLT3+ve)
MV4;11 (FLT3+ve)
Concentration (pg/ml)
10000
8000
6000
4000
2000
0
Mock
GFP
CD19
10E3-CHD
10E3-THD
8B5-CHD
8B5-THD
11F11-CHD
11F11-THD

FIG. 7B

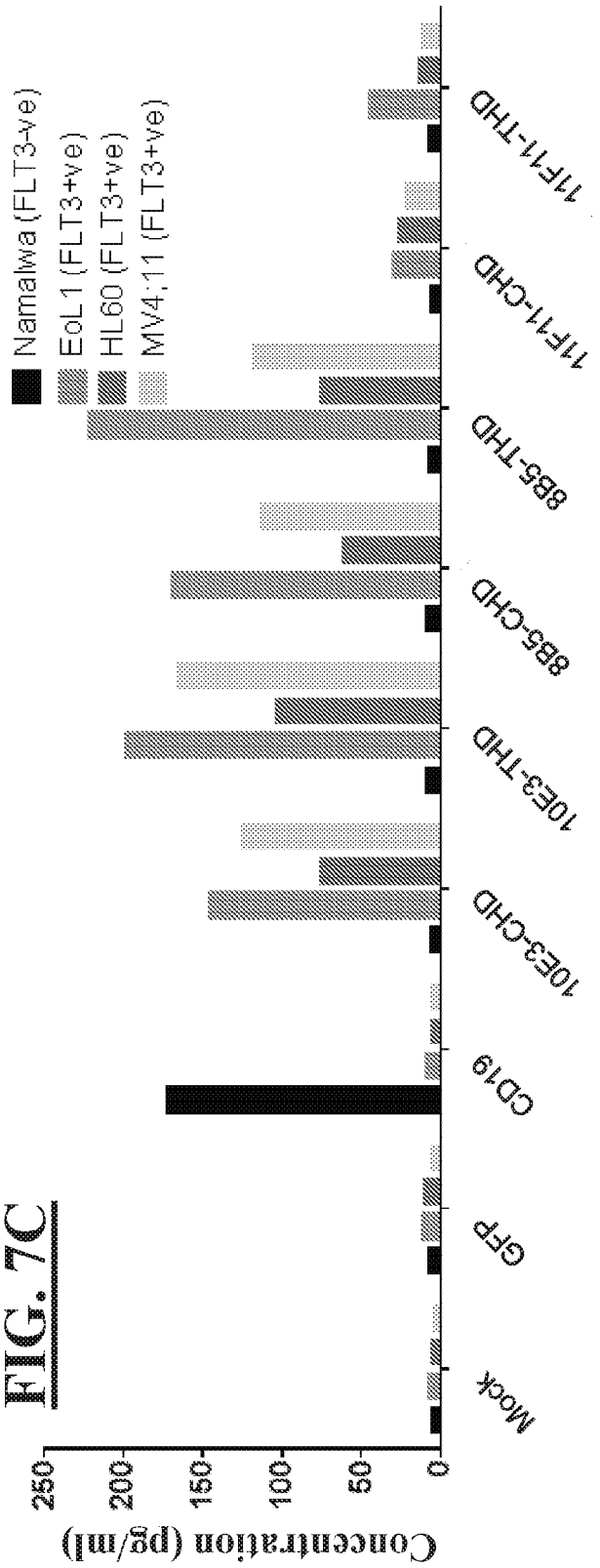

Namalwa (FLT3-ve)
EoL1 (FLT3+ve)
HL60 (FLT3+ve)
MV4;11 (FLT3+ve)
Concentration (pg/ml)
0
50
100
150
200
250
Mock
GFP
CD19
10E3-CHD
10E3-THD
8B5-CHD
8B5-THD
11F11-CHD
11F11-THD

FIG. 7C

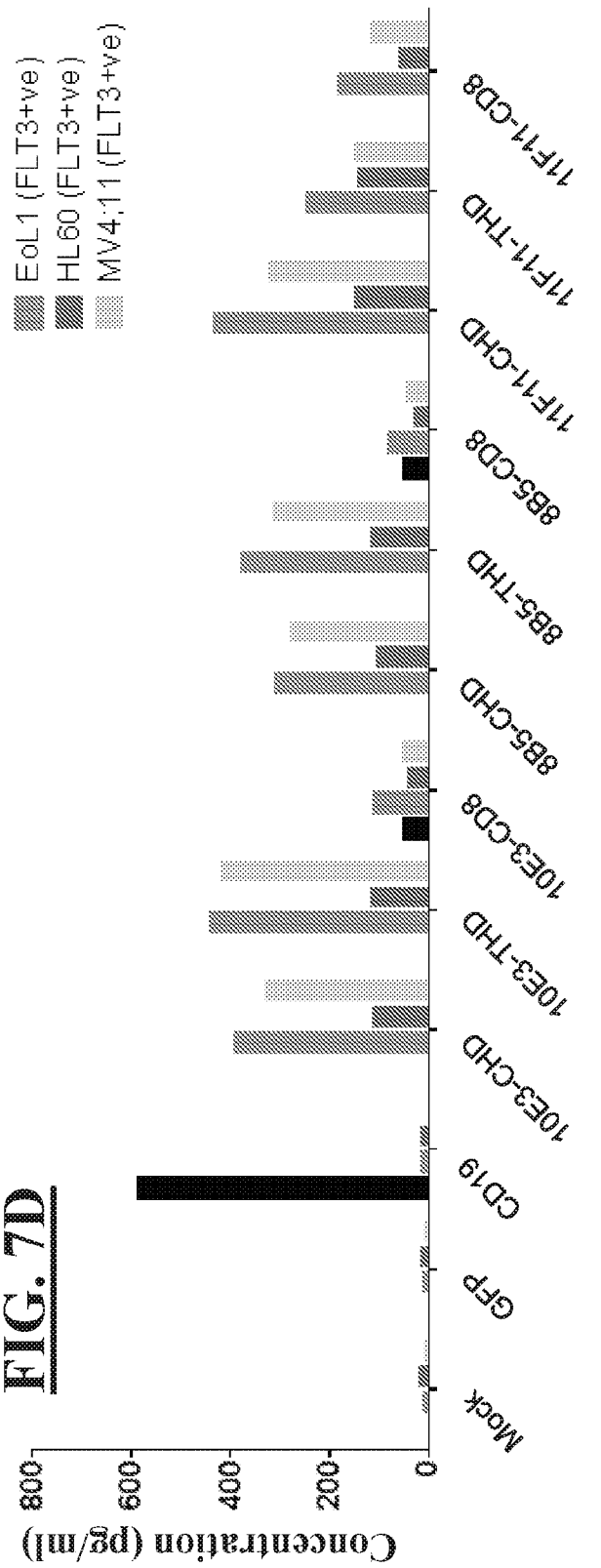

Namalwa (FLT3-ve)
EoL1 (FLT3+ve)
HL60 (FLT3+ve)
MV4;11 (FLT3+ve)
Concentration (pg/ml)
0
200
400
600
800
Mock
GFP
CD19
10E3-CHD
10E3-THD
10E3-CD8
8B5-CHD
8B5-THD
8B5-CD8
11F11-CHD
11F11-THD
11F11-CD8

FIG. 7D

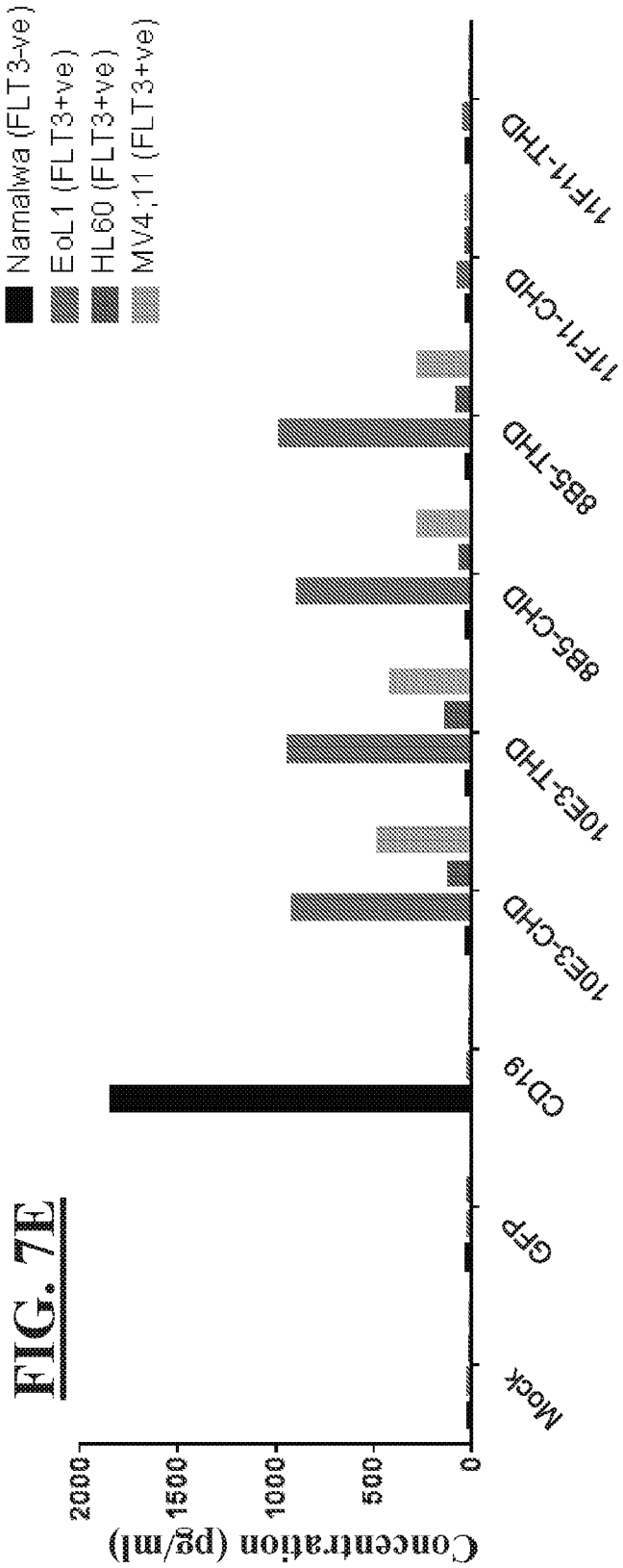

Namalwa (FLT3-ve)
EoL1 (FLT3+ve)
HL60 (FLT3+ve)
MV4;11 (FLT3+ve)
Concentration (pg/ml)
2000
1500
1000
500
0
Mock
GFP
CD19
10E3-CHD
10E3-THD
8B5-CHD
8B5-THD
11F11-CHD
11F11-THD

FIG. 7E

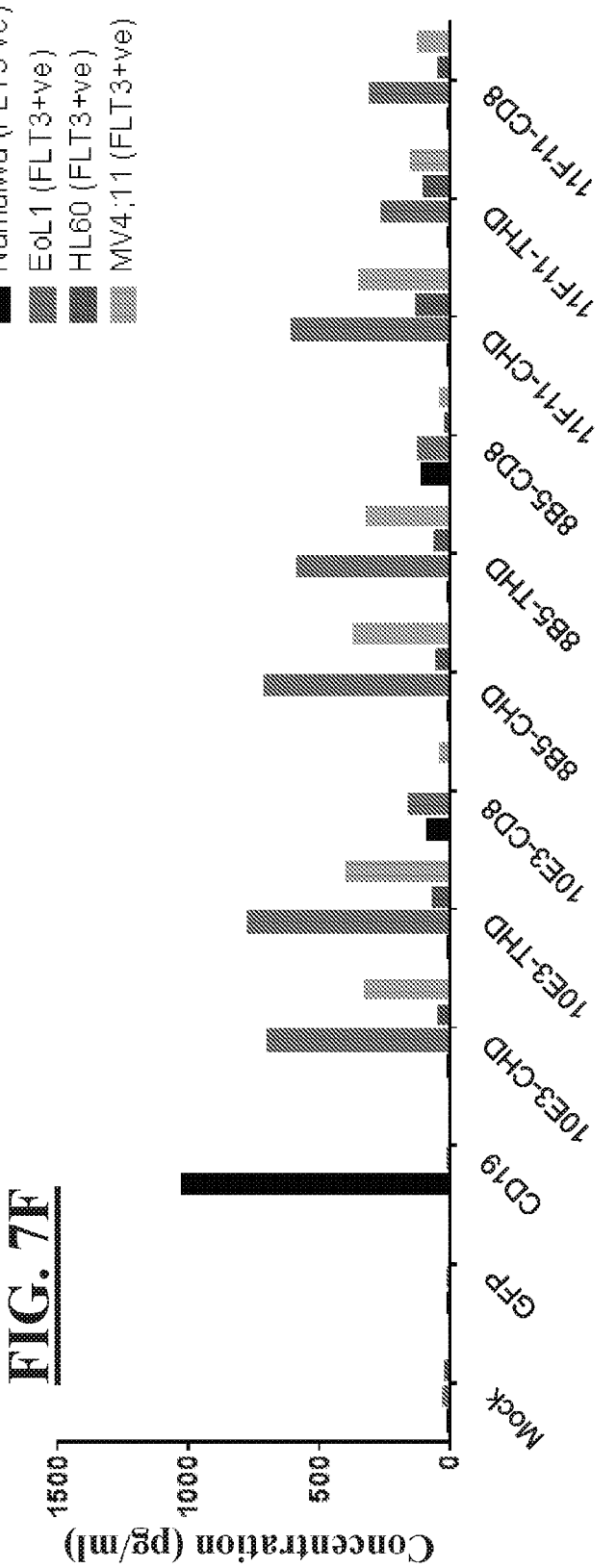

Namalwa (FLT3-ve)
EoL1 (FLT3+ve)
HL60 (FLT3+ve)
MV4;11 (FLT3+ve)
Concentration (pg/ml)
1500
1000
500
0
Mock
GFP
CD19
10E3-CHD
10E3-THD
10E3-CD8
8B5-CHD
8B5-THD
8B5-CD8
11F11-CHD
11F11-THD
11F11-CD8

FIG. 7F

FIG. 8A

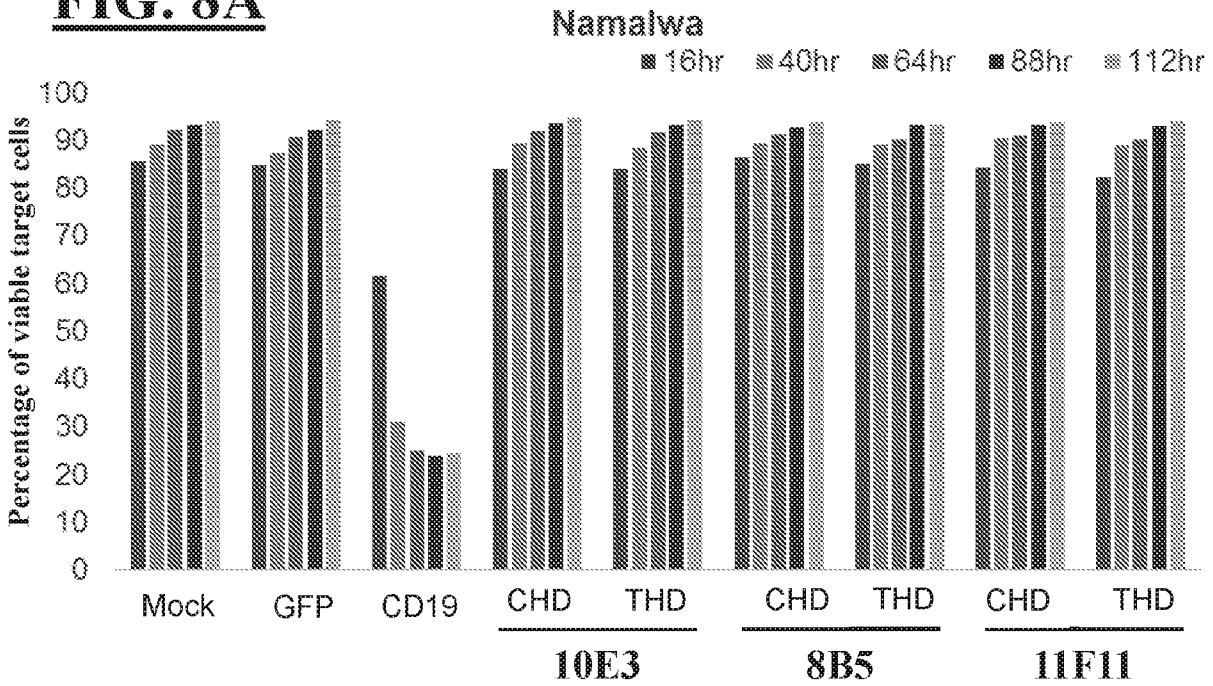

Namalwa
16hr
40hr
64hr
88hr
112hr
Percentage of viable target cells
100
90
80
70
60
50
40
30
20
10
0
Mock
GFP
CD19
CHD
THD
CHD
THD
CHD
THD
10E3
8B5
11F11

FIG. 8B

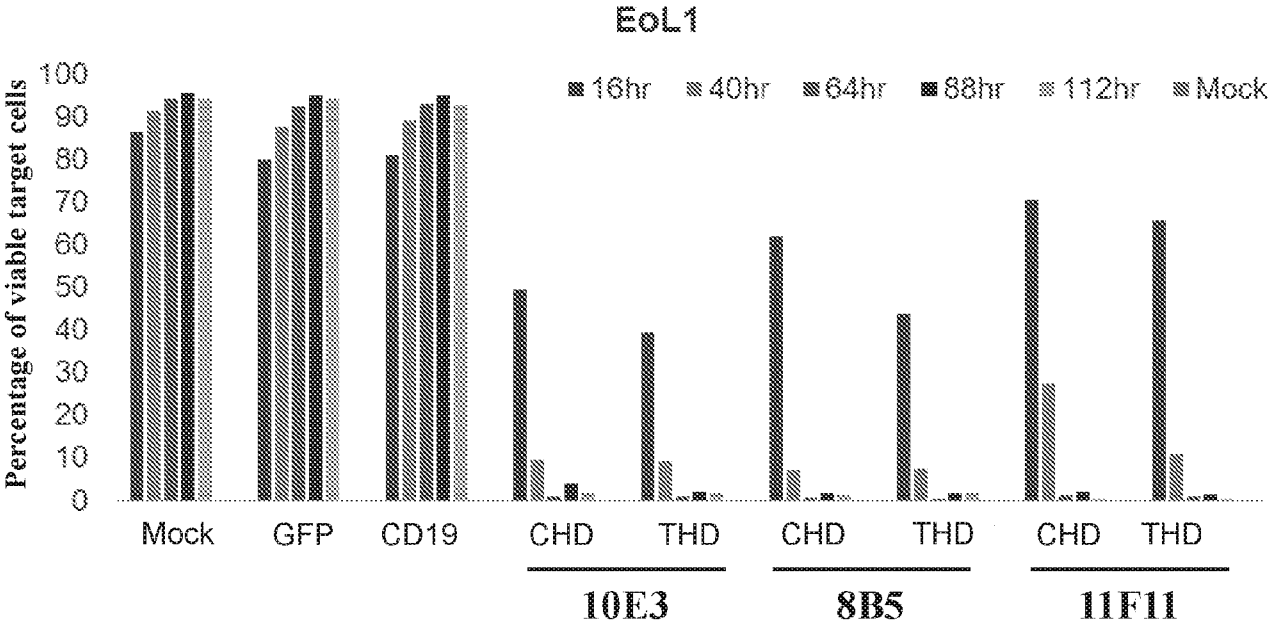

EoL1
16hr
40hr
64hr
88hr
112hr
Mock
Percentage of viable target cells
100
90
80
70
60
50
40
30
20
10
0
Mock
GFP
CD19
CHD
THD
CHD
THD
CHD
THD
10E3
8B5
11F11

FIG. 8C

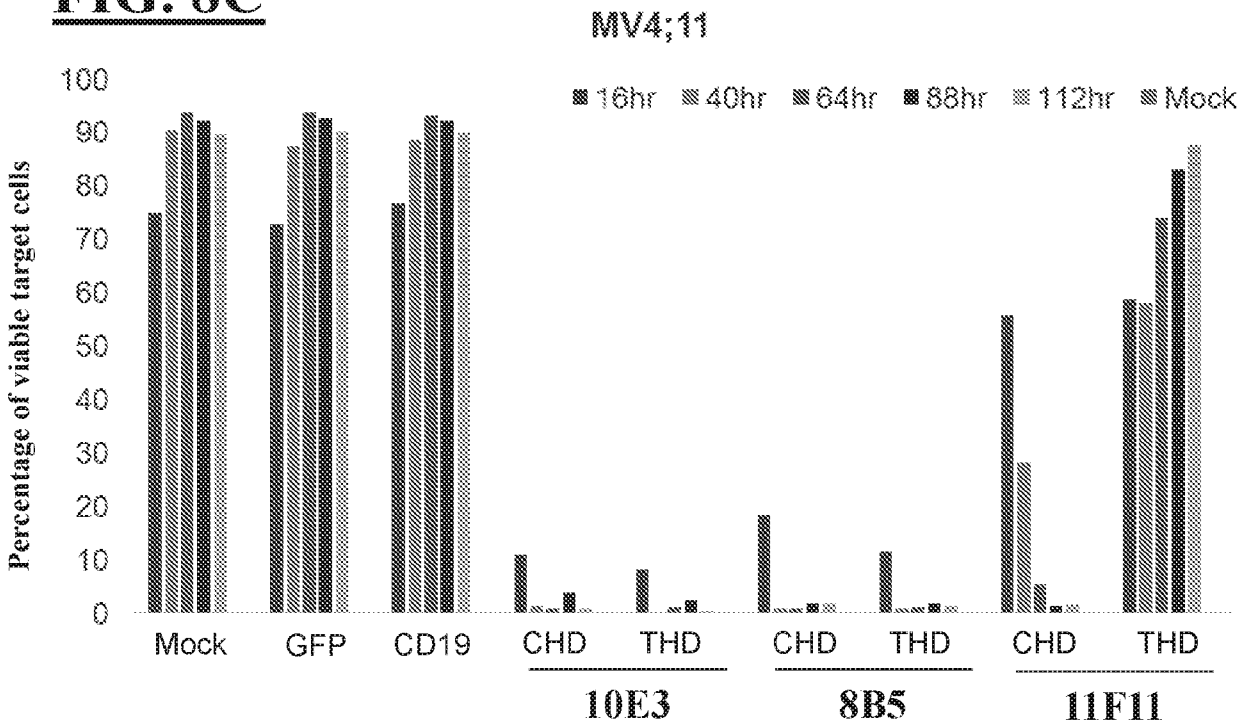

MV4;11
16hr
40hr
64hr
88hr
112hr
Mock
Percentage of viable target cells
100
90
80
70
60
50
40
30
20
10
0
Mock
GFP
CD19
CHD
THD
CHD
THD
CHD
THD
10E3
8B5
11F11

FIG. 8D

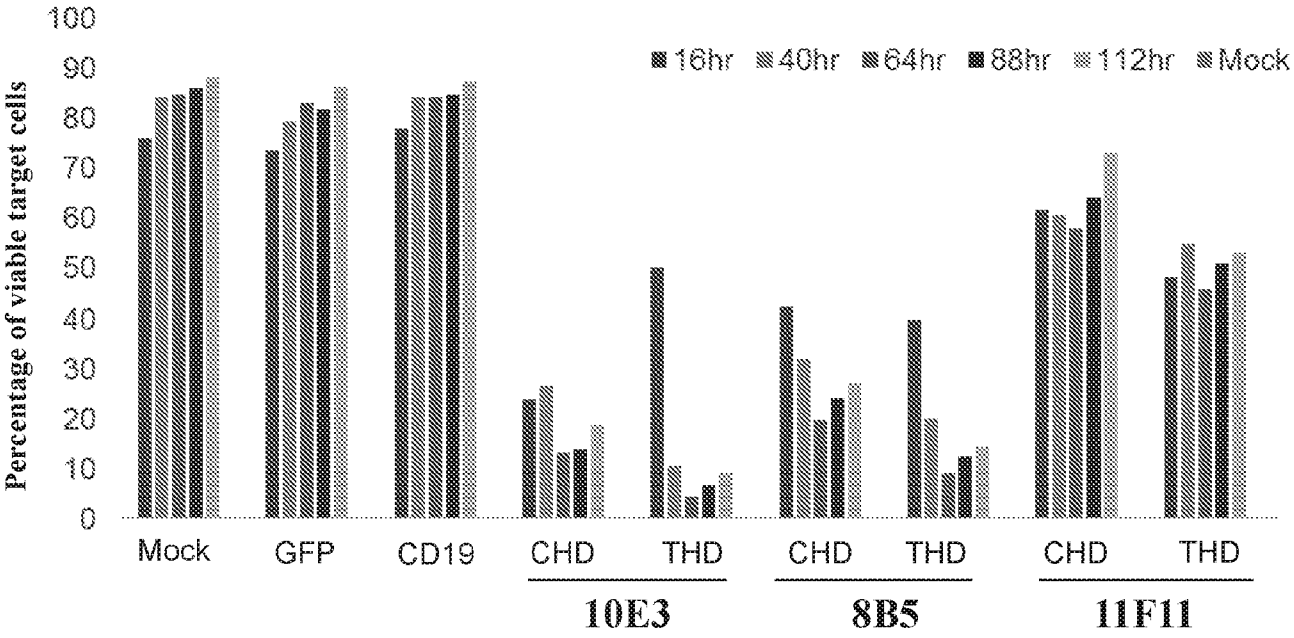
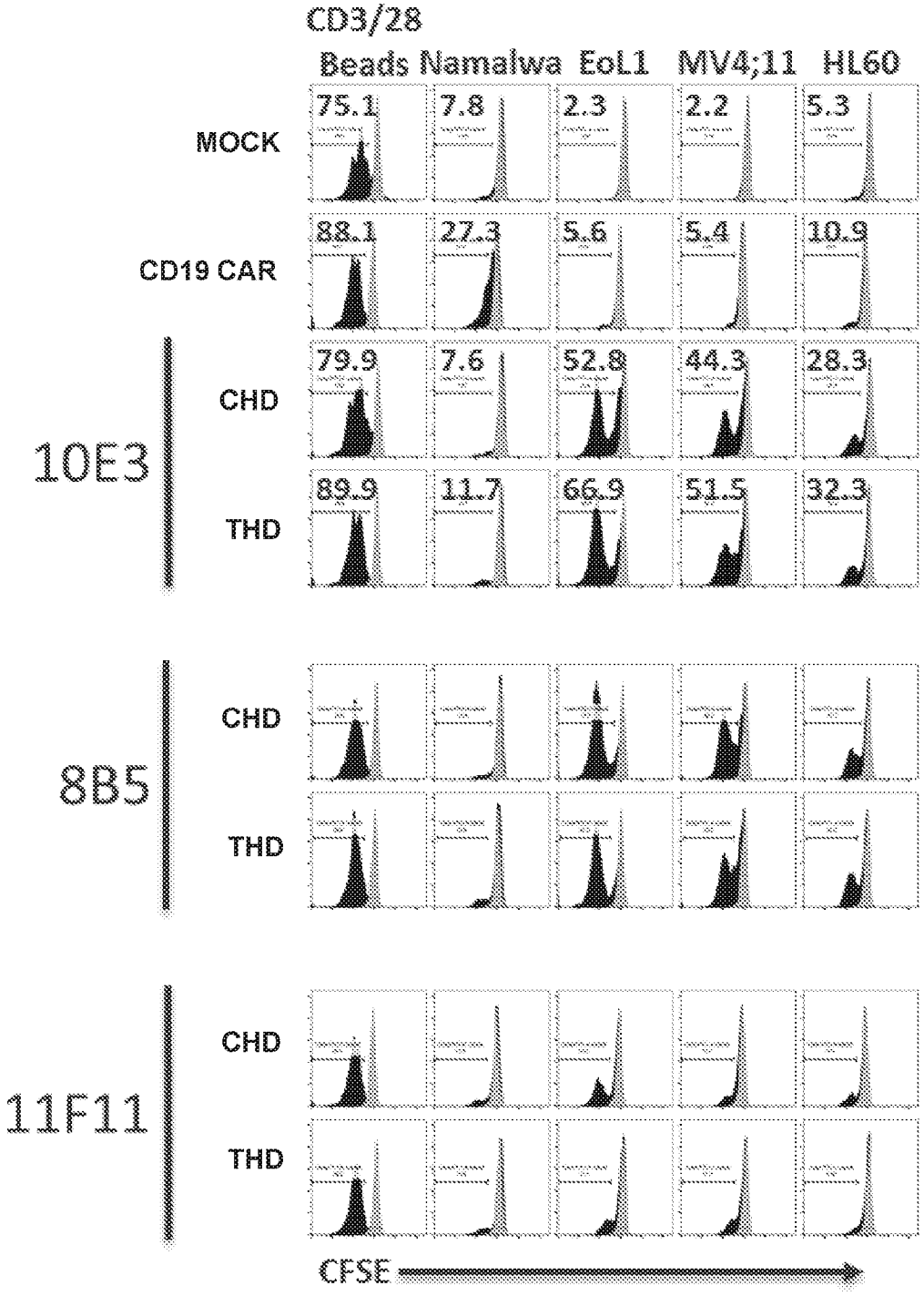
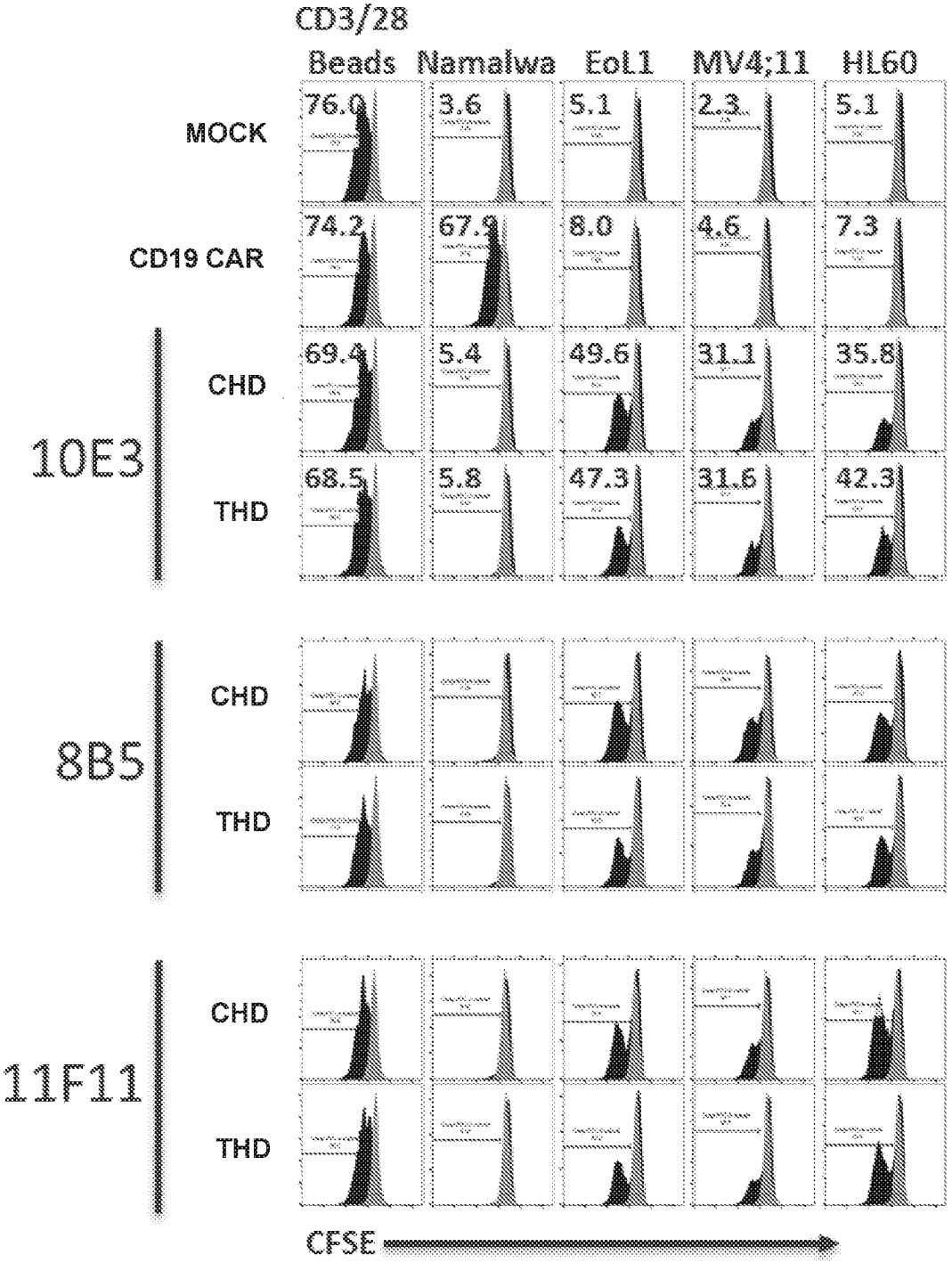

HL60
16hr
40hr
64hr
88hr
112hr
Mock
Percentage of viable target cells
100
90
80
70
60
50
40
30
20
10
0
Mock
GFP
CD19
CHD
THD
CHD
THD
CHD
THD
10E3
8B5
11F11

FIG. 9A **Donor 1**



Unstimulated T cells T cells + indicated stimulus

FIG. 9B **Donor 2**



Unstimulated T cells T cells + indicated stimulus

FIG. 10A

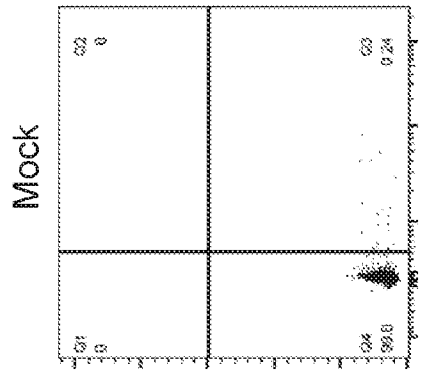


FIG. 10B

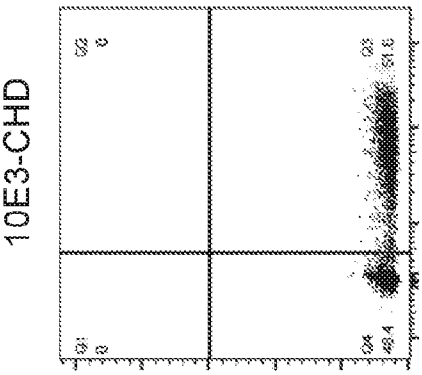


FIG. 10C

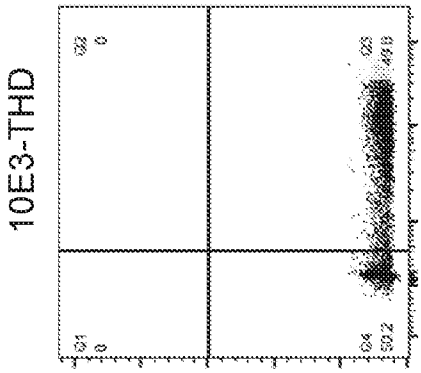


FIG. 10D

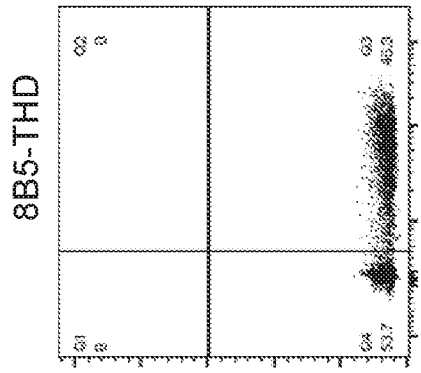


FIG. 10E

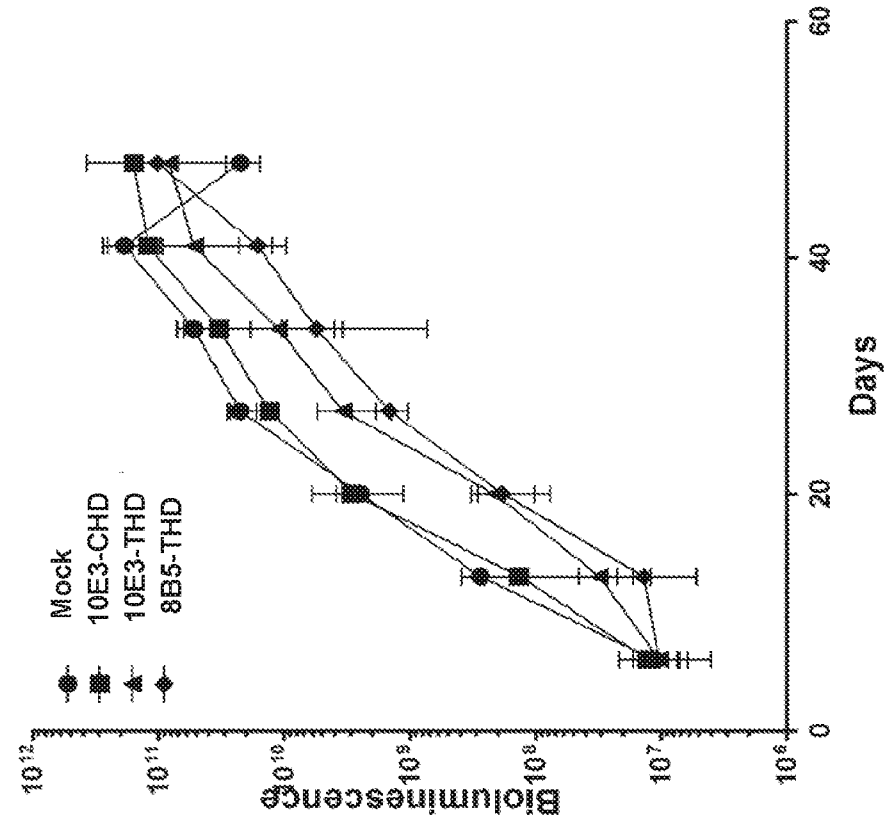


FIG. 10F

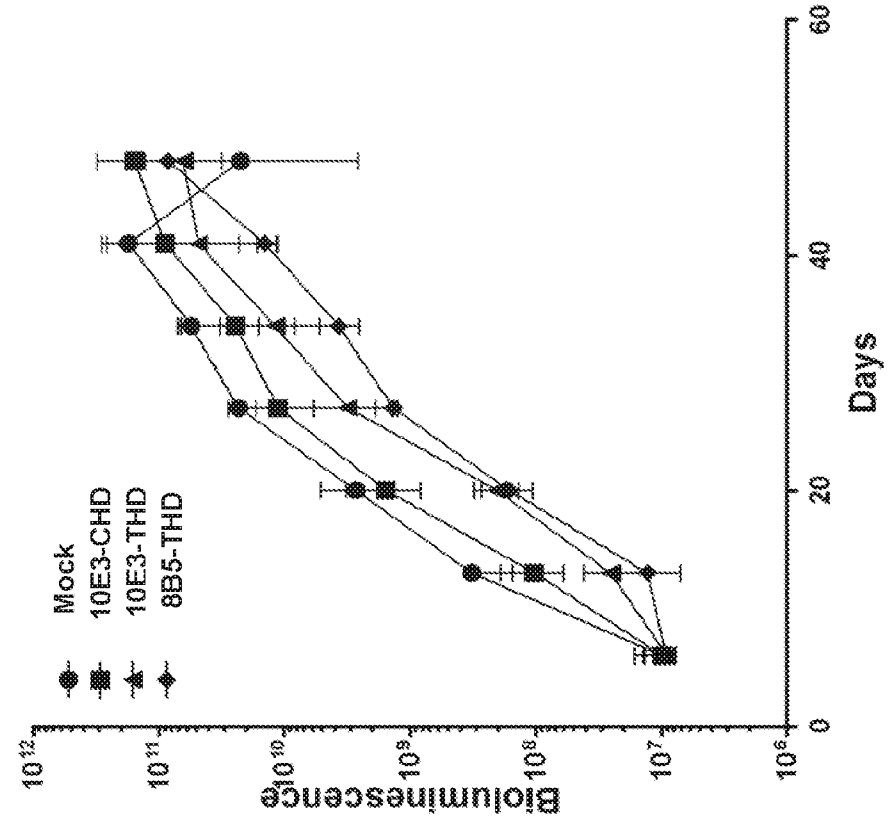


FIG. 10G

Day	Mock vs 10E3-CHD	Mock vs 10E3-THD	Mock vs 8B5-THD	10E3-THD vs 8B5-THD
6	0.756	0.657	0.690	0.959
13	0.067	0.0004	0.0002	0.028
20	0.777	0.0022	0.0020	0.639
27	0.158	<0.0001	<0.0001	0.042
34	0.200	0.0004	0.0001	0.142
41	0.376	0.0072	0.0009	0.054

FIG. 10H

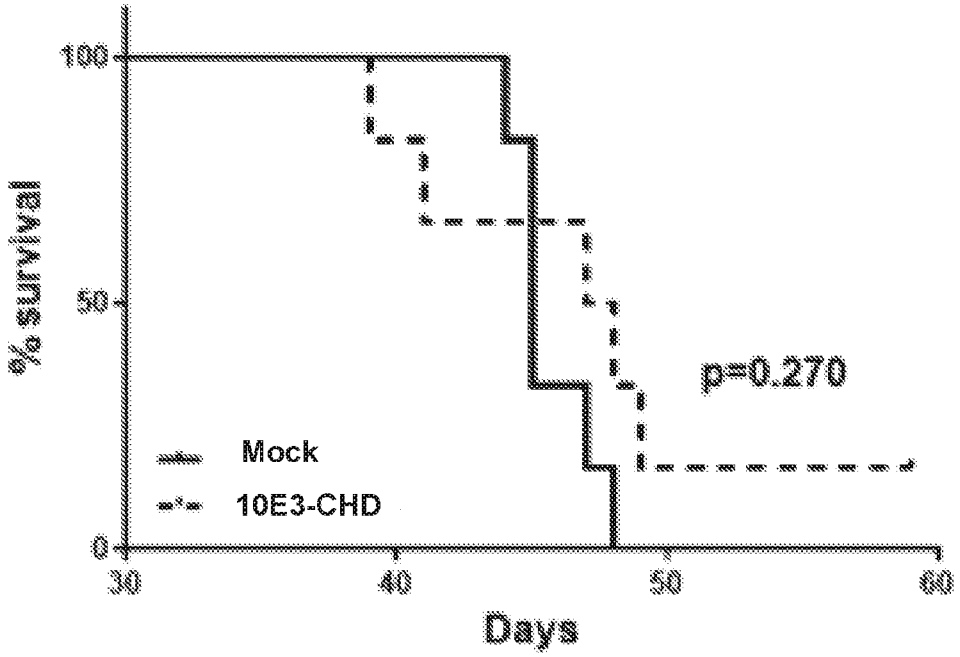


FIG. 10I

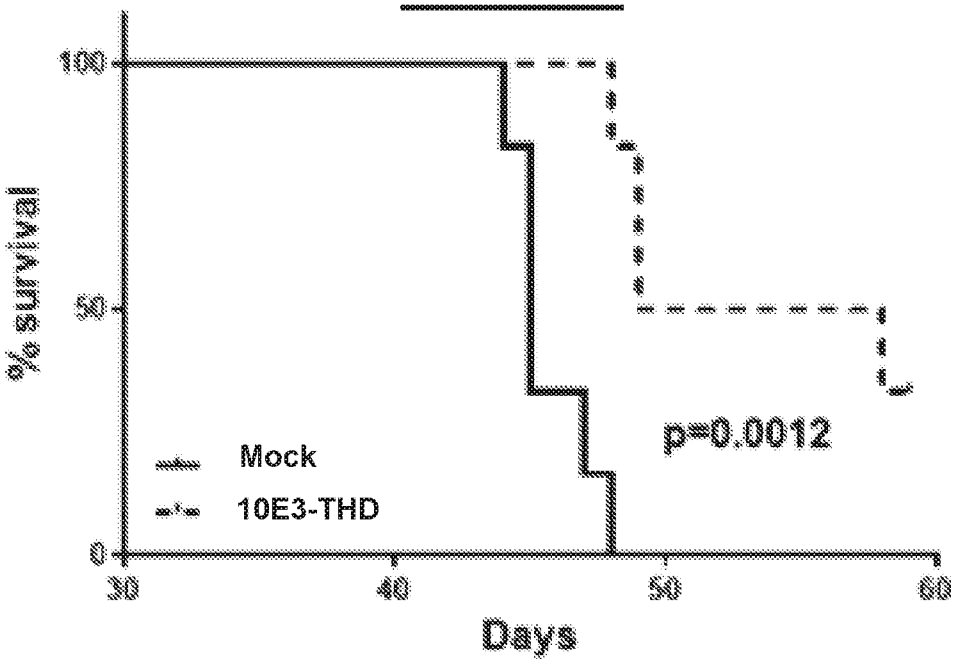


FIG. 10J

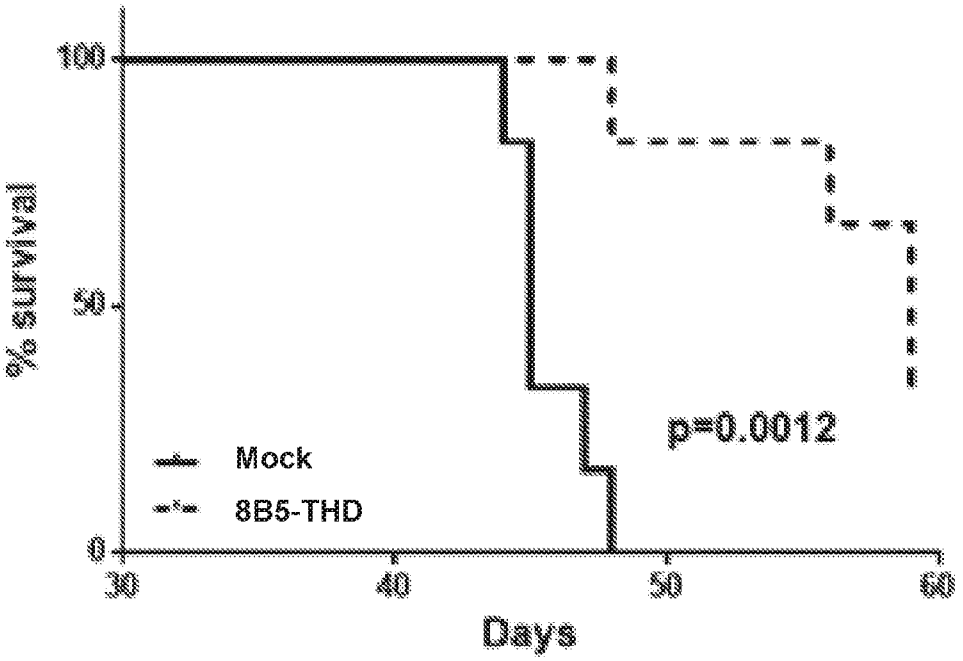


FIG. 10K

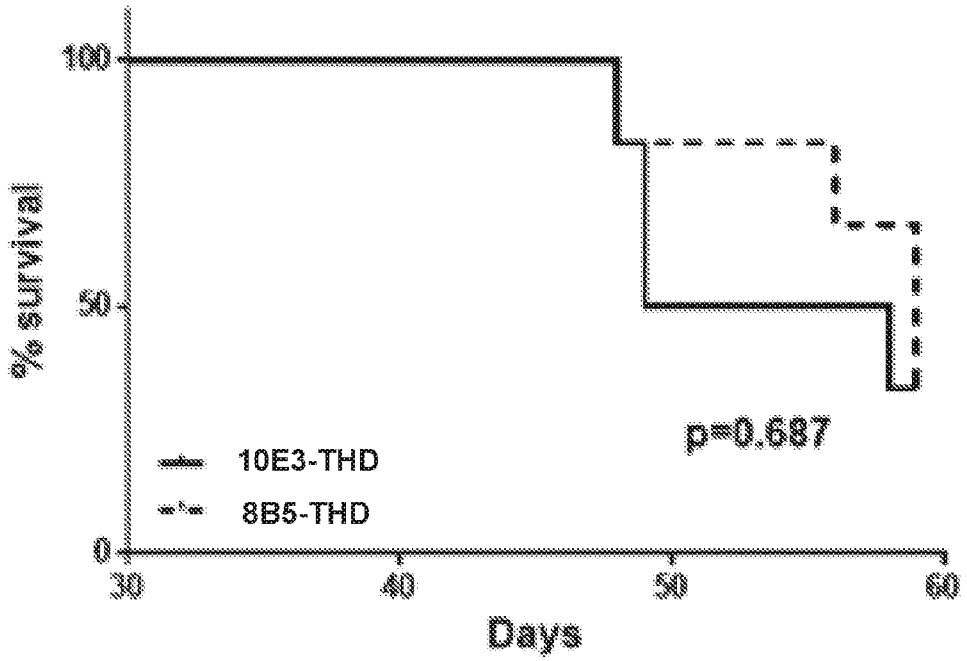


FIG. 11A

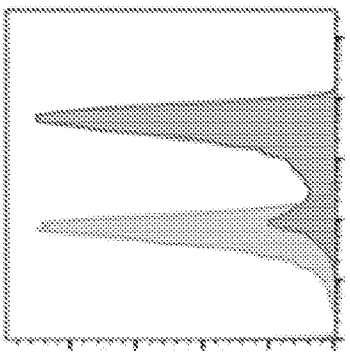
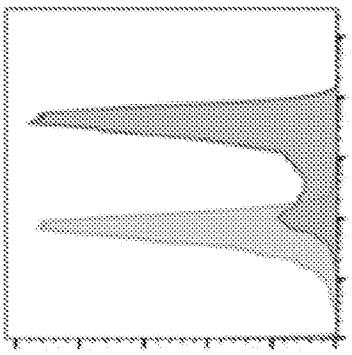


FIG. 11B



Protein L

FIG. 12A

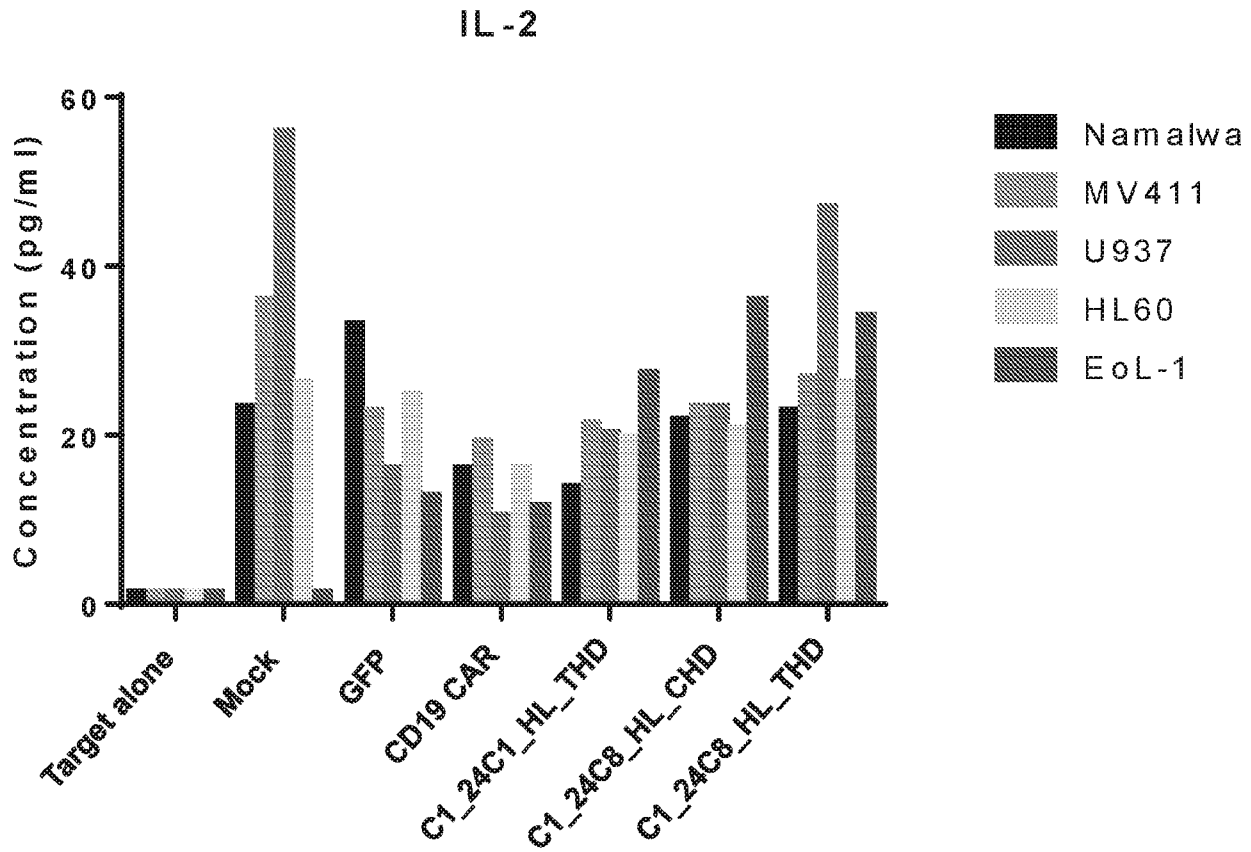

IL-2
Concentration (pg/ml)
60
40
20
0
Target alone
Mock
GFP
CD19 CAR
C1_24C1_HL_THD
C1_24C8_HL_CHD
C1_24C8_HL_THD
Namalwa
MV411
U937
HL60
EoL-1

FIG. 12B

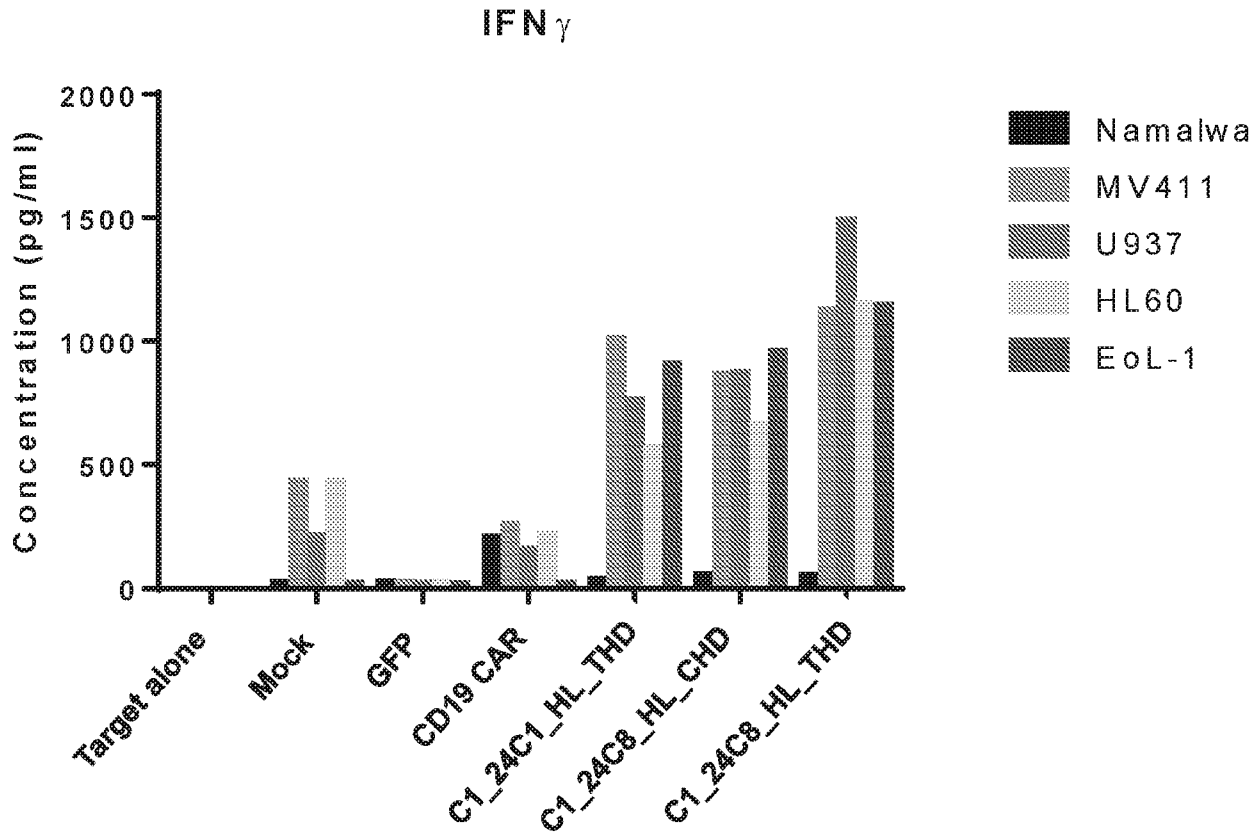
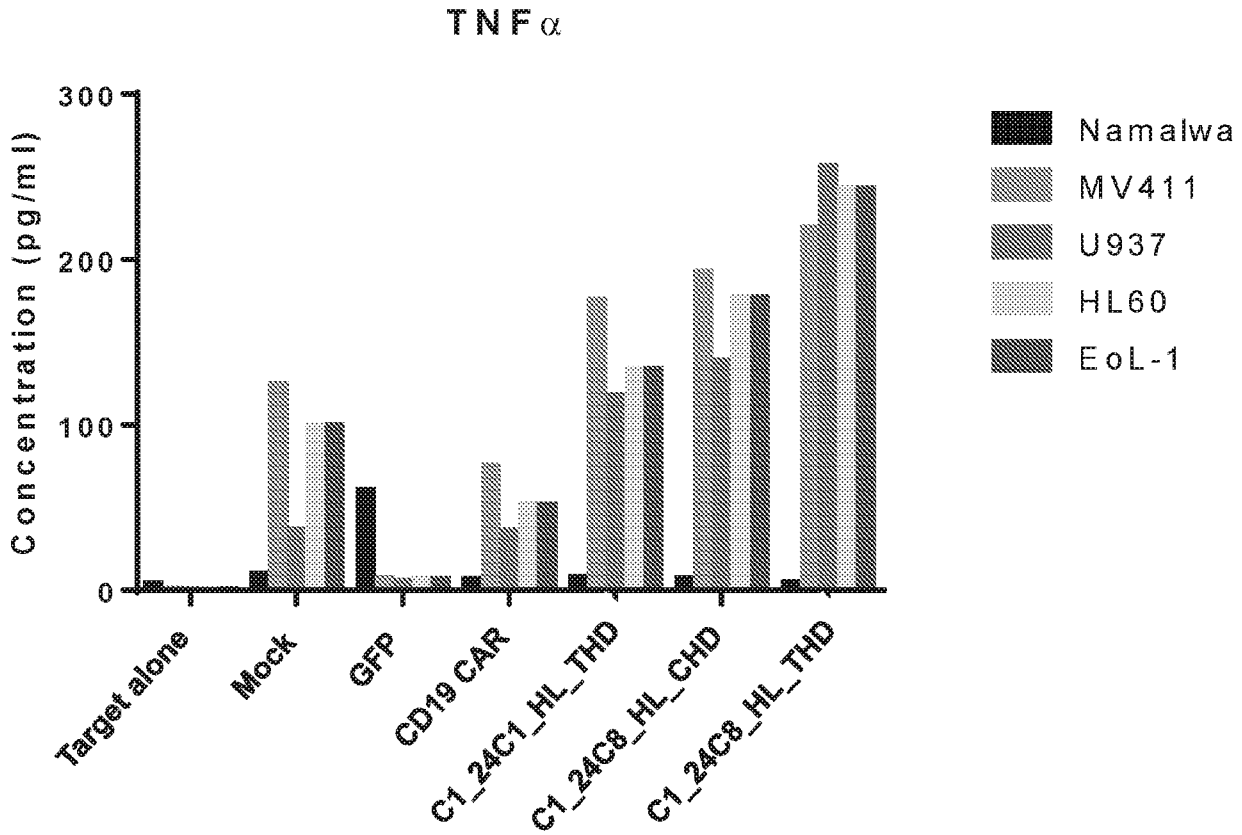

IFNγ
Concentration (pg/ml)
2000
1500
1000
500
0
Target alone
Mock
GFP
CD19 CAR
C1_24C1_HL_THD
C1_24C8_HL_CHD
C1_24C8_HL_THD
Namalwa
MV411
U937
HL60
EoL-1

FIG. 12C


TNFα
Concentration (pg/ml)
300
200
100
0
Target alone
Mock
GFP
CD19 CAR
C1_24C1_HL_THD
C1_24C8_HL_CHD
C1_24C8_HL_THD
Namalwa
MV411
U937
HL60
EoL-1

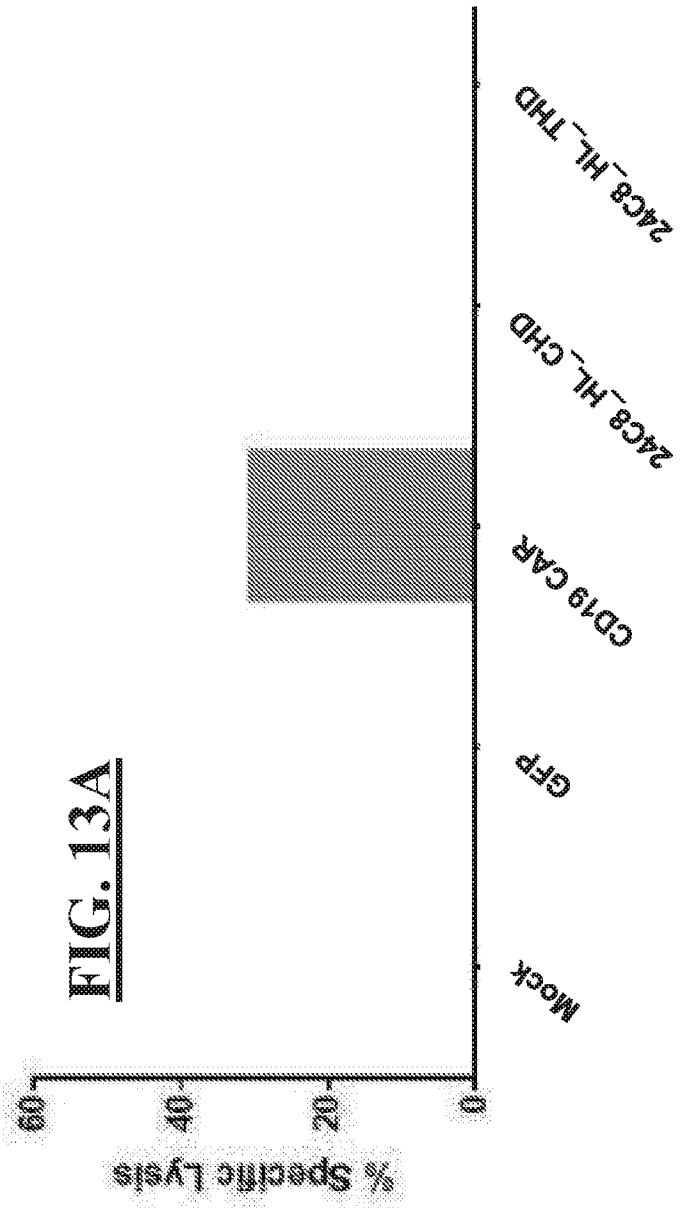


FIG. 13A

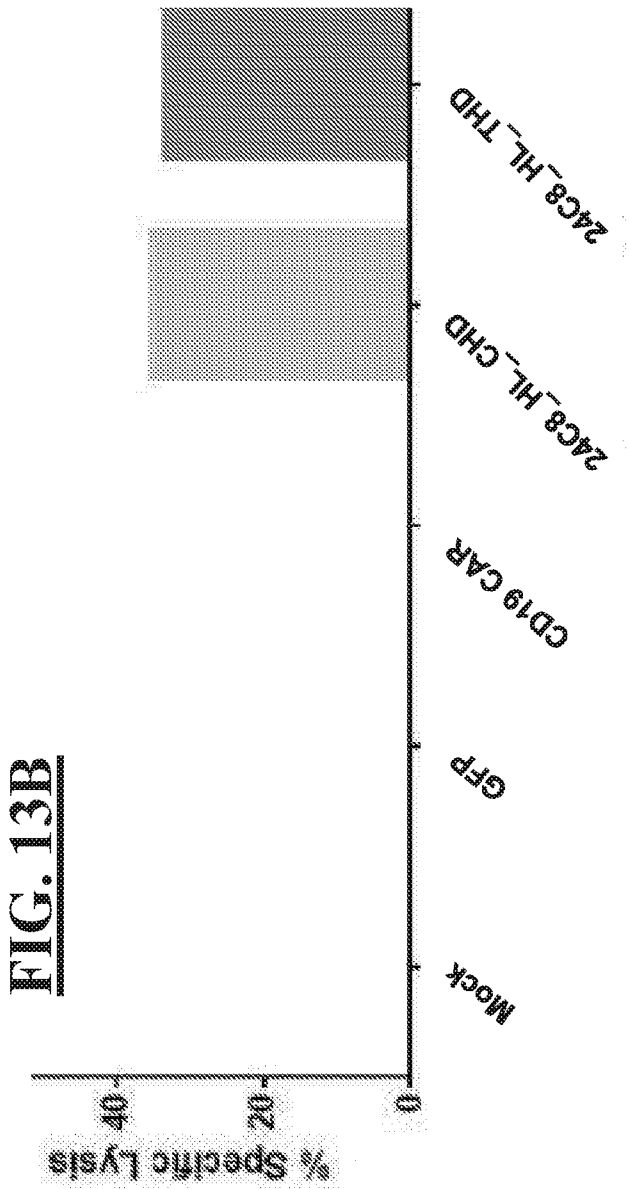


FIG. 13B

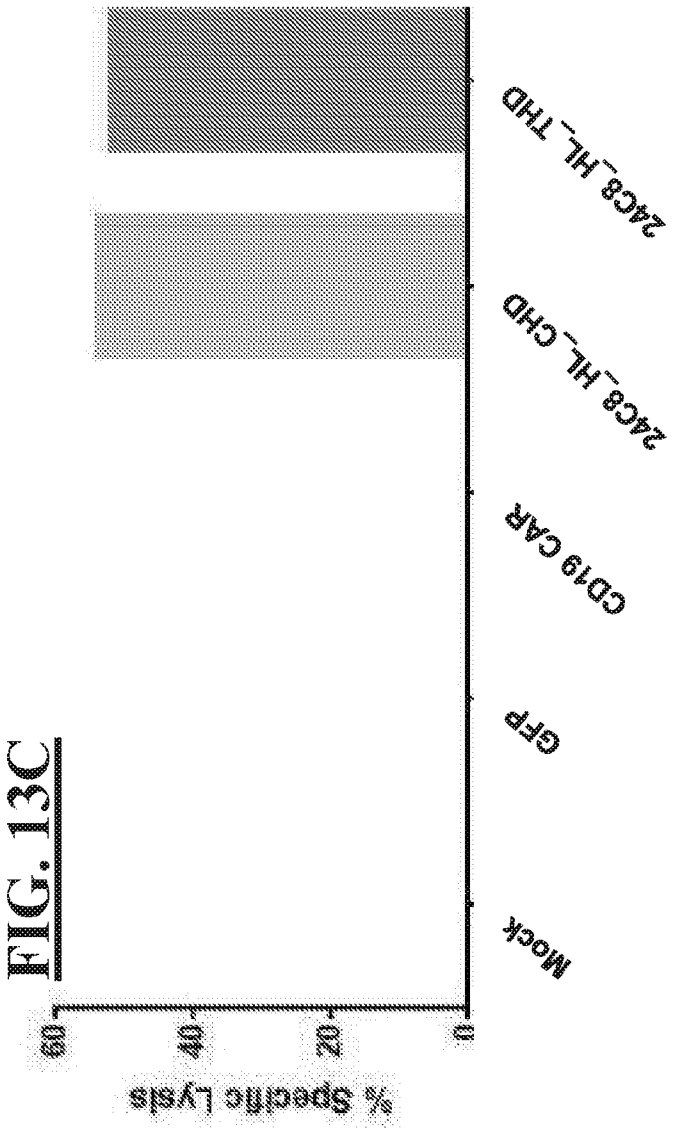


FIG. 13C

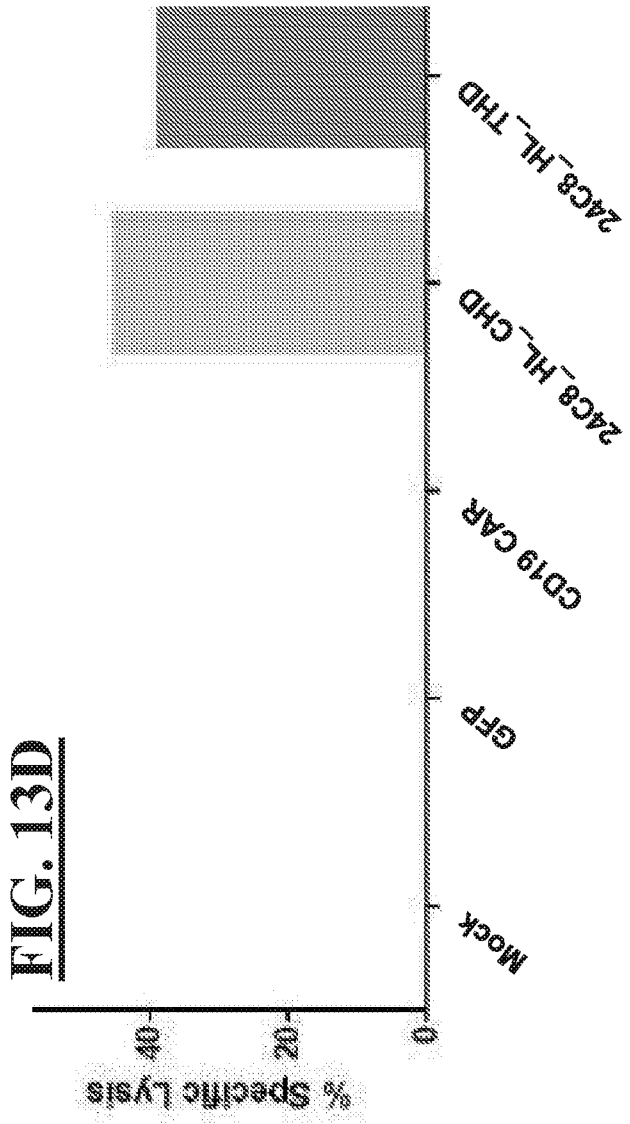


FIG. 13D

FIG. 13E

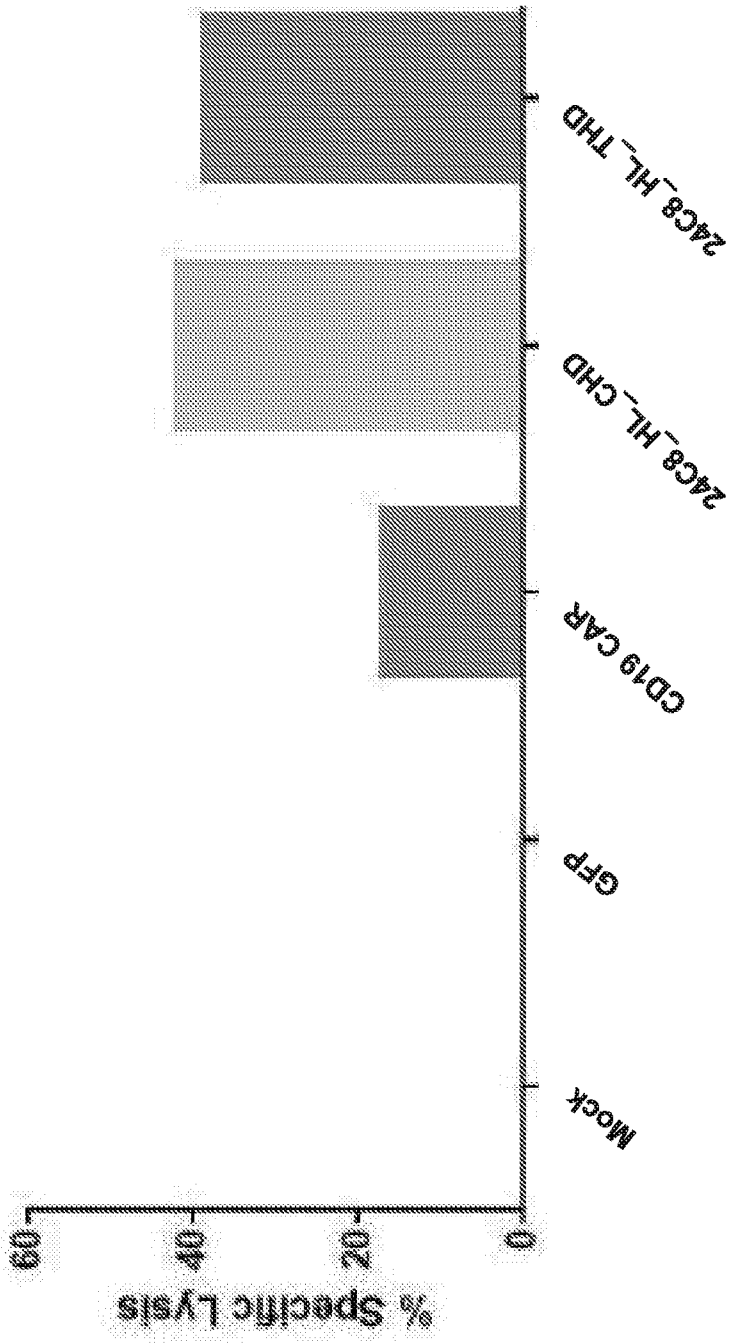

% Specific Lysis
0
20
40
60
Mock
GFP
CD19 CAR
24C8_HL_CHD
24C8_HL_THD

FIG. 14A

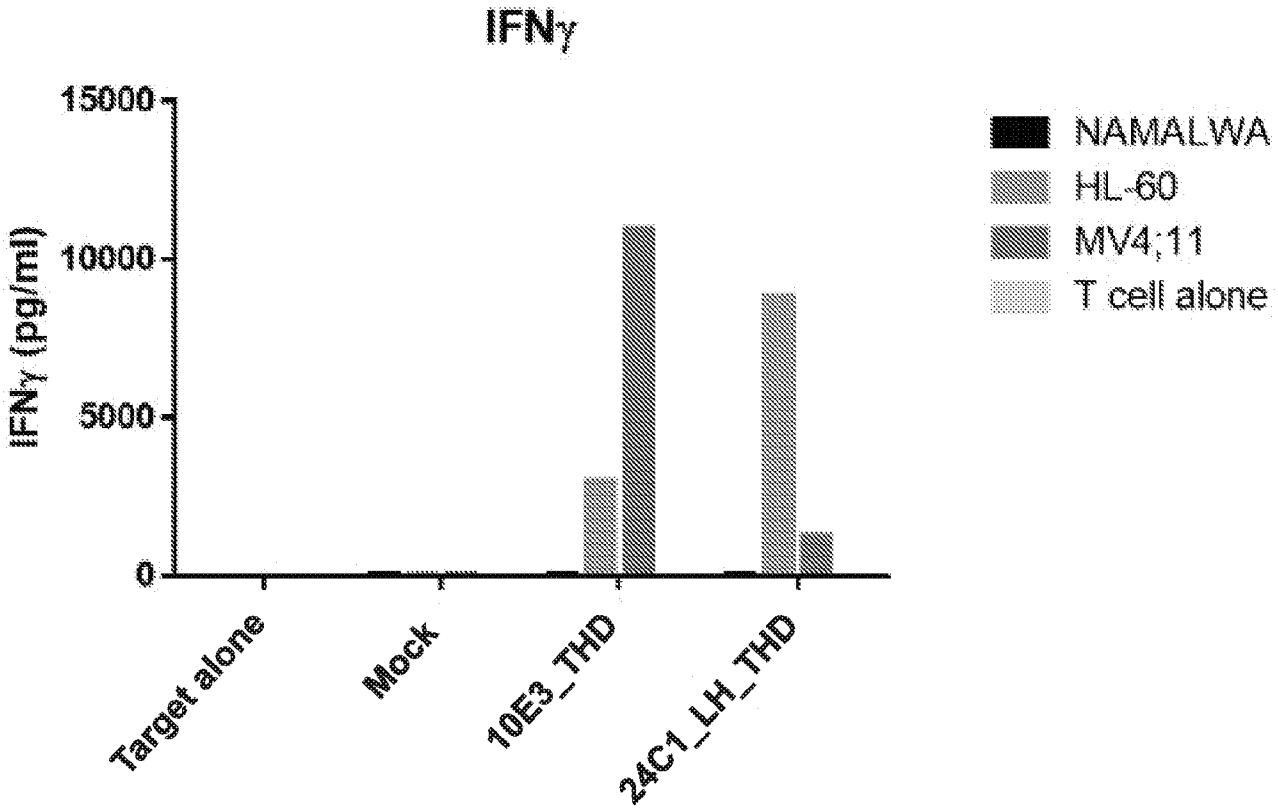

IFNγ
IFNγ (pg/ml)
15000
10000
5000
0
Target alone
Mock
10E3_THD
24C1_LH_THD
NAMALWA
HL-60
MV4;11
T cell alone

FIG. 14B

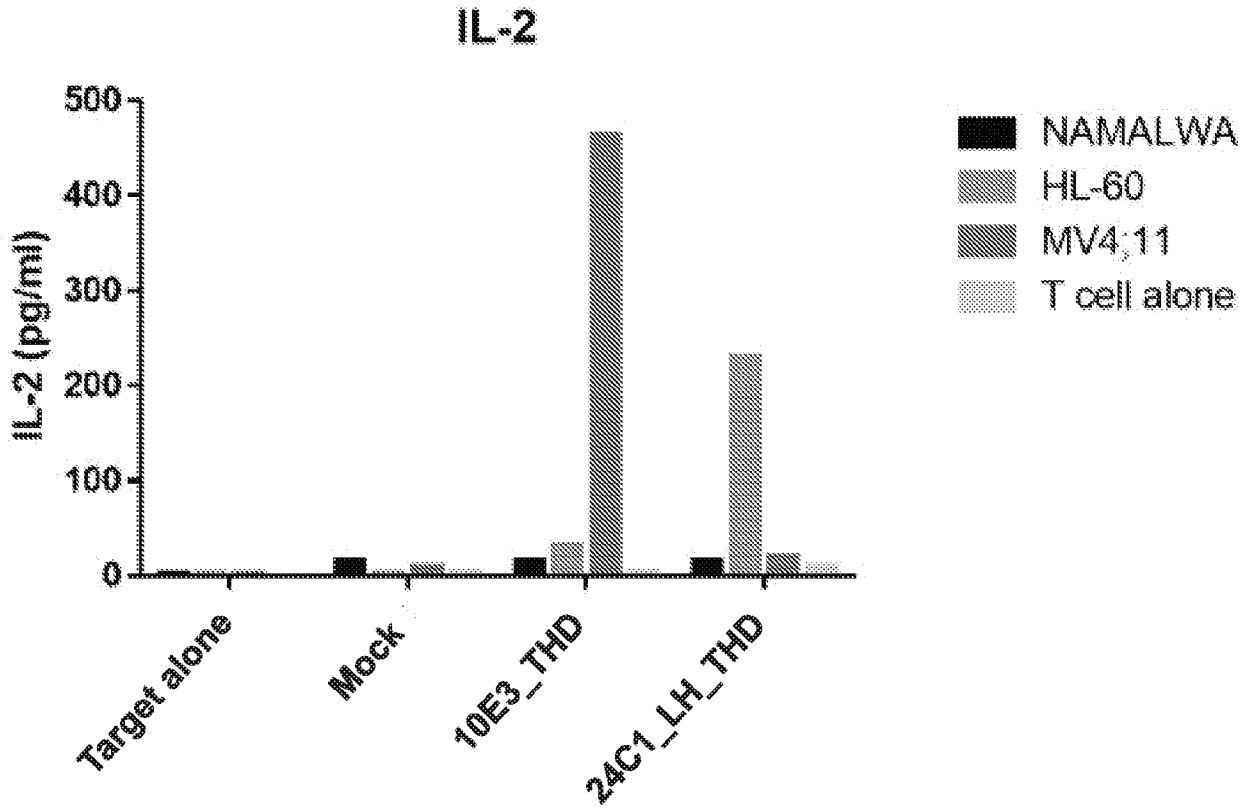

IL-2
IL-2 (pg/ml)
500
400
300
200
100
0
Target alone
Mock
10E3_THD
24C1_LH_THD
NAMALWA
HL-60
MV4;11
T cell alone

FIG. 14C

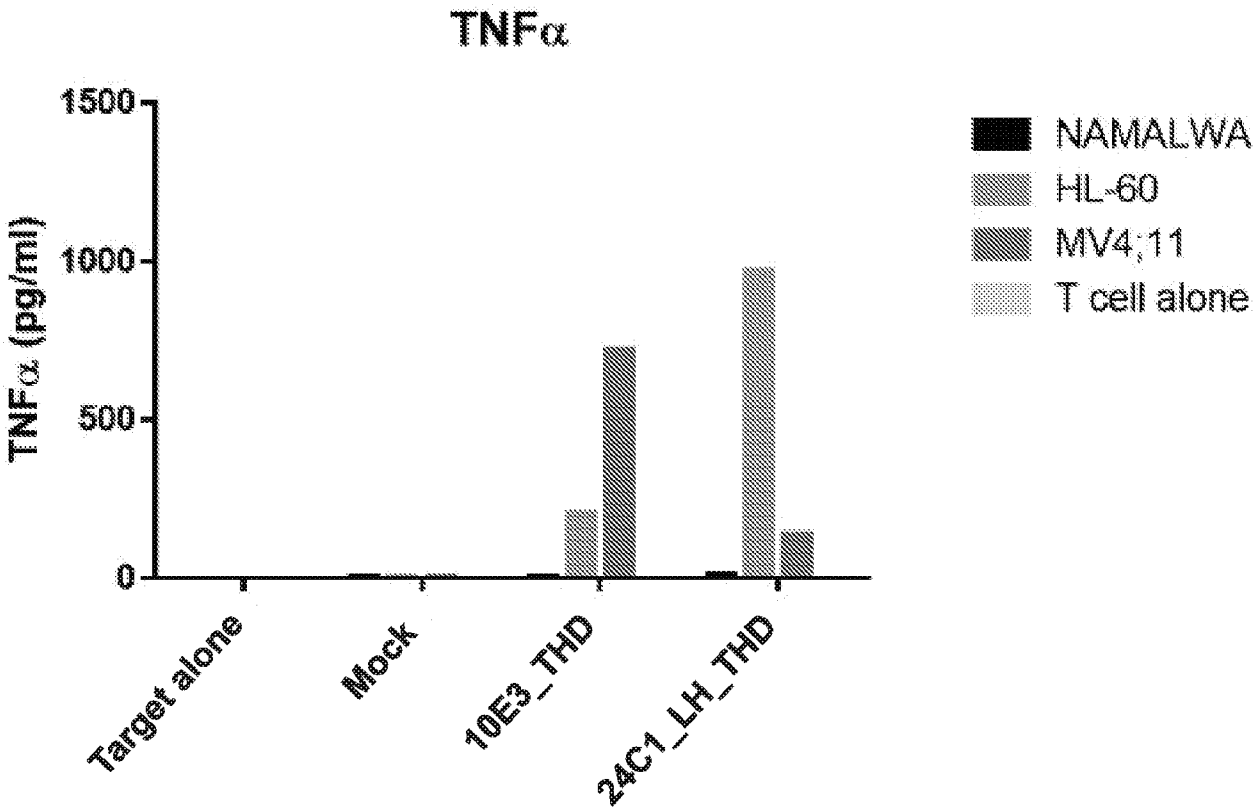

TNFα
1500
1000
500
0
TNFα (pg/ml)
Target alone
Mock
10E3_THD
24C1_LH_THD
NAMALWA
HL-60
MV4;11
T cell alone

FIG. 15A

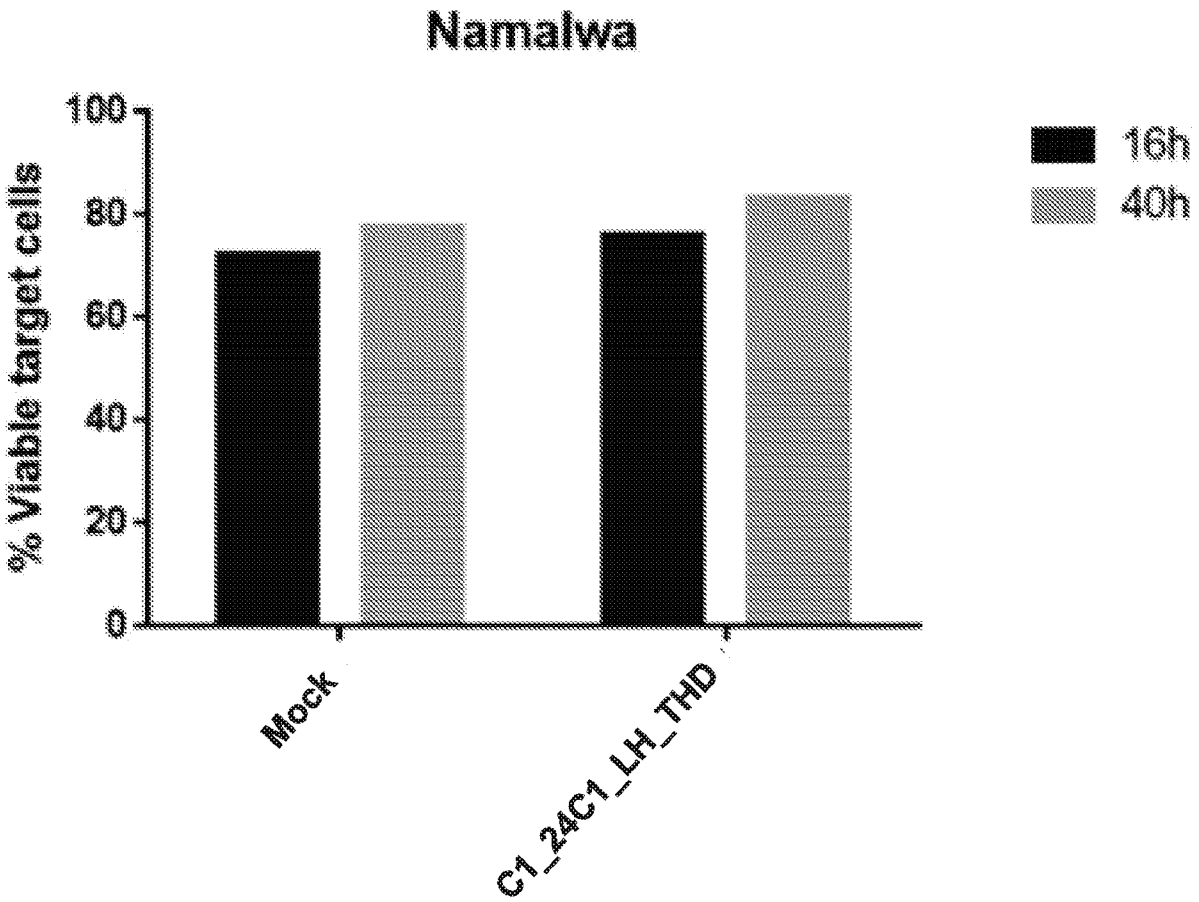

Namalwa
% Viable target cells
100
80
60
40
20
0
16h
40h
Mock
C1_24C1_LH_THD

FIG. 15B

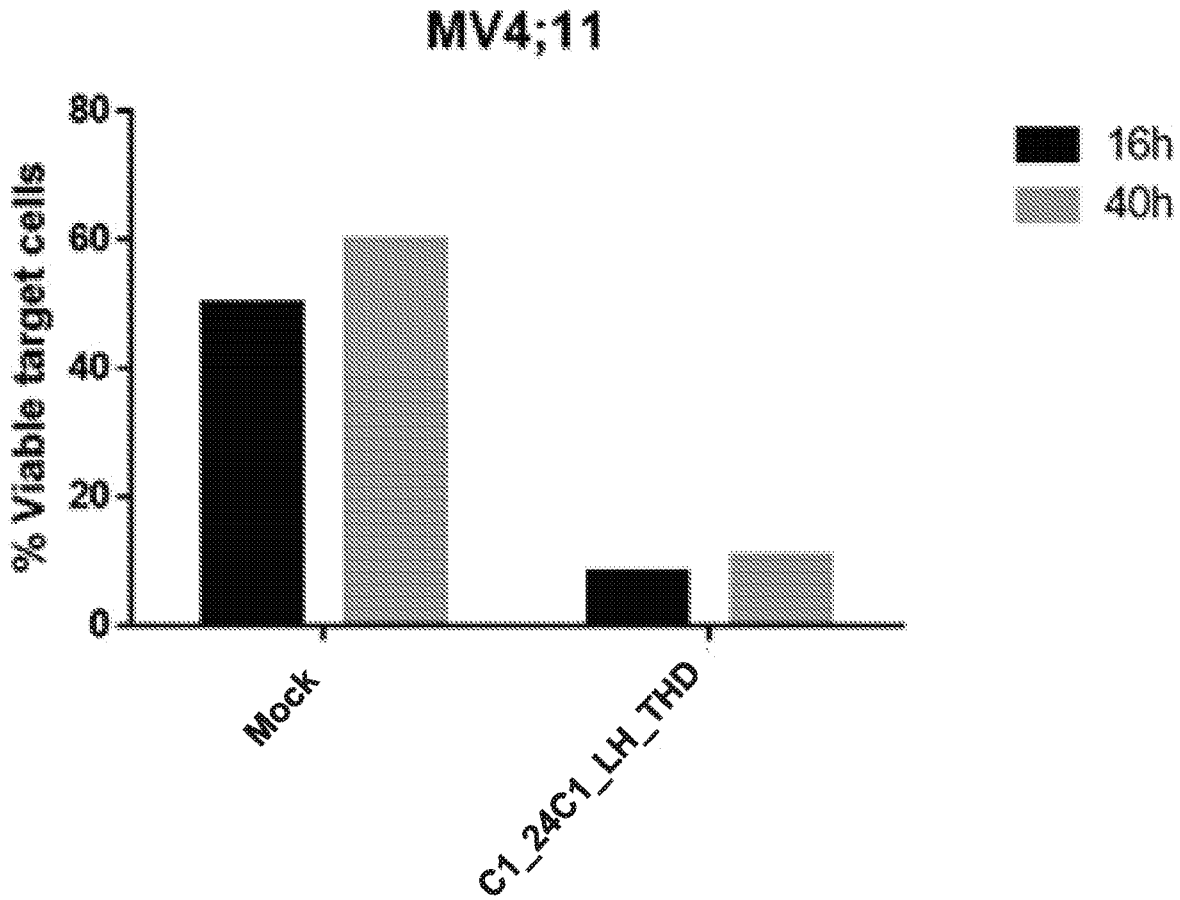

MV4;11
% Viable target cells
80
60
40
20
0
16h
40h
Mock
C1_24C1_LH_THD

FIG. 15C

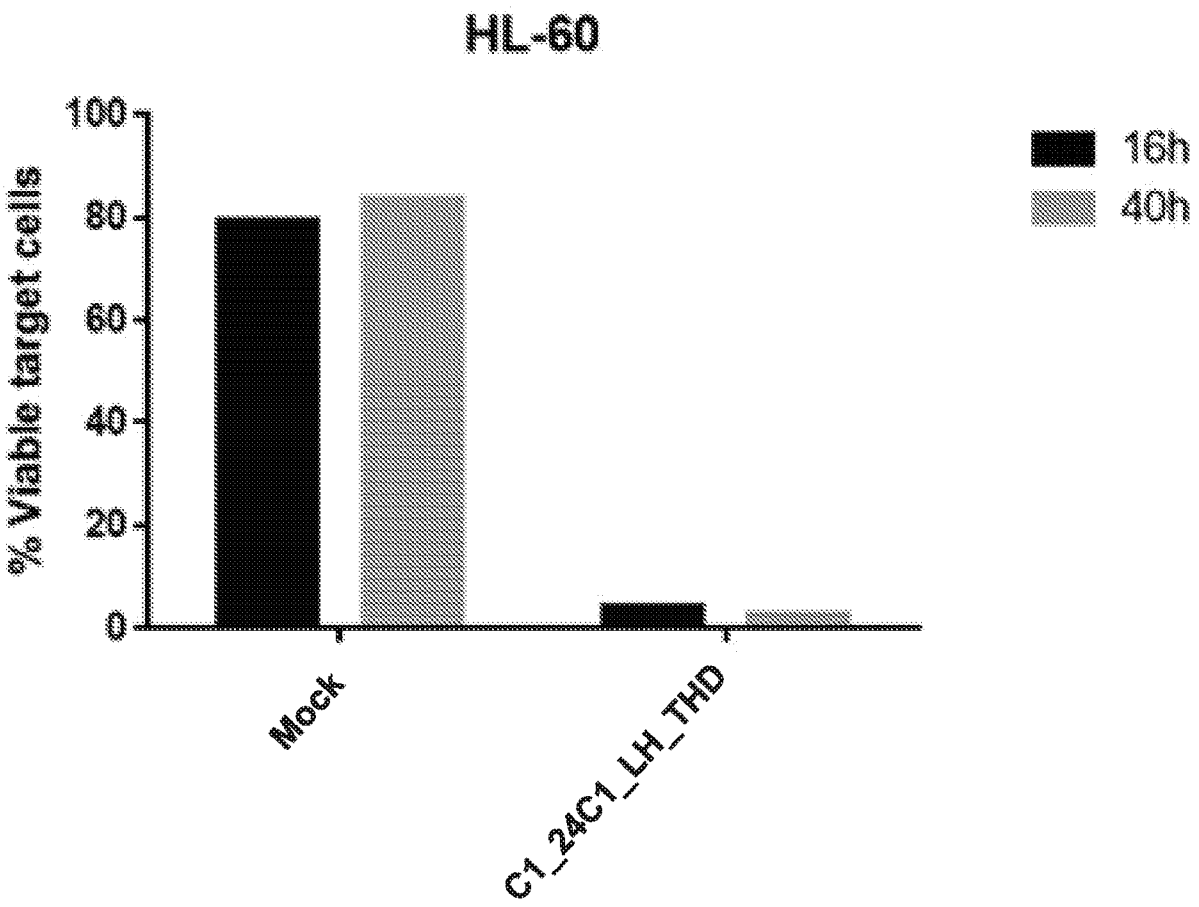

HL-60
% Viable target cells
100
80
60
40
20
0
16h
40h
Mock
C1_24C1_LH_THD

FIG. 16A

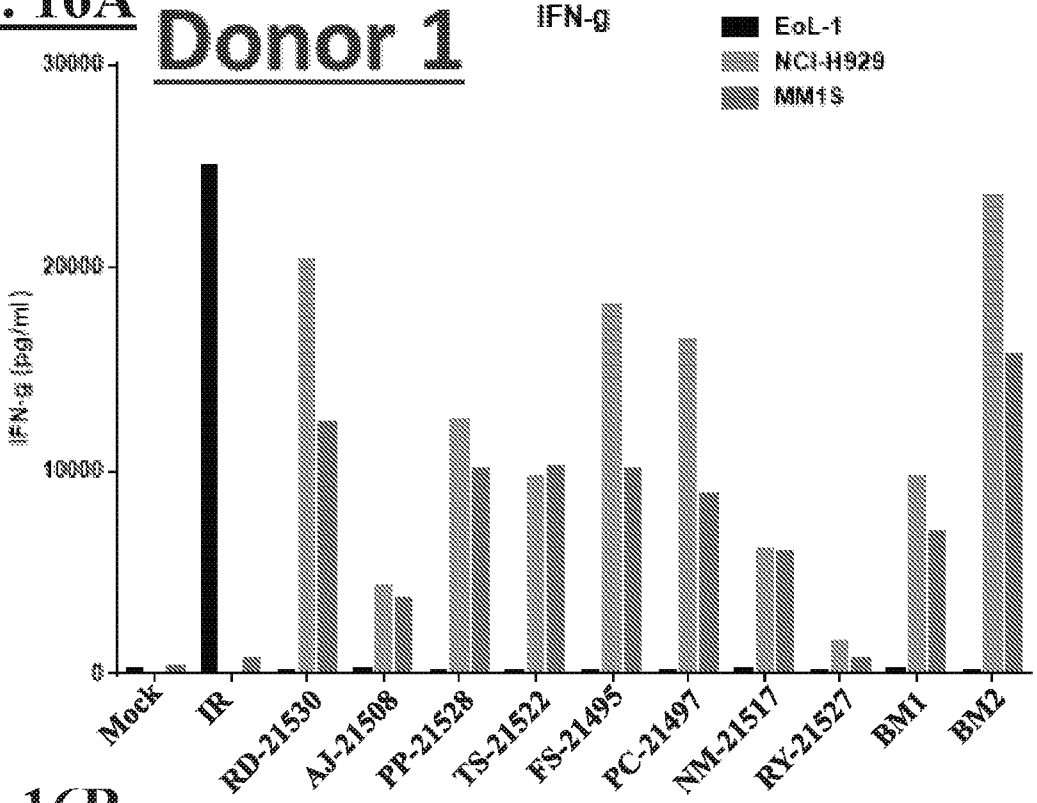


FIG. 16B

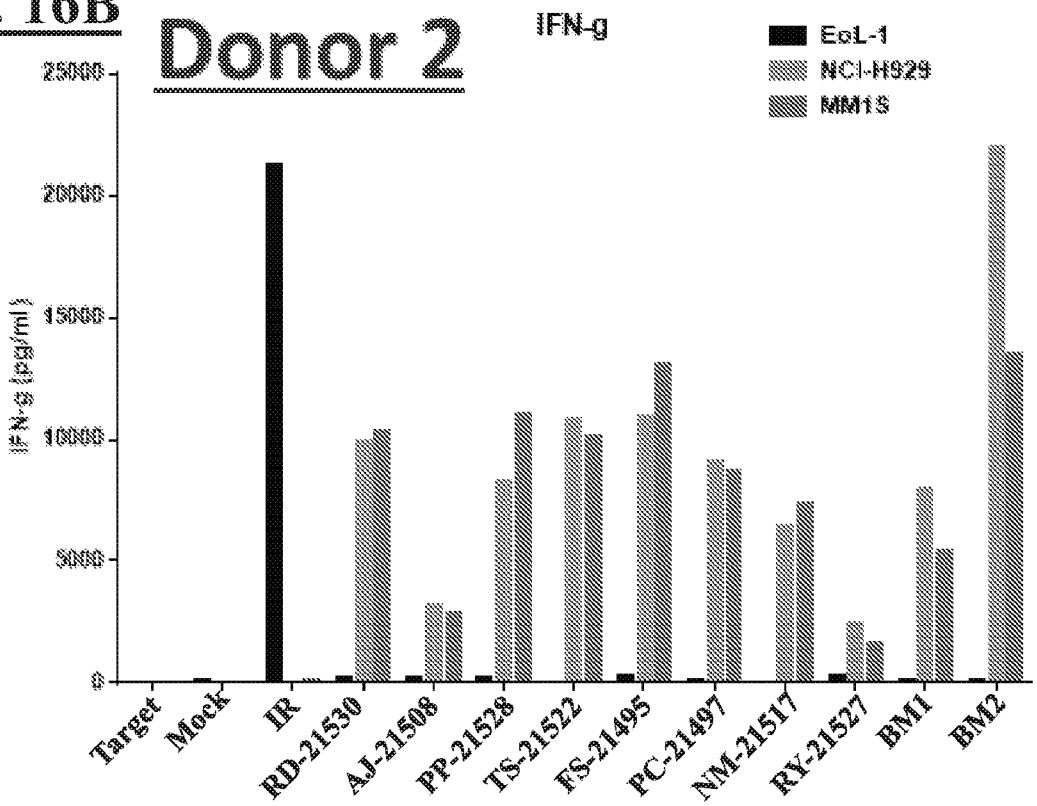


FIG. 16C

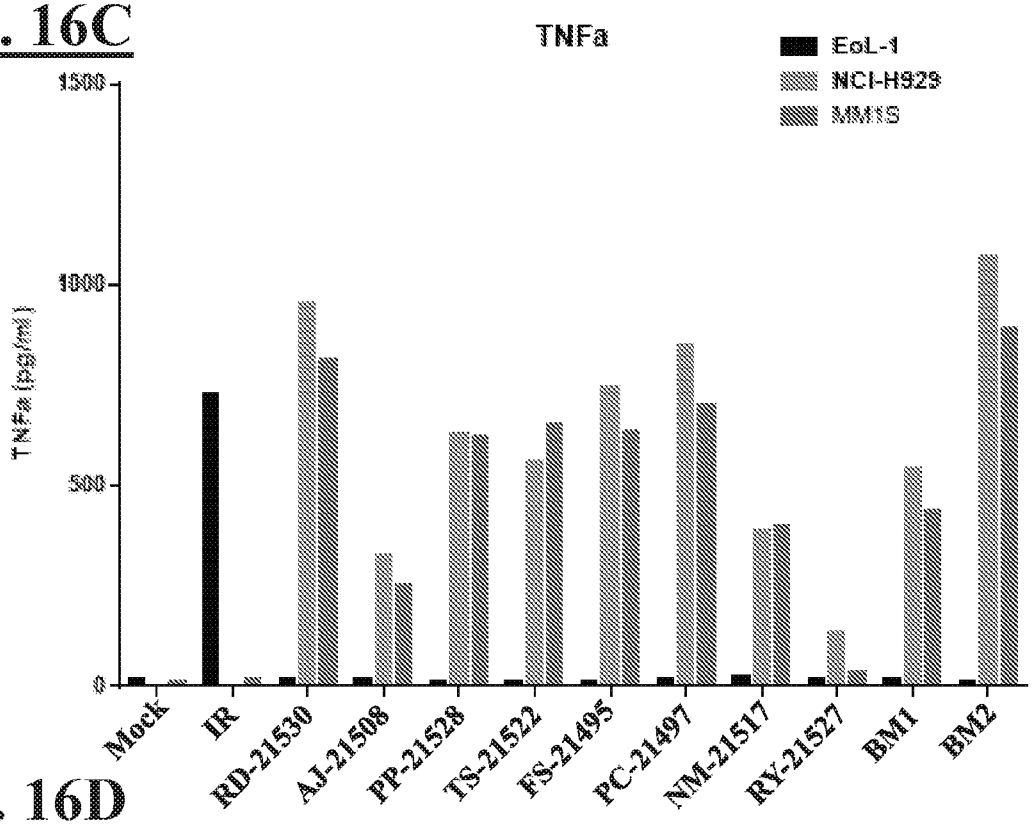


FIG. 16D

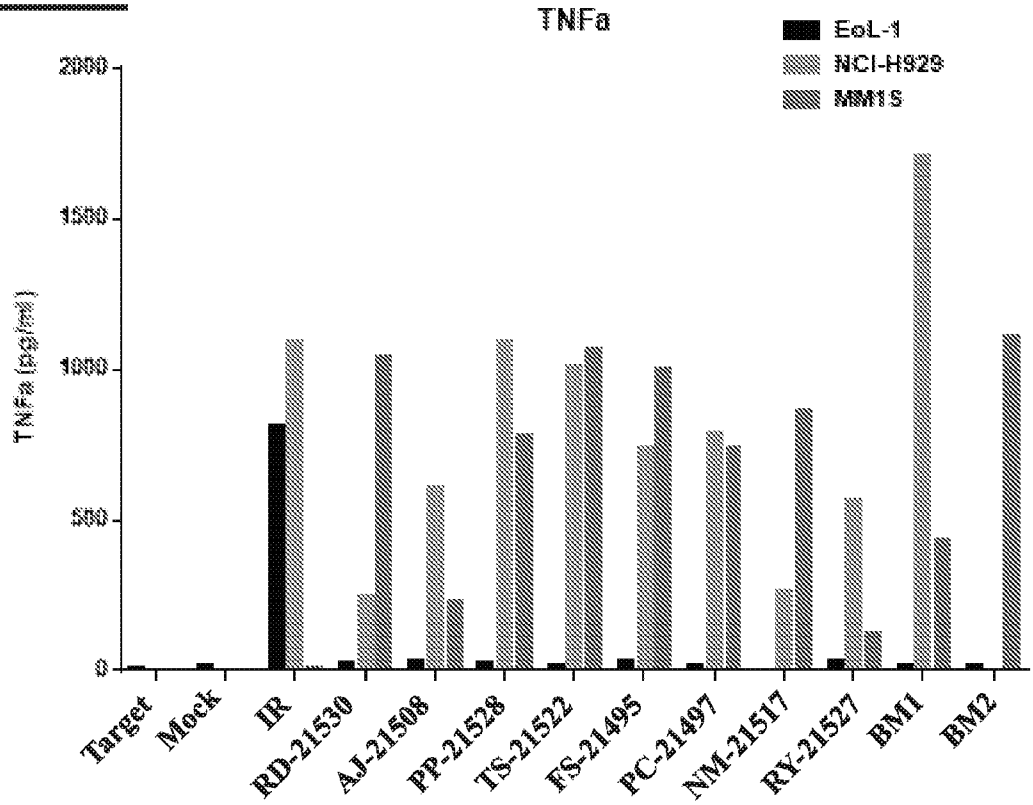


FIG. 16E

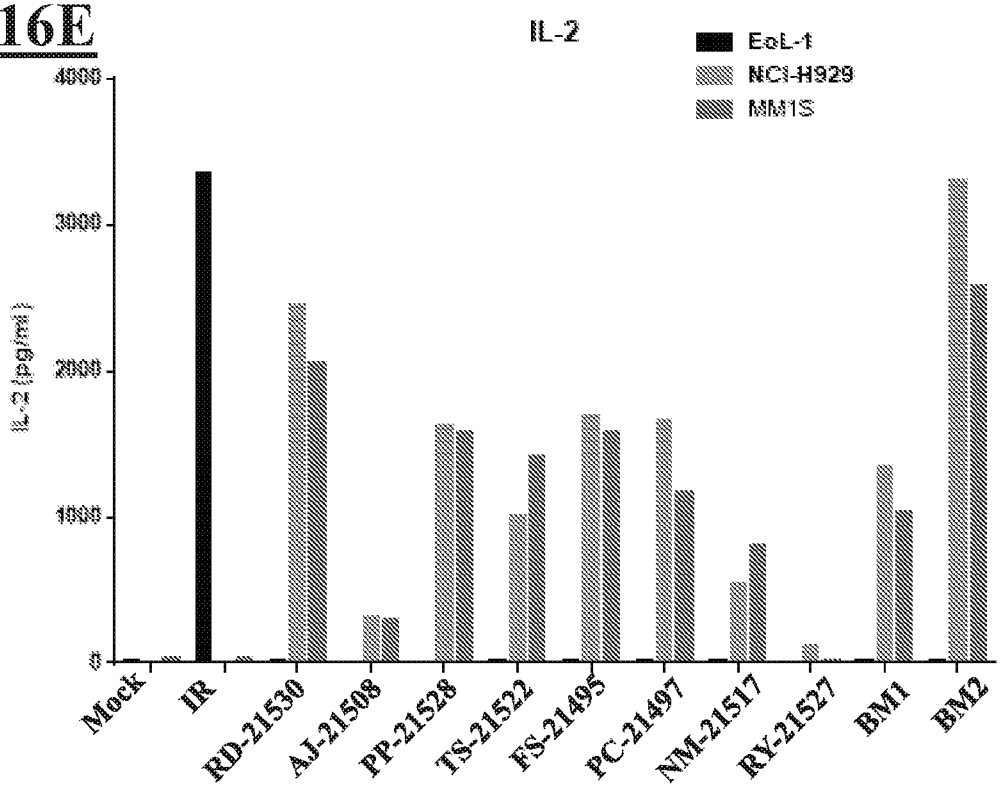


FIG. 16F

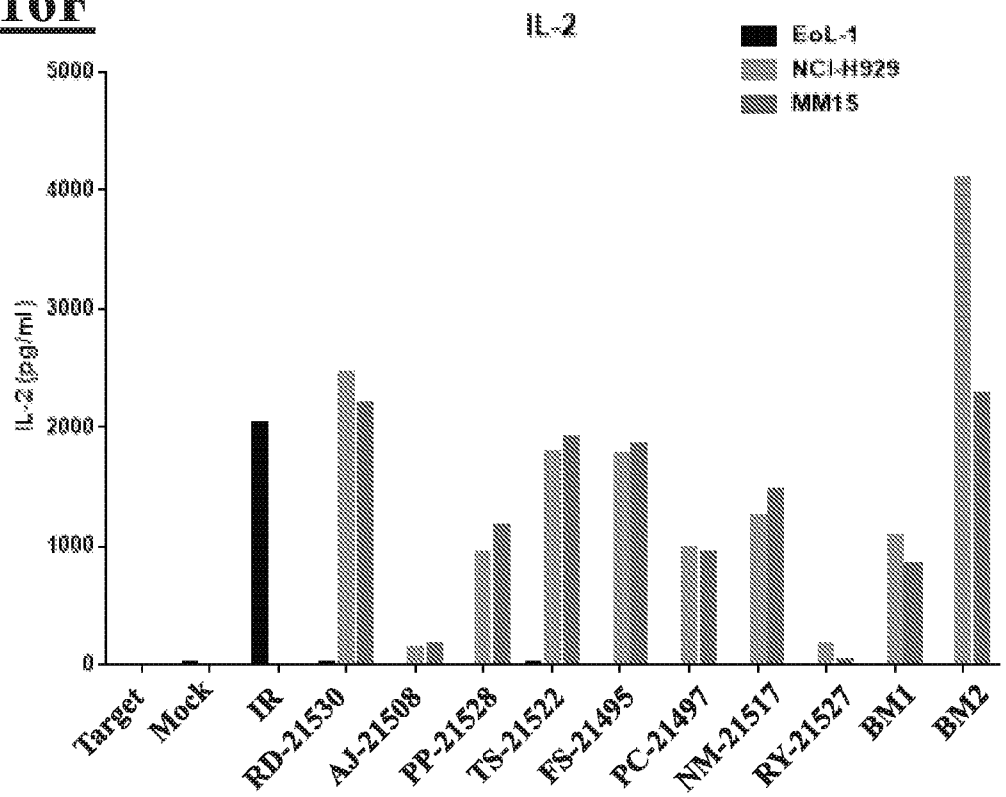


FIG. 17A

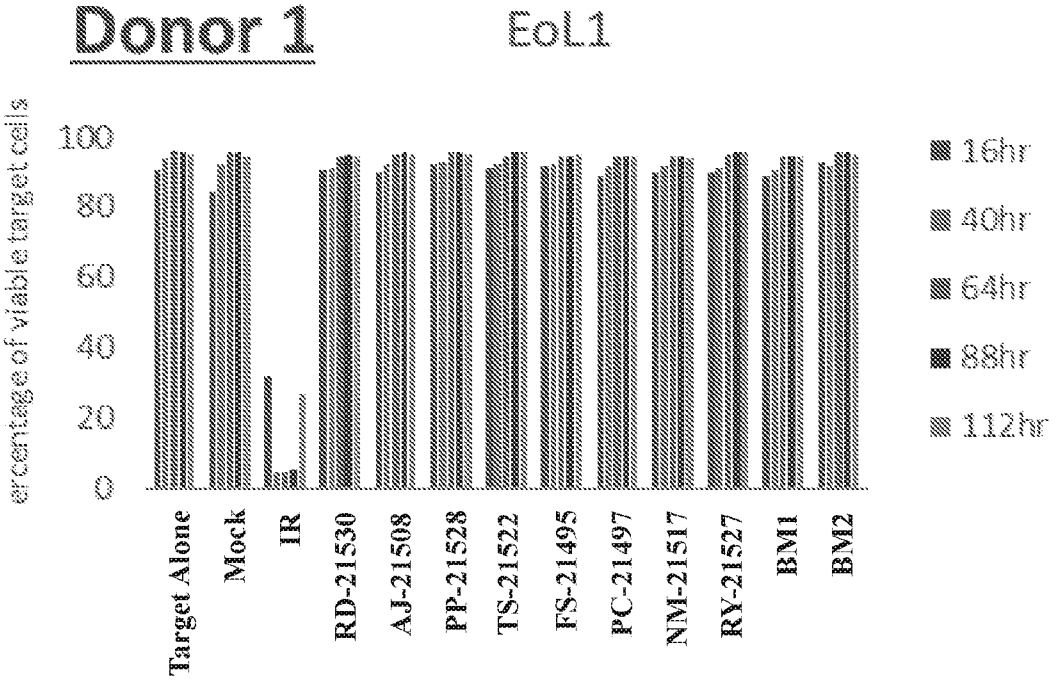


FIG. 17B

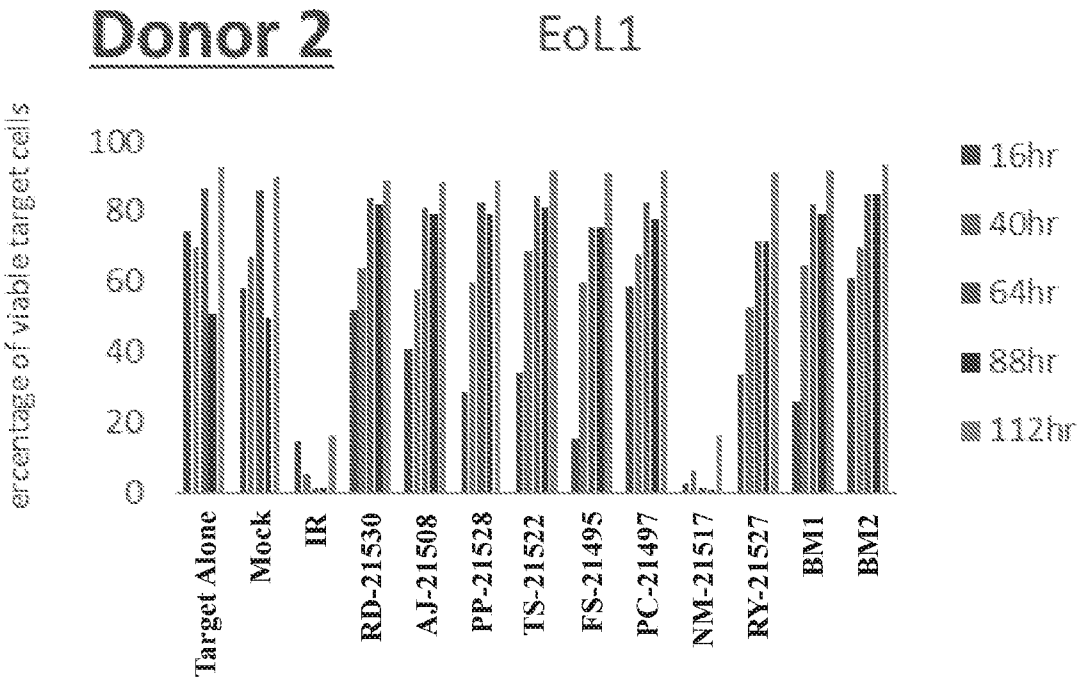


FIG. 17C

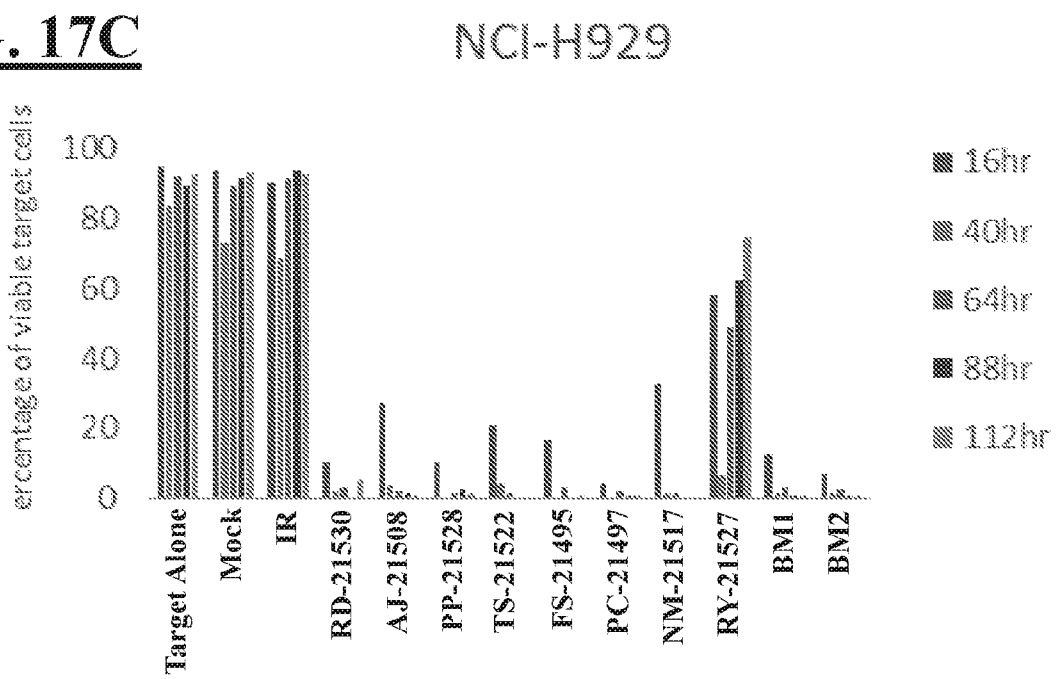


FIG. 17D

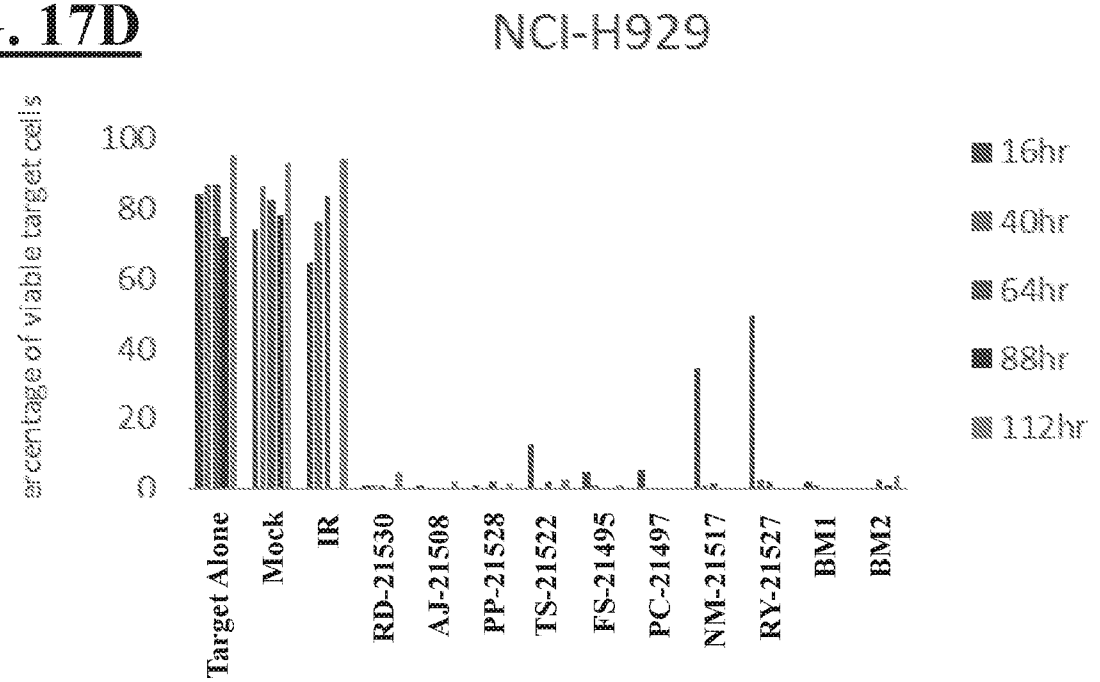


FIG. 17E

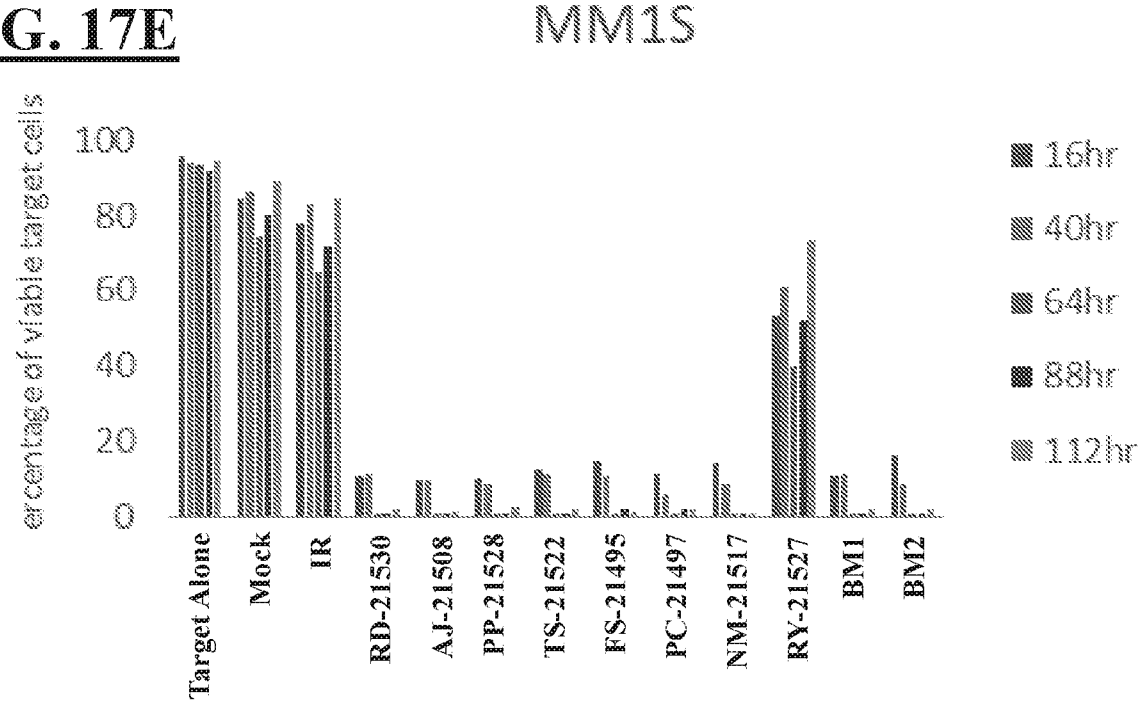
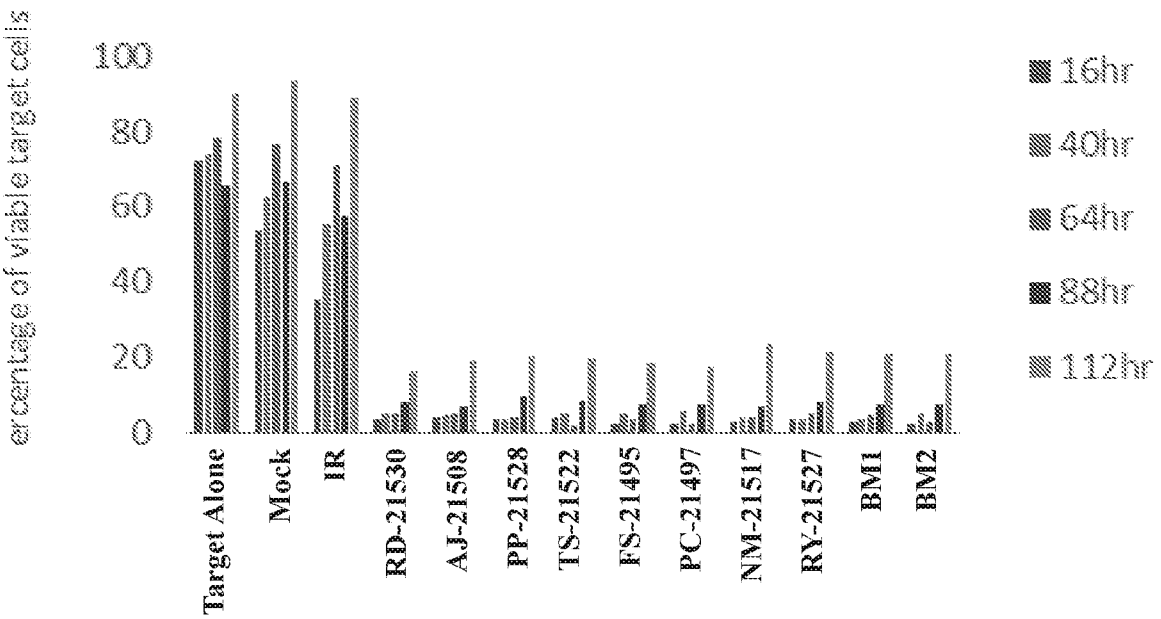


FIG. 17F



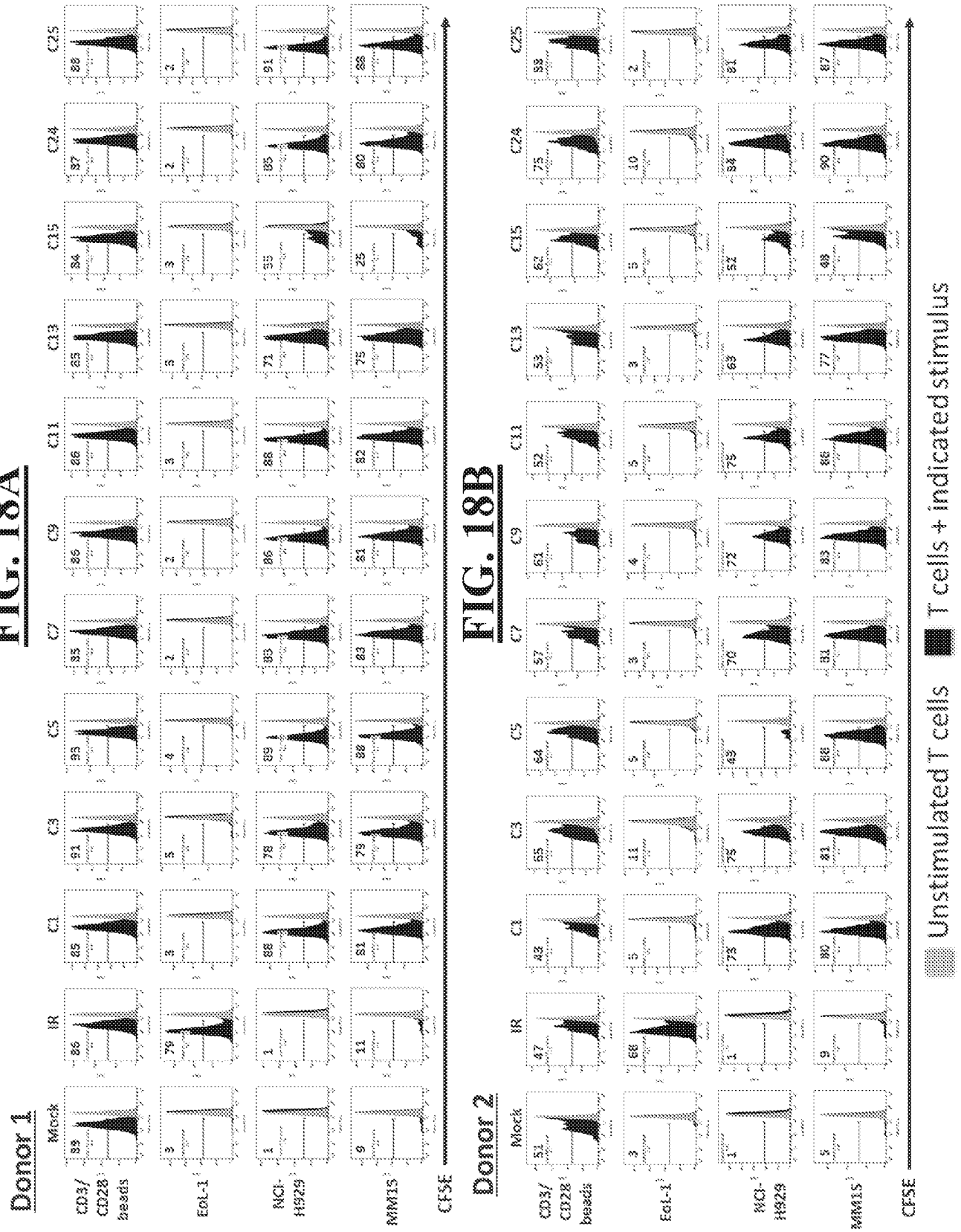

Donor 1
Mock
IR
C1
C3
C5
C7
C9
C11
C13
C15
C24
C25
CD3/CD28 beads
EoL-1
NCI-H929
MM1S
CFSE
FIG. 18A
Donor 2
Unstimulated T cells
T cells + indicated stimulus
FIG. 18B

FIG. 19A

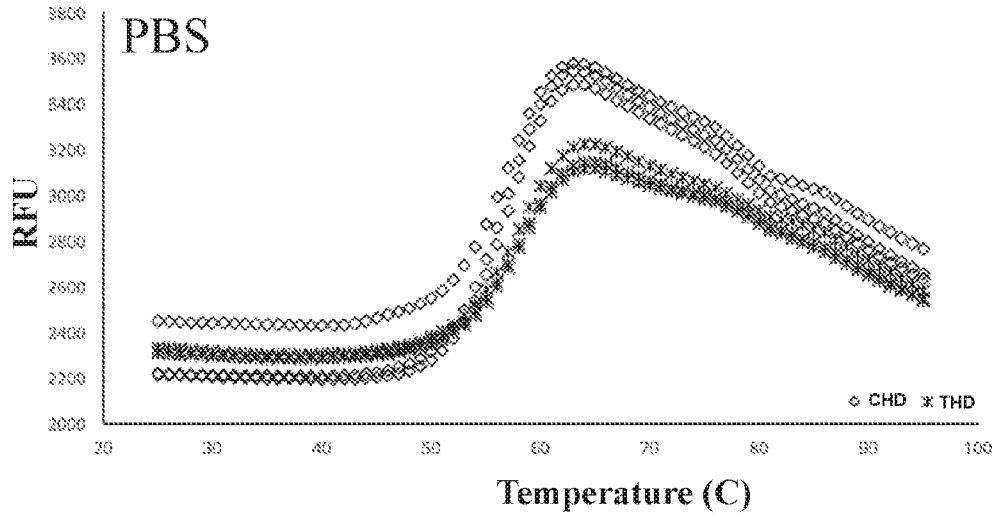


FIG. 19B

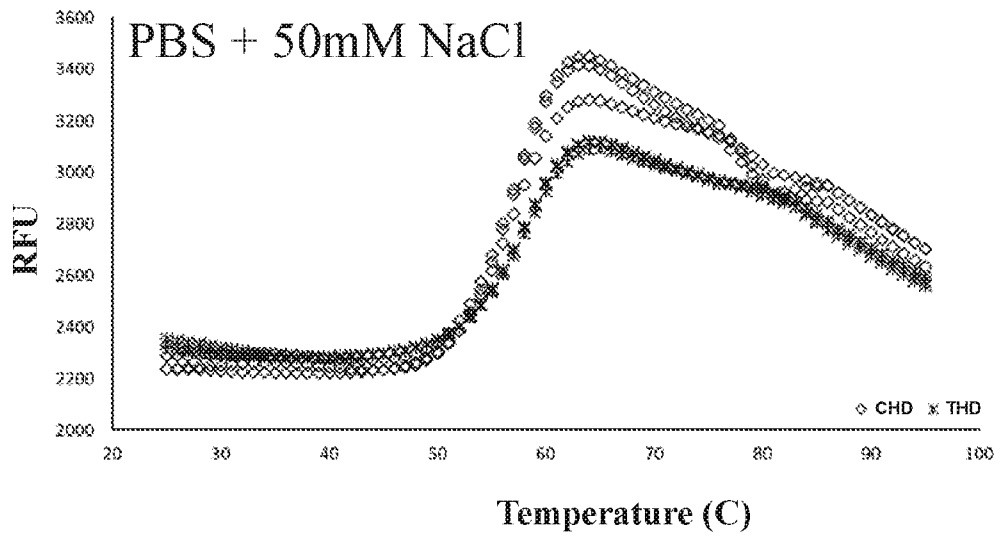


FIG. 1B