

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.

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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.

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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.

5 [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.

10 [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.*,
15 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
20 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
25 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
30 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.

5 **[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), CD11a, CD11b, CD11c, CD11d, 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, ITGB1, 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 (CD11a/CD18), MHC class I molecule, NKG2C, NKG2D, NKp30, NKp44, NKp46, NKp80 (KLRP1), 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, a Toll ligand receptor, TRANCE/RANKL, VLA1, or VLA-6, or a combination thereof.

5 **[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
10 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.

15 **[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 gp120, IL-11Ralpha, kappa chain, lambda chain, melanoma-associated antigen, mesothelin, MUC-1, mutated p53, mutated ras, prostate-specific antigen, ROR1, or VEGFR2, or a combination thereof.
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[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
30 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.

5 [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.

10 [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
15 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
20 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.

25 [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.

30 [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.

5 **[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
10 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
15 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.

20 **[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
25 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
30 lymphoma, monoclonal gammopathy 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 IFN γ , IL-2, and TNF α 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 IFN γ 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 TNF α 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 IFN γ (FIGs. 7A-7B), TNF α (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.

5 [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 intra-venous 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.

15 [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), IFN γ (FIG. 12B), and TNF α (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.

20 [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. IFN γ (FIG. 14A), IL-2 (FIG. 14B), and TNF α (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.

30 [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 IFN γ , TNF α , 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 IFN γ (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 TNF α (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
5 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
10 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.*, $\pm 10\%$). Thus, “about” can be understood to be within 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, 0.05%,
15 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
20 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
30 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.

5 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, 10 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 15 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, an antibody can comprise 20 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 25 chain constant region 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 30 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

- 5 **[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
- 10 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
- 15 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., IgG₁, IgG₂, IgG₃ and IgG₄.

[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 1×10^{-7} M. In some embodiments, the antigen binding molecule specifically binds an antigen with “high affinity” when the K_d is about 1×10^{-9} M to about 5×10^{-9} M. In some embodiments, the antigen binding molecule specifically binds an antigen with “very high affinity” when the K_d is 1×10^{-10} M to about 5×10^{-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 1×10^{-5} . In other embodiments, the antigen binding molecule binds human BCMA with a K_d of between about 1×10^{-7} M and about 1×10^{-13} M. In yet another embodiment, the antigen binding molecule binds human BCMA with a K_d of about 1×10^{-10} M to about 5×10^{-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
5 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
10 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
15 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),
20 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
25 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
30 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 1 α (MIP-1 α , MIP-1a), MIP-1 β (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

5 ((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

10 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

15 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

20 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

25 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,

30 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 malignancies, 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.

5 [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.

10 [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
15 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
20 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
25 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
30 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, BAFR, 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, CD40, CD49a, CD49D, CD49f, CD5, CD64, CD69, CD7, CD80, CD83 ligand, CD84, CD86, CD8alpha, CD8beta, CD9, CD96 (Tactile),

CDI-1a, CDI-1b, CDI-1c, CDI-1d, CDS, CEACAM1, CRT AM, DAP-10, DNAM1 (CD226), Fc gamma receptor, GADS, GTR, 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, ITGB1, KIRDS2, LAT, LFA-1, LFA-1, 5 LIGHT, LIGHT (tumor necrosis factor superfamily member 14; TNFSF14), LTBR, Ly9 (CD229), lymphocyte function-associated antigen-1 (LFA-1 (CD11a/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, 10 SLP-76, TNF, TNF α , 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 15 “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 20 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, 25 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 30 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 $\pm$ one amino acid, $\pm$ two amino acids, $\pm$ three amino acids, $\pm$ four amino acids, $\pm$ five amino acids, or $\pm$ 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.
- 15 [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 CTTGATAATGAAAAGTCAAACGGAACAATCATTACGTGAAGGGCAAGCACCTC TGTCCGTCACCCTTGTTCCCTGGTCCATCCAAGCCA.
- 20 [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.
- 25 [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%,
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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), CD11a, CD11b, CD11c, CD11d, 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, ITGB1, 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; CD11a/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; Lyl08), 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 LACYSLVTV 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
ATCGCTTCACAGCCTCTGTCCCTGCGCCCAGAGGCTTGCCGACCGGCCGAGGGG
GCGCTGTTTCATACCAGAGGACTGGATTTGCGCTGCGATATCTATATCTGGGCACC
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%,
 5 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
 10 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
 15 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
 20 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), CD11a, CD11b, CD11c, CD11d, 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, ITGB1, 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; CD11a/CD18), MHC class 1 molecule, NKG2C, NKG2D, NKp30, NKp44, NKp46, NKp80 (KLRP1), OX-40,
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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:
 RSKRSRLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS.

[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:
 CTTGATAATGAAAAGTCAAACGGAACAATCATTACGTGAAGGGCAAGCACCTC
 TGTCCTGTCACCCTTGTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTAGT
 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:
	LDNEKSNGTIIHVKGKHLCPSP	LPGPSKPFWVLVVVG	VLACYSLLVTVAFIHFWVR	
	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:
RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPPEMGGKPRRKNPQ
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:

RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPPEMGGKPRRKNPQ
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
 5 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
 10 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,
 15 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,
 20 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 (IGF1)-I, intestinal carboxyl esterase, kappa chain,
 25 LAGA-Ia, 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,
 30 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 AI 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
5 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
10 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
20 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
25 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
30 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 from 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 from 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.

10 **[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 from 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 from the group consisting of SEQ ID NOs: 121-124.

20 **[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
 5 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
 10 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.*,
 15 human BCMA, human FLT3, or human CLL-1) with a K_D of less than 1×10^{-6} M, less than 1×10^{-7} M, less than 1×10^{-8} M, or less than 1×10^{-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 1×10^{-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 1×10^{-8} M. In some embodiments, the antigen binding molecule binds a target antigen (*e.g.*,
 20 human BCMA, human FLT3, or human CLL-1) with a K_D of about 1×10^{-7} M, about 2×10^{-7} M, about 3×10^{-7} M, about 4×10^{-7} M, about 5×10^{-7} M, about 6×10^{-7} M, about 7×10^{-7} M, about 8×10^{-7} M, about 9×10^{-7} M, about 1×10^{-8} M, about 2×10^{-8} M, about 3×10^{-8} M, about 4×10^{-8} M, about 5×10^{-8} M, about 6×10^{-8} M, about 7×10^{-8} M, about 8×10^{-8} M, about 9×10^{-8} M, about 1×10^{-9} M, about 2×10^{-9} M, about 3×10^{-9} M, about 4×10^{-9} M, about 5×10^{-9} M, about 6×10^{-9} M, about 7×10^{-9} M, about 8×10^{-9} M, about 9×10^{-9} M, about 1×10^{-10} M, or about 5×10^{-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,
 30 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 $1 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$, less than $2 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$, less than $3 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$, less than $4 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$, less than $5 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$, less than $6 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$, less than $7 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$, less than $8 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$, less than $9 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$, less than $1 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$, less than $2 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$, less than $3 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$, less than $4 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$, less than $5 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$, less than $6 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$, less than $7 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$, less than $8 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$, less than $9 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$, less than $1 \times 10^{-6} \text{ M}^{-1} \text{ s}^{-1}$, less than $2 \times 10^{-6} \text{ M}^{-1} \text{ s}^{-1}$, less than $3 \times 10^{-6} \text{ M}^{-1} \text{ s}^{-1}$, less than $4 \times 10^{-6} \text{ M}^{-1} \text{ s}^{-1}$, less than $5 \times 10^{-6} \text{ M}^{-1} \text{ s}^{-1}$, less than $6 \times 10^{-6} \text{ M}^{-1} \text{ s}^{-1}$, less than $7 \times 10^{-6} \text{ M}^{-1} \text{ s}^{-1}$, less than $8 \times 10^{-6} \text{ M}^{-1} \text{ s}^{-1}$, less than $9 \times 10^{-6} \text{ M}^{-1} \text{ s}^{-1}$, or less than $1 \times 10^{-7} \text{ M}^{-1} \text{ s}^{-1}$. 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 a dissociation rate (k_{off}) of less than $1 \times 10^{-2} \text{ s}^{-1}$, less than $2 \times 10^{-2} \text{ s}^{-1}$, less than $3 \times 10^{-2} \text{ s}^{-1}$, less than $4 \times 10^{-2} \text{ s}^{-1}$, less than $5 \times 10^{-2} \text{ s}^{-1}$, less than $6 \times 10^{-2} \text{ s}^{-1}$, less than $7 \times 10^{-2} \text{ s}^{-1}$, less than $8 \times 10^{-2} \text{ s}^{-1}$, less than $9 \times 10^{-2} \text{ s}^{-1}$, less than $1 \times 10^{-3} \text{ s}^{-1}$, less than $2 \times 10^{-3} \text{ s}^{-1}$, less than $3 \times 10^{-3} \text{ s}^{-1}$, less than $4 \times 10^{-3} \text{ s}^{-1}$, less than $5 \times 10^{-3} \text{ s}^{-1}$, less than $6 \times 10^{-3} \text{ s}^{-1}$, less than $7 \times 10^{-3} \text{ s}^{-1}$, less than $8 \times 10^{-3} \text{ s}^{-1}$, less than $9 \times 10^{-3} \text{ s}^{-1}$, less than $1 \times 10^{-4} \text{ s}^{-1}$, less than $2 \times 10^{-4} \text{ s}^{-1}$, less than $3 \times 10^{-4} \text{ s}^{-1}$, less than $4 \times 10^{-4} \text{ s}^{-1}$, less than $5 \times 10^{-4} \text{ s}^{-1}$, less than $6 \times 10^{-4} \text{ s}^{-1}$, less than $7 \times 10^{-4} \text{ s}^{-1}$, less than $8 \times 10^{-4} \text{ s}^{-1}$, less than $9 \times 10^{-4} \text{ s}^{-1}$, less than $1 \times 10^{-4} \text{ s}^{-1}$, or less than $5 \times 10^{-4} \text{ s}^{-1}$. 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.

10 **[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
15 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	ATGGCACTCCCCGTAACCTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTGACCCTCAAAGAGTCTGGA CCCGTGCTCGTAAACCTACGGAGACCCT GACACTCACCTGCACAGTCTCCGGCTTCA GCCTCATCAATGCCAGGATGGGAGTTTCC TGGATCAGGCAACCGCCCGAAAGGCCCT GGAATGGCTCGCACATATTTTCAGTAACG CTGAAAAAGCTATCGGACTTCTCTGAAA AGTCGGCTCACGATTAGTAAGGACACATC CAAGAGCCAAGTGGTGCTTACGATGACTA ACATGGACCCTGTGGATACTGCAACCTAT TACTGTGCTCGAATCCCTGGTTATGGCGG AAATGGGGACTACCACTACTACGGTATGG ATGTCTGGGGCCAAGGGACACGGTTACT GTTTCAAGCGGAGGGGGAGGGAGTGGGGG TGGCGGATCTGGCGGAGGAGGCAGCGATA TCCAGATGACGCACTCCCTAGTTCACCT TCCGCATCCCTGGGGGATCGGGTTACCAT TACATCGCGCGCTCACAGGTATCCGGA ATGATCTGGGATGGTACCAGCAGAAGCCG GGAAAGGCTCCTAAGCGCCTCATCTACGC CAGCTCCACCTGCAGAGTGGAGTGCCCT CCCGGTTTTTCAGGCAGTGGCTCCGGTACG GAGTTTACTCTTACAATTAGCAGCCTGCA GCCAGAAGATTTTGAACCTACTACTGTT	242	MALPVTALLLPLALLL HAARPQVTLKESGPVL VKPTETLTLTCTVSGF SLINARMGVSWIRQPP GKALEWLAHIFSNAEK SYRTSLKSRLTISKDT SKSQVVLTMNMDPVD TATYYCARIPGYGGNG DYHYGMDVWVGQGTTV TVSSGGGGSGGGSGG GGSDIQMTQSPSSLSA SLGDRVITTCRASQGI RNDLGWYQQKPGKAPK RLIYASSTLQSGVPSR FSGSGSGTEFTLTISS LQPEDFATYYCLQHN FPWTFGQGTKVEIKRA AAIEVMYPPPYLDNEK SNGTIIHVKGKHLCP PLFPGSKFQFVLV GGVLACYSLLVTVAFI IFWVRSKRSRLHSDY MNMTPRRPGPTRKHYQ PYAPPRDFAAYSRVK FSRSDAPAYQGQNO LYNELNLGRREYDVL	243

	<p>TGCAGCATAATAATTTCCCTGGACCTTT GGTCAGGGCACCAAGGTGGAGATCAAAAG AGCAGCCGCCATCGAAGTAATGTATCCCC CCCCGTACCTTGACAATGAGAAGTCAAAT GGAACCATTTATCCATGTTAAGGGCAAACA CCTCTGCCCTTCTCCACTGTTCCCTGGCC CTAGTAAGCCGTTTTGGGTGCTGGTGGTA GTCCGTGGGGTGCTGGCTTGTACTCTCT TCTCGTGACCGTCGCCCTTTATAATCTTTT GGGTGAGATCCAAAAGAAGCCGCCTGCTC CATAGCGATTACATGAATATGACTCCACG CCGCCCTGGCCCCACAAGGAAACACTACC AGCCTTACGCACCACCTAGAGATTTTCGCT GCCTATCGGAGCCGAGTGAAATTTTCTAG ATCAGCTGATGCTCCCGCTATCAGCAGG GACAGAATCAACTTTACAATGAGCTGAAC CTGGGTGCGAGAGAAGGTACGACGTTTT GGACAAACGCCGGGGCCGAGATCCTGAGA TGGGGGGGAAGCCGAGAAGGAAGAATCCT CAAGAAGGCCTGTACAACGAGCTTCAAAA AGACAAAATGGCTGAGGCGTACTCTGAGA TCGGCATGAAGGGCGAGCGAGACGAGGC AAGGGTCACGATGGCTTGTATCAGGGCCT GAGTACAGCCACAAGGACACCTATGACG CCCTCCACATGCAGGCACTGCCCCCACGC TAG</p>		<p>DKRRGRDPEMGGKPRR KNPQEGLYNELQKDKM AEAYSEIGMKGERRRG KGHDGLYQGLSTATKD TYDALHMQALPPR</p>	
10E3_THD	<p>ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAAGTTACTTTGAAGGAGTCTGGA CCTGTACTGGTGAAGCCAACCGAGACACT GACACTCACGTGTACAGTGAGTGGTTTTT CCTTGATCAACGCAAGGATGGGCGTCAGC TGGATCAGGCAACCCCTGGCAAGGCTCT GGAATGGCTCGCTCACATATTCAGCAATG CCGAAAAAGCTACCGGACAAGCCTGAAA TCCCGCTGACTATTTCCAAGGACACTTC TAAGTCTCAGGTGGTGCTGACCATGACCA ACATGGACCCGGTGGACACCGCCACCTAT TACTGCGCAAGAATCCCTGGGTATGGTGG GAATGGTGACTACCATTTATGAGGATGG ATGTGTGGGGGCAAGGCACAACCGTAACG GTCTCAAGCGGTGGGGGAGGCTCAGGGGG CGGAGGCTCCGGAGGTGGCGGCTCCGACA TTCAGATGACCCAAAGCCCGTCCAGCCTG TCCGCCAGCCTGGGAGATAGAGTGACAAT CACGTGTAGAGCTTCCCAAGGGATAAGAA ATGATCTCGGGTGGTATCAGCAGAAGCCC GGCAAAGCCCCAAAAGGCTTATATATGC TAGTAGTACACTGCAGTCTGGAGTTCCTT CCCGATTTTCAGGTAGCGGCTCCGGTACA GAGTTCACCTCACGATAAGCTCACTCCA GCCTGAGGATTTGCAACGTACTACTGCC TCCAGCACACAATTTTCCCTGGACTTTC GGCCAGGGCACCAAGGTGGAGATCAAGAG GGCCGCTGCCCTTGATAATGAAAAGTCAA ACGGAACAATCATTACGTGAAGGGCAAG CACCTCTGTCCGTACCCCTGTTCCCTGG TCCATCCAAGCCATTCTGGGTGTTGGTCG TAGTGGGTGGAGTCCTCGCTTGTACTCT</p>	244	<p>MALPVTALLPLALLL HAARPQVTLKESGPVL VKPTETLTLTCTVSGF SLINARMGVSWIRQPP GKALEWLAHIFSNAEK SYRTSLKSRLTISKDT SKSQVVLTMNMDPVD TATYYCARIPGYGGNG DYHYYGMDVWQGTTV TVSSGGGGSGGGSGG GGSDIQMTQSPSSLSA SLGDRVTTICRASQGI RNDLGWYQQKPGKAPK RLIYASSTLQSGVPSR FSGSGSGTEFTLTIS LQPEDFATYYCLQHNN FPWTFGQGTKVEIKRA AALDNEKSNGTIIHVK GKHLCPSPLPFGPSKP FWVLVVVGGVLACYSL LVTVAFIIFWVRSKRS RLHSDYMNMTPRRPG PTRKHYQPYAPPRDFA AYRSRVKFSRSADAPA YQQGQNQLYNELNLGR REEYDVLDKRRGRDPE MGGKPRRKNPQEGLYN ELQKDKMAEAYSEIGM KGERRRGKGHDGLYQG LSTATKDTYDALHMQA LPPR</p>	245

	CTGCTCGTCACCGTGGCTTTTATAATCTT CTGGGTTAGATCCAAAAGAAGCCGCCTGC TCCATAGCGATTACATGAATATGACTCCA CGCCGCCCTGGCCCCACAAGGAAACACTA CCAGCCTTACGCACCACCTAGAGATTTGCG CTGCCTATCGGAGCCGAGTGAAATTTTCT AGATCAGCTGATGCTCCCGCTATCAGCA GGGACAGAATCAACTTTACAATGAGCTGA ACCTGGGTCGCAGAGAAGGTACGACGTT TTGGACAAAACGCCGGGGCCGAGATCCTGA GATGGGGGGGAAGCCGAGAAGGAAGAATC CTCAAGAAGGCCTGTACAACGAGCTTCAA AAAGACAAAATGGCTGAGGCGTACTCTGA GATCGGCATGAAGGGCGAGCGGAGACGAG GCAAGGGTCACGATGGCTTGTATCAGGGC CTGAGTACAGCCACAAAGGACACCTATGA CGCCCTCCACATGCAGGCACTGCCCCAC GCTAG			
8B5_CHD	ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTTGCTCCTGCACGCCGCAC GCCCGCAGATCCAGTTGGTGAATCAGGG GGCGGTGTGGTGCAGCCGGGTAGGAGCCT GAGACTGTATGCGTGGCGTCTGGCTTCA CATTCAAGAACTACGGCATGCACTGGGTG CGACAGGCCCCCGGAAAGGGTTTGGAGTG GGTCGCCGTGATCTGGTACGACGGATCTA ATGAGTATTACGGAGATCCTGTGAAGGGA AGGTTACCATCTCCCCGACAATAGCAA AAATATGCTCTACCTGCAATGAACTCAC TCAGGGCGGATGATACGGCGGTCTACTAT TGCGCTCGCTCAGGGATTGCTGTGGCCGG CGCATTTCGATTACTGGGACAGGGTACCC TGGTGACAGTATCAAGCGAGGCGGCGGC TCTGGCGGCGCGGATCTGGCGGGGGGG AAGTGAGATTGTGTTGACACAGTCTCCCG ATACCCTGTCACTGTCAACCGGCGAGAAG GCAACGCTGAGTTGCAGAGCAAGCCAGTC AGTCTCCTCTTCTTTCTGGCCTGGTATC AGCAAAAACAGGTCAAGCACCATCTCTC CTGATTTACGTTGCCAGCAGACGGGCGGC TGGCATTCCCGACAGGTTCTCTGGAAGCG GATCTGGGACCGATTTTACCCTGACAATT AGCCGCTTGGAGCCCGAAGACTTTGGTAT GTTTTACTGCCAGCACTACGGAAGGACAC CTTTCACATTTGGCCCGGGCACGAAAGTC GATATAAAACGCGCAGCCGCCATTGAAGT AATGTACCCACCACCTTATTTGGACAATG AAAAGTCCAATGGTACCATTATTCACGTC AAGGGAAAGCATCTCTGTCCAAGCCCTCT GTTCCCCGGCCCCCTCCAACCATTCTGGG TGCTGGTGGTCTGTCGGCGGAGTTCTGGCC TGCTATTCTCTGCTCGTGACTGTTGCATT CATCATTTTCTGGGTGAGATCCAAAAGAA GCCGCTGCTCCATAGCGATTACATGAAT ATGACTCCACGCCGCCCTGGCCCCACAAG GAAACACTACCAGCCTTACGCACCACCTA GAGATTTTCGCTGCCTATCGGAGCCGAGTG AAATTTTCTAGATCAGCTGATGCTCCCGC CTATCAGCAGGGACAGAATCAACTTTACA	246	MALPVTALLPLALLL HAARPQIQLVESGGGV VQPGRLRLSCVASGF TFKNYGMHWVRQAPGK GLEWVAVIWDGSNEY YGD PVKGRFTISRDN KNMLYLQMNLSLRADD AVYYCARSGLAVAGAF DYWGQGLVTVSSGGG GSGGGSGGGGSEIVL TQSPDTLSLSPGEKAT LSCRASQSVSSSFLAW YQQKPGQAPSLLIYVA SRRAAGIPDRFSGSGS GTDFTLTISRLEPEDF GMFYCQHYGRTPTFTF PGTKVDIKRAAAIEVM YPPPYLDNEKSNGTII HVKGKHLCPSPFPGP SKPFWVLVVGVLAC YSLLVTVAFIIFWVRS KRSRLHSDYMNMTPR RPGPTRKHYPYAPPR DFAAYRSRVKFSRSAD APAYQQGQNQLYNELN LGRREEYDVLDRRGR DPEMGGKPRKPNQEG LYNELQKDKMAEAYSE IGMKGERRRGKGDGL YQGLSTATKDTYDALH MQALPPR	247

	ATGAGCTGAACCTGGGTCGCAGAGAAGAG TACGACGTTTGGACAAACGCCGGGGCCG AGATCCTGAGATGGGGGGAAGCCGAGAA GGAAGAATCCTCAAGAAGGCCTGTACAAC GAGCTTCAAAAAGACAAAATGGCTGAGGC GTACTCTGAGATCGGCATGAAGGGCGAGC GGAGACGAGGCAAGGGTCACGATGGCTTG TATCAGGGCCTGAGTACAGCCACAAAGGA CACCTATGACGCCCTCCACATGCAGGCAC TGCCCCACGCTAG			
8B5_THD	ATGGCACTCCCCGTAACCTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGATTGAGCTCGTGGAGTCAGGT GGTGGCGTGGTTCAGCCCCGACGGTCCCT GCGACTCTCTGTGTGGCAAGCGGATTTA CCTTTAAGAACTATGGCATGCACTGGGTG AGGCAGGCCCTGGAAAAGGACTGGAGTG GGTTGCTGTGATCTGGTACGACGGGTCCA ACGAATATTATGGCGATCCTGTGAAGGGA CGGTTTACAACTCTACGCGATAACTCAA GAACATGCTGTACCTGCAAATGAACTCTC TGCGCGCTGATGACACTGCCGTGTATTAT TGCGCTCGGAGTGGTATCGCCGTCGCAGG AGCATTTGATTATTGGGGGCAAGGGACCC TCGTGACAGTGAGTTCCGAGGGGGAGGT TCTGGTGGAGGCGGCTCTGGTGGGGGAGG CAGCGAGATCGTTCTGACCCAGTCTCCTG ACACACTGTCACTGTCCCCTGGTAAAAG GCCACACTGTCTGTAGAGCGTCCCAGAG CGTTTCCAGTTCCTTCCCTGTCATGGTATC AACAAAAACCCGGGCAGGCTCCAAGCTTG CTGATCTACGTGGCCAGCCGCCGGGCCGC AGGCATCCCTGATAGGTTTAGCGGTTCTG GGAGCGGGACGGACTTCACCTTGACAATA TCACGGCTGGAACCCGAAGACTTCGGAAT GTTTTATTGCCAGCACTACGGAAGAACTC CATTACCTTTGGCCCCGGAACGAAGGTA GACATCAAGAGAGCAGCAGCCCTCGACAA CGAGAAATCCAATGGAACCATATCCATG TGAAGGGGAAACATCTCTGCCCTTACCA TTGTTCCCTGGACCCAGCAAGCCTTTTTG GGTTCTGGTCTGGTGGGGGGCGTCCTGG CTTGTTACTCCCTCCTCGTTACAGTCGCC TTCATAATCTTTTGGGTTAGATCCAAAAG AAGCCGCTGCTCCATAGCGATTACATGA ATATGACTCCACGCCGCCCTGGCCCCACA AGGAAACACTACCAGCCTTACGCACCACC TAGAGATTTGCTGCCTATCGGAGCCGAG TGAAATTTCTAGATCAGCTGATGCTCCC GCCTATCAGCAGGGACAGAATCAACTTA CAATGAGCTGAACCTGGGTGCGAGAGAAG AGTACGACGTTTGGACAAACGCCGGGGC CGAGATCCTGAGATGGGGGGAAGCCGAG AAGGAAGAATCCTCAAGAAGGCCTGTACA ACGAGCTTCAAAAAGACAAAATGGCTGAG GCGTACTCTGAGATCGGCATGAAGGGCGA GCGGAGACGAGGCAAGGGTCACGATGGCT TGTATCAGGGCCTGAGTACAGCCACAAAG	248	MALPVTALLLPLALLL HAARPQIQLVESGGGV VQPGRLRLSCVASGF TFKNYGMHWVRQAPGK GLEWVAVIWDGSNEY YGDPVKGRFTISRDN KNMLYLQMNLSRADDT AVYYCARSGIAVAGAF DYWGQGLTVTVSSGGG GSGGGSGGGGSEIVL TQSPDTLSLSPGEKAT LSCRASQSVSSSFLAW YQQKPGQAPSLLIYVA SRRAGIPDRFSGSGS GTDFTLTISRLEPEDF GMFYCQHYGRTPFTFG PGTKVDIKRAALDNE KSNGTIIHVKGKHLCP SPLFPGPSKPFWVLVV VGGVLACYSLLVTVAF IIFWVRSKSRLLHSD YNMTPRRPGPTRKHY QPYAPPRDFAAYRSRV KFSRSADAPAYQQQN QLYNELNLGRREYDV LDKRRGRDPEMGGKPR RKNPQEGLYNELQKDK MAEAYSEIGMKGERRR GKGHDGLYQGLSTATK DTYDALHMQALPPR	249

	GACACCTATGACGCCCTCCACATGCAGGC ACTGCCCCACGCTAG			
FS- 21495CARHx L	ATGGCACTCCCCGTAAC TGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCCGAGGTGCAGCTGTTGGAGTCTGGG GGAGGCTTGGTACAGCCTGGGGGGTCCCT GAGACTCTCCTGTGCAGCCTCTGGATTCA CCTTTAGCAGCTATGCCATGAGCTGGGTC CGCCAGGCTCCAGGGAAGGGGCTGGAGTG GGTCTCAGCTATTAGTGGTAGTGGTGGTA GCACATACTACGCAGACTCCGTGAAGGGC CGGTTACCATCTCCAGAGACAATTCCAA GAACACGCTGTATCTGCAAATGAACAGCC TGAGAGCCGAGGACACGGCGGTGTACTAC TGCGCAAGAGCCGAGATGGGAGCCGTATT CGACATATGGGCTCAGGTTACAATGGTCA CCGTCTCCTCAGGGTCTACATCCGGCTCC GGGAAGCCCCGAAGTGGCGAAGGTAGTAC AAAGGGGGAAATTGTGTTGACACAGTCTC CAGCCACCTGTCTTTGTCTCCAGGGGAA AGAGCCACCTCTCCTGCAGGGCCAGTCA GAGTGTTAGCAGGTACTTAGCCTGGTACC AACAGAACTTGGCCAGGCTCCCAGGCTC CTCATCTATGATGCATCCAACAGGGCCAC TGGCATCCCAGCCAGGTTCACTGGCAGTG GGTCTGGGACAGACTTCACTCTCACCATC AGCAGCCTAGAGCCTGAAGATTTTGCAGT TTATTACTGTCAGCAGAGAATCTCCTGGC CTTTCACTTTTGGCGGAGGGACCAAGGTT GAGATCAAACGGGCGCTGCCCTTGATAA TGAAAAGTCAAACGGAACAATCATTACG TGAAGGGCAAGCACCTCTGTCCGTCACCC TTGTTCCCTGGTCCATCCAAGCCATTCTG GGTGTTGGTCGTAGTGGGTGGAGTCCTCG CTTGTTACTCTCTGCTCGTCACCGTGGCT TTTATAATCTTCTGGGTTAGATCCAAAAG AAGCCGCCTGCTCCATAGCGATTACATGA ATATGACTCCACGCCGCCCTGGCCCCACA AGGAAACTACCAGCCTTACGCACCACC TAGAGATTTGCTGCCTATCGGAGCAGGG TGAAGTTTTCAGATCTGCAGATGCACCA GCGTATCAGCAGGGCCAGAACCAACTGTA TAACGAGCTCAACCTGGGACGCAGGGAAG AGTATGACGTTTTTGGACAAGCGCAGAGGA CGGGACCTGAGATGGGTGGCAAACCAAG ACGAAAAAACCCTCAGGAGGGTCTCTATA ATGAGCTGCAGAAGGATAAGATGGCTGAA GCCTATTCTGAAATAGGCATGAAAGGAGA GCGGAGAAGGGGAAAAGGGCACGACGGTT TGTACCAGGACTCAGCACTGCTACGAAG GATACTTATGACGCTCTCCACATGCAAGC CCTGCCACCTAGGTAA	133	MALPVTALLLPLALLL HAARPEVQLLES GGGL VQPGGSLRLSCAASGF TFSSYAMSWVRQAPGK GLEWVSAISGSGGSTY YADSVKGRFTISRDN KNTLYLQMNLSRAEDT AVYYCARAEMGAVFDI WGQGTMTVTVSSGSTSG SGKPGSGEGSTKGEIV LTQSPATLSLSPGERA TLSCRASQSVSRYLAW YQQKPGQAPRLLIYDA SNRATGIPARFSGSGS GTDFTLTITSSLEPEDF AVYYCQQRISWPF TFG GGTKVEIKRAAALDNE KSNGTIIHVKGKHLCP SPLFPGPSKPFWVLV VGGVLACYSLLVTVAF IIFWVRSKRSRLHSD YMNMTPRRPGPTRKHY QPYAPPRDFAAYRSRV KFSRSADAPAYQQGQN QLYNELNLGRREEYDV LDKRRGRDPEMGGKPR RKNPQEGLYNELQKDK MAEAYSEIGMKGERRR GKGHDGLYQGLSTATK DTYDALHMQALPPR	134
FS- 21495CARLx H	ATGGCACTCCCCGTAAC TGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCCGAAATGTGTTGACACAGTCTCCA GCCACCCTGTCTTTGTCTCCAGGGGAAAG AGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGGTACTTAGCCTGGTACCAA CAGAAACCTGGCCAGGCTCCCAGGCTCCT	135	MALPVTALLLPLALLL HAARPEIVLTQSPATL SLSPGERATLSCRASQ SVSRYLAWYQQKPGQA PRLLIYDASNRTGIP ARFSGSGSGTDFTLT SSLEPEDFAVYYCQQR	136

	<p>CATCTATGATGCATCCAACAGGGCCACTG GCATCCCAGCCAGGTTTCAGTGGCAGTGGG TCTGGGACAGACTTCACTCTCACCATCAG CAGCCTAGAGCCTGAAGATTTTGCAGTTT ATTACTGTCAGCAGAGAATCTCCTGGCCT TTCACTTTTGGCGGAGGGACCAAGGTTGA GATCAAACGGGGGTCTACATCCGGCTCCG GGAAGCCCGGAAGTGGCGAAGGTAGTACA AAGGGGGAGGTGCAGCTGTTGGAGTCTGG GGGAGGCTTGGTACAGCCTGGGGGGTCCC TGAGACTCTCCTGTGCAGCCTCTGGATTC ACCTTTAGCAGCTATGCCATGAGCTGGGT CCGCCAGGCTCCAGGGAAGGGCTGGAGT GGGTCTCAGCTATTAGTGGTAGTGGTGGT AGCACATACTACGCAGACTCCGTGAAGGG CCGGTTCACCATCTCCAGAGACAATTCCA AGAACACGCTGTATCTGCAAATGAACAGC CTGAGAGCCGAGGACACGGCGGTGTACTA CTGCGCAAGAGCCGAGATGGGAGCCGTAT TCGACATATGGGGTCAGGGTACAATGGTC ACCGTCTCCTCAGCCGCTGCCCTTGATAA TGAAAAGTCAAACGGAACAATCATTACG TGAAGGGCAAGCACCTCTGTCCGTCACCC TTGTTCCCTGGTCCATCCAAGCCATTCTG GGTGTGGTTCGTAGTGGGTGGAGTCCTCG CTTGTTACTCTCTGCTCGTACCGTGGCT TTTATAATCTTCTGGGTAGATCCAAAAG AAGCCGCTGCTCCATAGCGATTACATGA ATATGACTCCACGCCGCCCTGGCCCCACA AGGAAACACTACCAGCCTTACGCACCACC TAGAGATTTTCGCTGCCTATCGGAGCAGGG TGAAGTTTTCAGATCTGCAGATGCACCA GCGTATCAGCAGGGCCAGAACCAACTGTA TAACGAGCTCAACCTGGGACGCAGGGAAG AGTATGACGTTTTGGACAAGCGCAGAGGA CGGGACCTGAGATGGGTGGCAAACCAAG ACGAAAAAACCCCCAGGAGGGTCTCTATA ATGAGCTGCAGAAGGATAAGATGGCTGAA GCCTATTCTGAAATAGGCATGAAAGGAGA GCGGAGAAGGGGAAAAGGGCACGACGGTT TGTACCAGGGACTCAGCACTGCTACGAAG GATACTTATGACGCTCTCCACATGCAAGC CCTGCCACCTAGGTAA</p>		<p>ISWPFTFGGGTKVEIK RGSTSGSGKPGSGEGS TKGEVQLLESGGGLVQ PGGSLRLSCAASGFTF SSYAMSWVRQAPGKGL EWVSAISGSGSTYYA DSVKGRFTISRDN SKN TLYLQMNSLRAEDTAV YYCARAEMGAVFDIWG QGTMTVTVSSAAALDNE KSNGTIIHVKGKHLCP SPLFPGPSKPFWVLV VGGVLACYSLLVTVA IIFWVRSKRSLRLHSD YMNMTPRRPGPTRKHY QPYAPPRDFAAYRSRV KFSRSADAPAYQQGQN QLYNELNLGRREEYDV LDKRRGRDPEMGGKPR RKNPQEGLYNELQKDK MAEAYSEIGMKGERRR GKGHDGLYQGLSTATK DTYDALHMQALPPR</p>	
PC- 21497CARHx L	<p>ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTGCAGCTGGTGGAGTCTGGG GGAGGCGTGGTCCAGCCTGGGAGGTCCCT GAGACTCTCCTGTGCAGCGTCTGGATTCA CCTTCAGTAGCTATGGCATGCACTGGGTC CGCCAGGCTCCAGGCAAGGGGCTGGAGTG GGTGGCAGTTATATCGTATGATGGAAGTA ATAAATACTATGCAGACTCCGTGAAGGGC CGATTACCATCTCCAGAGACAATTCCAA GAACACGCTGTATCTGCAAATGAACAGCC TGAGAGCCGAGGACACGGCGGTGTACTAC TGCGCCAGAGACGGTACTTATCTAGGTGG TCTCTGGTACTTCGACTTATGGGGGAGAG GTACCTTGGTCACCGTCTCCTCAGGGTCT ACATCCGGCTCCGGGAAGCCCGGAAGTGG</p>	137	<p>MALPVTALLPLALLL HAARPQVQLVESGGGV VQPGRSLRLSCAASGF TFSSYGMHWVRQAPGK GLEWVAVISYDGSNKY YADSVKGRFTISRDN KNTLYLQMNSLRAEDT AVYYCARDGTYLGGLW YFDLWGRGTLVTVSSG STSGSGKPGSGEGSTK GDIVMTQSPLSLPVP GEPASISCRSSQSLH SNGYNYLDWYLQKPGQ SPQLLIYLGSNRASGV PDRFSGSGSGTDFTLK ISRVEAEDVGVYYCMQ</p>	138

	CGAAGGTAGTACAAAGGGGGATATTGTGA TGACTCAGTCTCCACTCTCCCTGCCCCGTC ACCCCTGGAGAGCCGGCCTCCATCTCCTG CAGGTCTAGTCAGAGCCTCCTGCATAGTA ATGGATACAACCTATTTGGATTGGTACCTG CAGAAGCCAGGGCAGTCTCCACAGCTCCT GATCTATTTGGGTTCTAATCGGGCCTCCG GGGTCCCTGACAGGTTCACTGGCAGTGGA TCAGGCACAGATTTTACACTGAAAATCAG CAGAGTGGAGGCTGAGGATGTTGGGGTTT ATTACTGCATGCAGGGACTCGGCCTCCCT CTCACTTTTGGCGGAGGGACCAAGGTTGA GATCAAACGGGCCGCTGCCCTTGATAATG AAAAGTCAAACGGAACAATCATTACAGTG AAGGGCAAGCACCTCTGTCCGTCAACCCTT GTTCCCTGGTCCATCCAAGCCATTCTGGG TGTTGGTCGTAGTGGGTGGAGTCCTCGCT TGTTACTCTCTGCTCGTCACCGTGGCTTT TATAATCTTCTGGGTTAGATCCAAAAGAA GCCGCCTGCTCCATAGCGATTACATGAAT ATGACTCCACGCCGCCCTGGCCCCACAAG GAAACACTACCAGCCTTACGCACCACCTA GAGATTTTCGCTGCCTATCGGAGCAGGGTG AAGTTTTCCAGATCTGCAGATGCACCAGC GTATCAGCAGGGCCAGAACCAACTGTATA ACGAGCTCAACCTGGGACGCAGGGAAGAG TATGACGTTTTGGACAAGCGCAGAGGACG GGACCCTGAGATGGGTGGCAAACCAAGAC GAAAAAACCCCCAGGAGGGTCTCTATAAT GAGCTGCAGAAGGATAAGATGGCTGAAGC CTATTCTGAAATAGGCATGAAAGGAGAGC GGAGAAGGGGAAAAGGGCACGACGGTTTG TACCAGGGACTCAGCACTGCTACGAAGGA TACTTATGACGCTCTCCACATGCAAGCCC TGCCACCTAGGTAA		GLGLPLTFGGGTKEVEI KRAAALDNEKSNGTII HVKGKHLCPSPFLFPGP SKPFWVLVVGGVLAC YSLLVTVAFIIFWVRS KRSRLHSDYMNMTPR RPGPTRKHYPYAPPR DFAAYRSRVKFSRSAD APAYQQGQNQLYNELN LGRREEYDVLDKRRGR DPEMGGKPRRKNPQEG LYNELQKDKMAEAYSE IGMKGERRRGKGDGL YQGLSTATKDTYDALH MQALPPR	
PC- 21497CARHx L	ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGGATATTGTGATGACTCAGTCTCCA CTCTCCCTGCCCGTCACCCCTGGAGAGCC GGCCTCCATCTCCTGCAGGTCTAGTCAGA GCCTCCTGCATAGTAATGGATACAACCTAT TTGGATTGGTACCTGCAGAAGCCAGGGCA GTCTCCACAGCTCCTGATCTATTTGGGTT CTAATCGGGCCTCCGGGTCCCTGACAGG TTCAGTGGCAGTGGATCAGGCACAGATTT TACACTGAAAATCAGCAGAGTGGAGGCTG AGGATGTTGGGGTTTATTACTGCATGCAG GGACTCGGCCTCCCTCTCACTTTTGGCGG AGGGACCAAGGTTGAGATCAAACGGGGGT CTACATCCGGCTCCGGGAAGCCCGGAAGT GGCGAAGGTAGTACAAAGGGGCAGGTGCA GCTGGTGGAGTCTGGGGGAGGCGTGCTCC AGCCTGGGAGGTCCCTGAGACTCTCCTGT GCAGCGTCTGGATTACCTTCAGTAGCTA TGGCATGCACTGGGTCCGCCAGGCTCCAG GCAAGGGGCTGGAGTGGGTGGCAGTTATA TCGTATGATGGAAGTAATAAATACTATGC AGACTCCGTGAAGGGCCGATTACCATCT CCAGAGACAATTCCAAGAACGCTGTAT	139	MALPVTALLLPLALLL HAARPDIVMTQSPLSL PVTPEPASISCRSSQ SLHNSNGYNDWYLQ KPGQSPQLLIYLGSR ASGVDPDRFSGSGSTD FTLKISRVEAEDVGVY YCMQGLGLPLTFGGGT KVEIKRGSTSGSGKPG SGEGSTKGQVQLVESG GGVVQPGRSRLRLSCAA SGFTFSSYGMHWVRQA PGKGLEWVAVISYDGS NKYYADSVKGRFTISR DNSKNTLYLQMNSLRA EDTAVYYCARDGTYLG GLWYFDLWGRGTLVTV SSAAALDNEKSNGTII HVKGKHLCPSPFLFPGP SKPFWVLVVGGVLAC YSLLVTVAFIIFWVRS KRSRLHSDYMNMTPR RPGPTRKHYPYAPPR DFAAYRSRVKFSRSAD	140

	<p>CTGCAATGAACAGCCTGAGAGCCGAGGA CACGGCGGTGTACTACTGCGCCAGAGACG GTACTTATCTAGGTGGTCTCTGGTACTTC GACTTATGGGGGAGAGGTACCTTGGTCAC CGTCTCCTCAGCCGCTGCCCTTGATAATG AAAAGTCAAACGGAACAATCATTACGTG AAGGGCAAGCACCTCTGTCCGTCAACCCTT GTTCCCTGGTCCATCCAAGCCATTCTGGG TGTTGGTTCGTAGTGGGTGGAGTCCTCGCT TGTTACTCTCTGCTCGTCACCGTGGCTTT TATAATCTTCTGGGTTAGATCCAAAAGAA GCCGCCTGCTCCATAGCGATTACATGAAT ATGACTCCACGCCGCCCTGGCCCCACAG GAAACACTACCAGCCTTACGCACCACCTA GAGATTTTCGTGCCTATCGGAGCAGGGTG AAGTTTTCCAGATCTGCAGATGCACCAGC GTATCAGCAGGGCCAGAACCAACTGTATA ACGAGCTCAACCTGGGACGCAGGGAAGAG TATGACGTTTTGGACAAGCGCAGAGGACG GGACCCTGAGATGGGTGGCAAACCAAGAC GAAAAAACCCCAAGGAGGTCTCTATAAT GAGCTGCAGAAGGATAAGATGGCTGAAGC CTATTCTGAAATAGGCATGAAAGGAGAGC GGAGAAGGGGAAAAGGGCACGACGTTTG TACCAGGGACTCAGCACTGCTACGAAGGA TACTTATGACGCTCTCCACATGCAAGCCC TGCCACCTAGGTAA</p>		<p>APAYQQGQNQLYNELN LGRREEYDVLDKRRGR DPFMGGKPRRKNPQEG LYNELQKDKMAEAYSE IGMKGERRRGKGDGL YQGLSTATKDTYDALH MQALPPR</p>	
AJ- 21508CARHx L	<p>ATGGCACTCCCCGTAACCTGCTCTGCTGCT GCCGTGGCATTTGCTCCTGCACGCCGCAC GCCCGCAGGTGCAGCTGGTGCAGTCTGGG GCTGAGGTGAAGAAGCCTGGGGCCTCAGT GAAGGTTTTCTGCAAGGCATCTGGATACA CCTTCACCAGCTACTATATGCACTGGGTG CGACAGGCCCTGGACAAGGGCTTGAGTG GATGGGAATAATCAACCCTGGTGGTGGTA GCACAAGCTACGCACAGAAGTTCCAGGGC AGAGTCACCATGACCAGGGACACGTCCAC GAGCACAGTCTACATGGAGCTGAGCAGCC TGAGATCTGAGGACACGGCGGTGTACTAC TGCGCCAGAGAGAGTTGGCCAATGGACGT ATGGGGCCAGGGAACAACCTGTCACCGTCT CCTCAGGGTCTACATCCGGCTCCGGGAAG CCCGGAAGTGGCGAAGGTAGTACAAAGGG GGAAATAGTGATGACGCAGTCTCCAGCCA CCCTGTCTGTGTCTCCAGGGGAAAGAGCC ACCCTCTCCTGCAGGGCCAGTCAGAGTGT TAGCAGCAACTTAGCCTGGTACCAGCAGA AACCTGGCCAGGCTCCCAGGCTCCTCATC TATGGTGCAATCCACCAGGGCCACTGGTAT CCCAGCCAGGTTTCAGTGGCAGTGGGTCTG GGACAGAGTTCACTCTCACCATCAGCAGC CTGCAGTCTGAAGATTTTGCAGTTTATTA CTGTGACAGTACGCCGCTACCCTACTT TTGGCGGAGGGACCAAGGTTGAGATCAA CGGGCCGCTGCCCTTGATAATGAAAAGTC AAACGGAACAATCATTACGTGAAGGGCA AGCACCTCTGTCCGTCAACCCTTGTTCCT GGTCCATCCAAGCCATTCTGGGTGTTGGT CGTAGTGGGTGGAGTCCTCGCTTGTTACT</p>	141	<p>MALPVTALLLPALLLL HAARPQVQLVQSGAEV KKPGASVKVSKASGY TFTSYMHWRQAPGQ GLEWMGIINPGGGSTS YAQKFQGRVTMTRDTS TSTVYMESSLRSED AVYYCARESWPMDVWG QGTTVTVSSGSTSGSG KPGSGEGSTKGEIVMT QSPATLSVSPGERATL SCRASQSVSSNLAWYQ QKPGQAPRLLIYGAST RATGIPARFSGSGSGT EFTLTISLQSEDFAV YYCQQYAAYPFTGGGT KVEIKRAALDNEKSN GTIIHVKGKHLCPSP FPGPSKPFVWLVVVG VLACYSLLVTVAFIIF WVRSKRSRLHSDYMN MTPRRPGPTRKHYQPY APPRDFAAYRSRVKFS RSADAPAYQQGQNQLY NELNLGRREEYDVLK RRGRDPFMGGKPRRKN PQEGLYNELQKDKMAE AYSEIGMKGERRRGK HDGLYQGLSTATKDTY DALHMQALPPR</p>	142

	CTCTGCTCGTCACCGTGGCTTTTATAATC TTCTGGGTTAGATCCAAAAGAAGCCGCCT GCTCCATAGCGATTACATGAATATGACTC CACGCCGCCCTGGCCCCACAAGGAAACAC TACCAGCCTTACGCACCACCTAGAGATTT CGCTGCCTATCGGAGCAGGGTGAAGTTT CCAGATCTGCAGATGCACCAGCGTATCAG CAGGGCCAGAACCAACTGTATAACGAGCT CAACCTGGGACGCAGGGAAGAGTATGACG TTTTGGACAAGCGCAGAGGACGGGACCCT GAGATGGGTGGCAAACCAAGACGAAAAA CCCCCAGGAGGGTCTCTATAATGAGCTGC AGAAGGATAAGATGGCTGAAGCCTATTCT GAAATAGGCATGAAAGGAGAGCGGAGAAG GGGAAAAGGGCACGACGGTTTGTACCAGG GACTCAGCACTGCTACGAAGGATACTTAT GACGCTCTCCACATGCAAGCCCTGCCACC TAGGTAA			
AJ- 21508CARLx H	ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGGAAATAGTGATGACGCAGTCTCCA GCCACCCTGTCTGTGTCTCCAGGGGAAAG AGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGCAACTTAGCCTGGTACCAG CAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATGGTGCATCCACCAGGGCCACTG GTATCCCAGCCAGGTTCACTGGCAGTGGG TCTGGGACAGAGTTCACTCTCACCATCAG CAGCCTGCAGTCTGAAGATTTTGCAGTTT ATTACTGTCAGCAGTACGCCGCCTACCCT ACTTTTGGCGGAGGGACCAAGGTTGAGAT CAAACGGGGGTCTACATCCGGCTCCGGGA AGCCCCGAAGTGGCGAAGGTAGTACAAAG GGGCAGGTGCAGCTGGTGCAGTCTGGGGC TGAGGTGAAGAAGCCTGGGGCCTCAGTGA AGGTTTCTGCAAGGCATCTGGATACACC TTCACCAGCTACTATATGCACTGGGTGCG ACAGGCCCCCTGGACAAGGGCTTGAGTGGA TGGGAATAATCAACCCTGGTGGTGGTAGC ACAAGCTACGCACAGAAAGTCCAGGGCAG AGTCACCATGACCAGGGACACGTCCACGA GCACAGTCTACATGGAGCTGAGCAGCCTG AGATCTGAGGACACGGCGGTGTACTACTG CGCCAGAGAGAGTTGGCCAATGGACGTAT GGGGCCAGGGAACAACTGTCACCGTCTCC TCAGCCGCTGCCCTTGATAATGAAAAGTC AAACGGAACAATCATTCACGTGAAGGGCA AGCACCTCTGTCCGTACCCCTGTTCCCT GGTCCATCCAAGCCATTCTGGGTGTTGGT CGTAGTGGGTGGAGTCCCTCGCTTGTACT CTCTGCTCGTCACCGTGGCTTTTATAATC TTCTGGGTTAGATCCAAAAGAAGCCGCCT GCTCCATAGCGATTACATGAATATGACTC CACGCCGCCCTGGCCCCACAAGGAAACAC TACCAGCCTTACGCACCACCTAGAGATTT CGCTGCCTATCGGAGCAGGGTGAAGTTT CCAGATCTGCAGATGCACCAGCGTATCAG CAGGGCCAGAACCAACTGTATAACGAGCT CAACCTGGGACGCAGGGAAGAGTATGACG	143	MALPVTALLPLALLL HAARPEIVMTQSPATL SVSPGERATLSCRASQ SVSSNLAWYQQKPGQA PRLLIYGASTRATGIP ARFSGSGSGTEFTLTI SSLQSEDFAVYYCQQY AAYPTFGGGTKVEIKR GSTSGSGKPGSGEGST KGQVQLVQSGAEVKKP GASVKVSKASGYTFT SYMHWVRQAPGQGLE WMGIINPGGGSTSYAQ KFQGRVTMTDRDSTST VYMESSLRSEDYAVY YCARSWPMQVWGQGT TVTVSSAAALDNEKSN GTIIHVKGKHLCPSP FPGPSKPEFVVLVVVG VLACYSLLVTVAFIIF WVRSKRSRLHSDYMN MTPRRPGPTRKHYQPY APPRDFAAYRSRVKFS RSADAPAYQQQNQLY NELNLGRREEYDVLDK RRGRDPEMGGKPRRKN PQEGLYNELQKDKMAE AYSEIGMKGERRRGKG HDGLYQGLSTATKDTY DALHMQALPPR	144

	TTTTGGACAAGCGCAGAGGACGGGACCCT GAGATGGGTGGCAAACCAAGACGAAAAA CCCCCAGGAGGGTCTCTATAATGAGCTGC AGAAGGATAAGATGGCTGAAGCCTATTCT GAAATAGGCATGAAAGGAGAGCGGAGAAG GGGAAAAGGGCACGACGGTTTGTACCAGG GACTCAGCACTGCTACGAAGGATACTTAT GACGCTCTCCACATGCAAGCCCTGCCACC TAGGTAA			
NM- 21517CARHx L	ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCCAGCTGCAGCTGCAGGAGTCGGGC CCAGGACTGGTGAAGCCTTCGGAGACCCT GTCCCTCACCTGCACTGTCTCTGGTGGCT CCATCAGCAGTAGTAGTTACTACTGGGGC TGGATCCGCCAGCCCCAGGGAAGGGGCT GGAGTGGATTGGGAGTATCTCCTATAGTG GGAGCACCTACTACAACCCGTCCTCAAG AGTCGAGTCACCATATCCGTAGACACGTC CAAGAACCAGTTCTCCCTGAAGCTGAGTT CTGTGACCGCCGAGACACGGCGGTGTAC TACTGCGCCAGAGGCAGGGGATATGCAAC CAGCTTAGCCTTCGATATCTGGGGTCAGG GTACAATGGTCACCGTCTCCTCAGGGTCT ACATCCGGCTCCGGGAAGCCCGGAAGTGG CGAAGGTAGTACAAAGGGGAAATTTGTGT TGACACAGTCTCCAGCCACCCTGTCTTTG TCTCCAGGGGAAAGAGCCACCCTCTCCTG CAGGGCCAGTCAGAGTGTTAGCAGCTACT TAGCCTGGTACCAACAGAAACCTGGCCAG GCTCCAGGCTCCTCATCTATGATGCATC CAACAGGGCCACTGGCATCCAGCCAGGT TCAGTGGCAGTGGGTCTGGGACAGACTTC ACTCTACCATCAGCAGCCTAGAGCCTGA AGATTTTGCAGTTTATTACTGTGAGCAGA GACACGTCTGGCCTCCTACTTTTGGCGGA GGGACCAAGGTTGAGATCAAACGGGCCGC TGCCCTTGATAATGAAAAGTCAAACGGAA CAATCATTACGTGAAGGGCAAGCACCTC TGTCCGTCAACCCTTGTTCCTGGTCCATC CAAGCCATTCTGGGTGTTGGTCGTAGTGG GTGGAGTCTCGCTTGTACTCTCTGCTC GTCACCGTGGCTTTTATAATCTTCTGGGT TAGATCCAAAAGAAGCCGCTGCTCCATA GCGATTACATGAATATGACTCCACGCCGC CCTGGCCCCACAAGGAAACACTACCAGCC TTACGCACCACCTAGAGATTTCTGCTGCCT ATCGGAGCAGGGTGAAGTTTCCAGATCT GCAGATGCACCAGCGTATCAGCAGGGCCA GAACCAACTGTATAACGAGCTCAACCTGG GACGCAGGGAAGAGTATGACGTTTTTGAC AAGCGCAGAGGACGGGACCCTGAGATGGG TGGCAAACCAAGACGAAAAACCCCCAGG AGGGTCTCTATAATGAGCTGCAGAAGGAT AAGATGGCTGAAGCCTATTCTGAAATAGG CATGAAAGGAGAGCGGAGAAGGGGAAAAG GGCACGACGGTTTGTACCAGGGACTCAGC ACTGCTACGAAGGATACTTATGACGCTCT CCACATGCAAGCCCTGCCACCTAGGTAA	145	MALPVTALLLPLALLL HAARPQLQLQESGPGL VKPSETLSLTCTVSGG SISSSSYWGWIRQPP GKGLEWIGSISYSGST YYNPSLKSRVTISVDT SKNQFSLKLSVTAAD TAVYYCARGRGYATSL AFDIWQGTMVTVSSG STSGSGKPGSGEGSTK GEIVLTQSPATLSLSP GERATLSCRASQSVSS YLAWYQQKPGQAPRL IYDASNRTGIPARFS GSGSGTDFTLTISLE PEDFAVYYCQQRHVWP PTFGGGTKVEIKRAAA LDNEKSNGTIIHVKGK HLCPSPLFPGPSKPFW VLVVVGVLACYSLLV TVAFIIFWVRSKRRL LHSDYMNMTPRRPGPT RKHYQPYAPPRDFAAY RSRVKFSRSADAPAYQ QGQNQLYNELNLGRRE EYDVLDKRRGRDPEMG GKPRRKNPQEGLYNEL QKDKMAEAYSEIGMKG ERRRGKGDGLYQGLS TATKDTYDALHMQALP PR	146

NM- 21517CARLx H	ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCCGAAATTGTGTTGACACAGTCTCCA GCCACCTGTCTTTGTCTCCAGGGGAAAAG AGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGCTACTTAGCCTGGTACCAA CAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATGATGCATCCAACAGGGCCACTG GCATCCCAGCCAGGTTCACTGGCAGTGGG TCTGGGACAGACTTCACTCTCACCATCAG CAGCCTAGAGCCTGAAGATTTTGAGTTT ATTACTGTCAGCAGAGACAGTCTGGCCT CCTACTTTTGGCGGAGGGACCAAGGTTGA GATCAAACGGGGGTCTACATCCGGCTCCG GGAAGCCCCGAAGTGGCGAAGGTAGTACA AAGGGGCAGCTGCAGCTGCAGGAGTCGGG CCCAGGACTGGTGAAGCCTTCGGAGACCC TGTCCCTCACCTGCACTGTCTCTGGTGGC TCCATCAGCAGTAGTAGTTACTACTGGGG CTGGATCCGCCAGCCCCCAGGGAAGGGG TGGAGTGGATTGGGAGTATCTCCTATAGT GGGAGCACCTACTACAACCCGTCCCTCAA GAGTCGAGTCACCATATCCGTAGACACGT CCAAGAACCAGTTCTCCCTGAAGCTGAGT TCTGTGACCGCCGCAGACACGGCGGTGTA CTACTGCGCCAGAGGCAGGGGATATGCAA CCAGCTTAGCCTTCGATATCTGGGTCAG GGTACAATGGTCAACCTCTCCTCAGCCGC TGCCCTTGATAATGAAAAGTCAAACGGAA CAATCATTACAGTGAAGGGCAAGCACCTC TGTCCGTCAACCTTGTTCCTGGTCCATC CAAGCCATTCTGGGTGTTGGTTCGTAGTGG GTGGAGTCCCTCGCTTGTACTCTCTGCTC GTCACCGTGGCTTTTATAATCTTCTGGGT TAGATCCAAAAGAAGCCGCTGCTCCATA GCGATTACATGAATATGACTCCACGCCGC CCTGGCCCCACAAGGAAACACTACCAGCC TTACGCACCACCTAGAGATTTTCGCTGCCT ATCGGAGCAGGGTGAAGTTTTCAGATCT GCAGATGCACAGCGTATCAGCAGGGCCA GAACCAACTGTATAACGAGCTCAACCTGG GACGCAGGGAAGAGTATGACGTTTTGGAC AAGCGCAGAGGACGGGACCTGAGATGGG TGGCAAACCAAGACGAAAAACCCCCAGG AGGGTCTCTATAATGAGCTGCAGAAGGAT AAGATGGCTGAAGCCTATTCTGAAATAGG CATGAAAGGAGAGCGGAGAAGGGGAAAAG GGCACGACGGTTTGTACCAGGGACTCAGC ACTGCTACGAAGGATACTTATGACGCTCT CCACATGCAAGCCCTGCCACCTAGGTAA	147	MALPVTALLLPLALLL HAARPEIVLTQSPATL SLSPGERATLSCRASQ SVSSYLAWYQQKPGQA PRLLIYDASNRATGIP ARFSGSGSGTDFTLTI SSLEPEDFAVYYCQQR HVWPPTFGGGTKVEIK RGSTSGSGKPGSGEGS TKGQLQLQESGPGLVK PSETLSLTCTVSGGSI SSSSYYWGWIQPPGK GLEWIGSISYSGSTYY NP SLKSRVTISVDTSK NQFSLKLSVTAADTA VYYCARGRGVATSLAF DIWQGQTMVTVSSAAA LDNEKSNGTIIHVKGK HLCPSPLFPGPSKPFW VLVVVGGVILACYSLLV TVAFIIIFWVRSKRSRL LHSDYMNMTPRRPGPT RKHYQPYAPPRDFAAY RSRVKFSRSADAPAYQ QQQNQLYNELNLGRRE EYDVLDKRRGRDPFEMG GKPRRKNPQEGLYNEL QKDKMAEAYSEIGMKG ERRRGKGDGLYQGLS TATKDTYDALHMQALP PR	148
TS- 21522CARHx L	ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCCGAGGTGCAGCTGGTGGAGTCTGGG GGAGGCTTGGTACAGCCTGGGGGGTCCCT GAGACTCTCCTGTGCAGCCTCTGGATTCA CCTTCAGTAGCTATAGCATGAACTGGGTC CGCCAGGCTCCAGGGAAGGGGCTGGAGTG GGTTTCAACCATTAGTAGTAGTAGTAGTA CCATATACTACGCAGACTCTGTGAAGGGC	149	MALPVTALLLPLALLL HAARPEVQLVESGGGL VQPGGSLRLSCAASGF TFSSYSMNWVRQAPGK GLEWVSTISSSSSTIY YADSVKGRFTISRDN KNSLYLQMNLSRAEDT AVYYCARGSQEHLIFD YWGQGLTLTVSSGSTS	150

	CGATTACCATCTCCAGAGACAATGCCAA GAACTCACTGTATCTGCAAATGAACAGCC TGAGAGCTGAGGACACGGCGGTGTACTAC TGCGCCAGAGGTTCTCAGGAGCACCTGAT TTTCGATTATTGGGGACAGGGTACATTGG TCACCGTCTCCTCAGGGTCTACATCCGGC TCCGGGAAGCCCGGAAGTGGCGAAGGTAG TACAAAGGGGAAATTTGTGTTGACACAGT CTCCAGCCACCCTGTCTTTGTCTCCAGGG GAAAGAGCCACCCTCTCCTGCAGGGCCAG TCAGAGTGTAGCAGGTACTTAGCCTGGT ACCAACAGAAACCTGGCCAGGCTCCCAGG CTCCTCATCTATGATGCATCCAACAGGGC CACTGGCATCCCAGCCAGGTTTCAGTGGCA GTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGCCTAGAGCCTGAAGATTTTGC AGTTTATTACTGTGTCAGCAGAGATTCTACT ACCCTTGGACTTTTGGCGAGGGACCAAG GTTGAGATCAAACGGGCCCTGCCCTTGA TAATGAAAAGTCAAACGGAACAATCATTC ACGTGAAGGGCAAGCACCTCTGTCCGTCA CCCTTGTTCCTGGTCCATCCAAGCCATT CTGGGTGTTGGTCGTAGTGGGTGGAGTCC TCGCTTGTACTCTCTGCTCGTCACCGTG GCTTTTATAATCTTCTGGGTTAGATCCAA AAGAAGCCGCTGCTCCATAGCGATTACA TGAATATGACTCCACGCCGCCCTGGCCCC ACAAGGAAACACTACCAGCCTTACGCACC ACCTAGAGATTTGCTGCCTATCGGAGCA GGGTGAAGTTTCCAGATCTGCAGATGCA CCAGCGTATCAGCAGGGCCAGAACCAACT GTATAACGAGCTCAACCTGGGACGCAGGG AAGAGTATGACGTTTTGGACAAGCGCAGA GGACGGGACCCTGAGATGGGTGGCAAACC AAGACGAAAAAACCCCAAGGAGGTCTCT ATAATGAGCTGCAGAAGGATAAGATGGCT GAAGCCTATCTGAAATAGGCATGAAAGG AGAGCGGAGAAGGGGAAAGGGCACGACG GTTTGTACCAGGGACTCAGCACTGCTACG AAGGATACTTATGACGCTCTCCACATGCA AGCCCTGCCACCTAGGTAA		GSGKPGSGEGSTKGEI VLTQSPATLSLSPGER ATLSCRASQSVSRYLA WYQQKPGQAPRLLIYD ASNRATGIPARFSGSG SGTDFTLTISLEPED FAVYYCQQRFYYPWTF GGGKTKVEIKRAAALDN EKSNGTIIHVKGKHL PSPLFPGPSKPFVVLV VVGGLVACYSLVTV FIIFWVRSKRSRLLS DYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSR VKFSRSADAPAYQQGQ NQLYNELNLRREEYD VLDKRRGRDPEMGGKP RRKNPQEGLYNELQKD KMAEAYSEIGMKGERR RGKGHDLGYQLSTAT KDTYDALHMQALPPR	
TS- 21522CARLx H	ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCCGAAATTTGTGTTGACACAGTCTCCA GCCACCCTGTCTTTGTCTCCAGGGGAAAG AGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGGTACTTAGCCTGGTACCAA CAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATGATGCATCCAACAGGGCCACTG GCATCCCAGCCAGGTTCACTGGCAGTGGG TCTGGGACAGACTTCACTCTCACCATCAG CAGCCTAGAGCCTGAAGATTTTGCAGTTT ATTACTGTCAGCAGAGATTCTACTACCCT TGGACTTTTGGCGGAGGGACCAAGGTTGA GATCAAACGGGGGTCTACATCCGGCTCCG GGAAGCCCGGAAGTGGCGAAGGTAGTACA AAGGGGAGGTGCAGCTGGTGGAGTCTGG GGGAGGCTTGGTACAGCCTGGGGGTCCC TGAGACTCTCCTGTGCAGCCTCTGGATTC	151	MALPVTALLPLALLL HAARPEIVLTQSPATL SLSPGERATLSCRASQ SVSRYLAWYQQKPGQA PRLLIYDASNRATGIP ARFSGSGSGTDFTLTI SSLEPEDFAVYYCQQR FYYPWTFGGGKTKVEIK RGSTSGSGKPGSGEGS TKGEVQLVESGGGLVQ PGGSLRLSCAASGFTF SSYSMNWVRQAPGKGL EWVSTISSSSSTIYYA DSVKGRFTISRDNKN SLYLQMNLSRAEDTAV YYCARGSQEHLIFDYW GQGTLVTVSSAAALDN EKSNGTIIHVKGKHL	152

	ACCTTCAGTAGCTATAGCATGAACTGGGT CCGCCAGGCTCCAGGGAAGGGCTGGAGT GGGTTTCAACCATTAGTAGTAGTAGT ACCATATACTACGCAGACTCTGTGAAGGG CCGATTACCATCTCCAGAGACAATGCCA AGAACTCACTGTATCTGCAAATGAACAGC CTGAGAGCTGAGGACACGGCGGTGTACTA CTGCGCCAGAGGTTCTCAGGAGCACCTGA TTTTCGATTATTGGGGACAGGGTACATTG GTCACCGTCTCCTCAGCCGCTGCCCTTGA TAATGAAAAGTCAAACGGAACAATCATTC ACGTGAAGGGCAAGCACCTCTGTCCGTCA CCCTTGTTCCCTGGTCCATCCAAGCCATT CTGGGTGTTGGTCGTAGTGGGTGGAGTCC TCGCTTGTTACTCTCTGCTCGTCACCGTG GCTTTTATAATCTTCTGGGTTAGATCCAA AAGAAGCCGCTGCTCCATAGCGATTACA TGAATATGACTCCACGCCGCCCTGGCCCC ACAAGGAAACACTACCAGCCTTACGCACC ACCTAGAGATTTTCGCTGCCTATCGGAGCA GGGTGAAGTTTTCAGATCTGCAGATGCA CCAGCGTATCAGCAGGGCCAGAACCAACT GTATAACGAGCTCAACCTGGGACGCAGGG AAGAGTATGACGTTTTGGACAAGCGCAGA GGACGGGACCCTGAGATGGGTGGCAAACC AAGACGAAAAACCCCCAGGAGGGTCTCT ATAATGAGCTGCAGAAGGATAAGATGGCT GAAGCCTATTCTGAAATAGGCATGAAAGG AGAGCGGAGAAGGGGAAAAGGGCACGACG GTTTGTACCAGGGACTCAGCACTGCTACG AAGGATACTTATGACGCTCTCCACATGCA AGCCCTGCCACCTAGGTAA		PSPLFPGPSKPFWVLV VVGGVLACYSLLVTV FIIFWVRSKRSRLHLS DYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSR VKFSRSADAPAYQQGQ NQLYNELNLGRREEYD VLDKRRGRDPEMGGKP RRKNPQEGLYNELQKD KMAEAYSEIGMKGERR RGKGDGLYQGLSTAT KDTYDALHMQALPPR	
RY- 21527CARHx L	ATGGCACTCCCCGTAAGTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTGCAGCTGGTGGAGTCTGGG GGAGGCGTGGTCCAGCCTGGGAGGTCCCT GAGACTCTCCTGTGCAGCGTCTGGATTCA CCTTCAGTAGCTATGGCATGCACTGGGTC CGCCAGGCTCCAGGCAAGGGGCTGGAGTG GGTGGCAGTTATATCGTATGATGGAAGTA ATAAATACTATGCAGACTCCGTGAAGGGC CGATTACCATCTCCAGAGACAATTCCAA GAACACGCTGTATCTGCAAATGAACAGCC TGAGAGCCGAGGACACGGCGGTGTACTAC TGCGCCAGAACTGACTTCTGGAGCGGATC CCCTCCAGGCTTAGATTACTGGGGACAGG GTACATTGGTCACCGTCTCCTCAGGGTCT ACATCCGGCTCCGGGAAGCCCGGAAGTGG CGAAGGTAGTACAAAGGGGACATCCAGT TGACCCAGTCTCCATCTTCCGTGTCTGCA TCTGTAGGAGACAGAGTCACCATCACTTG TCGGGCGAGTCAGGGTATTAGCAGCTGGT TAGCCTGGTATCAGCAGAAACCAGGGAAA GCCCCTAAGCTCCTGATCTATGGTGATC CAGTTTGCAAAGTGGGGTCCCATCAAGGT TCAGCGGCAGTGGATCTGGGACAGATTTC ACTCTACCATCAGCAGCCTGCAGCCTGA AGATTTTGCAACTTATTACTGTGACGAGA TATACACCTTCCCTTTCACTTTTGGCGGA	153	MALPVTALLPLALLL HAARPQVQLVESGGGV VQPGRLRLSCAASGF TFSSYGMHWVRQAPGK GLEWVAVISYDGSNKY YADSVKGRFTISRDN KNTLYLQMNSLRADET AVYYCARTDFWSSGSP GLDYWGQGLVTVSSG STSGSGKPGSGEGSTK GDIQLTQSPSSVSASV GDRVITICRASQGISS WLAWYQQKPGKAPKLL IYGASSLQSGVPSRFS SGSGTDFTLTISLQ PEDFATYYCQIYTFP FTFGGGTKVEIKRAA LDNEKSNGTIIHVKGK HLCPSPLFPGPSKPFW VLVVGGVLACYSLLV TVAFIIFWVRSKRSRL LHSDYMNMTPRRPGPT RKHYQPYAPPRDFAAY RSRVKFSRSADAPAYQ QGQNQLYNELNLGRRE EYDVLDRRGRDPEMG GKPRRKNPQEGLYNEL	154

	GGGACCAAGGTTGAGATCAAACGGGCGC TGCCCTTGATAATGAAAAGTCAAACGGAA CAATCATTCACGTGAAGGGCAAGCACCTC TGTCCGTACCCCTTGTTCCCTGGTCCATC CAAGCCATTCTGGGTGTTGGTCGTAGTGG GTGGAGTCCTCGCTTGTTACTCTCTGCTC GTCACCGTGGCTTTTATAATCTTCTGGGT TAGATCCAAAAGAAGCCGCTGCTCCATA GCGATTACATGAATATGACTCCACGCCGC CCTGGCCCCACAAGGAAACACTACCAGCC TTACGCACCACCTAGAGATTTCTGCTGCCT ATCGGAGCAGGGTGAAGTTTCCAGATCT GCAGATGCACCAGCGTATCAGCAGGGCCA GAACCAACTGTATAACGAGCTCAACCTGG GACGCAGGGAAGAGTATGACGTTTGGAC AAGCGCAGAGGACGGGACCCTGAGATGGG TGGCAAACCAAGACGAAAAAACCCCAAGG AGGGTCTCTATAATGAGCTGCAGAAGGAT AAGATGGCTGAAGCCTATTCTGAAATAGG CATGAAAGGAGAGCGGAGAAGGGGAAAAAG GGCAGGACGGTTTGTACCAGGGACTCAGC ACTGCTACGAAGGATACTTATGACGCTCT CCACATGCAAGCCCTGCCACCTAGGTAA		QKDKMAEAYSEIGMKG ERRRGKGHDGLYQGLS TATKDTYDALHMQALP PR	
RY- 21527CARLx H	ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCCGACATCCAGTTGACCCAGTCTCCA TCTTCCGTGTCTGCATCTGTAGGAGACAG AGTCACCATCACTTGTCGGGCGAGTCAGG GTATTAGCAGCTGGTTAGCCTGGTATCAG CAGAAACCAGGGAAAGCCCTAAGCTCCT GATCTATGGTGCATCCAGTTTGCAAAGTG GGGTCCCATCAAGGTTCAAGCGGCAAGTGA TCTGGGACAGATTTCACTCTCACCATCAG CAGCCTGCAGCCTGAAGATTTTGCAACTT ATTACTGTCAGCAGATATACACCTTCCCT TTCATTTTGGCGGAGGGACCAAGGTTGA GATCAAACGGGGGTCTACATCCGGCTCCG GGAAGCCCGGAAGTGGCGAAGGTAGTACA AAGGGGCAGGTGCAGCTGGTGGAGTCTGG GGGAGGCGTGGTCCAGCCTGGGAGGTCCC TGAGACTCTCCTGTGCAGCGTCTGGATTC ACCTTCAGTAGCTATGGCATGCACTGGGT CCGCCAGGCTCCAGGCAAGGGCTGGAGT GGGTGGCAGTTATATCGTATGATGGAAGT AATAAATACTATGCAGACTCCGTGAAGGG CCGATTACCATCTCCAGAGACAATTCCA AGAACACGCTGTATCTGCAAATGAACAGC CTGAGAGCCGAGGACACGGCGGTGTACTA CTGCGCCAGAACTGACTTCTGGAGCGGAT CCCCTCCAGGCTTAGATTACTGGGGACAG GGTACATTGGTCACCGTCTCCTCAGCCGC TGCCCTTGATAATGAAAAGTCAAACGGAA CAATCATTCACGTGAAGGGCAAGCACCTC TGTCCGTACCCCTTGTTCCCTGGTCCATC CAAGCCATTCTGGGTGTTGGTCGTAGTGG GTGGAGTCCTCGCTTGTTACTCTCTGCTC GTCACCGTGGCTTTTATAATCTTCTGGGT TAGATCCAAAAGAAGCCGCTGCTCCATA GCGATTACATGAATATGACTCCACGCCGC	155	MALPVTALLPLALLL HAARPDIQLTQSPSSV SASVGDRTVITCRASQ GISSWLAWYQQKPGKA PKLLIYGASSLQSGVP SRFSGSGSGTDFTLTI SSLQPEDFATYYCQOI YTFPFTFGGGTKVEIK RGSTSGSGKPGSGEGS TKGQVQLVESGGGVVQ PGRSLRLSCAASGFTF SSYGMHWVRQAPGKGL EWVAVISYDSNKKYYA DSVKGRFTISRDN SKN TLYLQMNSLRAEDTAV YYCARTDFWSSGSPGL DYWGQGTTLVTVSSAAA LDNEKSNGTIIHVKGK HLCPSPLFPGPSKPFW VLVVVGGLVACYSLLV TVAFIIFWVRSKRSRL LHSDYMNMTPRRPGPT RKHYQPYAPPRDFAAY RSRVKFSRSADAPAYQ QGQNQLYNELNLGRRE EYDVLDKRRGRDPEMG GKPRRKNPQEGLYNEL QKDKMAEAYSEIGMKG ERRRGKGHDGLYQGLS TATKDTYDALHMQALP PR	156

	<p>CCTGGCCCCACAAGGAAACACTACCAGCC TTACGCACCACCTAGAGATTTTCGCTGCCT ATCGGAGCAGGGTGAAGTTTTCCAGATCT GCAGATGCACCAGCGTATCAGCAGGGCCA GAACCAACTGTATAACGAGCTCAACCTGG GACGCAGGGAAGAGTATGACGTTTTGGAC AAGCGCAGAGGACGGGACCCTGAGATGGG TGGCAAACCAAGACGAAAAACCCCCAGG AGGGTCTCTATAATGAGCTGCAGAAGGAT AAGATGGCTGAAGCCTATTCTGAAATAGG CATGAAAGGAGAGCGGAGAAGGGGAAAAG GGCAGCAGGTTTGTACCAGGGACTCAGC ACTGCTACGAAGGATACTTATGACGCTCT CCACATGCAAGCCCTGCCACCTAGGTAA</p>			
PP- 21528CARHx L	<p>ATGGCACTCCCCGTAACGTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTGCAGCTGGTGCAGTCTGGG GCTGAGGTGAAGAAGCCTGGGTCTCGGT GAAGGTCTCCTGCAAGGCTTCTGGAGGCA CCTTCAGCAGCTATGCTATCAGCTGGGTG CGACAGGCCCTGGACAAGGGCTTGAGTG GATGGGAGGGATCATCCCTATCTTTGGTA CAGCAAACACGCACAGAAGTTCCAGGGC AGAGTCACGATTACCGCGACGAATCCAC GAGCACAGCCTACATGGAGCTGAGCAGCC TGAGATCTGAGGACACGGCGGTGTACTAC TGCGCCAGAACTCCTGAATACTCCTCCAG CATATGGCACTATTACTACGGCATGGACG TATGGGGCCAGGGAACAACTGTCACCGTC TCCTCAGGGTCTACATCCGGCTCCGGGAA GCCCCGAAGTGGCGAAGGTAGTACAAAGG GGGACATCGTGATGACCCAGTCTCCAGAC TCCCTGGCTGTGTCTCTGGGCGAGAGGGC CACCATCAACTGCAAGTCCAGCCAGAGTG TTTTATACAGCTCCAACAATAAGAACTAC TTAGCTTGGTACCAGCAGAAACCAGGACA GCCTCCTAAGCTGCTCATTACTGGGCAT CTACCCGGGAATCCGGGGTCCCTGACCGA TTCAGTGGCAGCGGGTCTGGGACAGATT CACTCTACCATCAGCAGCCTGCAGGCTG AAGATGTGGCAGTTTATTACTGTCAGCAG TTCGCCCACACTCCTTTCACTTTTGGCGG AGGGACCAAGGTTGAGATCAAACGGGCCG CTGCCCTTGATAATGAAAAGTCAAACGGA ACAATCATTCAGTGAAGGCAAGCACCT CTGTCCGTCAACCCTTGTCCCTGGTCCAT CCAAGCCATTCTGGGTGTTGGTCTGAGTG GGTGGAGTCTCGCTTGTACTCTCTGCT CGTCACCGTGGCTTTTATAATCTTCTGGG TTAGATCCAAAAGAAGCCGCTGCTCCAT AGCGATTACATGAATATGACTCCACGCCG CCCTGGCCCCACAAGGAAACACTACCAGC CTTACGCACCACCTAGAGATTTTCGCTGCC TATCGGAGCAGGGTGAAGTTTTCCAGATC TGCAGATGCACCAGCGTATCAGCAGGGCC AGAACCAACTGTATAACGAGCTCAACCTG GGACGCAGGGAAGAGTATGACGTTTTTGA CAAGCGCAGAGGACGGGACCCTGAGATGG GTGGCAAACCAAGACGAAAAACCCCCAG</p>	157	<p>MALPVTALLLPLALLL HAARPQVQLVQSGAEV KKPGSSVKVSCASGG TFSSYAI SWVRQAPGQ GLEWMGGIIPFGTAN YAQKFQGRVITADES TSTAYMELSSLRSED AVYYCARTPEYSSSIW HYYYGMDVWGQGT VSSGSTSGSGKPGSGE GSTKGDIVMTQSPDSL AVSLGERATINCKSSQ SVLYSSNNKNYLAWYQ QKPGQPPKLLIYWAST RESGVPDRFSGSGSGT DFTLTISSLQAEDVAV YYCQQFAHTPFTFGGG TKVEIKRAAALDNEKS NGTIIHVKGKHLCPSP LFPGPSKPFVWLTVVVG GVLACYSLLVTVAFII FWVRSKRRLHSDYM NMTPRRPGPTRKHYQP YAPPRDFAAYRSRVKF SRSADAPAYQQGQNL YNELNLGRREYDVL KRRGRDPEMGGKPRRK NPQEGLYNELQKDKMA EAYSEIGMKGERRRGK GHDGLYQGLSTATKDT YDALHMQALPPR</p>	158

	GAGGGTCTCTATAATGAGCTGCAGAAGGA TAAGATGGCTGAAGCCTATTCTGAAATAG GCATGAAAGGAGAGCGGAGAAGGGGAAAA GGGCACGACGGTTTGTACCAGGGACTCAG CACTGCTACGAAGGATACTTATGACGCTC TCCACATGCAAGCCCTGCCACCTAGGTAA			
PP- 21528CARLx H	ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCCGACATCGTGATGACCCAGTCTCCA GACTCCCTGGCTGTGTCTCTGGGCGAGAG GGCCACCATCAACTGCAAGTCCAGCCAGA GTGTTTTATACAGCTCCAACAATAAGAAC TACTTAGCTTGCTACCAGCAGAAACCAGG ACAGCCTCCTAAGCTGCTCATTTACTGGG CATCTACCCGGGAATCCGGGGTCCCTGAC CGATTCAGTGGCAGCGGGTCTGGGACAGA TTTCACTCTCACCATCAGCAGCCTGCAGG CTGAAGATGTGGCAGTTTATTACTGTCAG CAGTTCGCCCACACTCCTTCACTTTTGG CGGAGGGACCAAGGTTGAGATCAAACGGG GGTCTACATCCGGCTCCGGGAAGCCCGGA AGTGGCGAAGGTAGTACAAAGGGGCGAGT GCAGCTGGTGCAGTCTGGGGCTGAGGTGA AGAAGCCTGGGTCTCGGTGAAGGTCTCC TGCAAGGCTTCTGGAGGCACCTTCAGCAG CTATGCTATCAGCTGGGTGCGACAGGCC CTGGACAAGGGCTTGAGTGGATGGGAGGG ATCATCCCTATCTTTGGTACAGCAAACTA CGCACAGAAGTTCAGGGCAGAGTCACGA TTACCGCGGACGAATCCACGAGCACAGCC TACATGGAGCTGAGCAGCCTGAGATCTGA GGACACGGCGGTGTACTACTGCGCCAGAA CTCCTGAATACTCCTCCAGCATATGGCAC TATTACTACGGCATGGACGTATGGGGCCA GGGAACAACGTGCACCGTCTCCTCAGCCG CTGCCCTTGATAATGAAAAGTCAAACGGA ACAATCATTCACGTGAAGGCAAGCACCT CTGTCCGTCAACCTTGTTCCTGGTCCAT CCAAGCCATTCTGGGTGTTGGTCGTAGTG GGTGGAGTCCCTCGCTTGTACTCTCTGCT CGTCACCGTGGCTTTTATAATCTTCTGGG TTAGATCCAAAAGAAGCCGCTGCTCCAT AGCGATTACATGAATATGACTCCACGCCG CCCTGGCCCCACAAGGAAACACTACCAGC CTTACGCACCACTAGAGATTTCTGCTGCC TATCGGAGCAGGGTGAAGTTTCCAGATC TGCAGATGCACCAGCGTATCAGCAGGGCC AGAACCAACTGTATAACGAGCTCAACCTG GGACGCAGGGAAGAGTATGACGTTTTGGA CAAGCGCAGAGGACGGGACCCTGAGATGG GTGGCAAACCAAGACGAAAAAACCCTCAG GAGGGTCTCTATAATGAGCTGCAGAAGGA TAAGATGGCTGAAGCCTATTCTGAAATAG GCATGAAAGGAGAGCGGAGAAGGGGAAAA GGGCACGACGGTTTGTACCAGGGACTCAG CACTGCTACGAAGGATACTTATGACGCTC TCCACATGCAAGCCCTGCCACCTAGGTAA	159	MALPVTALLLPLALLL HAARPDIVMTQSPDSL AVSLGERATINCKSSQ SVLYSSNNKNYLAWYQ QKPGQPPKLLIYWAST RESGVPDRFSGSGSGT DFTLTISSLQAEADVAV YYCQQFAHTPFTFGGG TKVEIKRGSTSGSGKP GSGEGSTKGQVQLVQS GAEVKKPGSSSVKVSCK ASGGTFSSYAI SWVRQ APGQGLEWMGGIIPF GTANYAQKFQGRVTIT ADESTSTAYMELSSLR SEDVAVYYCARTPEYS SSIWHYYYGMDVWGQG TFTVTVSSAAALDNEKS NGTIIHVKGKHLCPSP LFPGPSKPFVFLVVG GVLACYSLLVTVAFII FWVRSKRSRLHSDYM NMTPRRPGPTRKHYQP YAPPRDFAAYRSRVKF SRADAPAYQQGQNQL YNELNLGRREEYDVLD KRRGRDPEMGGKPRRK NPQEGLYNELQDKMA EAYSEIGMKGERRRGK GHDGLYQGLSTATKDT YDALHMQALPFR	160

RD- 21530CARHx L	ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCCAGGTGCAGCTGGTGGAGTCTGGG GGAGGCGTGGTCCAGCCTGGGAGGTCCCT GAGACTCTCCTGTGCAGCGTCTGGATTCA CCTTCAGTAGCTATGGCATGCACTGGGTC CGCCAGGCTCCAGGCAAGGGGCTGGAGTG GGTGGCAGTTATATCGTATGATGGAAGTA ATAAATACTATGCAGACTCCGTGAAGGGC CGATTCACCATCTCCAGAGACAATTCCAA GAACACGCTGTATCTGCAATGAACAGCC TGAGAGCCGAGGACACGGCGGTGTACTAC TGCGTCAAGGGGCCGTTGCAGGAGCCGCC ATACGATTATGGAATGGACGTATGGGGCC AGGGAACAACTGTCACCGTCTCCTCAGGG TCTACATCCGGCTCCGGGAAGCCCGGAAG TGGCGAAGGTAGTACAAAGGGGGAATAG TGATGACGCAGTCTCCAGCCACCCTGTCT GTGTCTCCAGGGGAAAGAGCCACCCTCTC CTGCAGGGCCAGTCAGAGTGTTAGCAGCA ACTTAGCCTGGTACCAGCAGAAACCTGGC CAGGCTCCCAGGCTCCTCATCTATAGCGC ATCCACCAGGGCCACTGGTATCCCAGCCA GGTTCAGTGGCAGTGGGTCTGGGACAGAG TTCATCTCACCATCAGCAGCCTGCAGTC TGAAGATTTTGCAGTTTATTACTGTCAGC AGCACACGTCTGGCCTCTCACTTTTGGC GGAGGGACCAAGGTTGAGATCAAACGGGC CGCTGCCCTTGATAATGAAAAGTCAAACG GAACAATCATTCACGTGAAGGGCAAGCAC CTCTGTCCGTACCCCTGTTCCTGGTCC ATCCAAGCCATTCTGGGTGTTGGTCGTAG TGGGTGGAGTCCTCGCTTGTACTCTCTG CTCGTCACCGTGGCTTTTATAATCTTCTG GGTTAGATCCAAAAGAAGCCGCCTGCTCC ATAGCGATTACATGAATATGACTCCACGC CGCCCTGGCCCCACAAGGAAACACTACCA GCCTTACGCACCACCTAGAGATTTTCGTG CCTATCGGAGCAGGGTGAAGTTTTCAGA TCTGCAGATGCACCAGCGTATCAGCAGGG CCAGAACCACTGTATAACGAGCTCAACC TGGGACGCAGGGAAGAGTATGACGTTTGTG GACAAGCGCAGAGGACGGGACCCTGAGAT GGGTGGCAAACCAAGACGAAAAAACCC AGGAGGGTCTCTATAATGAGCTGCAGAAG GATAAGATGGCTGAAGCCTATTCTGAAAT AGGCATGAAAGGAGAGCGGAGAAGGGGAA AAGGGCACGACGGTTTGTACCAGGGACTC AGCACTGCTACGAAGGATACTTATGACGC TCTCCACATGCAAGCCCTGCCACCTAGGT AA	161	MALPVTALLLPLALLL HAARPQVQLVESGGGV VQFGRSLRLSCAASGF TFSSYGMHWVRQAPGK GLEWVAVISYDGSNKY YADSVKGRFTISRDN KNTLYLQMNLSRAEDT AVYYCVKGPLQEPYP YGMDEVWQGTTVTVSS GSTSGSGKPGSGEGST KGEIVMTQSPATLSVS PGERATLSCRASQSVS SNLAWYQQKPGQAPRL LIYSASTRATGIPARF SGSGSGTEFTLTISL QSEDFAVYYCQHHVW PLTFGGGTKEIKRAA ALDNEKSNGTIIHVKG KHLCPSPFPGPSKPF WVLVVVGVLACYSLL VTVAFIIFWVRSKRSR LLHSDYMNMTFRRPGP TRKHYQPYAPPRDFAA YRSRVKFSRSADAPAY QQGQNQLYNELNLGRR EEYDVLDRKRRDP GGKPRRKNPQEGLYNE LQKDKMAEAYSEIGMK GERRRGKGHDGLYQGL STATKDTYDALHMQAL PFR	162
RD- 21530CARLx H	ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCCGAAATAGTGATGACGCAGTCTCCA GCCACCCTGTCTGTGTCTCCAGGGGAAAG AGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGCAACTTAGCCTGGTACCAG CAGAAACCTGGCCAGGCTCCCAGGCTCCT CATCTATAGCGCATCCACCAGGGCCACTG	163	MALPVTALLLPLALLL HAARPEIVMTQSPATL SVSPGERATLSCRASQ SVSSNLAWYQQKPGQA PRLLIYSASTRATGIP ARFSGSGSGTEFTLT SSLQSEDFAVYYCQQH HVWPLTFGGGTKEIK	164

	<p>GTATCCCAGCCAGGTTTCAGTGGCAGTGGG TCTGGGACAGAGTTCACTCTCACCATCAG CAGCCTGCAGTCTGAAGATTTTGCAGTTT ATTACTGTCAGCAGCACCACGTCTGGCCT CTCACTTTTGGCGGAGGGACCAAGGTTGA GATCAAACGGGGGTCTACATCCGGCTCCG GGAAGCCCGAAGTGGCGAAGGTAGTACA AAGGGGCAGGTGCAGCTGGTGGAGTCTGG GGGAGGCGTGGTCCAGCCTGGGAGGTCCC TGAGACTCTCCTGTGCAGCGTCTGGATTC ACCTTCAGTAGCTATGGCATGCACTGGGT CCGCCAGGCTCCAGGCAAGGGGCTGGAGT GGGTGGCAGTTATATCGTATGATGGAAGT AATAAATACTATGCAGACTCCGTGAAGGG CCGATTACCATCTCCAGAGACAATTCCA AGAACACGCTGTATCTGCAATGAACAGC CTGAGAGCCGAGGACACGGCGGTGTACTA CTGCGTCAAGGGGCCGTTGCAGGAGCCGC CATACGATTATGGAATGGACGTATGGGGC CAGGGAACAACGTGTCAACGCTCTCCTCAGC CGCTGCCCCTTGATAATGAAAAGTCAAACG GAACAATCATTCACGTGAAGGGCAAGCAC CTCTGTCCGTCAACCTTGTTCCTGGTCC ATCCAAGCCATTCTGGGTGTTGGTCGTAG TGGGTGGAGTCCTCGCTTGTACTCTCTG CTCGTCACCGTGGCTTTTATAATCTTCTG GGTTAGATCCAAAAGAAGCCGCTGCTCC ATAGCGATTACATGAATATGACTCCACGC CGCCCTGGCCCCACAAGGAAACACTACCA GCCTTACGCACCACCTAGAGATTTTCGCTG CCTATCGGAGCAGGGTGAAGTTTTCCAGA TCTGCAGATGCACCAGCGTATCAGCAGGG CCAGAACCAACTGTATAACGAGCTCAACC TGGGACGCAGGGAAGAGTATGACGTTTTG GACAAGCGCAGAGGACGGGACCCTGAGAT GGGTGGCAAACCAAGACGAAAAAACCCCC AGGAGGGTCTCTATAATGAGCTGCAGAAG GATAAGATGGCTGAAGCCTATTCTGAAAT AGGCATGAAAGGAGAGCGGAGAAGGGGAA AAGGGCACGACGGTTTTGTACCAGGGACTC AGCACTGCTACGAAGGATACTTATGACGC TCTCCACATGCAAGCCCTGCCACCTAGGT AA</p>		<p>RGSTSGSGKPGSGEGS TKGQVQLVESGGGVVQ PGRSLRLSCAASGFTF SSYGMHWVRQAPGKGL EWVAVISYDGSNKYYA DSVKGRFTISRDN SKN TLYLQMNSLRAEDTAV YYCVKGPLQEPFYDYG MDVWGQGTTVTVSSAA ALDNEKSNGTIIHVKG KHLCPSPFLPGPSKPF WVLVVVGGVLACYSLL VTVAFIIFWVRSKRSR LLHSDYMNMTPRRPGP TRKHYQPYAPPRDFAA YRSRVKFSRSADAPAY QQGQNQLYNELNLGRR EEYDVLDKRRGRDPEM GGKPRRKNPQEGLYNE LQKDKMAEAYSEIGMK GERRRGKGDGLYQGL STATKDTYDALHMQAL PPR</p>	
Clone 24C1 THD CAR DNA HxL	<p>ATGGCACTCCCCGTAACGTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTCCAACGTGCAAGAAAGCGGA CCCGGACTGGTGAAGCCTTCTGAGACACT TAGTCTGACGTGCACGGTCAGTGGCGGCT CCATCTCCTCCTATTATTGGTCATGGATA CGACAACCCCGAGGTAAGGGCCTGGAATG GATTGGCTATATCTACTATTCAGGAAGCA CGAACTACAATCCCAGCCTGAAGTCCC GA GTGACAATTTAGTAGATACCAAGTAAAAA CCAGTTCAGTCTTAACTGTCAAGCGTGA CAGCTGCCGACACCGCTGTGTATTACTGC GTCTCACTGGTGTATTGTGGAGGGGATTG TTATAGCGGGTTCGATTATTGGGGACAGG GAACCCTGGTGAAGTGTATCTCCGGCGGC GGCGGCTCAGGGGGTGGCGGTAGTGGCGG</p>	165	<p>MALPVTALLPLALLL HAARPQVQLQESGPG VKPSETLSLTCTVSGG SISSYYWSWIRQPPGK GLEWIGYIYSGSTNY NPSLKSRTVISVDTSK NQFSLKLSSVTAADTA VYYCVSLVYCGGDCYS GFDYWGQGTLVTVSSG GGSGGGSGGGGSDI QLTQSPSSLASVGD VSFTCQASQDINNFLN WYQQKPKAPKLLIYD ASNLETGVPSPRFSGS SGTDFTFTISSLQPED IATYYCQYGNLPFTF</p>	166

	<p>TGGGGGTTCCGATATTCAACTGACACAAT CCCCCAGCTCACTCAGCGCCAGCGTGGGG GACAGGGTTAGCTTTACCTGTCAAGCCTC TCAGGATATAAATAACTTTCTGAAGTGGT ATCAACAGAAAGCCTGGGAAGGCGCCCAA CTCCTGATCTATGATGCGTCCAACCTGGA AACTGGCGTGCTTTCACGCTTTAGCGGCT CTGGCAGTGGTACAGACTTCACTTTTACC ATCTCTTCACTTCAGCCGGAGGACATCGC CACATATTACTGTCAACAGTACGGAACCT TGCCCTTTACTTTTGGAGGCGGCACCAAA GTTGAAATCAAAGGGCCGCTGCCCTGGA TAACGAAAAGAGCAATGGGACTATAATAC ATGTTAAAGGAAAACACCTGTGTCCATCT CCCCTGTTCCCTGGACCGTCAAAGCCATT TTGGGTGCTCGTGGTTGTGCGTGGCGTTC TCGCCTGTTATAGCTTGCTGGTGACAGTA GCCTTCATTATCTTTTGGGTGAGATCCAA AAGAAGCCGCTGCTCCATAGCGATTACA TGAATATGACTCCACGCCGCCCTGGCCCC ACAAGGAAACACTACCAGCCTTACGCACC ACCTAGAGATTTGCTGCTATCGGAGCA GGGTGAAGTTTCCAGATCTGCAGATGCA CCAGCGTATCAGCAGGGCCAGAACCACT GTATAACGAGCTCAACCTGGGACGCAGGG AAGAGTATGACGTTTGGACAAGCGCAGA GGACGGGACCCTGAGATGGGTGGCAAACC AAGACGAAAAAACCCCGAGAGGGTCTCT ATAATGAGCTGCAGAAGGATAAGATGGCT GAAGCCTATTCTGAAATAGGCATGAAAGG AGAGCGGAGAAGGGGAAAAGGGCACGACG GTTTGTACCAGGGACTCAGCACTGCTACG AAGGATACTTATGACGCTCTCCACATGCA AGCCCTGCCACCTAGGTAA</p>		<p>GGGTKVEIKRAAALDN EKSNGTIIHVKGKHL PSPLFPGPSKPFVWL VVGGLVACYSLLVTV FIIFWVRSKRSRLHS DYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSR VKFSRSADAPAYQQGQ NQLYNELNLGRREEYD VLDKRRGRDPEMGGKP RRKNPQEGLYNELQKD KMAEAYSEIGMKGERR RGKGHDGLYQGLSTAT KDTYDALHMQALPPR</p>	
<p>(CAR1.1) Clone 24C1 THD CAR DNA HxL</p>	<p>CAGGTCCAAGTGAAGAAAGCGGACCCGG ACTGGTGAAGCCTTCTGAGACACTTAGTC TGACGTGCACGGTCACTGGCGGCTCCATC TCCTCCTATTATTGGTCATGGATACGACA ACCCCCAGGTAAGGGCCTGGAATGGATTG GCTATATCTACTATTTCAGGAAGCACGAAC TACAATCCCAGCCTGAAGTCCCGAGTGAC AATTTCAGTAGATACAGTAAAAACCACT TCAGTCTTAACTGTCAAGCGTGACAGCT GCCGACACCGCTGTGTATTACTGCGTCTC ACTGGTGTATTGTGGAGGGATTGTTATA GCGGGTTCGATTATTGGGGACAGGGAACC CTGGTGACTGTATCTTCCGGCGGCGGCGG CTCAGGGGGTGGCGGTAGTGGCGGTGGGG GTTCCGATATTCAACTGACACAATCCCC AGCTCACTCAGCGCCAGCGTGGGGGACAG GGTTAGCTTTACCTGTCAAGCCTCTCAGG ATATAAATAACTTTCTGAACTGGTATCAA CAGAAGCCTGGGAAGGCGCCAACTCCT GATCTATGATGCGTCCAACCTGGAACTG GCGTGCTTTCACGCTTTAGCGGCTCTGGC AGTGGTACAGACTTCACTTTTACCATCTC TTCACCTCAGCCGGAGGACATCGCCACAT ATTACTGTCAACAGTACGGAACCTTGCCC TTTACTTTTGGAGGCGGCACCAAAGTTGA</p>	167	<p>QVQLQESGPGLVKPS E TLSLTCTVSGGSISS Y YWSWIRQPPGKGLEW I GYIYYSGSTNYPNPSL K SRVTISVDTSKNQFSL L KLSSVTAADTAVYYCV S SLVYCGGDCYSGFDYW G GQGTLTVTVSSGGGSG G GGGSGGGGSDIQLTQS P PSSLSASVGRVSTFC Q QASQDINNFLNWWYQK P PGKAPKLLIYDASNLE T TGVPSRFSGSGSGTDF T TFTISSLQPEDIATYY C CQQYGNLPFTFGGGTK V VEIKRAAALDNEKSN G TIIHVKGKHLCPSP L PGPSKPFVWLTVVVG G LACYSLLVTVAFIIFW V VRSKRSRLHSDYMN M TPRRPGPTRKHYPYA P PPRDFAYRSRVKFSR S SADAPAYQQGNQLYN E ELNLGRREEYDVLDR K RGRDPEMGGKPRKNP</p>	168

	AATCAAAGGGCCGCTGCCCTGGATAACG AAAAGAGCAATGGGACTATAATACATGTT AAAGGAAAACACCTGTGTCCATCTCCCT GTTCCCTGGACCGTCAAAGCCATTTTGGG TGCTCGTGGTTGTGGTGGCGTTCTCGCC TGTTATAGCTTGCTGGTGACAGTAGCCTT CATTATCTTTTGGGTGAGATCCAAAAGAA GCCGCCTGCTCCATAGCGATTACATGAAT ATGACTCCACGCCGCCCTGGCCCCACAAG GAAACACTACCAGCCTTACGCACCACCTA GAGATTTTCGCTGCCTATCGGAGCAGGGTG AAGTTTTCCAGATCTGCAGATGCACCAGC GTATCAGCAGGGCCAGAACCAACTGTATA ACGAGCTCAACCTGGGACGCAGGGAAGAG TATGACGTTTTGGACAAGCGCAGAGGACG GGACCCTGAGATGGGTGGCAAACCAAGAC GAAAAAACCCCAAGGAGGGTCTCTATAAT GAGCTGCAGAAGGATAAGATGGCTGAAGC CTATTCTGAAATAGGCATGAAAGGAGAGC GGAGAAGGGGAAAAGGGCACGACGGTTTG TACCAGGGACTCAGCACTGCTACGAAGGA TACTTATGACGCTCTCCACATGCAAGCCC TGCCACCTAGG		QEGLYNELQKDKMAEA YSEIGMKGERRRGKGH DGLYQGLSTATKDTYD ALHMQUALPPR	
(CAR1.2) Clone 24C1 CHD CAR DNA HxL	ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTGCAGCTGCAGGAATCCGGA CCGGGGCTGGTGAAGCCAGCGAGACTCT GAGTCTCACGTGTACAGTTTCTGGAGGTA GCATTAGCTCCTACTATTGGTCATGGATA AGGCAGCCCCCGGGAAGGGATTGGAATG GATCGGCTATATTTACTACAGTGGGAGCA CCAATTACAACCCCTCACTGAAGTCTAGA GTTACAATCAGCGTTGACACCTCAAAGAA TCAGTTCAAGTTTGAAATTGTCTAGCGTCA CAGCAGCTGATACAGCCGTCTATTATTGT GTTTCTCTGGTCTATTGCGGTGGGGATTG TTACAGTGGCTTTGACTATTGGGGGCAGG GTAATCTGGTTACAGTTTCTTCCGGGGGG GGAGGCTCTGGGGCGGAGGCTCAGGTGG TGGAGGCAGCGACATCCAGTTGACACAGA GCCCGAGTTCCTTGTCCGCTCCGTCCGGG GATAGAGTGTCAATTTACCTGTGAGGCCTC TCAGGATATTAATAACTTTCTGAATTGGT ATCAGCAAAGCCCCGGAAGGCACCCAAG CTGTTGATTTACGACGCCAGTAACCTGGA GACAGGCGTGCCCTCCCGGTTTAGTGGTA GCGGAAGCGGTACGGATTTTACCTTTACT ATCAGCTCTCTCCAACCGAAGACATTGC AACCTACTATTGTCAACAATATGGAAACC TGCCTTTTACATTTGGCGGCGGCACCAAG GTGGAGATTAAGCGGGCGGCAGCTATTGA GGTGATGTATCCACCGCCTTACCTGGATA ACGAAAAGAGTAACGGTACCATCATTCAC GTGAAAGGTAAACACCTGTGTCCTTCTCC CCTCTTCCCCGGGCCATCAAAGCCCTTCT GGGTTCTTGTGGTCTGTTGGGAGGCGTCTT GCTTGTTATTCTCTGCTCGTTACCGTGGC GTTTATCATTTTTTGGGTTAGATCCAAA GAAGCCGCTGCTCCATAGCGATTACATG	169	MALPVTALLPLALLL HAARPQVQLQESGPG VKPSETLSLTCTVSGG SISSYYWSWIRQPPGK GLEWIGYIYSGSTNY NPSLKSRTISVDTSK NQFSLKLSSVTAADTA VYYCVSLVYCGGDCYS GFDYWGQGTILTVSSG GGSGGGSGGGSGSDI QLTQSPSSLSASVGD VSFTCQASQDINNFLN WYQQKPGKAPKLLIYD ASNLETGVPSTRFSGS SGTDFTFTISSLPED IATYYCQYGNLPFTF GGGKVEIKRAAAIEV MYPPPYLDNEKSNGTI IHVKGKHLCPSPFP PSKPFWLVVVGGLA CYSLLVTVAFIIFWVR SKRSRLHSDYMNMT RRPGPTRKHYQPYAPP RDFAAYSRVKFSRSA DAPAYQQQNQLYNEL NLGRREEYDVLKRRG RDPFMGGKPRRKNPQE GLYNELQKDKMAEAYS EIGMKGERRRGKGDH LYQGLSTATKDTYDAL HMQUALPPR	170

	AATATGACTCCACGCCGCCCTGGCCCCAC AAGGAAACACTACCAGCCTTACGCACCAC CTAGAGATTTTCGCTGCCTATCGGAGCAGG GTGAAGTTTTCCAGATCTGCAGATGCACC AGCGTATCAGCAGGGCCAGAACCAACTGT ATAACGAGCTCAACCTGGGACGCAGGGAA GAGTATGACGTTTTGGACAAGCGCAGAGG ACGGGACCCTGAGATGGGTGGCAAACCAA GACGAAAAAACCCCAAGGAGGGTCTCTAT AATGAGCTGCAGAAGGATAAGATGGCTGA AGCCTATTCTGAAATAGGCATGAAAGGAG AGCGGAGAAGGGGAAAAGGGCACGACGGT TTGTACCAGGGACTCAGCACTGCTACGAA GGATACTTATGACGCTCTCCACATGCAAG CCCTGCCACCTAGGTAA			
(CAR1.2) Clone 24C1 CHD CAR DNA HxL	CAGGTGCAGCTGCAGGAATCCGACCGGG GCTGGTGAAGCCCAGCGAGACTCTGAGTC TCACGTGTACAGTTTCTGGAGGTAGCATT AGCTCCTACTATTGGTCATGGATAAGGCA GCCCCCGGGGAAGGGATTGGAATGGATCG GCTATATTTACTACAGTGGGAGCACCAAT TACAACCCCTCACTGAAGTCTAGAGTTAC AATCAGCGTTGACACCTCAAAGAATCAGT TCAGTTTGAAATTGTCTAGCGTCACAGCA GCTGATACAGCGTCTATATTGTGTTC TCTGGTCTATTGCGGTGGGGATTGTACA GTGGCTTTGACTATTGGGGCAGGGTACT CTGGTTACAGTTTCTTCCGGGGGGGAGG CTCTGGGGCGGAGGCTCAGGTGGTGGAG GCAGCGACATCCAGTTGACACAGAGCCCG AGTTCCTTGTCCGCCTCCGTCGGGGATAG AGTGTCAATTTACCTGTCAGGCCTCTCAGG ATATTAATAACTTTCTGAATTGGTATCAG CAAAAGCCCCGAAAGGCACCCAAGCTGTT GATTTACGACGCCAGTAACCTGGAGACAG GCGTGCCCTCCCGGTTTAGTGGTAGCGGA AGCGGTACGGATTTTACCTTTACTATCAG CTCTCTCCAACCCGAAGACATTGCAACCT ACTATTGTCAACAATATGAAACCTGCCT TTTACATTTGGCGGCGGCACCAAGGTGGA GATTAAGCGGGCGGCAGCTATTGAGGTGA TGTATCCACGCTTACCTGGATAACGAA AAGAGTAACGGTACCATCATTACGTGAA AGGTAAACACCTGTGTCTTCTCCCCTCT TCCCCGGCCATCAAAGCCCTTCTGGGTT CTTGTGGTCGTGGGAGGCGTGCTTGCTTG TTATTCTCTGCTCGTTACCGTGGCGTTTA TCATTTTTTTGGGTTAGATCCAAAAGAAGC CGCCTGCTCCATAGCGATTACATGAATAT GACTCCACGCCGCCCTGGCCCCACAAGGA AACACTACCAGCCTTACGCACCACCTAGA GATTTTCGCTGCCTATCGGAGCAGGGTGAA GTTTTCCAGATCTGCAGATGCACCAGCGT ATCAGCAGGGCCAGAACCAACTGTATAAC GAGCTCAACCTGGGACGCAGGGAAGAGTA TGACGTTTTGGACAAGCGCAGAGGACGGG ACCTTGAGATGGGTGGCAAACCAAGACGA AAAAACCCCAAGGAGGGTCTCTATAATGA GCTGCAGAAGGATAAGATGGCTGAAGCCT	171	QVQLQESGPGLVKPSSE TSLTCTVSGGSISSY YWSWIRQPPKGLEWI GYIYYSGSTNYPNPSLK SRVTISVDTSKNQFSL KLSSVTAADTAVYYCY SLVYCGGDCYSGFDYW GQGTLVTVSSGGGSG GGSGGGGSDIQLTQS PSSLASVGDVRSFTC QASQDINNFLNWFYQQK PGKAPKLLIYDASNLE TGVPSRFSGSGSGTDF TFTISSLQPEDATYY CQQYGNLPFTFGGGTK VEIKRAAAIEVMYPPP YLDNEKSNGTIIHVKG KHLCPSPFPFGPSKPF WVLVVVGGVLACYSLL VTVAFIIIFWVRKRSR LLHSDYMNMTFRRPGP TRKHYQPYAPPRDFAA YRSRVKFSRSADAPAY QQGQNQLYNELNLGR EEYDVLDRGRDPEM GGKPRRNKPQEGLYNE LQKDKMAEAYSEIGMK GERRRGKGDGLYQGL STATKDTYDALHMQAL PPR	172

	ATTCTGAAATAGGCATGAAAGGAGAGCGG AGAAGGGGAAAAGGGCACGACGGTTTGT CCAGGGACTCAGCACTGCTACGAAGGATA CTTATGACGCTCTCCACATGCAAGCCCTG CCACCTAGG			
(CAR1.3) Clone 24C1 CD8 CAR DNA HxL	ATGGCACTCCCCGTAACCTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCCGAGGTGCAATTGCAAGAGTCCGGC CCCGGACTCGTTAAACCCAGTGAGACGCT TAGCCTGACCTGTACCGTCTCAGGGGGCA GCATCTCCTCTTATTACTGGAGCTGGATC AGGCAGCCTCCAGGAAAAGGCCTTGAATG GATTGGGTACATCTACTACTCTGGCTCAA CAAATTATAATCCATCCCTGAAGTCCCGC GTGACTATCTCTGTGGACACCAGCAAGAA TCAGTTTTCACTGAAGTTGTCTAGTGTTA CCGCGGCCGACACCGCCGTATACTACTGT GTGTCTCTTGTGTACTGTGGCGGCGACTG CTATTCGGGTTCGACTACTGGGGCCAAG GGACTCTGGTAACCGTGTCTCAGGCGGC GGCGGGTCAGGAGGAGCGGCAGTGGAGG TGGCGGCTCCGACATCCAGCTGACACAAT CACCATCTTCCCTTTCAGCTTCAGTCGGG GACAGAGTGTCTTACATGCCAGGCCAG CCAGGATATCAATAACTTCTGAAGTGGT ACCAACAGAAACCCGGAAGGCTCCAAAG CTCCTGATCTATGATGCTTCCAACCTGGA GACCGGCGTGCCCTCCAGTTTCAGTGTT CAGGATCAGGCACTGACTTTACGTTCAAC ATATCCAGTCTTCAGCCCGAAGACATTGC AACCTATTACTGCCAACATAACGGGAACC TTCCCTTTTACATTCCGAGGCGGCACCAAG GTGGAAATCAAAGGGCTGCAGCATTGAG CAACTCAATAATGTATTTTAGTCACTTTG TACCAGTGTCTTGGCGGCTAAGCCTACT ACCACACCCGCTCCACGGCCACCTACCCC AGCTCCTACCATCGCTTCACAGCCTCTGT CCCTGCGCCCAGAGGCTTGCCGACCGGCC GCAGGGGGCGCTGTTATACAGAGGACT GGATTTTCGCTGCGATATCTATATCTGGG CACCCCTGGCCGGAACCTGCGGCGTACTC CTGCTGTCCCTGGTCATCAGCTCTATTG TAATCACAGGAACAGATCCAAAAGAAGCC GCCTGCTCCATAGCGATTACATGAATATG ACTCCACGCGCCCTGGCCCCACAAGGAA ACACTACCAGCCTTACGCACCACCTAGAG ATTTGCTGCCTATCGGAGCAGGGTGAAG TTTTCCAGATCTGCAGATGCACCAGCGTA TCAGCAGGGCCAGAACCAGTGTATAACG AGCTCAACCTGGGACGCAGGGAAGAGTAT GACGTTTTGGACAAGCGCAGAGGACGGGA CCCTGAGATGGGTGGCAAACCAAGACGAA AAAACCCCCAGGAGGGTCTCTATAATGAG CTGCAGAAGGATAAGATGGCTGAAGCCTA TTCTGAAATAGGCATGAAAGGAGAGCGGA GAAGGGGAAAAGGGCACGACGGTTTGTAC CAGGGACTCAGCACTGCTACGAAGGATAC TTATGACGCTCTCCACATGCAAGCCCTGC CACCTAGGTAA	173	MALPVTALLLPLALLL HAARPQVQLQESGPGL VKPSETLSLTCTVSGG SISSYYWSWIRQPPGK GLEWIGYIYYSGSTNY NPSLKSRVTISVDTSK NQFSLKLSSVTAADTA VYYCVSLVYCGGDCYS GFDYWGGQTLVTVSSG GGGSGGGSGGGGSDI QLTQSPSSLSASVGD VSFTCQASQDINNFLN WYQQKPGKAPKLLIYD ASNLETGVPSTRFSGS SGTDFTFTISSLQPED IATYYCQYGNLPTF GGGKVEIKRAAALSN SIMYFSHFVPVFLPAK PTTTPAPRPPTPPTI ASQPLSLRPEACRPAA GGAVHTRGLDFACDIY IWAPLAGTCGVLLLSL VITLYCNHRNRSKRSR LLHSDYMNMTPRRPGP TRKHYPYAPPRDFAA YRSRVKFSRSADAPAY QQGQNQLYNELNLGRR EEYDVLDKRRGRDPEM GGKPRRKNPQEGLYNE LQKDKMAEAYSEIGMK GERRRGKGHDLGYQGL STATKDTYDALHMQAL PPR	174

(CAR1.3) Clone 24C1 CD8 CAR DNA HxL	CAGGTGCAATTGCAAGAGTCCGGCCCCGG ACTCGTTAAACCCAGTGAGACGCTTAGCC TGACCTGTACCGTCTCAGGGGCGAGCATC TCCTCTTATTACTGGAGCTGGATCAGGCA GCCTCCAGGAAAAGGCCTTGAATGGATTG GGTACATCTACTACTCTGGCTCAACAAAT TATAATCCATCCCTGAAGTCCCGCGTGAC TATCTCTGTGGACACCAGCAAGAATCAGT TTTCACTGAAGTTGTCTAGTGTACCGCG GCCGACACCGCGGTATACTACTGTGTGTC TCTTGTGTACTGTGGCGGCGACTGCTATT CCGGGTTCTGACTACTGGGGCCAAGGGACT CTGGTAACCGTGTCTCAGCGGCGCGCGG GTCAGGAGGAGGCGGCAGTGGAGGTGGCG GCTCCGACATCCAGCTGACACAATCACCA TCTTCCCTTTCAGCTTCAGTCGGGGACAG AGTGTCTTTCACATGCCAGGCCAGCCAGG ATATCAATAACTTCTGAAGTGGTACCAA CAGAAACCCGAAAGGCTCCAAAGCTCCT GATCTATGATGCTTCCAACCTGGAGACCG GCGTGCCCTCCAGGTTCACTGGTTCAGGA TCAGGCACTGACTTTACGTTCAACATATC CAGTCTTCAGCCGAAGACATTGCAACCT ATTACTGCCAACAATACGGGAACCTTCCC TTTACATTTCGAGGCGGCACCAAGGTGGA AATCAAAGGGCTGCAGCATTGAGCAACT CAATAATGTATTTTAGTCACTTTGTACCA GTGTTCTTGCCGGCTAAGCTACTACCAC ACCCGCTCCACGGCCACCTACCCAGCTC CTACCATCGCTTCACAGCCTCTGTCCCTG CGCCCAGAGGCTTGCCGACCGGCCGAGG GGGCGCTGTTTCATACCAGAGGACTGGATT TCGCCTGCGATATCTATATCTGGGCACCC CTGGCCGGAACCTGCGGCGTACTCCTGCT GTCCCTGGTCATCACGCTCTATTGTAATC ACAGGAACAGATCCAAAAGAAGCCGCTG CTCCATAGCGATTACATGAATATGACTCC ACGCCGCCCTGGCCCCACAAGGAAACACT ACCAGCCTTACGCACCACCTAGAGATTTC GCTGCCTATCGGAGCAGGGTGAAAGTTTC CAGATCTGCAGATGCACCAGCGTATCAGC AGGGCCAGAACCAACTGTATAACGAGCTC AACCTGGGACGCAGGGAAGAGTATGACGT TTTGGACAAGCGCAGAGGACGGGACCCCTG AGATGGGTGGCAAACCAAGACGAAAAAAC CCCCAGGAGGTCTCTATAATGAGCTGCA GAAGGATAAGATGGCTGAAGCCTATTCTG AAATAGGCATGAAAGGAGAGCGGAGAAGG GGAAAAGGGCACGACGGTTTGTACCAGGG ACTCAGCACTGCTACGAAGGATACTTATG ACGCTCTCCACATGCAAGCCCTGCCACCT AGG	175	QVQLQESGPGLVKPS E TSLTCTVSGGSISS Y YWSWIRQPPGKLEW I GYIYYSGSTNYPNPS L K SRVTISVDTSKNQFSL KLSSVTAADTAVYYCV SLVYCGGDCYSGFDYW GGQTLVTVSSGGGGSG GGGSGGGSDIQLTQS PSSLSASVGDVSVFTC QASQDINNFLNWFYQQ K PGKAPKLLIYDASNLE TGVPSRFSGSGSGTDF TFTISSLPEDIATYY CQQYGNLPFTFGGGTK VEIKRAAALSNSIMYF SHFVPVFLPAKPTTTP APRPPTPAPTIASQPL SLRPEACRPAAGGAVH TRGLDFACDIYIWAPL AGTCGVLLLSLVITLY CNHRNRSKRSLHSD YMNMTPRRPGPTRKHY QPYAPPRDFAAYRSRV KFSRSADAPAYQQGQN QLYNELNLGRREYDV LDKRRGRDPEMGGKPR RKNPQEGLYNELQKDK MAEAYSEIGMKGERRR GKGHDGLYQGLSTATK DTYDALHMQALPPR	176
(CAR1.4) Clone 24C1 THD CAR DNA LxH	ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGGATATCCAGCTCACGCAATCCCC TCAAGCTTGAGTGCCCTCCGTGGGCGACCG GGTGTCTTTCACATGTGAGGCAAGCCAAG ACATAAATAATTTCTGAATTGGTACCAA CAAAAACCCGGCAAGGCTCCCAAACCTCT	177	MALPVTALLPLALLL HAARPDIQLTQSPSSL SASVGDVSVFTCQASQ DINNFLNWFYQQKPGKA PKLLIYDASNLETGVP SRFSGSGSGTDFFTI SSLPEDIATYYCQQY	178

	GATTTATGATGCCTCCAATCTGGAGACCG GGGTCCCTTCTAGATTACAGCGGAAGTGGC AGCGGCACAGACTTTACATTTACTATCTC TTCTCTGCAACCAGAGGACATCGCCACAT ACTATTGCCAGCAATACGGCAATCTGCCC TTCACCTTCGGAGGCGGAACCAAGGTAGA AATTAAAAGGGGCGGTGGAGGCTCCGGAG GGGGGGGCTCTGGCGGAGGGGCTCCCAA GTACAATTGCAGGAGTCAGGGGCTGGACT CGTGAAGCCTTCAGAACTTTGTCACTGA CATGTACAGTGTCCGGCGGAAGCATTTC AGTTACTATTGGTCCTGGATTAGACAGCC ACCCGGCAAAGGACTGGAATGGATTGGAT ATATCTACTACTCTGGATCTACAACTAT AATCCCAGCCTCAAATCCAGGGTCACTAT TAGTGTGGATACATCAAAGAATCAGTTCT CCTTGAAGCTGAGCTCAGTCACTGCTGCC GACACCGCAGTGTACTATTGTGTGAGCCT GGTCTACTGCGGCGGAGATTGCTACAGCG GTTTCGATTACTGGGGCCAGGGCACCCCTG GTTACCGTTAGTTCGCGGCTGCTCTTGA TAACGAGAAGTCCAACGCTACGATTATCC ACGTTAAGGGTAAGCACCTTTGCCCTAGC CCGCTGTTCCAGGCCCCAGTAAGCCCTT TTGGGTCCCTCGTTGTGGTAGGTGGGGTAC TCGCCTGCTACTCCCTGCTCGTCACTGTC GCATTTCATCATCTTCTGGGTCAAGTCCAA AAGAAGCCGCTGCTCCATAGCGATTACA TGAATATGACTCCACGCCGCCCTGGCCCC ACAAGGAAACACTACCAGCCTTACGCACC ACCTAGAGATTTGCTGCCTATCGGAGCA GGGTGAAGTTTTCCAGATCTGCAGATGCA CCAGCGTATCAGCAGGGCCAGAACCAACT GTATAACGAGCTCAACCTGGGACGCAGGG AAGAGTATGACGTTTTGGACAAGCGCAGA GGACGGGACCCTGAGATGGGTGGCAAACC AAGACGAAAAAACCCCAAGAGGGTCTCT ATAATGAGCTGCAGAAGGATAAGATGGCT GAAGCCTATTCTGAAATAGGCATGAAAGG AGAGCGGAGAAGGGGAAAAGGGCACGACG GTTTGTACCAGGGACTCAGCACTGCTACG AAGGATACTTATGACGCTCTCCACATGCA AGCCCTGCCACCTAGGTAA		GNLPFTFGGGTKVEIK RGGGSGGGSGGGGS QVQLQESGPGLVKPS TSLTCTVSGGSISSY YWSWIRQPPGKLEWI GYIYSGSTNYPNPSLK SRVTISVDTSKNQFSL KLSSVTAADTAVYYCV SLVYCGDCYSGFDYW GQGTLVTVSSAAALDN EKSNGTIIHVKGKHL PSPLFPGPSKPFVWL VVGGLVACYLLVTVA FIIFWVRSKRSRLLS DYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSR VKFSRSADAPAYQQGQ NQLYNELNLGRREEYD VLDKRRGRDPEMGGKP RRKNPQEGLYNELQKD KMAEAYSEIGMKGERR RGKGDGLYQGLSTAT KDTYDALHMQALPPR	
(CAR1.4) Clone 24C1 THD CAR DNA LxH	GATATCCAGCTCAGCAATCCCCCTCAAG CTTGAGTGCCTCCGTGGGCGACCGGGTGT CCTTCACATGTACAGCAAGCCAAGACATA AATAATTTCCCTGAATTGGTACCAACAAAA ACCCGGCAAGGCTCCCAAACCTCTGATTT ATGATGCCTCCAATCTGGAGACCGGGGTC CCTTCTAGATTACAGCGAAGTGGCAGCGG CACAGACTTTACATTTACTATCTCTTCTC TGCAACCAGAGGACATCGCCACATACTAT TGCCAGCAATACGGCAATCTGCCCTTCAC CTTCGGAGGCGGAACCAAGGTAGAAATTA AAAGGGGCGGTGGAGGCTCCGGAGGGGGG GGCTCTGGCGGAGGGGGCTCCCAAGTACA ATTGCAGGAGTCAGGGCTGGACTCGTGA AGCCTTCAGAACTTTGTCACTGACATGT ACAGTGTCCGGCGGAAGCATTTCCAGTTA	179	DIQLTQSPSSLSASVG DRVSFTCQASQDINNF LNWYQQKPKGKAPKLLI YDASNLETGVPSRFSG SGSGTDFTFTISSLQP EDIATYYCQQYGNLPP TFGGGTKEIKRGGGG SGGGSGGGGSQVQLQ ESGPGLVKPSETLSLT CTVSGGSISSYYWSWI RQPPGKLEWIGYIYY SGSTNYPNPSLKSRVTI SVDTSKNQFSLKLSSV TAADTAVYYCVSLVYC GGDCYSGFDYWQGT VTVSSAAALDNEKSNG	180

	<p>CTATTGGTCCTGGATTAGACAGCCACCCG GCAAAGGACTGGAATGGATTGGATATATC TACTACTCTGGATCTACAACTATAATCC CAGCCTCAAATCCAGGGTCACTATTAGTG TGGATACATCAAAGAATCAGTTCTCCTTG AAGCTGAGCTCAGTCACTGCTGCCGACAC CGCAGTGTACTATTGTGTGAGCCTGGTCT ACTGCGGCGGAGATTGTACAGCGGTTTC GATTACTGGGGCCAGGGCACCCCTGGTTAC CGTTAGTTCCGCGGCTGCTCTTGATAACG AGAAGTCCAACGGTACGATTATCCACGTT AAGGGTAAGCACCTTTGCCCTAGCCCGCT GTTCACAGGCCCCAGTAAGCCCTTTTGGG TCCTCGTTGTGGTAGGTGGGGTACTCGCC TGCTACTCCCTGCTCGTCACTGTGCGATT CATCATCTTCTGGGTGAGATCCAAAAGAA GCCGCCTGCTCCATAGCGATTACATGAAT ATGACTCCACGCGCCCTGGCCCCACAAG GAAACACTACCAGCCTTACGCACCACCTA GAGATTTTCGCTGCCTATCGGAGCAGGGTG AAGTTTTCCAGATCTGCAGATGCACCAGC GTATCAGCAGGGCCAGAACCACCTGTATA ACGAGCTCAACCTGGGACGCAGGGAAGAG TATGACGTTTTGGACAAGCGCAGAGGACG GGACCCTGAGATGGGTGGCAAACCAAGAC GAAAAAACCCCAAGGAGGTCTCTATAAT GAGCTGCAGAAGGATAAGATGGCTGAAGC CTATTCTGAAATAGGCATGAAAGGAGAGC GGAGAAGGGGAAAAGGGCACGACGGTTTG TACCAGGGACTCAGCACTGCTACGAAGGA TACTTATGACGCTCTCCACATGCAAGCCC TGCCACCTAGG</p>		<p>TIIHVKGKHLCPSPLF PGPSKPFWVLVVVGGV LACYSLLVTVAFIIFW VRSKRSRLHSDYMN TPRRPGPTRKHYQPYA PPRDFAAYSRVKFSR SADAPAYQQGQNQLYN ELNLGRREEYDVLDR RGRDPEMGGKPRRKNP QEGLYNELQDKMAEA YSEIGMKGERRRGKGH DGLYQGLSTATKDTYD ALHMQALPPR</p>	
(CAR1.5) Clone 24C1 CHD CAR DNA LxH	<p>ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGGATATCCAGCTGACCCAGTCTCCA TCCTCTTTGAGTGCCTCCGTGGGTGACCG CGTCTCTTTCACTTGCCAAGCCAGCCAAG ACATCAACAACTTTCTGAATTGGTACCAG CAGAAACCAGGCAAAGCACCAAGCTCCT CATCTACGACGCCTCCAACCTGGAACCG GGGTGCCCAGCAGGTTTAGCGGGAGCGGT TCTGGCACGGATTTTACGTTACCATCTC CTCTCTGCAGCCCGAGGATATAGCTACTT ATTACTGTGAGCAGTACGGGAATCTGCCA TTTACTTTTGGGGGTGGAATAAGGTGGA AATCAAAAGGGGCGCGGGGGAAGCGGGG GCGGGGGCTCAGGTGGCGGAGGGAGCCAG GTGCAACTCCAGGAAAGTGGCCAGGATT GGTGAAGCCAGCGAGACCCTTTCCCTTA CTTGACTGTAGCGGAGGCAGCATAAGC AGCTACTATTGGTCCTGGATCAGACAGCC ACCAGGGAAGGGCTTGAATGGATTGGCT ACATTTACTATTCCGGGTCCACCAACTAC AACCCATCCCTCAAGTCCCGCGTGACAAT TTCCGTCGACACAAGCAAGAACCAGTTCT CCCTGAACTTAGTAGCGTCACTGCTGCA GATACAGCAGTGTACTATTGTGTGAGCCT TGTCTACTGTGGCGGCGACTGCTACAGTG GCTTTGATTACTGGGGACAGGGCACGCTC</p>	181	<p>MALPVTALLPLALLL HAARPDILTQSPSSL SASVGDVRSFTCQASQ DINNFLNWYQQKPGKA PKLLIYDASNLETGVP SRFSGSGSGDFTFTI SSLQPEDIATYYCQY GNLPFTFGGGTKVEIK RGGGGSGGGSGGGGS QVQLQESGPGLVKPS TSLTCTVSGGSISSY YWSWIRQPPGKLEWI GYIYSGSTNYPNPSLK SRVTISVDTSKNQFSL KLSSVTAADTAVYYCV SLVYCGGDCYSGFDYW GQGTLVTVSSAAAEV MYPPPYLDNEKSNGTI IHVKGKHLCPSPLPFG PSKPFWVLVVVGGVLA CYSLLVTVAFIIFWVR SKRSRLHSDYMNMT RRPGPTRKHYQPYAPP RDFAAYS RVKFSRSA DAPAYQQGQNQLYNEL NLGRREEYDVLDRRG RDPPEMGGKPRRKNPQE</p>	182

	<p>GTGACAGTGTCCAGCGCTGCGGCTATCGA GGTAATGTATCCGCCACCGTATCTGGACA ACGAGAAGTCTAATGGGACAATCATTAC GTGAAGGGAAGCACCTGTGTCCATCCCC CCTGTTTCCGGGTCCCAGTAAACCCTTCT GGGTGCTTGTGTGCTTGGCGGGGTGCTG GCCTGCTATTCCCTGCTGGTGACCGTCGC GTTTATTATTTTCTGGGTAGATCCAAA GAAGCCGCCTGCTCCATAGCGATTACATG AATATGACTCCACGCCGCCCTGGCCCCAC AAGGAAACACTACCAGCCTTACGCACCAC CTAGAGATTTGCTGCTATCGGAGCAGG GTGAAGTTTTCCAGATCTGCAGATGCACC AGCGTATCAGCAGGGCCAGAACCAACTGT ATAACGAGCTCAACCTGGGACGCAGGGAA GAGTATGACGTTTTGGACAAGCGCAGAGG ACGGGACCCTGAGATGGGTGGCAAACCAA GACGAAAAACCCCCAGGAGGGTCTCTAT AATGAGCTGCAGAAGGATAAGATGGCTGA AGCCTATTCTGAAATAGGCATGAAAGGAG AGCGGAGAAGGGGAAAAGGACACGACGGT TTGTACCAGGGACTCAGCACTGCTACGAA GGATACTTATGACGCTCTCCACATGCAAG CCCTGCCACCTAGGTAA</p>		<p>GLYNELQDKMAEAYS EIGMKGERRRGKGHG LYQGLSTATKDTYDAL HMQALPPR</p>	
<p>(CAR1.5) Clone 24C1 CHD CAR DNA LxH</p>	<p>GATATCCAGCTGACCCAGTCTCCATCCTC TTTGAGTGCTCCGTGGGTGACCGCGTCT CTTTCACCTTGCCAAGCCAGCCAAGACATC AACAACTTTCTGAATTGGTACCAGCAGAA ACCAGGCAAAGCACCAAAGCTCCTCATCT ACGACGCCTCCAACCTGGAACCGGGGTG CCCAGCAGGTTTAGCGGGAGCGGTTCTGG CACGGATTTTACGTTACCATCTCCTCTC TGCAGCCCCAGGATATAGCTACTTATTAC TGTCAGCAGTACGGGAATCTGCCATTTAC TTTTGGGGGTGGAATAAGGTGGAATCA AAAGGGGCGGCGGGGAAGCGGGGCGGG GGCTCAGGTGGCGGAGGGAGCCAGGTGCA ACTCCAGGAAAGTGGCCCAGGATTGGTGA AGCCCAGCGAGACCCTTTCCCTTACTTGT ACTGTTAGCGGAGGCAGCATAAGCAGCTA CTATTGGTCTCGGATCAGACAGCCACCAG GGAAAGGGCTTGAATGGATTGGCTACATT TACTATTCCGGGTCCACCAACTACAACCC ATCCCTCAAGTCCCGCGTGACAATTTCCG TCGACACAAGCAAGAACCAGTTCTCCCTG AAACTTAGTAGCGTCACTGCTGCAGATAC AGCAGTGACTATTGTGTGACGCTTGTCT ACTGTGGCGGCGACTGCTACAGTGGCTTT GATTACTGGGACAGGGCACGCTCGTGAC AGTGTCCAGCGCTGCGGCTATCGAGGTAA TGTATCCGCCACCGTATCTGGACAACGAG AAGTCTAATGGGACAATCATTACAGTGAA GGGGAAGCACCTGTGTCCATCCCCCTGT TTCCGGGTCCCAGTAAACCCTTCTGGGTG CTTGTTGTGCTTGGCGGGGTGCTGGCCTG CTATCCCCTGCTGGTGACCGTCGCGTTTA TTATTTTCTGGGTAGATCCAAAAGAAGC CGCCTGCTCCATAGCGATTACATGAATAT GACTCCACGCCGCCCTGGCCCCACAAGGA</p>	183	<p>DIQLTQSPSSLSASVG DRVSFTCQASQDINNF LNWYQQKPKGKAPKLLI YDASNLETGVPSRFSG SGSGTDFFTISSLQP EDIATYYCQQYGNLPF TFGGGTKVEIKRGGG SGGGSGGGGSQVQLQ ESGPGLVKPSSETLSLT CTVSGGSISSYYWSWI RQPPGKGLEWIGYIYY SGSTNYPNPSLKSRVTI SVDTSKNQFSLKLSSV TAADTAVYYCVSLVYC GGDCYSGFDIWGQGT VTVSSAAAEVMPFP YLDNEKSNGTIIHVKG KHLCPSPLEFPGPSKPF WVLVVGGLACYSLL VTVAFIIFWVRKRSR LLHSDYMNMTFRRPGP TRKHYQPYAPPRDFAA YRSRVKFSRSADAPAY QQGQNQLYNELNLGRR EEYDVLDKRRGRDPEM GGKPRRKNPQEGLYNE LQDKMAEAYSEIGMK GERRRGKGHGGLYQGL STATKDTYDALHMQAL PPR</p>	184

	AACACTACCAGCCTTACGCACCACCTAGA GATTTTCGCTGCCTATCGGAGCAGGGTGAA GTTTTCCAGATCTGCAGATGCACCAGCGT ATCAGCAGGGCCAGAACCACTGTATAAC GAGCTCAACCTGGGACGCAGGGAAGAGTA TGACGTTTTGGACAAGCGCAGAGGACGGG ACCCTGAGATGGGTGGCAAACCAAGACGA AAAAACCCCCAGGAGGGTCTCTATAATGA GCTGCAGAAGGATAAGATGGCTGAAGCCT ATTCTGAAATAGGCATGAAAGGAGAGCGG AGAAGGGGAAAAGGGCACGACGGTTTGTA CCAGGGACTCAGCACTGCTACGAAGGATA CTTATGACGCTCTCCACATGCAAGCCCTG CCACCTAGG			
(CAR1.6) Clone 24C1 CD8 CAR DNA LxH	ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGACATTCAATTGACCCAGTCCCCT AGCAGTCTCTCAGCAAGTGTGGGAGATAG GGTGTCAATCACCTGTGAGGCTTCACAGG ACATCAACAACCTTCTCAATTGGTATCAG CAGAAGCCAGGGAAGGCACCAAGCTGCT CATATATGACGCTTCAAACCTTGAAACCG GAGTACCTAGCCGCTTCAGCGGAAGCGGA TCAGGGACTGACTTCACTTTTACCATCTC TTCAGTGCAGCCGAAGACATCGCCACAT ACTACTGCCAGCAGTACGGAACCTTGCCCT TTTACATTTGGGGGCGGCACCAAGTGGA GATTAAGCGAGGGGGAGGCGGCTCAGGAG GCGGTGGCTCCGAGGCGGGGGTTCCCAG GTCCAGCTCCAGGAATCCGGCCCAGGTCT GGTTAAGCCAGTGAACTTTGTCCCTCA CGTGTACTGTGAGCGGTGGTTCAATCTCC TCATACTATTGGTCTTGGATACGGCAACC TCCTGGAAAGGGCCTCGAGTGGATCGGCT ATATCTACTATAGTGGCTCCACTAATTAC AACCCTTCCCTCAAGTCCAGAGTCACCAT TTCCGTGGACACATCTAAGAACCAGTTCA GTCTGAAGTTGTCCAGCGTTACAGCCGCA GACACAGCCGTTTATTACTGTGTGTCTCT TGTTTACTGCGGGGAGACTGTTATAGCG GCTTCGATTACTGGGGCCAGGGCACCTTG GTCACAGTCTCTTCCGCGCCGCCCTCTC TAACAGTATTATGTACTTTTCTCATTTTG TACCCGTGTTCTTCCCGCTAAGCCAACCT ACTACCCGGCCCCACGGCCGCTACCCC TGCACCCACAATAGCCAGTCAGCCTTTGA GCCTGAGACCTGAGGCTTGTCCGCCGGCT GCTGGGGGTGAGTGCACACACGAGGTCT TGATTTTGCTTGCGACATATACATCTGGG CCCCTCTGGCCGGGACCTGTGGGGTGCTG CTTCTGAGCTTGGTCTATCACGCTCTATTG CAACCATCGCAACAGATCCAAAAGAAGCC GCCTGCTCCATAGCGATTACATGAATATG ACTCCACGCCGCCCTGGCCCCACAAGGAA ACACTACCAGCCTTACGCACCACCTAGAG ATTTTCGCTGCCTATCGGAGCAGGGTGAAG TTTTCCAGATCTGCAGATGCACCAGCGTA TCAGCAGGGCCAGAACCACTGTATAACG AGCTCAACCTGGGACGCAGGGAAGAGTAT	185	MALPVTALLLPLALLL HAARPDIQLTQSPSSL SASVGDRVSTCQASQ DINNFLNWYQQKPGKA PKLLIYDASNLETGVP SRFSGSGSGTDFTFTI SSLQPEDIATYYCQQY GNLPFTFGGGTKVEIK RGGGSGGGSGGGGS QVQLQESGPGLVKPS TSLTCTVSGGSISSY YWSWIRQPPGKLEWI GYIYSGSTNYPNPSLK SRVTISVDTSKNQFSL KLSSVTAADTAVYYCV SLVYCGGDCYSGFDYW GQGTLVTVSSAAALSN SIMYFSHFVPVFLPAK PTTTPAPRPPTPAPT ASQPLSLRPEACRPAA GGAVHTRGLDFACDIY IWAPLAGTCGVLLLSL VITLYCNHRNRSKRSR LLHSDYMNMTPRRPGP TRKHYPYAPPRDFAA YRSRVKFSRSADAPAY QQGQNQLYNELNLGRR EEYDVLDRKRRDPEM GGKPRRKNPQEGLYNE LQKDKMAEAYSEIGMK GERRRGKHDGLYQGL STATKDTYDALHMQAL PPR	186

	GACGTTTTGGACAAGCGCAGAGGACGGGA CCCTGAGATGGGTGGCAAACCAAGACGAA AAAACCCCCAGGAGGGTCTCTATAATGAG CTGCAGAAGGATAAGATGGCTGAAGCCTA TTCTGAAATAGGCATGAAAGGAGAGCGGA GAAGGGGAAAAGGGCACGACGGTTTGTAC CAGGGACTCAGCACTGCTACGAAGGATAC TTATGACGCTCTCCACATGCAAGCCCTGC CACCTAGGTAA			
(CAR1.6) Clone 24C1 CD8 CAR DNA LxH	GACATTCAATTGACCCAGTCCCCTAGCAG TCTCTCAGCAAGTGTGGGAGATAGGGTGT CATTACCTGTCAGGCTTCACAGGACATC AACAACTTCCTCAATTGGTATCAGCAGAA GCCAGGGAAGGCACCAAAGCTGCTCATAT ATGACGCTTCAAACCTTGAAACCGGAGTA CCTAGCCGCTTCAGCGGAAGCGGATCAGG GACTGACTTCACTTTTACCATCTCTTCAC TGCAGCCCAGACATCGCCACATACTAC TGCCAGCAGTACGGAACTTGCCTTTTAC ATTTGGGGGCGGCACCAAAGTGGAGATTA AGCGAGGGGGAGGCGGCTCAGGAGGCGGT GGCTCCGGAGGCGGGGGTTCCCAGGTCCA GCTCCAGGAATCCGGCCCAGGTCTGGTTA AGCCAGTGAAACTTTGTCCCTCACGTGT ACTGTGAGCGGTGGTTCAATCTCCTCATA CTATTGGTCTTGATACGGCAACCTCCTG GAAAGGGCCTCGAGTGGATCGGCTATATC TACTATAGTGGCTCCACTAATTACAACCC TTCCCTCAAGTCCAGAGTCACCATTTCCG TGGACACATCTAAGAACCAGTTCAGTCTG AAGTTGTCCAGCGTTACAGCCGCAGACAC AGCCGTTTATTACTGTGTCTCTTGTTT ACTGCGGGGAGACTGTTATAGCGGCTTC GATTACTGGGGCCAGGGCACCTTGGTCAC AGTCTCTTCCGCGGCCGCCCTCTCTAACA GTATTATGTACTTTTCTCATTTTGTACCC GTGTTCTTCCCGCTAAGCCAACACTACTAC CCCGGCCCCACGGCCGCCCTACCCCTGCAC CCACAATAGCCAGTCAGCCTTTGAGCCTG AGACCTGAGGCTTGTGCGCGGCTGCTGG GGGTGCAGTGCACACACGAGGTCTTGATT TTGCTTGCGACATATACATCTGGGCCCT CTGGCCGGGACCTGTGGGGTGTGCTTCT GAGCTTGGTCATCACGCTCTATTGCAACC ATCGCAACAGATCCAAAGAAGCCGCTG CTCCATAGCGATTACATGAATATGACTCC ACGCCGCCCTGGCCCCACAAGGAAACACT ACCAGCCTTACGCACCACCTAGAGATTTT GCTGCCTATCGGAGCAGGGTGAAGTTTTC CAGATCTGCAGATGCACCAGCGTATCAGC AGGGCCAGAACCAACTGTATAACGAGCTC AACCTGGGACGCAGGGAAGAGTATGACGT TTTGGACAAGCGCAGAGGACGGGACCCTG AGATGGGTGGCAAACCAAGACGAAAAAAC CCCCAGGAGGGTCTCTATAATGAGCTGCA GAAGGATAAGATGGCTGAAGCCTATTCTG AAATAGGCATGAAAGGAGAGCGGAGAAGG GGAAAAGGGCACGACGGTTTGTACCAGGG ACTCAGCACTGCTACGAAGGATACTTATG	187	DIQLTQSPSSLSASVG DRVSFTCQASQDINNF LNWYQQKPKAPKLLI YDASNLETGVPSRFSG SGSGTDFTFITISLQP EDIATYYCQQYGNLFF TFGGGKVEIKRGGGG SGGGSGGGGSQVQLQ ESGPGLVKPSSETLSLT CTVSGGSISSYYWSWI RQPPGKGLEWIGYIYY SGSTNYPNLSKSRVTI SVDTSKNQFSLKLSSV TAADTAVYYCVSLVYC GGDCYSGFDYWGQTL VTVSSAAALNSIMYF SHFVPVFLPAKPTTTP APRPPTPAPTIASQPL SLRPEACRPAAGGAVH TRGLDFACDIYIWAPL AGTCGVLLLSLVITLY CNHRNRSKRSLHSD YMNMTPRRPGPTRKHY QPYAPPRDFAAYRSRV KFSRSADAPAYQQQN QLYNELNLGRREEYDV LDKRRGRDPENGGKPR RKNPQEGLYNELQKDK MAEAYSEIGMKGERRR GKGHDGLYQGLSTATK DTYDALHMQALPPR	188

	ACGCTCTCCACATGCAAGCCCTGCCACCT AGG			
(CAR2.1) Clone 24C8 THD CAR DNA HxL	ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCCGAGGTACAGCTGCAGGAATCTGGG CCCGGACTTGTCAAGCCAAGTCAGACACT TTCTCTTACATGTACCGTGAGCGCGGAA GTATAAGCAGTGGAGGCTTTTACTGGTCT TGGATACGGCAGCACCCAGGCAAAGGCTT GGAGTGGATTGGATACATTCATTCAG GATCTACACACTATAATCCATCCCTTAAG TCCCGGCTCACCATTAGCATTGATACGTC TAAGAATCTGTTCAAGTCTCAGGCTGTCCT CCGTCACTGCTGCCGACACAGCCGTGTAC TACTGCGCCTCCTTGGTTTACTGCGGAGG CGACTGTTATAGCGGCTTGTATTATTGGG GGCAGGGGACCTCGTAACCGTGAGCTCT GGAGGGGGTGGGAGCGGGGAGGAGGTTC AGGGGGGGCGGCTCCGATATCCAGCTCA CTCAAAGCCCTCTAGTCTCTCTGCCTCA GTGGGGGATCGGGTCAGTTTACTTGTCA AGCTTCACAGGATATCAACAACCTCCTTA ATTGGTATCAGCAGAAGCCAGGAAAAGCA CCCAAGCTGCTCATCTATGATGCCTCAAA TTTGGAGACGGGTGTTCCAGTCGATTCT CTGGGTCAAGGTCCGGGACCGACTTTACG TTTACGATCTCCTCTCTGCAGCCCGAAGA CATCGCCACATACTATTGTCAACAGTACG GCAACTTGCCTTTCACATTGGGGGCGGG ACTAAGGTTGAAATCAAGAGGGCCGCTGC ACTGGACAATGAGAAGTCCAACGGCACCA TCATCCACGTGAAGGGCAGCACCTGTGC CCTAGTCTCTGTTCCAGGCCCATCCAA ACCTTTTTGGGTTCTTGTGTGGTCCGGG GGGTGCTGGCCTGCTATTCTCTGCTGGTC ACGGTGGCCTTCATAATTTCTGGGTTAG ATCCAAAAGAAGCCGCCTGCTCCATAGCG ATTACATGAATATGACTCCACGCCGCCCT GGCCCCACAAGGAAACACTACCAGCCTTA CGCACCACCTAGAGATTTGCTGCCTATC GGAGCAGGGTGAAGTTTCCAGATCTGCA GATGCACCAGCGTATCAGCAGGGCCAGAA CCAACTGTATAACGAGCTCAACCTGGGAC GCAGGGAAGAGTATGACGTTTTGGACAAG CGCAGAGGACGGGACCTGAGATGGGTGG CAAACCAAGACGAAAAAAGCCAGGAGG GTCTCTATAATGAGCTGCAGAAGGATAAG ATGGCTGAAGCCTATTCTGAAATAGGCAT GAAAGGAGAGCGGAGAAGGGGAAAAGGCG ACGACGGTTTGTACCAGGACTCAGCACT GCTACGAAGGATACTTATGACGCTCTCCA CATGCAAGCCCTGCCACCTAGGTAA	189	MALPVTALLLPLALLL HAARPQVQLQESGPG VKPSQTLSTCTVSGG SISSGGFYWSWIRQHP GKLEWIGYIHHSGST HYNPSLKSRVTISIDT SKNLFSLRLSSVTAAD TAVYYCASLVYCGGDC YSGFDYWGQGLVTVS SGGGSGGGSGGGGS DIQLTQSPSSLSASVG DRVSFTCQASQDINNF LNWYQQKPKAPKLLI YDASNLETGVPSRFSG SGSGTDFTFITSSLP EDIATYYCQYGNLPF TFGGGKVEIKRAAAL DNEKSNGTIIHVKGKH LCPSPLFPGPSKPFVW LVVVGVLACYSLVLT VAFIIFWVRSKRSRL HSDYMNMTPRPGPTR KHYQPYAPPRDFAAYR SRVKFSRSADAPAYQQ GQNQLYNELNLGRREE YDVLDRRRGRDPEMGG KPRRKNPQEGLYNELQ KDKMAEAYSEIGMKGE RRRGKGHDLGYQGLST ATKDTYDALHMQALPP R	190
(CAR2.1) Clone 24C8 THD CAR DNA HxL	CAGGTACAGCTGCAGGAATCTGGGCCCGG ACTTGTCAAGCCAAGTCAGACACTTTCTC TTACATGTACCGTGAGCGCGGAAGTATA AGCAGTGGAGGCTTTTACTGGTCTTGGAT ACGGCAGCACCCAGGCAAAGGCTTGGAGT GGATTGGATACATTCATTCAGGATCT ACACACTATAATCCATCCCTTAAGTCCCG	191	QVQLQESGPGLVKPSQ TLSTCTVSGGSISSG GFYWSWIRQHPGKLE WIGYIHHSGSTHYNPS LKSRVTISIDTSKNLF SLRLSSVTAADTAVYY CASLVYCGGDCYSGFD	192

	GGTCACCATTAGCATTGATACGTCTAAGA ATCTGTTTCAGTCTCAGGCTGTCTCCGTC ACTGCTGCCGACACAGCCGTGTACTACTG CGCCTCCTTGTTTACTGCGGAGGCGACT GTTATAGCGGCTTTGATTATTGGGGGAG GGGACCTCGTAACCGTGAGCTCTGGAGG GGGTGGGAGCGGGGAGGAGTTTCAGGGG GGGGCGGCTCCGATATCCAGCTCACTCAA AGCCCCCTCTAGTCTCTCTGCTCAGTGGG GGATCGGGTCAGTTTTACTTGTCAAGCTT CACAGGATATCAACAACCTCCTTAATTGG TATCAGCAGAAGCCAGGAAAAGCACCCAA GCTGCTCATCTATGATGCCTCAAATTTGG AGACGGGTGTTCCAGTCGATTCTCTGGG TCAGGGTCCGGGACCGACTTTACGTTTAC GATCTCCTCTCTGCAGCCGAAGACATCG CCACATACTATTGTCAACAGTACGGCAAC TTGCCTTTTACATTTGGGGCGGGACTAA GGTTGAAATCAAGAGGGCGCTGCACTGG ACAATGAGAAGTCCAACGGCACCATCATC CACGTGAAGGGCAAGCACCTGTGCCCTAG TCCTCTGTTCCAGGCCCATCCAACCTT TTTGGGTTCTTGTGTGGTCTGGGGGGTG CTGGCCTGCTATTCTCTGCTGGTCACGGT GGCCTTCATAATTTTCTGGGTTAGATCCA AAAGAAGCCGCTGCTCCATAGCGATTAC ATGAATATGACTCCACGCCGCCCTGGCCC CACAAGGAAACACTACCAGCCTTACGCAC CACCTAGAGATTTGCTGCCTATCGGAGC AGGGTGAAGTTTTCCAGATCTGCAGATGC ACCAGCGTATCAGCAGGGCCAGAACCAC TGTATAACGAGCTCAACCTGGGACGCAGG GAAGAGTATGACGTTTTGGACAAGCGCAG AGGACGGGACCCTGAGATGGGTGGCAAC CAAGACGAAAAAACCCCGAGGAGGTCTC TATAATGAGCTGCAGAAGGATAAGATGGC TGAAGCCTATTCTGAAATAGGCATGAAAG GAGAGCGGAGAAGGGGAAAAGGGCACGAC GGTTTGTACCAGGGACTCAGCACTGCTAC GAAGGATACTTATGACGCTCTCCACATGC AAGCCCTGCCACCTAGG		YWGQGTTLVTSSGGGG SGGGGSGGGGSDIQLT QSPSSLSASVGDVRSF TCQASQDINNFLNWFQ QKPGKAPKLLIYDASN LETGVPSRFSGSGSGT DFTFTISSLPEDIAT YYCQQYGNLPFTFGGG TKVEIKRAAALDNEKS NGTIIHVKGKHLCPSP LFPGPSKPFVVLVVVG GVLACYSLLVTVAFII FWVRSKRSLLHSDYM NMTPRRPGPTRKHYQP YAPPRDFAAYRSRVKF SRADAPAYQQGQNL YNELNLGRREEYDVLD KRRGRDPEMGKPRRK NPQEGLYNELQKDKMA EAYSEIGMKGERRRGK GHDGLYQGLSTATKDT YDALHMQALPFR	
(CAR2.2) Clone 24C8 CHD CAR DNA HxL	ATGGCACTCCCCGTAAGTCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCCGAGGTGCAGCTGCAGGAAAGCGGT CCGGGACTTGTCAAGCGTCCCAAACGCT GAGTCTGACGTGTACTGTCTCTGGTGGCT CTATTTCTTCCGGGGGCTTTTATTGGTCT TGGATCAGACAACACCCTGGCAAAGGGCT GGAGTGGATAGGGTATATTCACTACTCTG GGTCCACTCACTACAACCCATCATTGAAA TCCAGAGTGACTATCTCAATCGACACATC CAAGAACCCTTTTCAGCCTGAGGTTGTCT CAGTTACCGCCGCTGACACCGCGGTGTAT TATTGCGCCTCTCTCGTGTACTGCGGTGG CGATTGTTATAGTGGCTTTGACTACTGGG GGCAGGGGACATTGGTTACCGTTTCAAGT GGAGGCGGTGGGTCTGGCGGGGCGGTAG CGGAGGTGGGGGAGCGACATACAGCTTA CGCAGAGCCCTCCAGCCTTTCAGCCTCC	193	MALPVTALLLPLALLL HAARPQVQLQESGPG VKPSQTLSTCTVSGG SISSGGFYWSWIRQHP GKGLEWIGYIHHSGST HYNPSLSRVTISIDT SKNLFSLRLSSVTAAD TAVYYCASLVYCGGDC YSGFDYWQGTTLVTVS SGGGGSGGGGSGGGG DIQLTQSPSSLSASVG DRVSFTCQASQDINN LNWYQQKPGKAPKLLI YDASNLETGVPSRFSG SGSGTDFTFTISSLP EDIATYYCQQYGNLP TFGGGTKEIKRAAAI EVMPYPYLDNEKSNG	194

	<p>GTGGGGGATAGGGTGTCTTTACCTGCCA GGCTTCCCAGGACATAAACAACTTCCTCA ATTGGTATCAGCAAAAGCCCGGAAAGCA CCAAAGCTGCTCATCTACGATGCCAGCAA CCTGGAACCGGAGTGCCGTCTCGCTTCT CTGGAAGTGGCAGTGGGACCGATTTCCT TTTACAATCTCAAGTTTGAGCCAGAAGA CATTGCAACATACTACTGTCAACAGTACG GCAATCTCCCCTTTACATTTGGGGGGGGA ACTAAAGTGGAGATTAAGCGCGCTGCAGC CATTGAAGTTATGTATCCGCCCCGTATC TGGATAACGAGAAATCTAATGGTACCATA ATACATGTGAAGGGGAAGCACCTCTGTCC ATCACCGCTGTTCCCCGGCCCTTCAAAC CTTTCTGGGTACTCGTTGTCGTGGGTGGA GTTCTGGCCTGCTATAGTCTGCTGGTGAC CGTGGCGTTTATCATCTTCTGGGTAAGAT CCAAAAGAAGCCGCTGCTCCATAGCGAT TACATGAATATGACTCCACGCCGCCCTGG CCCCACAAGGAAACACTACCAGCCTTACG CACCACCTAGAGATTTTCGTGCCTATCGG AGCAGGGTGAAGTTTTCAGATCTGCAGA TGCACCAGCGTATCAGCAGGGCCAGAACC AACTGTATAACGAGCTCAACCTGGGACGC AGGGAAGAGTATGACGTTTGGACAAGCG CAGAGGACGGGACCCTGAGATGGGTGGCA AACCAAGACGAAAAACCCCAGGAGGGT CTCTATAATGAGCTGCAGAAGGATAAGAT GGCTGAAGCCTATTCTGAAATAGGCATGA AAGGAGAGCGGAGAAGGGGAAAAGGGCAC GACGGTTTGTACCAGGGACTCAGCACTGC TACGAAGGATACTTATGACGCTCTCCACA TGCAAGCCCTGCCACCTAGGTAA</p>		<p>TIIHVKGKHLCPSPFLF PGPSKPFWVLVVVGGV LACYSLLVTVAFIIFW VRSKRSRLHSDYMN TPRRPGPTRKHYQPYA PPRDFAAYSRVKFSR SADAPAYQQQNQLYN ELNLGRREEYDVLDR RGRDPEMGGKPRRKNP QEGLYNELQDKMAEA YSEIGMKGERRRGKGH DGLYQGLSTATKDTYD ALHMQALPPR</p>	
(CAR2.2) Clone 24C8 CHD CAR DNA HxL	<p>CAGGTGCAGCTGCAGGAAAGCGGTCCGGG ACTTGTCAAGCCGTCCCAAACGCTGAGTC TGACGTGTACTGTCTCTGGTGGCTCTATT TCTTCCGGGGGCTTTTATTTGGTCTTGGAT CAGACAACACCCTGGCAAAGGGCTGGAGT GGATAGGGTATATTACCACTCTGGGTCC ACTCACTACAACCCATCATTGAAATCCAG AGTGACTATCTCAATCGACACATCCAAGA ACCTTTTCAGCCTGAGGTTGTCTCATCAGTT ACCGCCGCTGACACCGCGGTGTATTATTG CGCCTCTCTCGTGTACTGCGGTGGCGATT GTTATAGTGGCTTTGACTACTGGGGGCAG GGGACATTGGTTACCGTTTCAAGTGGAGG CGGTGGGTCTGGCGGGGGCGGTAGCGGAG GTGGGGGGAGCGACATACAGCTTACGCAG AGCCCCTCCAGCCTTTTACGCTCCGTGGG GGATAGGGTGTCTTTACCTGCCAGGCTT CCCAGGACATAAACAACTTCCTCAATTGG TATCAGCAAAAGCCCGGAAAGCACCAAA GCTGCTCATCTACGATGCCAGCAACCTGG AAACCGGAGTGCCGTCTCGCTTCTCTGGA AGTGGCAGTGGGACCGATTCACTTTTAC AATCTCAAGTTTGAGCCAGAAGACATTG CAACATACTACTGTCAACAGTACGGCAAT CTCCCCTTTACATTTGGGGGGGAACTAA AGTGGAGATTAAGCGCGCTGCAGCCATTG</p>	195	<p>QVQLQESGPGLVKPSQ TSLTCTVSGGSISSG GFYWSWIRQHPGKLE WIGYIHHSGSTHYNPS LKSRVTISIDTSKNLF SLRLSSVTAADTAVYY CASLVYCGGDCYSGFD YWGQGLTVTVSSGGGG SGGGSGGGGSDIQLT QSPSSLSASVGDVRSF TCQASQDINNFLNWFY QKPGKAPKLLIYDASN LETGVPSRFSGSGSGT DFTFTISSLPEDIAT YYCQQYGNLPFTFGGG TKVEIKRAAAIEVMYP PPYLDNEKSNGTIIHV KGKHLCPSPFLPGPSK PFWVLVVVGGVLACYS LLVTVAFIIFWVRSKR SRLHSDYMNMTPRRP GPTRKHYQPYAPPRDF AAYRSRVKFSRSADAP AYQQQNQLYNELNLG RREEYDVLDRGRDP EMGGKPRRKNPQEGLY</p>	196

	AAGTTATGTATCCGCCCCGTATCTGGAT AACGAGAAATCTAATGGTACCATAATACA TGTGAAGGGAAGCACCTCTGTCCATCAC CGCTGTTCCCCGGCCCTTCAAAACCTTTC TGGGTACTCGTTGTCTGGGTGGAGTTCT GGCCTGCTATAGTCTGCTGGTGACCGTGG CGTTTATCATCTTCTGGGTAAGATCCAAA AGAAGCCGCCTGCTCCATAGCGATTACAT GAATATGACTCCACGCCGCCCTGGCCCCA CAAGGAAACACTACCAGCCTTACGCACCA CCTAGAGATTTCGCTGCCTATCGGAGCAG GGTGAAGTTTTCCAGATCTGCAGATGCAC CAGCGTATCAGCAGGGCCAGAACCAACTG TATAACGAGCTCAACCTGGGACGCAGGGA AGAGTATGACGTTTTGGACAAGCGCAGAG GACGGGACCCTGAGATGGGTGGCAAACCA AGACGAAAAAACCCCAAGGAGGTCTCTA TAATGAGCTGCAGAAGGATAAGATGGCTG AAGCCTATTCTGAAATAGGCATGAAAGGA GAGCGGAGAAGGGGAAAAGGGCACGACGG TTTGTACCAGGGACTCAGCACTGCTACGA AGGATACTTATGACGCTCTCCACATGCAA GCCCTGCCACCTAGG		NELQKDKMAEAYSEIG MKGERRRGKGDGLYQ GLSTATKDTYDALHMQ ALPPR	
(CAR2.3) Clone 24C8 CD8 CAR DNA HxL	ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTGCAGTTGCAGGAAAGCGGG CCTGGCCTTGTGAAACCAAGCCAGACACT GAGCCTGACATGCACTGTGTCCGGCGGGT CCATATCTTCCGGGGGTTTTTATTGGTCC TGGATACGCCAGCATCCCCGGAAGGACT TGAATGGATTGGATATATCCACCATTCCG GAAGCACCCTACTACAATCCAAGCCTTAAA TCCCGGGTGACAATCTCCATCGACACCTC AAAGAATCTTTTTCCCTGCGGTTGTCTT CAGTAACTGCCGCCGATACCGCTGTGTAC TACTGTGCCAGCCTCGTCTATTGCGGCGG AGATTGTTATTCTGGGTCGATTATTGGG GTCAAGGCACACTGGTAACTGTCAGCAGC GGAGCGGGCGGTTCCGGGGCGGGGGCAG TGGAGGGGGCGGATCTGACATTGAGCTTA CGCAGTCCCCATCTTCACTTAGCGCCAGC GTTGGCGATCGGGTCAGCTTACGTGTCA AGCAAGTCAGGATATCAACAACCTTTCTTA ACTGGTACCAGCAGAAGCCAGGCAAGGCA CCCAAGTTGCTGATTTACGATGCTTCTAA CCTCGAGACGGGAGTGCTAGCCGCTTCT CCGGGAGCGGCAGCGGCACAGACTTTACC TTTACGATTTCCAGTCTGCAGCCAGAGGA TATAGCAACTTATTACTGTCAGCAGTATG GCAACCTCCCTTTTACCTTCGGTGGTGGC ACAAAGGTCGAGATTAAAAGAGCCGCAGC GTTGTCCAACCTCCATAATGTATTTTTCTC ATTTTGTGCCGCTTTTCTGCCTGCCAAA CCTACCACCACCCCGCCCCACGACCACC TACTCCAGCCCCACCATCGCCTCCCAGC CCCTCAGCCTGAGGCCAGAGGCTTGTGCG CCTGCTGCGGGGGCGCTGTCCATACCAG AGGACTCGACTTCGCCTGCGATATTTATA TATGGGCCCCCTCGCCGCACCTGCGGA	197	MALPVTALLPLALLL HAARPQVQLQESGPG VKPSQTLSTCTVSGG SISSGGFYWSWIRQHP GKLEWIGYIHHSST HYNPSLKSRTVISIDT SKNLFSLRLSSVTAAD TAVYYCASLVYCGGDC YSGFDYWGQGLVTVS SGGGSGGGSGGGGS DIQLTQSPSSLASVG DRVSFTCQASQDINN LNWYQQKPKAPKLLI YDASNLETGVPSRFS SGSGTDFFTISSLP EDIATYYCQYGNLP TFGGGKVEIKRAAL SNSIMYFSHFVPVFLP AKPTTTPAPRPPTPAP TIASQPLSLRPEACRP AAGGAVHTRGLDFACD IYIWAPLAGTCGVLL SLVITLYCNHRNRSKR SRLHSDYMNMTPRRP GPTRKHYQPYAPPRDF AAYRSRVKFSRSADAP AYQQGQNQLYNELNLG RREEYDVLDRGRDP EMGGKPRRKNPQEGLY NELQKDKMAEAYSEIG MKGERRRGKGDGLYQ GLSTATKDTYDALHMQ ALPPR	198

	GTCTTGCTCCTGAGCCTTGTGATCACGCT TTATTGTAACCATCGGAATAGATCCAAA GAAGCCGCCTGCTCCATAGCGATTACATG AATATGACTCCACGCCGCCCTGGCCCCAC AAGGAAACACTACCAGCCTTACGCACCAC CTAGAGATTTGCTGCCTATCGGAGCAGG GTGAAGTTTTCCAGATCTGCAGATGCACC AGCGTATCAGCAGGGCCAGAACCAACTGT ATAACGAGCTCAACCTGGGACGCAGGGAA GAGTATGACGTTTTGGACAAGCGCAGAGG ACGGGACCCTGAGATGGGTGGCAAACCAA GACGAAAAACCCCCAGGAGGGTCTCTAT AATGAGCTGCAGAAGGATAAGATGGCTGA AGCCTATTCTGAAATAGGCATGAAAGGAG AGCGGAGAAGGGGAAAAGGGCAGCAGCGT TTGTACCAGGGACTCAGCACTGCTACGAA GGATACTTATGACGCTCTCCACATGCAAG CCTGCCACCTAGGTAA			
(CAR2.3) Clone 24C8 CD8 CAR DNA HxL	CAGGTGCAGTTGCAGGAAAGCGGGCCTGG CCTTGTGAAACCAAGCCAGACACTGAGCC TGACATGCACTGTGTCCGGCGGGTCCATA TCTTCCGGGGGTTTTATTTGGTCTGGAT ACGCCAGCATCCCGGGAAGGACTTGAAT GGATTGGATATATCCACCATTCCGGAAGC ACCCACTACAATCCAAGCCTTAAATCCCG GGTGACAATCTCCATCGACACCTCAAAGA ATCTTTTTTCCCTGCGGTTGTCTTCAGTA ACTGCCGCCGATAACCGCTGTGTACTACTG TGCCAGCCTCGTCTATTGCGGCGGAGATT GTTATTCTGGGTTTCGATTATTGGGGTCAA GGCACACTGGTAACTGTGACGAGCGGAGG CGGCGGTTCCGGGGGCGGGGGCAGTGGAG GGGGCGGATCTGACATTGAGCTTACGCAG TCCCCATCTTCACTTAGCGCCAGCGTTGG CGATCGGGTCAGCTTACGTGTCAAGCAA GTCAGGATATCAACAACCTTCTTAACTGG TACCAGCAGAAGCCAGGCAAGGCACCCAA GTTGCTGATTTACGATGCTTCAACCTCG AGACGGGAGTGCCTAGCCGCTTCTCCGGG AGCGGCAGCGGCACAGACTTTACCTTTAC GATTTCCAGTCTGCAGCCAGAGGATATAG CAACTTATTACTGTGACGAGTATGGCAAC CTCCCTTTTACCTTCGGTGGTGGCACAAA GGTCGAGATTAAAAGAGCCGACGCTTGT CCAACTCCATAATGTATTTTCTCATTTT GTGCCCCTCTTTCTGCCTGCCAAACCTAC CACCACCCCGCCCCACGACCACCTACTC CAGCCCCACCATCGCCTCCAGCCCCCTC AGCCTGAGGCCAGAGGCTTGTGCGCCCTGC TGCGGGGGGCGCTGTCCATACCAGAGGAC TCGACTTCGCCTGCGATATTTATATATGG GCCCCCTCGCCGGCACCTGCGGAGTCTT GCTCCTGAGCCTTGTGATCACGCTTTATT GTAACCATCGGAATAGATCCAAAAGAAGC CGCCTGCTCCATAGCGATTACATGAATAT GACTCCACGCCGCCCTGGCCCCACAAGGA AACACTACCAGCCTTACGACCACTAGTA GATTTGCTGCCTATCGGAGCAGGGTGAA GTTTTCCAGATCTGCAGATGCACCAGCGT	199	QVQLQESGPGLVKPSQ TSLTCTVSGGSISSG GFYWSWIRQHPGKGLE WIGYIHHSGSTHYNPS LKSRVTISIDTSKNLF SLRLSSVTAADTAVYY CASLVYCGGDCYSGFD YWGQGTLVTVSSGGGG SGGGSGGGGSDIQLT QSPSSLSASVGDVRSF TCQASQDINNFLNWYQ QKPGKAPKLLIYDASN LETGVPSRFSGSGSGT DFTFTISSLPEDIAT YYCQQYGNLPFTFGGG TKVEIKRAAALSNSIM YFSHFVPVFLPAKPTT TPAPRPPTPAPTIASQ PLSLRPEACRPAAGGA VHTRGLDFACDIYIWA PLAGTCGVLLLSLVIT LYCNHRNRSKRSRLH SDYMNMTPRRPGPTRK HYQPYAPPRDFAAYRS RVKFSRSADAPAYQQG QNQLYNELNLGRREEY DVLDKRRGRDPEMGGK PRRKNPQEGLYNELQK DKMAEAYSEIGMKGER RRGKGHDGLYQGLSTA TKDITYDALHMQALPPR	200

	ATCAGCAGGGCCAGAACCAACTGTATAAC GAGCTCAACCTGGGACGCAGGGAAGAGTA TGACGTTTTGGACAAGCGCAGAGGACGGG ACCCTGAGATGGGTGGCAACCAAGACGA AAAAACCCCAGGAGGGTCTCTATAATGA GCTGCAGAAGGATAAGATGGCTGAAGCCT ATTCTGAAATAGGCATGAAAGGAGAGCGG AGAAGGGGAAAAGGGCACGACGGTTTTGTA CCAGGGACTCAGCACTGCTACGAAGGATA CTTATGACGCTCTCCACATGCAAGCCCTG CCACCTAGG			
(CAR3.1) Clone 20C5.1 THD CAR DNA HxL	ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTCCAAGTGGTGCAGTCCGGA GCCGAAGTCAAGAAACAGGTGCCTCCGT TAAAGTGAGTTGCAAAGTCTCTGGATACA CTCTGACCGAGCTCTCTATGCACTGGGTC CGGCAGGCCCCCGCAAGGGATTGGAATG GATGGGCGGGTTCGATCCTGAGGACGGAG AGACTATCTACGCTCAAAAATCCAGGGA CGAGTGACTGTGACCGAAGACACTAGTAC CGACACTGCCTACATGGAAGTCTTCCCTC TGCGATCAGAAGATACCGCAGTGTACTAC TGTGCTACTGAATCTAGGGGCATTGGATG GCCCTACTTCGATTACTGGGGTCAGGGAA CTCTGGTGACTGTCTCCAGCGGTGGAGGT GGCAGCGGTGGTGGCGGAAGCGGGGGGGG CGGCTCTGATATTAGATGACTCAATCTC CTTCTTCTGTCCGCTTCCGTGGGCGAT AGAGTGACCATTAAGTGTAGGGCGTCCCA GTCAATCTCCAGTTATTTGAATTGGTATC AGCAGAAGCCCGGGAAGCACCTAAGCTG TTGATCAGCGGGGCTTCTAGCCTGAAGAG TGGGGTACCTTCACGGTTCAGCGGAAGCG GAAGCGGAACCGATTTCACCTGACTATC AGCAGCCTGCCACCTGAGGACTTTGCAAC TTACTACTGCCAACAGTCATACAGCACTC CGATCACTTTCGGCCAGGGCACCCGGCTC GAAATCAAGCGCGCTGCTGCTTTGGACAA TGAGAAGTCAAACGGCACCATCATACTG TTAAAGGTAAACATCTGTGTCCCTCCCCG CTGTTCCCCGGCCCTTCCAAACCGTTCTG GGTTCTGGTGGTGGTGGAGGCGTACTCG CTTGCTATAGTCTGCTGGTAACTGTCGCC TTCATCATCTTTTGGGTGAGATCCAAAAG AAGCCGCTGCTCCATAGCGATTACATGA ATATGACTCCACGCGCCCTGGCCCCACA AGGAAACACTACCAGCCTTACGCACCACC TAGAGATTTTCGCTGCCTATCGGAGCAGGG TGAAGTTTTCCAGATCTGCAGATGCACCA GCGTATCAGCAGGGCCAGAACCAACTGTA TAACGAGCTCAACCTGGGACGCAGGGAAG AGTATGACGTTTTGGACAAGCGCAGAGGA CGGGACCTGAGATGGGTGGCAAACCAAG ACGAAAAACCCCCAGGAGGGTCTCTATA ATGAGCTGCAGAAGGATAAGATGGCTGAA GCCTATTCTGAAATAGGCATGAAAGGAGA GCGGAGAAGGGGAAAAGGGCACGACGGTT TGTACCAGGGACTCAGCACTGCTACGAAG	201	MALPVTALLLPLALLL HAARPQVQLVQSGAEV KKPGASVKVSCKVS TLTELSMHVWRQAPGK GLEWMGGFDPEDGETI YAQKFQGRVTVTEDTS TDTAYMELSSLRSEDT AVYYCATESRGIGWPY FDYWGQGTIVTVSSGG GGSGGGSGGGGSDIQ MTQSPSSLSASVGRV TITCRASQSISSYLNW YQQKPGKAPKLLISGA SSLKSGVPSRFSGSGS GTDFTLTISSLPPEDF ATYYCQSYSTPITFG QGTRLEIKRAAALDNE KSNGTIIHVKGKHLCP SPLFPGPSKPFWVLV VGGVLACYSLLVTVAF IIFWVRSKRSRLHSD YMNMTPRRPGPTRKHY QPYAPPRDFAAYRSRV KFSRSADAPAYQQGQN QLYNELNLGRREEYDV LDKRRGRDPEMGKPR RKNPQEGLYNELQKDK MAEAYSEIGMKGERR GKGHDGLYQGLSTATK DTYDALHMQALPPR	202

	GATACTTATGACGCTCTCCACATGCAAGC CCTGCCACCTAGGTAA			
(CAR3.1) Clone 20C5.1 THD CAR DNA HxL	CAGGTCCAACTGGTGCAGTCCGGAGCCGA AGTCAAGAAACCAGGTGCCCTCCGTAAAAG TGAGTTGCAAAGTCTCTGGATACACTCTG ACCGAGCTCTCTATGCACTGGGTCCGGCA GGCCCCCGCAAGGGATTGGAATGGATGG GCGGGTTCGATCCTGAGGACGGAGAGACT ATCTACGCTCAAAAATTCAGGGACGAGT GACTGTGACCGAAGACACTAGTACCGACA CTGCCTACATGGAACCTTCTCTCTGCGA TCAGAAGATACCGCAGTGTACTACTGTGC TACTGAATCTAGGGGCATTGGATGGCCCT ACTTTCGATTACTGGGGTCAGGGAACCTG GTGACTGTCTCCAGCGGTGGAGGTGGCAG CGGTGGTGGCGGAAGCGGGGGGCGGCT CTGATATTGAGATGACTCAATCTCCTTCT TCTCTGTCCGCTTCCGTGGGCGATAGAGT GACCATTACTTGTAGGGCGTCCCAGTCAA TCTCCAGTTATTTGAATTGGTATCAGCAG AAGCCCGGAAAGCACCTAAGCTGTTGAT CAGCGGGGCTTCTAGCCTGAAGAGTGGGG TACCTTCACGGTTCAGCGGAAGCGGAAGC GGAACCGATTTACCCCTGACTATCAGCAG CCTGCCACCTGAGGACTTTGCAACTTACT ACTGCCAACAGTCATACAGCACTCCGATC ACTTTCGGCCAGGGCACCCGGCTCGAAAT CAAGCGCGCTGCTGCTTTGGACAATGAGA AGTCAAACGGCACCATCATACATGTTAAA GGTAAACATCTGTGTCCCTCCCCGCTGTT CCCCGGCCCTTCCAAACCGTTCTGGGTTC TGGTGGTGGTCGGAGGCGTACTCGCTTGC TATAGTCTGCTGGTAACGTGCGCTTCAT CATCTTTTGGGTGAGATCCAAAAGAAGCC GCCTGCTCCATAGCGATTACATGAATATG ACTCCACGCCGCCCTGGCCCCACAAGGAA ACACTACCAGCCTTACGCACCACCTAGAG ATTTTCGCTGCCTATCGGAGCAGGGTGAAG TTTTCCAGATCTGCAGATGCACCAGCGTA TCAGCAGGGCCAGAACCAACTGTATAACG AGCTCAACCTGGGACGCAGGGAAGAGTAT GACGTTTTGGACAAGCGCAGAGGACGGGA CCCTGAGATGGGTGGCAAACCAAGACGAA AAAACCCCCAGGAGGTTCTCTATAATGAG CTGCAGAAGGATAAGATGGCTGAAGCCTA TTCTGAAATAGGCATGAAAGGAGAGCGGA GAAGGGGAAAAGGGCACGACGGTTTGTAC CAGGGACTCAGCACTGCTACGAAGGATAC TTATGACGCTCTCCACATGCAAGCCCTGC CACCTAGG	203	QVQLVQSGAEVKKPGA SVKVSCKVSGYTLTEL SMHWVRQAPGKGLEWM GGFDPEDGETIYAQKF QGRVTVTEDTSTDYAY MELSSLRSEDYAVYYC ATESRGIGWPYFDYWG QGTTLVTVSSGGGSGG GGSGGGGSDIQMTQSP SSLSASVGDVITICR ASQSISSYLNWYQQKP GKAPKLLISGASSLKS GVPSRFSGSGSGTDFT LTISLPPEDFATYYC QQSYSTPITFGQGTRL EIKRAALDNEKSNGT IIHVKGKHLCPSPFLP GPSKPFWVVLVVGVL ACYSLLVTVAFIIIFWV RSKRSRLHSDYMNMT PRRPGPTRKHYQPYAP PRDFAAYRSRVKFSRS ADAPAYQQGQNQLYNE LNLGRREYDVLDRR GRDPEMGGKPRRKNPQ EGLYNELQDKMAEAY SEIGMKGERRRGKHD GLYQGLSTATKDTYDA LHMQALPPR	204
(CAR3.2) Clone 20C5.1 CHD CAR DNA HxL	ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTGCAGCTTGTGCAGAGCGGG GCCGAGGTGAAGAAGCCCGGGCCAGCGT CAAAGTGTCTGTAAAGGTGAGCGTTACA CCCTCACCAGCTGAGCATGCACTGGGTA CGGCAGGCTCCCGGCAAAGGTCTTGAGTG GATGGGTGGATTGATCCAGAAGATGGAG AGACTATCTACGCCCAGAAGTTCAGGGC	205	MALPVTALLPLALLL HAARPQVQLVQSGAEV KKPGASVKVSKVSGY TLTELSMHWVRQAPGK GLEWMGGFDPEDGETI YAQKFQGRVTVTEDTS TDTAYMELSSLRSEDY AVYYCATESRGIGWPY FDYWGQGTTLVTVSSG	206

	CGGGTCACCGTAACAGAAGACACCTCAAC TGACACCGCTTACATGGAGCTGAGTTCAC TGCGGTCCGAGGACACGGCCGTGTATTAT TGTGCCACCGAGAGCCGCGGAATCGGATG GCCTTACTTCGACTACTGGGGACAGGGTA CACTTGTTACAGTATCATCCGGGGGTGGC GGCTCTGGTGGGGGCGGCTCCGGAGGGGG TGGATCAGATATCCAAATGACTCAAAGTC CAAGTTCCTGTCTGCCTCAGTCGGAGAT AGAGTCACCATAACCTGCAGGGCAAGTCA GTCCATCTCCTCTATCTGAACTGGTACC AACAGAAACCTGGAAAGGCGCCTAAGCTC CTGATCTCCGGAGCCTCATCTTTGAAATC CGGTGTCCCATCTCGCTTCAGTGGCTCTG GAAGCGGTACAGATTTTACTTTGACCATT AGCAGCCTCCACCGGAAGACTTTGCTAC ATATTACTGCCAGCAGTCTTACTCAACCC CAATCACCTTCGGGCAAGGCACCAGACTC GAAATAAAAAGAGCAGCTGCTATCGAGGT TATGTACCCACCGCCGTACTTGGATAACG AAAAAAGCAATGGGACCATCATTCATGTG AAGGGTAAGCACCTTTGCCCTAGCCCACT GTTTCCTGGCCCGAGTAACCCCTTTTGGG TACTTGTGGTCGTGCGCGCGTGTGGCC TGCTACTCACTCCTGGTTACCGTCGCATT CATCATCTTTTGGGTGAGATCCAAAAGAA GCCGCCTGCTCCATAGCGATTACATGAAT ATGACTCCACGCCGCCCTGGCCCCACAAG GAAACACTACCAGCCTTACGCACCACCTA GAGATTTGCTGCCTATCGGAGCAGGGTG AAGTTTTCCAGATCTGCAGATGCACCAGC GTATCAGCAGGGCCAGAACCAACTGTATA ACGAGCTCAACCTGGGACGCAGGGAAGAG TATGACGTTTGGACAAGCGCAGAGGACG GGACCCTGAGATGGGTGGCAAACCAAGAC GAAAAAACCCCAAGGAGGTCTCTATAAT GAGCTGCAGAAGGATAAGATGGCTGAAGC CTATTCTGAAATAGGCATGAAAGGAGAGC GGAGAAGGGGAAAAGGGCACGACGGTTTG TACCAGGGACTCAGCACTGCTACGAAGGA TACTTATGACGCTCTCCACATGCAAGCCC TGCCACCTAGGTAA		GGSGGGSGGGGSDIQ MTQSPSSLSASVGD TITCRASQSISSYL YQOKPGKAPKLLIS SSLKSGVPSRFSGS GTDFTLTISLPPED ATYYCQQSYSTPIT QGTRLEIKRAAAIE YPPPYLDNEKSNGT HVKGKHLCPSPFP SKPFWVLVVVGGVL YSLLVTVAFIIFWV KRSRLLSHYMNMTP RPGPTRKHYQPYAP DFAAYRSRVKFSRS APAYQQGQNLYNEL LGRREEYDVLDRGR DFEMGGKPRRKNPQ LYNELQKDKMAEAY IGMKGERRRKGHDGL YQGLSTATKDTYDAL MQALPPR	
(CAR3.2) Clone 20C5.1 CHD CAR DNA HxL	CAGGTGCAGCTTGTGCAGAGCGGGGCCGA GGTGAAGAAGCCCGGGGCCAGCGTCAAAG TGTCTGTAAAGTCAAGGTTACACCTC ACCGAGCTGAGCATGCACTGGGTACGGCA GGCTCCCGGCAAAGTCTTGAGTGGATGG GTGGATTGTATCCAGAAGATGGAGAGACT ATCTACGCCCAAGATTCCAGGGCCGGGT CACCGTAACAGAAGACACCTCAACTGACA CCGCTTACATGGAGCTGAGTTCACTGCGG TCCGAGGACACGGCCGTGTATTATTGTGC CACCGAGAGCCGCGGAATCGGATGGCCTT ACTTCGACTACTGGGGACAGGGTACACTT GTTACAGTATCATCCGGGGGTGGCGGCTC TGGTGGGGGCGGCTCCGGAGGGGGTGGAT CAGATATCCAAATGACTCAAAGTCCAAGT TCCCTGTCTGCCTCAGTCGGAGATAGAGT CACCATAACCTGCAGGGCAAGTCAGTCCA	207	QVQLVQSGAEVKKPGA SVKVSCKVSGYTLTEL SMHWVRQAPGKLEWM GGFDPEDGETIYAQKF QGRVTVTEDTSTDY MELSSLRSEDYVYYC ATESRGIWPFYDYWG QGTLVTVSSGGGGSGG GGSGGGSDIQMTQSP SSLSASVGDRTITCR ASQSISSYLNWYQOKP GKAPKLLISGASSLKS GVPSRFSGSGSGTDF LTISLPPEDFATYYC QQSYSTPITFGQGTRL EIKRAAAIEVMYPPPY LDNEKSNGTIHVKGK	208

	<p>TCTCCTCCTATCTGAACTGGTACCAACAG AAACCTGGAAAGGCGCCTAAGCTCCTGAT CTCCGGAGCCTCATCTTTGAAATCCGGTG TCCCATCTCGCTTCAGTGGCTCTGGAAGC GGTACAGATTTTACTTTGACCATTAGCAG CCTCCCACCGGAAGACTTTGCTACATATT ACTGCCAGCAGTCTTACTCAACCCCAATC ACCTTCGGGCAAGGCACAGACTCGAAAT AAAAAGAGCAGCTGCTATCGAGGTTATGT ACCCACCGCGTACTTGGATAACGAAAAA AGCAATGGGACCATCATTCATGTGAAGGG TAAGCACCTTTGCCCTAGCCCACTGTTTC CTGGCCCCGAGTAAACCTTTTGGGTACTT GTGGTCGTCGGCGGCGTGCTGGCCTGCTA CTCACTCCTGGTTACCGTCGCATTTCATCA TCTTTTGGGTGAGATCCAAAAGAAGCCGC CTGCTCCATAGCGATTACATGAATATGAC TCCACGCGCCCTGGCCCCACAAGGAAAC ACTACCAGCCTTACGCACCACCTAGAGAT TTCGCTGCCTATCGGAGCAGGGTGAAGTT TTCCAGATCTGCAGATGCACGAGCGTATC AGCAGGGCCAGAACCAACTGTATAACGAG CTCAACCTGGGACGCAGGGAAGAGTATGA CGTTTTGGACAAGCGCAGAGGACGGGACC CTGAGATGGGTGGCAAACCAAGACGAAAA AACCCCCAGGAGGGTCTCTATAATGAGCT GCAGAAGGATAAGATGGCTGAAGCCTATT CTGAAATAGGCATGAAAGGAGAGCGGAGA AGGGGAAAAGGGCACGACGGTTTGTACCA GGGACTCAGCACTGCTACGAAGGATACTT ATGACGCTCTCCACATGCAAGCCCTGCCA CCTAGG</p>		<p>HLCPSPFLFPGPSKPFW VLVVVGGVLCYSLLV TVAFIIFWVRSKRSRL LHSDYMNMTPRRPGPT RKHYQPYAPPRDFAAY RSRVKFSRSADAPAYQ QGQNQLYNELNLGRRE EYDVLDRRGRDPEMG GKPRRKNPQEGLYNEL QKDKMAEAYSEIGMKG ERRRGKGHDGLYQGLS TATKDTYDALHMQALP PR</p>	
<p>(CAR3.3) Clone 20C5.1 CD8 CAR DNA HxL</p>	<p>ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTGCAGTTGGTGCAAAGCGGC GCAGAAGTTAAGAAACCTGGGCGTCACT TAAGGTGTCTTGCAAAGTATCTGGCTATA CCCTCACTGAGCTGTCCATGCATTGGGTA AGGCAGGCTCCTGGAAGGGGCTCGAATG GATGGGAGGATTTGACCTGAAGACGGAG AGACCATCTACGCCCAGAAATTCCAGGGT AGAGTAACAGTGACTGAGGACACTAGCAC TGACACAGCGTACATGGAGCTGAGTTCTC TGAGAAGTGAGGACACAGCCGTTTACTAC TGCGCTACCGAGTCCAGAGGTATTGGCTG GCCATACTTCGACTATTGGGGTCAGGGCA CCCTGGTTACAGTGAGTTCAGGAGGCGGG GGCTCTGGGGGGGGCGGTTCCGGAGGGGG GGGCTCAGATATACAGATGACGCAGAGTC CATCAAGTCTCTCAGCCAGCGTGGGAGAT CGCGTGACTATTACTTGCCGCGCCAGCCA GAGTATTAGCTCCTATCTGAATTGGTACC AGCAAAAGCCCGGAAGGCCCTAAGCTT CTGATTTCTGGCGCCTCCTTTTGAAGTC AGGTGTGCCAAGCAGATTTAGCGGGTCTG GAAGTGGCACTGACTTTTACTTACTATC TCCAGCCTGCCCCCAGAGGATTTTGCCAC ATATTACTGTGCAAGCTACTCTACTC CAATCACTTTCCGCCAGGGCACAAGATTG</p>	209	<p>MALPVTALLPLALLL HAARPQVQLVQSGAEV KKPGASVKVSKVSGY TLTELSMHWRQAPGK GLEWMGGFDPEDGETI YAQKFQGRVTVTEDTS TDTAYMELSSLRSED AVYYCATESRGIWPFY FDYWGQGLTVTVSSGG GGSGGGSGGGGSDIQ MTQSPSSLSASVGDV TITCRASQSISSYLNW YQQKPGKAPKLLISGA SSLKSGVPSRFSGSGS GTDFTLTISLPPEDF ATYYCQQSYSTPITFG QGTRLEIKRAAALSNS IMYFSHFVPVFLPAKP TTTPAPRPPTPAPTIA SQPLSLRPEACRPAAG GAVHTRGLDFACDIYI WAPLAGTCGVLLLSLV ITLYCNHRNRSKRSRL LHSDYMNMTPRRPGPT RKHYQPYAPPRDFAAY RSRVKFSRSADAPAYQ QGQNQLYNELNLGRRE</p>	210

	<p>GAGATTAAGAGGGCTGCCGCACTTTCAAA TTCCATCATGTATTTAGCCATTTTGTGC CTGTTTTTCTTCCGGCCAAACCTACAACC ACTCCCGCCCCACGCCACCTACTCCCGC CCCTACCATTGCCTCCCAGCCTCTGTCTC TTAGACCTGAGGCTTGTAGACCTGCTGCC GGCGGAGCCGTGCACACTCGCGGTCTGGA CTTCGCCTGCGACATCTATATCTGGGCC CTCTGGCCGGCACCTGCGGCGTTCTCCTT CTCTCACTCGTAATCACACTCTATTGCAA TCACAGGAACAGATCCAAAAGAAGCCGCC TGCTCCATAGCGATTACATGAATATGACT CCACGCCGCCCTGGCCCCACAAGGAAACA CTACCAGCCTTACGCACCACCTAGAGATT TCGCTGCCTATCGGAGCAGGGTGAAGTTT TCCAGATCTGCAGATGCACCAGCGTATCA GCAGGGCCAGAACCAACTGTATAACGAGC TCAACCTGGGACGCAGGGAAGAGTATGAC GTTTTGGACAAGCGCAGAGGACGGGACCC TGAGATGGGTGGCAAACCAAGACGAAAAA ACCCCCAGGAGGGTCTCTATAATGAGCTG CAGAAGGATAAGATGGCTGAAGCCTATTC TGAAATAGGCATGAAAGGAGAGCGGAGAA GGGAAAAGGGCACGACGGTTTGTACCAG GGACTCAGCACTGCTACGAAGGATACTTA TGACGCTCTCCACATGCAAGCCCTGCCAC CTAGGTAA</p>		<p>EYDVLDKRRGRDPEMG GKPRRKNPQEGLYNEL QKDKMAEAYSEIGMKG ERRRGKHDGLYQGLS TATKDTYDALHMQALP PR</p>	
<p>(CAR3.3) Clone 20C5.1 CD8 CAR DNA HxL</p>	<p>CAGGTGCAGTTGGTGCAAAGCGGCGCAGA AGTTAAGAAACCTGGGGCGTCAGTTAAGG TGTCTTGCAAAGTATCTGGCTATACCCTC ACTGAGCTGTCCATGCATTGGGTAAGGCA GGCTCCTGGAAAGGGGCTCGAATGGATGG GAGGATTTGACCCTGAAGACGGAGAGACC ATCTACGCCCAGAAATTCCAGGGTAGAGT AACAGTGACTGAGGACACTAGCACTGACA CAGCGTACATGGAGCTGAGTTCTCTGAGA AGTGAGGACACAGCCGTTTACTACTGCGC TACCGAGTCCAGAGGTATTGGCTGGCCAT ACTTCGACTATTGGGGTCAGGGCACCCCTG GTTACAGTGAGTTTAGGAGCGGGGGGCTC TGGGGGGGGCGGTTCCGGAGGGGGGGGCT CAGATATACAGATGACGCAGAGTCCATCA AGTCTCTCAGCCAGCGTGGGAGATCGCGT GACTATTACTTGCCGCGCCAGCCAGAGTA TTAGCTCCTATCTGAATTGGTACCAGCAA AAGCCCGGGAAGGCCCCTAAGCTTCTGAT TTCTGGCGCCTCCTCTTTGAAGTCAGGTG TGCCAAGCAGATTTAGCGGGTCTGGAAGT GGCACTGACTTTTACTTACTATCTCCAG CCTGCCCCCAGAGGATTTTGCCACATATT ACTGTCAGCAAAGCTACTCTACTCCAATC ACTTTCGGCCAGGGCACAGATTGGAGAT TAAGAGGGCTGCCGCACTTTCAAATTCCA TCATGTATTTAGCCATTTTGTGCCTGTT TTTCTTCCGGCCAAACCTACAACCACTCC CGCCCCACGCCACCTACTCCGCCCCCTA CCATTGCCCTCCAGCCTCTGTCTCTTAGA CCTGAGGCTTGTAGACCTGCTGCCGGCGG AGCCGTGCACACTCGCGGTCTGGACTTCG</p>	211	<p>QVQLVQSGAEVKKPGA SVKVSCKVSGYTLTEL SMHWVRQAPGKLEWM GGFDPEDGETIYAQKF QGRVTVTEDTSTDY MELSSLRSEDYVYYC ATESRGIWPFYDWG QGTLVTVSSGGGSGG GGSGGGSDIQMTQSP SSLSASVGDRTITCR ASQSISSYLNWYQQK GKAPKLLISGASSLKS GVPSRFSGSGSDFT LTISSLPPEDFATYYC QQSYSTPITFGQTRL EIKRAALNSIMYFS HFVPVFLPAKPTTPA PRPPTPAPTIASQPLS LRPEACRPAAGGAVHT RGLDFACDIYIWAPLA GTCGVLLLSLVITLYC NHRNRSKRSLHSDY MNMTPRRPGPTRKHYQ PYAPPRDFAAYRSRVK FSRSADAPAYQQGQNG LYNELNLGRREYDVL DKRRGRDPEMGKPRR KNPQEGLYNELQKDKM AEAYSEIGMKGERRRG KHDGLYQGLSTATKD TYDALHMQALPPR</p>	212

	CCTGCGACATCTATATCTGGGCCCTCTG GCCGGCACCTGCGGCGTTCTCCTTCTCTC ACTCGTAATCACACTCTATTGCAATCACA GGAACAGATCCAAAAGAAGCCGCCTGCTC CATAGCGATTACATGAATATGACTCCACG CCGCCCTGGCCCCACAAGGAAACACTACC AGCCTTACGCACCACCTAGAGATTTTCGCT GCCTATCGGAGCAGGGTGAAGTTTTCCAG ATCTGCAGATGCACCAGCGTATCAGCAGG GCCAGAACCAACTGTATAACGAGCTCAAC CTGGGACGCAGGGAAGAGTATGACGTTTT GGACAAGCGCAGAGGACGGGACCCTGAGA TGGGTGGCAAACCAAGACGAAAAACCCC CAGGAGGGTCTCTATAATGAGCTGCAGAA GGATAAGATGGCTGAAGCCTATTCTGAAA TAGGCATGAAAGGAGAGCGGAGAAGGGGA AAAGGGCACGACGGTTTGTACCAGGGACT CAGCACTGCTACGAAGGATACTTATGACG CTCTCCACATGCAAGCCCTGCCACCTAGG			
(CAR4.1) Clone 20C5.2 THD CAR DNA HxL	ATGGCACTCCCCGTAACCTGCTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTCCAGTTGGTCGAAAGTGGC GGTGGTGTAGTGACGCCGGCCGCAGTTT GAGGCTTTCTGTGCGGCTTCAGGCTTTA CTTTTTCCAGCTATGGAATGCACTGGGTG CGGCAGGCCCCCGGCAAAGGACTTGAGTG GGTGGCGTCATTTCTTATGACGGATCAG ATAAGTACTACGTGGACACGCTCAAGGGC AGATTCACCATCTCTAGGGACAACAGTAA AAATAGACTCTACCTCCAGATGAATAGCC TCAGAGCTGAAGACACGGCGTCTACTAT TGTGCTCGGGAGCGGTATAGTGGCAGAGA CTACTGGGGGCAGGGCACACTCGTTACAG TGAGTAGCGCGGAGGAGGAGTGGGGGC GGTGGCTCCGGTGGAGGAGGTCTGAGAT TGTTATGACCCAGAGTCTCGCACCCTCT CAGTCAGCCCCGGGGAGCGCGCAACTTTG TCTTGACAGCTAGTCAGTCCGTGTCTC TCTTCTGACATGGTACCAGCAAAAGCCCG GGCAGGCTCCGCGCCTTTTGATCTTTGGG GCTTCAACAAGAGCCACTGGGATTCCCGC ACGATTCTCTGGCTCCGGGAGCGGTACTG GTTTCACCTGACGATTAGCAGTCTCCAG AGCGAGGACTTCGCCGTATACTACTGCCA GCAGTACGATACGTGGCCATTCACTTTTG GACCAGGACTAAAGTGGATTTTAAGCGC GCCGCCGTCTCGATAACGAAAAGTCAAA TGGCACCATAATCCACGTCAAAGGCAAGC ACCTGTGCCCTTCCCCGCTCTTCCCCGGA CCCAGTAAACCATTTTGGGTGCTGTTGT TGTGGGGGGCGTGCTGGCCTGCTATAGCC TTTTGGTCACTGTAGCCTTCATTATTTTT TGGGTGAGATCCAAAAGAAGCCGCTGCT CCATAGCGATTACATGAATATGACTCCAC GCCGCCCTGGCCCCACAAGGAAACACTAC CAGCCTTACGCACCACCTAGAGATTTTCGC TGCTATCGGAGCAGGGTGAAGTTTTCCA GATCTGCAGATGCACCAGCGTATCAGCAG GGCCAGAACCAACTGTATAACGAGCTCAA	213	MALPVTALLLPLALLL HAARPQVQLVESGGGV VQPGRSLRLSCAASGF TFSSYGMHWVRQAPGK GLEWVAVISYDGSDKY YVDSVKGRFTISRDN KNRLYLQMNLSRAEDT AVYYCARERYSGRDY GQGTLVTVSSGGGSG GGSGGGGSEIVMTQS PATLSVSPGERATLSC RASQSVSSLLTWYQQK PGQAPRLIFGASTRA TGIPARFSGSGSGTGF TLTISSLQSEDFAVYY CQQYDTPFTFGPGTK VDFKRAAALDNEKSNG TIIHVKGKHLCPSPLF PGPSKPFVWLVVVG LACYSLLVTVAFIIFW VRSKRSRLHSDYMN TPRRPGPTRKHYQPYA PPRDFAAYSRVKFSR SADAPAYQQGQNQLYN ELNLGRREYDVLDR RGRDPEMGKPRRKNP QEGLYNELQDKMAEA YSEIGMKGERRRGKGH DGLYQGLSTATKDTYD ALHMQALPPR	214

	CCTGGGACGCAGGGAAGAGTATGACGTTT TGGACAAGCGCAGAGGACGGGACCTGAG ATGGGTGGCAAACCAAGACGAAAAACCC CCAGGAGGGTCTCTATAATGAGCTGCAGA AGGATAAGATGGCTGAAGCCTATTCTGAA ATAGGCATGAAAGGAGAGCGGAGAAGGGG AAAAGGGCACGACGGTTTGTACCAGGGAC TCAGCACTGCTACGAAGGATACTTATGAC GCTCTCCACATGCAAGCCCTGCCACCTAG GTAA			
(CAR4.1) Clone 20C5.2 THD CAR DNA HxL	CAGGTCCAGTTGGTTCGAAAGTGGCGGTGG TGTAAGTGCAGCCGGGCGCAGTTTGAGGC TTTCCTGTGGGCTTCAGGCTTTACTTTT TCCAGCTATGGAATGCACTGGGTGCGGCA GGCCCCGGCAAAGGACTTGAGTGGGTGG CCGTCAATTTCTATGACGGATCAGATAAG TACTACGTGGACAGCGTCAAGGGCAGATT CACCATCTCTAGGGACAACAGTAAAAATA GACTCTACCTCCAGATGAATAGCCTCAGA GCTGAAGACACGGCCGTCTACTATTGTGC TCGGGAGCGGTATAGTGGCAGAGACTACT GGGGGCAGGGCACACTCGTTACAGTGAGT AGCGGCGGAGGAGGGAGTGGGGCGGTGG CTCCGGTGGAGGAGTTCTGAGATTGTTA TGACCCAGAGTCCTGCGACCTCTCAGTC AGCCCCGGGAGCGCGCACTTTGTCTTG CAGAGCTAGTCAGTCCGTGCTCTCTCTC TGACATGGTACCAGCAAAAGCCCGGGCAG GCTCCGCGCCTTTTGATCTTTGGGGCTTC AACAAGAGCCACTGGGATTCCCGCACGAT TCTCTGGCTCCGGGAGCGTACTGGTTTC ACCCTGACGATTAGCAGTCTCCAGAGCGA GGACTTCGCGTATACTACTGCCAGCAGT ACGATACGTGGCCATTCACTTTTGACCA GGGACTAAAGTGGATTTTAAAGCGCGCCGC CGCTCTCGATAACGAAAAGTCAAATGGCA CCATAATCCACGTCAAAGGCAAGCACCTG TGCCCTTCCCCGCTCTTCCCCGGACCCAG TAAACCATTTTGGGTGCTGTTGTTGTGG GGGGCGTGCTGGCCTGCTATAGCCTTTTG GTCAGTGTAGCCTTCATTATTTTGGGT CAGATCCAAAAGAAGCCGCTGCTCCATA GCGATTACATGAATATGACTCCACGCCGC CCTGGCCCCACAAGGAAACACTACCAGCC TTACGCACCACTAGAGATTTGCTGCCT ATCGGAGCAGGGTGAAGTTTCCAGATCT GCAGATGCACCAGCGTATCAGCAGGGCCA GAACCAACTGTATAACGAGCTCAACCTGG GACGCAGGGAAGAGTATGACGTTTGGAC AAGCGCAGAGGACGGGACCCTGAGATGGG TGGCAAACCAAGACGAAAAACCCCGAGG AGGGTCTCTATAATGAGCTGCAGAAGGAT AAGATGGCTGAAGCCTATTCTGAAATAGG CATGAAAGGAGAGCGGAGAAGGGGAAAAG GGCACGACGGTTGTACCAGGGACTCAGC ACTGCTACGAAGGATACTTATGACGCTCT CCACATGCAAGCCCTGCCACCTAGG	215	QVQLVESGGGVVQPGR SLRLSCAASGFTFSSY GMHWVRQAPGKGLEWV AVISYDGS DKYYVDSV KGRFTISRDN SKNRLY LQMNSLRAEDTAVYYC ARERYSGRDYWGQGT L VTVSSGGGSGGGGSG GGGSEIVMTQSPATLS VSPGERATLSCRASQS VSSLLTWYQQKPGQAP RLLI FGASTRATGIPA RFSGSGSGTGFTLTIS SLQSEDFAVYYCQDYD TWPFTFGPGTKVDFKR AAALDNEKSNGTIIHV KGKHLCPSP LFPGPSK PFWVLVVVGVLACYS LLVTVAFIIFWVRSKR SRLLHSDYMNMTPRRP GPTRKHYQPYAPPRDF AAYRSRVKFSRSADAP AYQQGQNQLYNELNLG RREEYDVLDRRGRDP EMGGKPRRKNPQEGLY NELQDKMAEAYSEIG MKGERRRGKGDGLYQ GLSTATKDTYDALHMQ ALPPR	216
(CAR4.2) Clone	ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC	217	MALPVTALLLPLALLL HAARPQVQLVESGGGV	218

20C5.2 CHD CAR DNA HxL	GCCCCGAGGTGCAGCTCGTGGAGTCTGGC GGCGGCGTGGTCCAGCCCCGCCGGTCCCT GCGCCTGTCTGCGCCGCCAGCGGGTTTA CTTTTCTCCTACGGCATGCACTGGGTG CGCCAGGCTCCCGGCAAGGGCCTCGAGTG GGTCGCGTGATCTCATACGATGGGTGAG ACAAATACTATGTCGATTCTGTTAAAGGG CGGTTTACCATTTCAAGAGATAACTCTAA GAATAGGCTGTATTTGCAGATGAACAGCC TGAGGGCTGAAGATACCGCAGTGTACTAT TGCGCTAGGGAGCGGTATAGTGGCCGCGA TTACTGGGGACAGGGTACACTGGTGACCG TGAGCTCTGGGGGTGGCGAAGCGGGGT GGCGGAAGCGGCGGAGGGGTAGTGAAAT TGTGATGACCCAGTCTCCGGCTACACTTT CAGTCTCCCTGGGGAGAGAGCTACACTG TCATGCAGAGCGTCCCAGTCCGTCTCTTC TCTCCTTACCTGGTATCAGCAGAAGCCCG GCCAGGCTCCTCGACTGCTGATCTTCGGT GCCTCCACAAGGGCGACCGGGATTCCAGC CCGCTTCTCAGGTTCTGGGAGCGGAAGT GTTTCACTTTGACAATCAGTTCACTGCAG TCAGAGGATTTGCGCGTGTACTACTGCCA GCAATACGACACATGGCCATTCACTTTG GACCCGGTACCAAAGTCGATTTCAAGAGA GCCGCGGCCATCGAGGTTATGTACCCACC ACCATATCTGGACAATGAAAAAGCAATG GAACCATTTATCCATGTGAAGGGTAAACAC CTCTGCCCTAGCCCACTTTTCCCTGGCCC ATCAAAGCCCTTCTGGGTCTTGGTGGTGG TGGGGGGTGTGCTGGCCTGTTACAGCCTT CTGGTGACGGTTGCTTTTCACTATCTTCTG GGTTAGATCCAAAAGAAGCCGCTGCTCC ATAGCGATTACATGAATATGACTCCACGC CGCCCTGGCCCCACAAGGAAACACTACCA GCCTTACGCACCACCTAGAGATTTGCTG CCTATCGGAGCAGGGTGAAGTTTCCAGA TCTGCAGATGCACCAGCGTATCAGCAGGG CCAGAACCAACTGTATAACGAGCTCAACC TGGGACGCAGGGAAGAGTATGACGTTTGT GACAAGCGCAGAGGACGGGACCTGAGAT GGGTGGCAAACCAAGACGAAAAACCCCG AGGAGGGTCTCTATAATGAGCTGCAGAAG GATAAGATGGCTGAAGCCTATTCTGAAAT AGGCATGAAAGGAGAGCGGAGAAGGGGAA AAGGGCACGACGGTTTGTACCAGGGACTC AGCACTGCTACGAAGGATACTTATGACGC TCTCCACATGCAAGCCCTGCCACCTAGGT AA		VQPGRSLRLSCAASGF TFSSYGMHWVRQAPGK GLEWVAVISYDGS DKY YVDSVKGRFTISRDN KNRLYLQMNLSRAEDT AVYYCARERYSGRDY WGQTLVTVSSGGGSG GGGSGGGSEIVMTQS PATLSVSPGERATLSC RASQSVSSLLTWYQK PGQAPRLIFGASTRA TGIPARFSGSGSGTGF TLTISSLQSEDFAVYY CQQYDTPFTFGPGTK VDFKRAAAIEVMYPP YLDNEKSNGTIIHVKG KHLCPSPLEPGPSKPF WVLVVVGGVLACYSL VTVAFIIFWVRSKRSR LLHSDYMNMTPRRPGP TRKHYQPYAPPRDFAA YRSRVKFSRSADAPAY QQGQNQLYNELNLGRR EEYDVLDKRRGRDPEM GGKPRRKNPQEGLYNE LQKDKMAEAYSEIGMK GERRRKGHDGLYQGL STATKDTYDALHMQAL PPR	
(CAR4.2) Clone 20C5.2 CHD CAR DNA HxL	CAGGTGCAGCTCGTGGAGTCTGGCGGCGG CGTGGTCCAGCCCGGCCGGTCCCTGCGCC TGTCCTGCGCCGCCAGCGGGTTTACTTTT TCCTCCTACGGCATGCACTGGGTGCGCCA GGCTCCCGGCAAGGGCCTCGAGTGGGTG CCGTGATCTCATACGATGGGTGAGACAAA TACTATGTCGATTCTGTTAAAGGGCGGTT TACCATTTCAAGAGATAACTCTAAGAATA GGCTGTATTTGCAGATGAACAGCCTGAGG GCTGAAGATACCGCAGTGTACTATTGCGC	219	QVQLVESGGGVVQPGR SLRLSCAASGFTFSSY GMHWVRQAPGKGLEWV AVISYDGS DKYYVDSV KGRFTISRDN SKNRLY LQMNLSRAEDTAVYYC ARERYSGRDYWGQTL VTVSSGGGSGGGGSG GGGSEIVMTQSPATLS VSPGERATLSCRASQS	220

	<p>TAGGGAGCGGTATAGTGGCCGCGATTACT GGGGACAGGGTACACTGGTGACCGTGAGC TCTGGGGGTGGCGGAAGCGGGGTGGCGG AAGCGCGGAGGGGGTAGTGAAATTGTGA TGACCCAGTCTCCGGCTACACTTTCAGTC TCCCCTGGGGAGAGAGCTACACTGTCATG CAGAGCGTCCAGTCCGTCTCTTCTCTCC TTACCTGGTATCAGCAGAGCCCCGGCCAG GCTCCTCGACTGCTGATCTTCGGTGCCCTC CACAAAGGCGACCGGGATTCCAGCCCGCT TCTCAGGTTCTGGGAGCGGAAGTGGTTTC ACTTTGACAATCAGTTCAGTGCAGTCAGA GGATTTTCGCCGTGTACTACTGCCAGCAAT ACGACACATGGCCATTCACTTTCGGACCC GGTACCAAAGTCGATTTCAAGAGAGCCGC GGCCATCGAGGTTATGTACCCACCACCAT ATCTGGACAATGAAAAAGCAATGGAACC ATTATCCATGTGAAGGGTAAACACCTCTG CCCTAGCCCACTTTTCCCTGGCCCATCAA AGCCCTTCTGGGTCTTGGTGGTCTGGGG GGTGTGCTGGCCTGTTACAGCCTTCTGGT GACGGTTGCTTTCATTATCTTCTGGGTTA GATCCAAAAGAAGCCGCTGCTCCATAGC GATTACATGAATATGACTCCACGCCGCC TGGCCCCACAGGAACACTACCAGCCTT ACGCACCACCTAGAGATTTTCGCTGCCTAT CGGAGCAGGGTGAAGTTTTCCAGATCTGC AGATGCACCAGCGTATCAGCAGGGCCAGA ACCAACTGTATAACGAGCTCAACCTGGGA CGCAGGGAAGAGTATGACGTTTTGGACAA GCGCAGAGGACGGGACCCTGAGATGGGTG GCAAACCAAGACGAAAAACCCCCAGGAG GGTCTCTATAATGAGCTGCAGAAGGATAA GATGGCTGAAGCCTATTCTGAAATAGGCA TGAAAGGAGAGCGGAGAAGGGGAAAAGGG CACGACGGTTGTACCAGGACTCAGCAC TGCTACGAAGGATACTTATGACGCTCTCC ACATGCAAGCCCTGCCACCTAGG</p>		<p>VSSLLTWYQQKPGQAP RLLIFGASTRATGIPA RFSGSGSGTGFTLTIS SLQSEDFAVYYCQYD TWPFTFGPGTKVDFKR AAAEIVMPPPYLDNE KSNGTIIHVKGKHLCP SPLFPGPSKPFWVLV VGGVLACYSLLVTVA IIFWVRSKRSRLHSD YMNMTPRRPGPTRKHY QPYAPPRDFAAYRSRV KFSRSADAPAYQQGQN QLYNELNLGRREYDV LDKRRGRDPMEGGKPR RKNPQEGLYNELQKDK MAEAYSEIGMKGERRR GKGHDGLYQGLSTATK DTYDALHMQALPPR</p>	
<p>(CAR4.3) Clone 20C5.2 CD8 CAR DNA HxL</p>	<p>ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGCAGGTGCAGTTGGTTGAATCAGGA GGGGGTGTGGTGCAACCCGGTCGGTCACT GCGCCTCAGTTGTGCTGCTCCGGGTTTA CTTTCAGCTCATATGGGATGCACTGGGTA CGGCAGGCTCCAGGTAAAGGCTTGGAATG GGTGGCGGTGATCAGCTATGACGGCTCTG ACAAATATTATGTGGACTCCGTGAAAGGC AGATTACCATCAGTCGAGACAACCTCAA GAATAGACTCTACTTGAGATGAATAGCC TCCGGGCCGAAGATACTGCAGTCTATTAT TGCGCCCGGAGCGCTACAGTGGAAGAGA CTATTGGGGGCAAGGAAGTCTTGTACAG TCTCATCTGGCGGCGGCGGAGCGGTGGG GGCGGATCTGGCGGGGCGGCGAGCGAAAT CGTTATGACTCAGAGTCTGCCACACTGA GCGTTAGCCCTGGTGAGAGAGCAACACTT AGCTGCAGAGCTAGTCAGAGTGTTTCCAG TCTTTTGACATGGTACCAACAGAAGCCCG GTCAAGCTCCACGACTGCTCATCTTCGGT</p>	221	<p>MALPVTALLLPALLL HAARPQVQLVESGGV VQPGRLRLSCLASGF TFSSYGMHWVRQAPGK GLEWVAVISYDGSCKY YVDSVKGRFTISRDN KNRLYLQMNLSRAEDT AVYYCARERYSGRDY GQGTLLTVSSGGGSG GGSGGGGSEIVMTQS PATLSVSPGERATLSC RASQSVSSLLTWYQQK PGQAPRLIFGASTRA TGIPARFSGSGSGTGF TLTISSLQSEDFAVYY CQQYDTWPFTFGPGTK VDFKRAAALSNSIMYF SHFVPVFLPAKPTTTP APRPPTPAPTIASQPL SLRPEACRPAAGGAVH TRGLDFACDIYIWAPL</p>	222

	GCATCCACCCGCGCAACCGGGATACCCGC CCGGTTTTCCGGTTCTGGAAGTGGCACAG GATTACAGCTCACCATTCTTCTCTGCAG TCTGAAGACTTTGCCGTGATTACTGCCA GCAGTACGATACCTGGCCCTTTACCTTTG GCCAGGTACTAAAGTGGATTTTAAACGA GCTGCTGCACTTTCCAATAGTATTATGTA CTTTTCACATTTTGTGCCCGTGTTCCCTGC CTGCGAAGCCTACGACAACCCAGCCCTT AGGCCGCCCACACCGGCCCAACTATTGC CTCCCAGCCATTGTCTCTGAGACCCGAAG CTTGACAGCTGCTGCTGGAGGCGCCGTT CACACCCGAGGATTGGATTTCGCATGTGA CATTTACATCTGGGCCCCCTTTGGCCGGAA CCTGCGGTGTGCTGCTGCTGCTCACTCGTG ATTACACTTTACTGCAACCACCGAAACAG ATCCAAAAGAAGCCGCCTGCTCCATAGCG ATTACATGAATATGACTCCACGCGCCCT GGCCCCACAAGGAAACACTACCAGCCTTA CGCACCACCTAGAGATTTGCTGCCTATC GGAGCAGGGTGAAGTTTTCCAGATCTGCA GATGCACCAGCGTATCAGCAGGGCCAGAA CCAAGTGTATAACGAGCTCAACCTGGGAC GCAGGGAAGAGTATGACGTTTTGGACAAG CGCAGAGGACGGGACCCCTGAGATGGGTGG CAAACCAAGACGAAAAACCCCCAGGAGG GTCTCTATAATGAGCTGCAGAAGGATAAG ATGGCTGAAGCCTATTCTGAAATAGGCAT GAAAGGAGAGCGGAGAAGGGGAAAAGGGC ACGACGGTTTGTACCAGGGACTCAGCACT GCTACGAAGGATACTTATGACGCTCTCCA CATGCAAGCCCTGCCACCTAGGTAA		AGTCGVLLLLSLVITLY CNHRNRSKRSLHSD YMNMTPRRPGPTRKHY QPYAPPRDFAAYRSRV KFSRSADAPAYQQGQN QLYNELNLGRREEYDV LDKRRGRDPEMGGKPR RKNPQEGLYNELQKDK MAEAYSEIGMKGERRR GKGHDGLYQGLSTATK DTYDALHMQALPPR	
(CAR4.3) Clone 20C5.2 CD8 CAR DNA HxL	CAGGTGCAGTTGGTTGAATCAGGAGGGG TGTGGTGCAACCCGGTCGGTCACTGCGCC TCAGTTGTGCTGCTTCCGGGTTTACTTTC AGCTCATATGGGATGCACTGGGTACGGCA GGCTCCAGGTAAAGGCTTGAATGGGTGG CGGTGATCAGCTATGACGGCTCTGACAAA TATTATGTGGACTCCGTGAAAGGCAGATT CACCATCAGTCGAGACAACCTCAAAGAATA GACTCTACTTGACAGATGAATAGCCTCCGG GCCGAAGATACTGCAGTCTATTATTGCGC CCGGGAGCGCTACAGTGAAGAGACTATT GGGGGCAAGGAACCTCTGTACAGTCTCA TCTGGCGGCGCGCGCAGCGGTGGGGCGG ATCTGGCGGGGGCGGCAGCGAAATCGTTA TGACTCAGAGTCCTGCCCACTGAGCGTT AGCCCTGGTGAGAGAGCAACACTTAGCTG CAGAGCTAGTCAGAGTGTTCCAGTCTTT TGACATGGTACCAACAGAAGCCCGGTCAA GCTCCACGACTGCTCATCTTCGGTGATC CACCCGCGCAACCGGGATACCCGCCCGGT TTTCCGGTTCTGGAAGTGGCACAGGATTC ACGCTCACCATTTCTTCTCTGCAGTCTGA AGACTTTGCCGTGTATTACTGCCAGCAGT ACGATACCTGGCCCTTTACCTTTGGCCCA GGTACTAAAGTGGATTTTAAACGAGCTGC TGCACTTTCCAATAGTATTATGTACTTTT CACATTTTGTGCCCGTGTTCTCTGCCTGCG	223	QVQLVESGGGVVQPGR SLRLSCAASGFTFSSY GMHWVRQAPGKGLEWV AVISYDGS DKYYVDSV KGRFTISRDN SKNRLY LQMN SLRAEDTAVYYC ARERYSGRDYWGQGT LTVSSGGGSGGGGSG GGGSEIVMTQSPATLS VSPGERATLSCRASQS VSSLLTWYQQKPGQAP RLLI FGA STRATGIPA RFSGSGSGTFTLTIS SLQSEDFAVYYCQQYD TWPFTFGPGTKVDFKR AAALSNSIMYFSHFVP VFLPAKPTTTPAPRPP TPAPTIASQPLSLRPE ACRPAAGGAVHTRGLD FACDIYIWAPLAGTCG VLLLSLVITLYCNHRN RSKRSLHSDYMNMT PRRPGPTRKHYQPYAP PRDFAAYRSRVKFSRS ADAPAYQQGQNQLYNE LNLGRREEYDVLDRR GRDPEMGGKPRRKNPQ	224

	AAGCCTACGACAACCCAGCCCTAGGCC GCCCACACCGGCCCCAACTATTGCCTCCC AGCCATTGTCTCTGAGACCCGAAGCTTGC AGACCTGCTGCTGGAGGCGCCGTTACACAC CCGAGGATTGGATTTTCGCATGTGACATTT ACATCTGGGCCCCCTTTGGCCGGAACCTGC GGTGTGCTGCTGCTGTCACTCGTGATTAC ACTTTACTGCAACCACCGAAACAGATCCA AAAGAAGCCGCTGCTCCATAGCGATTAC ATGAATATGACTCCACGCCGCCCTGGCCC CACAAGGAAACACTACCAGCCTTACGCAC CACCTAGAGATTTTCGCTGCCTATCGGAGC AGGGTGAAGTTTCCAGATCTGCAGATGC ACCAGCGTATCAGCAGGGCCAGAACCAC TGTATAACGAGCTCAACCTGGGACGCAGG GAAGAGTATGACGTTTTTGACAAGCGCAG AGGACGGGACCCTGAGATGGGTGGCAAAC CAAGACGAAAAAACCCCGAGGAGGTCTC TATAATGAGCTGCAGAAGGATAAGATGGC TGAAGCCTATTCTGAAATAGGCATGAAAG GAGAGCGGAGAAGGGGAAAAGGGCACGAC GGTTTGTACCAGGGACTCAGCACTGCTAC GAAGGATACTTATGACGCTCTCCACATGC AAGCCCTGCCACCTAGG		EGLYNELQDKMAEAY SEIGMKGERRRGKGH GLYQGLSTATKDTYDA LHMQALPPR	
(CAR4.4) Clone 20C5.2 THD CAR DNA LxH	ATGGCACTCCCCGTAACCTGCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCCGAGATTGTGATGACCCAGTCCCCT GCTACCCGTCCGTCAGTCCGGGCGAGAG AGCCACCTTGTCTGTCAGCCGGCCAGCCAGT CCGTGAGCAGTCTCCTGACTTGGTATCAG CAAAAACCCAGGGCAGGCACCGCGGCTTTT GATTTTGGTGCAAGCACACGCGCCACTG GCATTCCAGCTAGGTTTTCTGGAAGTGGA TCTGGGACAGGCTTCACTCTGACAATCAG TAGCCTGCAGAGTGAGGACTTTGCTGTTT ACTACTGTCAACAGTACGACACCTGGCCA TTCACATTCCGGGCCCCGGCACCAAGGTCGA CTTCAAGAGGGGCGGTGGAGGTTAGGTG GTGGCGGGTCAGGCGGCGGTGGGTCTCAG GTTCAACTGGTGGAATCAGGTGGCGGCGT TGTCCAACCGGGGCGATCACTTCGACTTT CCTGTGCTGCCTCAGGCTTACTTTTTTCA TCCTATGGGATGCACTGGGTTCCGGCAGGC TCCCGGAAAAGGACTCGAGTGGGTGTCAG TGATCTCTTACGATGGCTCAGACAAGTAT TATGTGGACTCAGTCAAGGGGAGATTAC AATAAGCCGAGACAACCTCAAAAACCGGC TTTATCTCCAGATGAACAGCCTTAGAGCG GAAGATACCGCGGTATACTACTGTGCCCG CGAGAGGTATCCGGCAGAGACTACTGGG GACAGGGCACACTGGTCACCGTGAGTTCT GCCGCAGCGCTCGATAACGAAAAGAGCAA CGGAACCATTATCCACGTTAAGGGCAAGC ACCTGTGCCCCAGTCCCCTCTTCCAGGA CCATCTAAACCCCTTCTGGGTTCTGGTAGT AGTTGGAGGGGTCCTTGTCATGTTACTCCC TTTTGGTCAACGTCGCTTCATTATTTTC TGGGTGAGATCCAAAAGAGCCGCTGCT CCATAGCGATTACATGAATATGACTCCAC	225	MALPVTALLPLALLL HAARPEIVMTQSPATL SVSPGERATLSCRASQ SVSSLLTWYQQKPGQA PRLIFGASTRATGIP ARFSGSGSGTGFTLTI SSLQSEDFAVYYCQQY DTWPFYFGPGTKVDFK RGGGSGGGSGGGGS QVQLVESGGGVVQPGR SLRLSCAASGFTFSSY GMHWVRQAPGKLEWV AVISYDGSCKYYVDSV KGRFTISRDNKSNRLY LQMNSLRADTAVYYC ARERYSGRDYWGQGT VTVSSAAALDNEKSNG TIIHVKGKHLCPSPFL PGPSKPFWVLVVGGV LACYSLLVTVAFIIFW VRSKRSRLHSDYMN TPRRPGPTRKHYPYA PPRDFAAYRSRVKFSR SADAPAYQQQNQLYN ELNLGRREEYDVLDKR RGRDPEMGGKPRRKNP QEGLYNELQDKMAEA YSEIGMKGERRRGKGH DGLYQGLSTATKDTYD ALHMQALPPR	226

	GCCGCCCTGGCCCCACAAGGAAACACTAC CAGCCTTACGCACCACCTAGAGATTTTCGC TGCCTATCGGAGCAGGGTGAAGTTTTCCA GATCTGCAGATGCACCAGCGTATCAGCAG GGCCAGAACCAACTGTATAACGAGCTCAA CCTGGGACGCAGGGAAGAGTATGACGTTT TGGACAAGCGCAGAGGACGGGACCCTGAG ATGGGTGGCAAACCAAGACGAAAAAACCC CCAGGAGGGTCTCTATAATGAGCTGCAGA AGGATAAGATGGCTGAAGCCTATTCTGAA ATAGGCATGAAAGGAGAGCGGAGAAGGGG AAAAGGGCACGACGGTTTGTACCAGGGAC TCAGCACTGCTACGAAGGATACTTATGAC GCTCTCCACATGCAAGCCCTGCCACCTAG GTAA			
(CAR4.4) Clone 20C5.2 THD CAR DNA LxH	GAGATTGTGATGACCCAGTCCCCTGCTAC CCTGTCCGTCACTCCGGGCGAGAGAGCCA CCTTGTTCATGCCGGGCCAGCCAGTCCGTC AGCAGTCTCCTGACTTGGTATCAGCAAAA ACCAGGGCAGGCACCGCGCTTTTGAATTT TTGGTGCAAGCACACGCCCACTGGCATT CCAGCTAGGTTTTCTGGAAGTGGATCTGG GACAGGCTTCACTCTGACAATCAGTAGCC TGCAGAGTGAGGACTTTGCTGTTTACTAC TGTC AACAGTACGACACCTGGCCATTAC ATTCCGGGCCCGGCACCAAGGTCGACTTCA AGAGGGGCGGTGGAGGTTCAAGGTGGTGGC GGGTCAAGGCGCGGTGGGTCTCAGGTTCA ACTGGTGGAATCAGGTGGCGGCGTTGTCC AACC GGCGGATCACTTCGACTTTTCTGT GCTGCCTCAGGCTTTACTTTTTCATCCTA TGGGATGCACTGGGTTCGGCAGGCTCCCG GAAAAGGACTCGAGTGGGTGCAAGTATG TCTTACGATGGCTCAGACAAGTATTATGT GGACTCAGTCAAGGGGAGATTACAATAA GCCGAGACAACTCCAAAAACCGGCTTTAT CTCCAGATGAACAGCCTTAGAGCGGAAGA TACCGCGGTATACTACTGTGCCCGCGAGA GGTATTCGGCAGAGACTACTGGGGACAG GGCACACTGGTCACCGTGAGTTCTGCCGC AGCGCTCGATAACGAAAAGAGCAACGGAA CCATTATCCAGTTAAGGGCAAGCACCTG TGCCCCAGTCCCCTCTTCCAGGACCATC TAAACCCTTCTGGGTCTGGTAGTAGTTG GAGGGGTCTTGCATGTTACTCCCTTTTG GTCACCGTCGCCTTCATTATTTTCTGGGT GAGATCCAAAAGAAGCCGCTGCTCCATA GCGATTACATGAATATGACTCCACGCCGC CCTGGCCCCACAAGGAAACACTACCAGCC TTACGCACCACCTAGAGATTTGCTGCT ATCGGAGCAGGGTGAAGTTTTCCAGATCT GCAGATGCACCAGCGTATCAGCAGGGCCA GAACCAACTGTATAACGAGCTCAACCTGG GACGCAGGGAAGAGTATGACGTTTTTGAC AAGCGCAGAGGACGGGACCCTGAGATGGG TGGCAAACCAAGACGAAAAAACCCAGG AGGGTCTCTATAATGAGCTGCAGAAGGAT AAGATGGCTGAAGCCTATTCTGAAATAGG CATGAAAGGAGAGCGGAGAAGGGGAAAAG	227	EIVMTQSPATLSVSPG ERATLSCRASQSVSSL LTWYQQKPGQAPRLLI FGASTRATGIPARFSG SGSGTGFTLTISLQS EDFAVYYCQQYDTWPF TFGPGTKVDFKRGGGG SGGGSGGGGSQVQLV ESGGGVVQPGRSRLRS CAASGFTFSSYGMHWV RQAPGKGLEWVAVISY DGS DKYYVDSVKGRFT ISRDNSKNRLYLQMNS LRAEDTAVYYCARERY SGRDYWGQGLVTVSS AAALDNEKSNGTIIHV KGKHLCPSPFPGPSK PFWVLVVGGVLACYS LLVTVAFIIFWVRSKR SRLHSDYMNMTPRRP GPTRKHYQPYAPPRDF AAYRSRVKFSRSADAP AYQQGQNQLYNELNLG RREEYDVLDKRRGRDP EMGGKPRRNKPQEGLY NELQKDKMAEAYSEIG MKGERRRGKHDGLYQ GLSTATKDTYDALHMQ ALPPR	228

	GGCACGACGGTTTGTACCAGGGA CTGCTACGAAGGATACTTATGACGCTCT CCACATGCAAGCCCTGCCACCTAGG			
(CAR4.5) Clone 20C5.2 CHD CAR DNA LxH	ATGGCACTCCCCGTAAGTCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGGAGATCGTCATGACACAGAGTCCA GCTACCTGAGCGTGTCCCCTGGAGAGAG AGCCACCCTGTCCTGTAGGGCTAGTCAGA GTGTGTCCAGCCTCCTCACCTGGTATCAA CAGAAGCCTGGTCAAGCTCCCCGGCTGCT TATCTTCGGGGCCAGCACGCGAGCCACAG GCATCCCGGCCAGATTCTCTGGCTCTGGC AGTGGCACCGGGTTCACTCTCACGATCTC ATCCCTGCAGTCAGAGGATTTCTGCTGTGT ATTACTGTGAGCAGTACGATACATGGCCC TTCACCTTCGGCCCGGGCAGAAAAGTAGA TTTCAAGCGCGCGCGGGGGTAGTGGGG GCGGGGGATCAGGAGGAGGGGGCTCCCAA GTACAGCTGGTTGAGAGCGCGCGGGGT GGTTCAGCCCGGGCGCAGCCTCAGGCTGA GTTGCGCAGCATCAGGATTCACATTCAGT TCTTATGGAATGCATTGGGTGAGACAGGC TCCCGGGAAGGGCCTTGAATGGGTGGCAG TCATTAGCTACGACGGAAGCGATAAGTAC TATGTGGACTCAGTTAAAGGGAGATTTAC TATCAGCCGCGACAATTCCAAAACAGAT TGTATTTGCAGATGAATCCCTCAGGGCG GAGGACACTGCTGTATATTACTGCGCACG AGAGAGATACTCCGGCCGAGACTATTGGG GCCAAGGAACATTGGTAACTGTGAGCTCC GCCGCAGCTATTGAGGTGATGTACCCCC ACCTTATCTCGATAATGAGAAGAGTAATG GGACTATAATTCACGTAAAGGGCAAACAC CTGTGCCCTTCCCCGCTGTTCCAGGTCC AAGTAAGCCGTTCTGGGTCTGGTTGTGG TGGGAGGGGTGCTGGCCTGCTATTCTCTG TTGGTTACCGTGGCCTTTATCATTTTCTG GGTGAGATCCAAAAGAAGCCGCTGCTCC ATAGCGATTACATGAATATGACTCCACGC CGCCCTGGCCCCACAAGGAAACACTACCA GCCTTACGCACCACCTAGAGATTTCTGCTG CCTATCGGAGCAGGGTGAAGTTTTCCAGA TCTGCAGATGCACCAGCGTATCAGCAGGG CCAGAACCACTGTATAACGAGCTCAACC TGGGACGCAGGGAAGAGTATGACGTTTTG GACAAGCGCAGAGGACGGGACCCTGAGAT GGGTGGCAAACCAAGACGAAAAACCCCC AGGAGGGTCTCTATAATGAGCTGCAGAAG GATAAGATGGCTGAAGCCTATTCTGAAAT AGGCATGAAAGGAGAGCGGAGAAGGGGAA AAGGGCACGACGTTTTGTACCAGGACTC AGCACTGCTACGAAGGATACTTATGACGC TCTCCACATGCAAGCCCTGCCACCTAGGT AA	229	MALPVTALLLPLALLL HAARPEIVMTQSPATL SVSPGERATLSCRASQ SVSSLLTWYQQKPGQA PRLLI FGASTRATGIP ARFSGSGSGTGFTLTI SSLQSEDFAVYYCQQY DTWPF TFGPGTKVDFK RGGGSGGGSGGGGS QVQLVESGGGVVQPGR SLRLSCAASGFTFSSY GMHWVRQAPGKGLEWV AVISYDGS D KYVDSV KGRFTISRDN SKNRLY LQMN SLRAEDTAVYYC ARERYSGRDYWGQGT VTVS SAAAEVMYPPP YLDNEKSNGTIIHVKG KHLCPSP LFPGPSKPF WVLVVVGVLACYSLL VTVAFIIFWVRSKRSR LLHSDYMNMTPRRPGP TRKHYQPYAPPRDFAA YRSRVKFSRSADAPAY QQGQNQLYNELNLGRR EEYDVL DKRRGRDPEM GGKPRRKNPQEGLYNE LQKDKMAEAYSEIGMK GERRRGKGHDGLYQGL STATKDTYDALHMQAL PFR	230
(CAR4.5) Clone 20C5.2 CHD CAR DNA LxH	GAGATCGTCATGACACAGAGTCCAGCTAC CCTGAGCGTGTCCCCTGGAGAGAGGCCA CCCTGTCTGTAGGGCTAGTCAGAGTGTG TCCAGCCTCCTCACCTGGTATCAACAGAA GCCTGGTCAAGCTCCCCGCTGCTTATCT	231	EIVMTQSPATLSVSPG ERATLSCRASQSVSSL LTWYQQKPGQAPRLLI FGASTRATGIPARFSG SGSGTGFTLTISLQS	232

	TCGGGGCCAGCACGCGAGCCACAGGCATC CCGGCCAGATTCTCTGGCTCTGGCAGTGG CACC GGTTCACTCTCACGATCTCATCCC TGCAGTCAGAGGATTTCTGTGTATTAC TGTCAGCAGTACGATACATGGCCCTTCAC CTTCGGCCCCGGGCACAAAAGTAGATTTCA AGCGCGGGCGCGGGGGTAGTGGGGCGGG GGATCAGGAGGAGGGGGCTCCCAAGTACA GCTGGTTGAGAGCGGGCGGGGTGGTTC AGCCCCGGGCGCAGCCTCAGGCTGAGTTGC GCAGCATCAGGATTCACATTCAGTTCTTA TGGAATGCATTGGGTGAGACAGGCTCCCG GGAAGGGCCTTGAATGGGTGGCAGTCATT AGCTACGACGGAAGCGATAAGTACTATGT GGACTCAGTTAAAGGGAGATTTACTATCA GCCGCGACAATTCCAAAAACAGATTGTAT TTGCAGATGAACTCCCTCAGGGCGGAGGA CACTGCTGTATATTACTGCGCACGAGAGA GATACTCCGGCCGAGACTATTGGGGCCAA GGAACATTGGTAACTGTGAGCTCCGCCGC AGCTATTGAGGTCATGTACCCCCACCTT ATCTCGATAATGAGAAGAGTAATGGGACT ATAATTACGTAAAGGGCAAACACCTGTG CCCTTCCCCGCTGTTTCCAGGTCCAAGTA AGCCGTTCTGGGTCCTGGTTGTGGTGGGA GGGGTGCTGGCCTGCTATTCTCTGTTGGT TACCGTGGCCTTTATCATTTTCTGGGTGA GATCCAAAAGAAGCCGCTGCTCCATAGC GATTACATGAATATGACTCCACGCCGCC TGGCCCCACAAGGAAACACTACCAGCCTT ACGCACCACCTAGAGATTTCTGCTGCCTAT CGGAGCAGGGTGAAGTTTTCCAGATCTGC AGATGCACCAGCGTATCAGCAGGGCCAGA ACCAACTGTATAACGAGCTCAACCTGGGA CGCAGGGAAGAGTATGACGTTTTGGACAA GCGCAGAGGACGGGACCCTGAGATGGGTG GCAAACCAAGACGAAAAACCCCGAGGAG GGTCTCTATAATGAGCTGCAGAAGGATAA GATGGCTGAAGCCTATTCTGAAATAGGCA TGAAAGGAGAGCGGGAAGGGGAAAAGGG CACGACGGTTTGTACCAGGGAAGTACGAC TGCTACGAAGGATACTTATGACGCTCTCC ACATGCAAGCCCTGCCACCTAGG		EDFAVYYCQQYDTWPF TFGPGTKVDFKRGGGG SGGGSGGGGSQVQLV ESGGGVVQPGRSLRLS CAASGFTFSSYGMHWV RQAPGKGLEWVAVISY DGSDKYYVDSVKGRFT ISRDN SKNRLYLQMN LRAEDTAVYYCARERY SGRDYWGQGLVTVSS AAAIEVMYPPPYLDNE KSNGTIIHVKGKHLCP SPLFPGPSKPFWVLV VGGVLACYSLLVTFAF IIFWVRSKRSRLHSD YMNMTPRRPGPTRKHY QPYAPPRDFAAYRSRV KFSRSADAPAYQQGQN QLYNELNLGRREYDV LDKRRGRDPEMGGKPR RKNPQEGLYNELQDK MAEAYSEIGMKGERRR GKGHDGLYQGLSTATK DTYDALHMQALPPR	
(CAR4.6) Clone 20C5.2 CD8 CAR DNA LxH	ATGGCACTCCCCGTAAGTCTGCTGCTGCT GCCGTTGGCATTGCTCCTGCACGCCGCAC GCCCGGAAATAGTGATGACTCAGTCCCCG GCCACCCTCAGCGTGTCCCCGGGGAGCG AGCGACCCTGTCATGCAGGCTTCCCAGA GTGTCAGCTCCCTGCTCACTTGGTATCAG CAAAAGCCGGGGCAGGCTCCCCGCCCTCCT CATCTTCGGGGCATCAACTAGGGCCACCG GCATTCTGCAAGATTTTCCGGGTCTGGC AGCGGCACCGGCTTCACCTTACCATTAG CTCTCTGCAGTCTGAGGACTTCGCCGTTT ACTATTGTGACGAGTATGATACTTGGCCC TTTACCTTCGGTCCCGGAACTAAGGTGGA CTTCAAGCGCGGGGGGGTGGATCTGGAG GTGGTGGCTCCGGGGGCGGTGGAAGCCAG GTCCAGTTGGTTGAGAGCGGCGGCGGAGT	233	MALPVTALLLPLALLL HAARPEIVMTQSPATL SVSPGERATLSCRASQ SVSSLLTWYQQKPGQA PRLLI FGASTRATGIP ARFSGSGSGTGFTLT SSLQSEDFAVYYCQQY DTWPF TFGPGTKVDFK RGGGSGGGSGGGGS QVQLVESGGGVVQPGR SLRLSCAASGFTFSSY GMHWVRQAPGKLEWV AVISYDGSDKYYVDSV KGRFTISRDN SKNRLY LQMN SLRAEDTAVYYC ARERYSGRDYWGQGL	234

	GGTGCAGCCCGGGAGGTCCTTGCGGCTGA GCTGTGCAGCCTCCGGTTTACTTTTTCT AGCTATGGAATGCATTGGGTAAGACAGGC TCCCGGAAAAGGCCTCGAGTGGGTGGCGG TCATTAGCTATGATGGATCTGATAAATAC TATGTGGACTCAGTTAAGGGGCGCTTCAC AATCTCAAGAGACAATAGCAAAAATAGAC TGTACCTGCAGATGAATAGTCTGCGCGCC GAGGACACTGCCGTGTACTACTGCGCCCG CGAGAGATACAGCGGACGGGATTACTGGG GCCAGGGTACCCTCGTAACGGTGTCTCC GCTGCCGCCCTTAGCAACAGCATTATGTA CTTTTCTCATTTCTGCGCCAGTCTTTCTCC CAGCAAAGCCCACTACTACCCCGCCCCC AGGCCGCTACTCCTGCCCCACTATCGC GTCTCAGCCTCTCTCCTTGGGCGCGAGG CCTGCCGGCCAGCCGAGGGGCGCCGTA CATACTCGGGGTTTGGATTTCGCTTGCGA CATATATATTGGGCCCCCTCGCCGGCA CATGTGGAGTGCTGCTCCTGAGTCTCGTT ATAACCTCTATTGCAACCATAGAACAG ATCCAAAAGAAGCCGCTGCTCCATAGCG ATTACATGAATATGACTCCACGCGCCCT GGCCCCACAAGGAAACTACCAGCCTTA CGCACCACCTAGAGATTTGCTGCCTATC GGAGCAGGGTGAAGTTTCCAGATCTGCA GATGCACCAGCGTATCAGCAGGGCCAGAA CCAACTGTATAACGAGCTCAACCTGGGAC GCAGGGAAGAGTATGACGTTTTGGACAAG CGCAGAGGACGGGACCCTGAGATGGGTGG CAAACCAAGACGAAAAACCCCCAGGAGG GTCTCTATAATGAGCTGCAGAAGGATAAG ATGGCTGAAGCCTATTCTGAAATAGGCAT GAAAGGAGAGCGGAGAAGGGGAAAAGGC ACGACGGTTTGTACCAGGGACTCAGCACT GCTACGAAGGATACTTATGACGCTCTCCA CATGCAAGCCCTGCCACCTAGGTAA		VTVSSAAALSNSIMYF SHFVPVFLPAKPTTTP APRPPTPAPTIASQPL SLRPEACRPAAGGAVH TRGLDFACDIYIWAPL AGTCGVLLLSLVITLY CNHRNRSKRSRLHSD YMNMTPRRPGETRKH QPYAPPRDFAAYRSRV KFSRSADAPAYQQQN QLYNELNLGRREYDV LDKRRGRDPEMGGKPR RKNPQEGLYNELQKDK MAEAYSEIGMKGERRR GKGHDGLYQGLSTATK DTYDALHMQALPPR	
(CAR4.6) Clone 20C5.2 CD8 CAR DNA LxH	GAAATAGTGATGACTCAGTCCCCGGCCAC CCTCAGCGTGTCCCCGGGGAGCGAGCGA CCCTGTCTGAGAGGCTTCCAGAGTGTC AGCTCCCTGCTCACTTGGTATCAGCAAAA GCCGGGGCAGGCTCCCCGCTCCTCATCT TCGGGGCATCAACTAGGGCCACCGGCATT CCTGCAAGATTTTCCGGGTCTGGCAGCGG CACCGGCTTACCCTTACCATTAGCTCTC TGCAGTCTGAGGACTTCGCCGTTTACTAT TGTCAGCAGTATGATACTTGGCCCTTTAC CTTCGGTCCCGGAATAAGGTGGACTTCA AGCGCGGGGGGGTGGATCTGGAGGTGGT GGCTCCGGGGGCGGTGGAAGCCAGGTCCA GTTGGTTGAGAGCGGCGGCGGAGTGGTGC AGCCCCGGAGGTCCTTGCGGCTGAGCTGT GCAGCCTCCGGTTTTACTTTTTCTAGCTA TGGAATGCATTGGGTAAGACAGGCTCCCG GAAAAGGCCCTCGAGTGGGTGGCGGTCAAT AGCTATGATGGATCTGATAAATACTATGT GGACTCAGTTAAGGGGCGCTTCACAATCT CAAGAGACAATAGCAAAAATAGACTGTAC CTGCAGATGAATAGTCTGCGCGCCGAGGA	235	EIVMTQSPATLSVSPG ERATLSCRASQSVSSL LTWYQQKPGQAPRLLI FGASTRATGIPARFSG SGSGTGFTLTISLQS EDFAVYYCQYDTWPF TFGPGTKVDFKRGGGG SGGGSGGGGSQVQLV ESGGGVVQPGRSLRLS CAASGFTFSSYGMHWV RQAPGKLEWVAVISY DGS DKYYVDSVKGRFT ISRDN SKNRLYLQMNS LRAEDTAVYYCARERY SGRDYWGQGLTVTVSS AAALSNSIMYF SHFVP VFLPAKPTTTPAPRPP TPAPTIASQPLSLRPE ACRPAAGGAVHTRGLD FACDIYIWAPLAGTCG VLLLSLVITLYCNHRN RSKRSRLHSDYMNMT	236

	<p> CACTGCCGTGTACTACTGCGCCCGCGAGA GATACAGCGGACGGGATTACTGGGGCCAG GGTACCCCTCGTAACGGTGTCTCCGCTGC CGCCCTTAGCAACAGCATTATGTACTTTT CTCATTTTCGTGCCAGTCTTTCTCCAGCA AAGCCCACTACTACCCCGCCCCAGGCC GCCTACTCCTGCCCCACTATCGCGTCTC AGCCTCTCTCCTTGCGGCCGAGGCCTGC CGGCCAGCCGAGGGGGCGCCGTACATAC TCGGGGTTTGGATTTCGCTTGCGACATAT ATATTTGGGCCCCCTCGCCGGCACATGT GGAGTGCTGCTCCTGAGTCTCGTTATAAC CCTCTATTGCAACCATAGAAACAGATCCA AAAGAAGCCGCTGCTCCATAGCGATTAC ATGAATATGACTCCACGCCGCCCTGGCCC CACAAGGAAACACTACCAGCCTTACGCAC CACCTAGAGATTTTCGCTGCCTATCGGAGC AGGGTGAAGTTTTCAGATCTGCAGATGC ACCAGCGTATCAGCAGGGCCAGAACCAC TGTATAACGAGCTCAACCTGGGACGCAGG GAAGAGTATGACGTTTTGGACAAGCGCAG AGGACGGGACCCTGAGATGGGTGGCAAAC CAAGACGAAAAACCCCCAGGAGGGTCTC TATAATGAGCTGCAGAAGGATAAGATGGC TGAAGCCTATTCTGAAATAGGCATGAAAG GAGAGCGGAGAAGGGGAAAAGGGCACGAC GGTTTGTACCAGGGACTCAGCACTGCTAC GAAGGATACTTATGACGCTCTCCACATGC AAGCCCTGCCACCTAGG </p>		<p> PRRPGPTRKHYQPYAP PRDFAAYRSRVKFSRS ADAPAYQQGQNQLYNE LNLGRREEYDVLKRR GRDPEMGGKPRRNPQ EGLYNELQDKMAEAY SEIGMKGERRRGKGHD GLYQGLSTATKDTYDA LHMQUALPPR </p>	
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[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 a 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*

5 [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
10 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.

15 [0221] In an embodiment, a vector that can be employed in the context of the present invention is pGAR and has the coding sequence:

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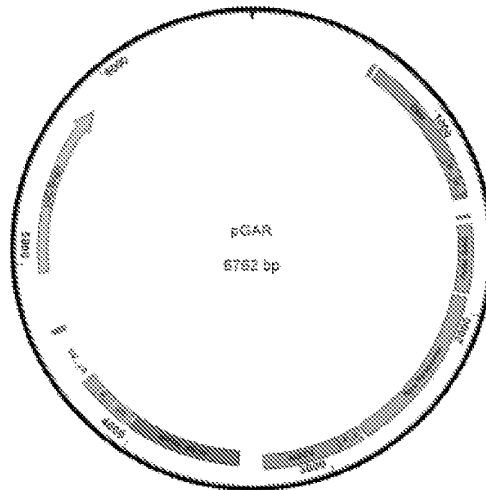
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GCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTTCGCTTTCTTCCCT
TCCTTTCTCGCCACGTTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCC
20 TTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAACTTGATTAG
GGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTCGCCCTTTGA
CGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACT
CAACCCTATCTCGGTCTATTCTTTTGATTATAAGGGATTTTGCCGATTTTCGGCCT
ATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAAT
25 ATTAACGCTTACAATTTGCCATTTCGCCATTCAGGCTGCGCAACTGTTGGGAAGGG
CGATCGGTGCGGGCCTCTTCGCTATTACGCCAGCTGGCGAAAGGGGGATGTGCTG
CAAGGCGATTAAAGTTGGGTAACGCCAGGGTTTTCCCAGTCACGACGTTGTAAAAC
GACGGCCAGTGAATTGTAATACGACTCACTATAGGGCGACCCGGGGATGGCGCG
CCAGTAATCAATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCGCGGTT
30 ACATAACTTACGGTAAATGGCCCCGCCTGGCTGACCGCCCAACGACCCCCGCCCAT
TGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTG
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TATCATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCCGCCT
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35 CGTATTAGTCATCGCTATTACCATGCTGATGCGGTTTTGGCAGTACATCAATGGG
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5 TGCTGAAGCGCGCACGGCAAGAGGCGAGGGGCGGCGACTGGTGAGTACGCCAA
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TCTTAACATATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTAAATGCCTTTGT
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AGAATCAGGGGATAACGCAGGAAAGAACATGTGAGCAAAAGGCCAGCAAAAGG
20 CCAGGAACCGTAAAAAGGCCGCGTTGCTGGCGTTTTTCCATAGGCTCCGCCCCC
TGACGAGCATCACAAAAATCGACGCTCAAGTCAGAGGTGGCGAAACCCGACAGG
ACTATAAAGATACCAGGCGTTTCCCCCTGGAAGCTCCCTCGTGCGCTCTCCTGTT
CCGACCCTGCCGCTTACCGGATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTGG
CGCTTTCTCATAGCTCACGCTGTAGGTATCTCAGTTCGGTGTAGGTGCTTCGCTCC
25 AAGCTGGGCTGTGTGCACGAACCCCCGTTTCAGCCCGACCGCTGCGCCTTATCCG
GTAATATCGTCTTGAGTCCAACCCCGTAAGACACGACTTATCGCCACTGGCAGC
AGCCACTGGTAACAGGATTAGCAGAGCGAGGTATGTAGGCGGTGCTACAGAGTT
CTTGAAGTGGTGGCCTAACTACGGCTACACTAGAAGAACAGTATTTGGTATCTGC
GCTCTGCTGAAGCCAGTTACCTTCGGAAAAAGAGTTGGTAGCTCTTGATCCGGCA
30 AACAAACCACCGCTGGTAGCGGTGGTTTTTTTTGTTTGCAAGCAGCAGATTACGCG
CAGAAAAAAGGATCTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCT
CAGTGGAACGAAAACCTACGTTAAGGGATTTTGGTTCATGAGATTATCAAAAAGG
ATCTTCACCTAGATCCTTTTAAATTAATAAATGAAGTTTTAAATCAATCTAAAGTA
TATATGAGTAACTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGCACCTAT
35 CTCAGCGATCTGTCTATTTTCGTTTCATCCATAGTTGCCTGACTCCCCGTCGTGTAGA
TAACTACGATACGGGAGGGGCTTACCATCTGGCCCCAGTGCTGCAATGATACCGCG
AGACCCACGCTCACC GGCTCCAGATTTATCAGCAATAAACCAGCCAGCCGGAAG
GGCCGAGCGCAGAAGTGGTCTGCAACTTTATCCGCTCCATCCAGTCTATTAAT
TGTTGCCGGGAAGCTAGAGTAAGTAGTTCGCCAGTTAATAGTTTGCACAACGTTG
40 TTGCCATTGCTACAGGCATCGTGGTGTACGCTCGTCGTTTGGTATGGCTTCATTC
AGCTCCGGTTCCCAACGATCAAGGCGAGTTACATGATCCCCCATGTTGTGCAAAA
AAGCGGTTAGCTCCTTCGGTCCCTCCGATCGTTGTGAGAAGTAAGTTGGCCGCAGT
GTTATCACTCATGGTTATGGCAGCACTGCATAATTCTCTTACTGTGATGCCATCCG
TAAGATGCTTTTCTGTGACTGGTGAAGTCAACCAAGTCATTCTGAGAATAGTG
45 TATGCGGCGACCGAGTTGCTCTTGCCCGGCGTCAATACGGGATAATACCGCGCCA
CATAGCAGAACTTTAAAAGTGCTCATCATTGGAAAACGTTCTTCGGGGCGAAAA
CTCTCAAGGATCTTACCGCTGTTGAGATCCAGTTTCGATGTAACCCACTCGTGCAC
CCAAGTATCTTACGATCTTTTACTTTACCAGCGTTTCTGGGTGAGCAAAAAC
AGGAAGGCAAAATGCCGCAAAAAGGGAATAAGGGCGACACGGAAATGTTGAA

[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.

[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, *Enterobacteriaceae* 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
5 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
10 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
15 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
20 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
25 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
30 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.

5 **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
10 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
15 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
20 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
25 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
30 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 2×10^6 cells/kg, about 3×10^6 cells/kg, about 4×10^6 cells/kg, about 5×10^6 cells/kg, about 6×10^6 cells/kg, about 7×10^6 cells/kg, about 8×10^6 cells/kg, about 9×10^6 cells/kg, about 1×10^7 cells/kg, about 2×10^7 cells/kg, about 3×10^7 cells/kg, about 4×10^7 cells/kg, about 5×10^7 cells/kg, about 6×10^7 cells/kg, about 7×10^7 cells/kg, about 8×10^7 cells/kg, or about 9×10^7 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
5 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
10 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
15 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,
20 large cell granuloma, leukocyte adhesion deficiency, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, monoclonal gammopathy 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.,
25 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-
30 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
5 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
10 therapy comprising administering to the patient specified beneficial doses of cyclophosphamide (between 200 mg/m²/day and 2000 mg/m²/day) and specified doses of fludarabine (between 20 mg/m²/day and 900 mg/m²/day). One such dose regimen involves treating a patient comprising administering daily to the patient about 500 mg/m²/day of cyclophosphamide and about 60 mg/m²/day of fludarabine for three days prior to
15 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-
20 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 thiotepea and cyclophosphamide (CYTOXANTM); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine,
25 triethylenemelamine, trietylenephosphoramide, triethylenethiophosphoramide and trimethylolomelamine; 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,
30 ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabycin, 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-mercaptapurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, 5-FU; androgens such as calusterone, dromostanolone propionate, epitio stanol, mepitio stanol, 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 (Cytosan[®]), 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
 5 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
 10 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[®]),
 15 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,
 20 cediranib, lenvatinib, nintedanib, pazopanib, regorafenib, semaxanib, sorafenib, sunitinib, tivozanib, toceranib, vandetanib, entrectinib, cabozantinib, imatinib, dasatinib, nilotinib, ponatinib, radotinib, bosutinib, lestaurtinib, ruxolitinib, pacritinib, cobimetinib, selumetinib,
 25 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
 30 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 propoxyphene hydrochloride. Exemplary glucocorticoids include cortisone, 5 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 10 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 15 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; 20 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- 25 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, 30 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
5 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
10 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).
15 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
20 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,
25 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 2.5×10^7 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
30 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 IFN γ (FIGs. 4A, 4B, 4G, 4H, 4M, 4N, 4S, and 4T), IL-2 (FIGs. 4C, 4D, 4I, 4J, 4O, 4P, 4U, and 4V), and TNF α (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 μ g of DNA and 22.5 μ l of polyethileneimine (Polysciences, 1 mg/ml) in 600 μ l of OptiMEM medium. The mix was incubated for 5 minutes at room temperature. Simultaneously, 293T cells (ATCC) were trypsinized, counted and a total of 10×10^6 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 μ m 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 $0.5\text{--}2.0 \times 10^6$ cells/ml prior to use in activity assays. To examine CAR expression, T cells were stained with FLT3-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 IFN γ (FIGs. 7A-7B), TNF α (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 (2×10^6 cells/animal) were injected intravenously into 5 to 6 week-old female NSG mice. After 6 days, 6×10^6 T cells (~50% CAR+) in 200 μ l 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), IFN γ (FIG. 12B), and TNF α (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 MV4;11 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 IFN γ (FIG. 14A), IL-2 (FIG. 14B),

and TNF α (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
5 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
10 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
15 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 IFN γ (FIGs. 16A-16B), TNF α (FIGs. 16C-16D), and IL-2 (FIGs. 16E-16F). IFN γ (FIGs. 16A-16B), TNF α (FIGs. 16C-16D), and IL-2 (FIGs.
20 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, IFN γ (FIGs. 16A-16B), TNF α (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).

25 [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).
30 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).

5 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.

10 [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
15 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
20 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.