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(54) Title: CD70 BINDING MOLECULES AND METHODS OF USE THEREOF

(57) Abstract: The disclosure provides anti-CD70 antibodies, antigen binding fragments thereof, chimeric antigen receptors (CARs) and engineered T cell receptors (TCRs) comprising an antigen binding molecule that specifically binds to CD70, polynucleotides encoding the same, and in vitro cells comprising the same. The polynucleotides, polypeptides, and in vitro cells described herein can be used in an engineered TCR and/or CAR T cell therapy for the treatment of a patient suffering from a cancer. In one embodiment, the polynucleotides, polypeptides, and in vitro cells described herein can be used for the treatment of multiple myeloma.



CD70 BINDING MOLECULES AND METHODS OF USE THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to United States Provisional Patent Application serial number 62/458,879 filed February 14, 2017, the entirety of which is hereby incorporated by reference.

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 February 8, 2018, is named K-1034_02_SL.txt and is 183,361 kilobytes in size.

TECHNICAL FIELD

[0003] This instant disclosure relates to chimeric antigen receptors (CARs) and engineered T cell receptors (TCRs) comprising an antigen binding molecule which binds to CD70, polynucleotides encoding the same, and methods of treating a cancer in a patient using the same.

BACKGROUND

[0004] 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.

[0005] Human 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.

5 [0006] Current therapies for hematologic malignancies have shown varying levels of effectiveness. Therefore, a need exists to identify novel and improved therapies for treating CD70-related diseases and disorders.

SUMMARY

[0007] In one aspect, an isolated polynucleotide encoding a chimeric antigen
 10 receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to CD70 is provided. In one embodiment the antigen binding molecule comprises: (a) a heavy chain variable region (VH) complementarity determining region (CDR) 1 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of GFTFSSY (SEQ ID NO: 71), GDSIISGGY (SEQ ID
 15 NO: 73) and GYTFTSY (SEQ ID NO: 75); (b) a heavy chain variable region (VH) complementarity determining region (CDR) 2 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of WYDGSN (SEQ ID NO: 72), FYSGS (SEQ ID NO: 74) and DPSGGS (SEQ ID NO: 76); (c) a heavy chain variable region (VH) complementarity determining region (CDR) 3 comprising,
 20 consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of DLLRGVKGYAMDV (SEQ ID NO: 64), SGYSYALFDH (SEQ ID NO: 67) and DYGDYVFDY (SEQ ID NO: 76); (d) a light chain variable region (VL) complementarity determining region (CDR) 1 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of
 25 RASQSLRRIYLA (SEQ ID NO: 53), RASQFIGRYFN (SEQ ID NO: 56), and SGSSSNIGTNTVN (SEQ ID NO: 59); (e) a light chain variable region (VL) complementarity determining region (CDR) 2 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of DVFDRAT (SEQ ID NO: 54), AESSLQS (SEQ ID NO: 57), and INNQRPS (SEQ ID NOL 60); (f) a
 30 light chain variable region (VL) complementarity determining region (CDR) 3 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of QQYSDSPFT (SEQ ID NO: 55), QQSYSTPFT (SEQ ID NO: 58), and

ATWDDSLNGPVV (SEQ ID NO: 61). In one embodiment the VH CDR3 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 64, 67 and 70.

[0008] In another aspect, an isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to CD70 is disclosed. In one embodiment the antigen binding molecule comprises a VH CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 64, 67 and 70. In one embodiment the VH CDR1 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 71, 73 and 75.

[0009] In another embodiment the VH CDR2 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 72, 74 and 76.

[0010] In another embodiment the VL CDR1 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 53, 56 and 59. In another embodiment the VL CDR2 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 54, 57 and 60. In another embodiment the VL CDR3 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 55, 58 and 61.

[0011] In another embodiment the VH CDR1, VH CDR2, and VH CDR3 each comprise the amino acid sequence of the VH CDR1, VH CDR2, and VH CDR3 of a variable light chain shown in FIGURES 7A, 7C or 7E.

[0012] In another embodiment the VL CDR1, VL CDR2, and VL CDR3 each comprise the amino acid sequence of the VL CDR1, VL CDR2, and VL CDR3 of an antibody in FIGURES 7B, 7D or 7F. In another embodiment the antigen binding molecule comprises a heavy chain variable region sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 11.

[0013] In another embodiment the antigen binding molecule comprises a light chain variable region sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 9 and 13.

[0014] In another embodiment the antigen binding molecule comprises one of: (a) a VH CDR1 region comprising the amino acid sequence of SEQ ID NO: 71; a VH CDR2 region comprising the amino acid sequence of SEQ ID NO: 72; a VH CDR3 region comprising the amino acid sequence of SEQ ID NO: 64; a VL CDR1 region comprising the amino acid sequence of SEQ ID NO: 53; a VL CDR2 region comprising the amino acid sequence of SEQ ID NO: 54; and a VL CDR3 region comprising the amino acid sequence of SEQ ID NO: 55; (b) a VH CDR1 region comprising the amino acid sequence of SEQ ID

NO: 73; a VH CDR2 region comprising the amino acid sequence of SEQ ID NO: 74; a VH CDR3 region comprising the amino acid sequence of SEQ ID NO: 67; a VL CDR1 region comprising the amino acid sequence of SEQ ID NO: 56; a VL CDR2 region comprising the amino acid sequence of SEQ ID NO: 57; and a VL CDR3 region comprising the amino acid sequence of SEQ ID NO: 58; or (c) a VH CDR1 region comprising the amino acid sequence of SEQ ID NO: 75; a VH CDR2 region comprising the amino acid sequence of SEQ ID NO: 76; a VH CDR3 region comprising the amino acid sequence of SEQ ID NO: 70; a VL CDR1 region comprising the amino acid sequence of SEQ ID NO: 59; a VL CDR2 region comprising the amino acid sequence of SEQ ID NO: 60; and a VL CDR3 region comprising the amino acid sequence of SEQ ID NO: 61. In another embodiment the antigen binding molecule comprises one of: (a) a VH comprising the amino acid sequence of SEQ ID NO: 3; and a VL comprising the amino acid sequence of SEQ ID NO: 5; (b) a VH comprising the amino acid sequence of SEQ ID NO: 7; and a VL comprising the amino acid sequence of SEQ ID NO: 9; or (c) a VH comprising the amino acid sequence of SEQ ID NO: 11; and a VL comprising the amino acid sequence of SEQ ID NO: 13.

[0015] In another embodiment the nucleotide sequence is 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: 2 and 4.

[0016] In another embodiment the nucleotide sequence is 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: 6 and 8.

[0017] In another embodiment the nucleotide sequence is 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: 10 and 12.

[0018] In another embodiment the antigen binding molecule is single chained.

[0019] In various embodiments the antigen binding molecule is selected from the group consisting of scFv, Fab, Fab', Fv, F(ab')₂, dAb, and any combination thereof, and in a specific embodiment the antigen binding molecule comprises an scFv.

[0020] In another embodiment the VH and the VL are joined by a linker. In a specific embodiment the VH is located at the N terminus of the linker and the VL is located at the C terminus of the linker, and in another embodiment the VL is located at the N terminus of the linker and the VH is located at the C terminus of the linker.

[0021] In another embodiment 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, and in another embodiment the linker comprises an amino acid sequence at least 75%, at least 85%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of one of SEQ ID NOs: 80 and 81.

[0022] In another embodiment the antigen binding molecule binds to CD70 with a K_D of less than about 1×10^{-6} M, less than about 1×10^{-7} M, less than about 1×10^{-8} M, or less than about 1×10^{-9} M.

[0023] In another embodiment the CAR or TCR further comprises a constant region, and in another embodiment the CAR or TCR further comprises a transmembrane domain and in still further embodiments. the transmembrane domain is a transmembrane domain of CD28, 4-1BB/CD137, CD8 alpha, CD4, CD19, CD3 epsilon, CD45, CD5, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154, an alpha chain of a T cell receptor, a beta chain of a T cell receptor, a zeta chain of a T cell receptor, or any combination thereof. In a specific embodiment the transmembrane domain is a CD28T transmembrane domain. In another embodiment the CD28T 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: 15 or 19.

[0024] In another embodiment the CD28T 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: 16 or 18.

[0025] In another embodiment the transmembrane domain is a CD8 alpha transmembrane domain. In another embodiment the CD8 alpha 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: 17, 21 or 94.

[0026] In another embodiment the CD8 alpha 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: 16 or 20.

[0027] In another embodiment the CAR or TCR further comprises a hinge region between the transmembrane domain and the antigen binding molecule. In another embodiment the hinge region comprises all or a fragment of IgG1, IgG2, IgG3, IgG4, IgA, IgD, IgE, IgM, CD28, or CD8 alpha. In another embodiment the hinge region is of CD28T. In another embodiment wherein the hinge region 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 a sequence selected from the group consisting of SEQ ID NOs: 15, and 83. In another embodiment the hinge region 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 a sequence selected from the group consisting of SEQ ID NOs: 14 and 82.

[0028] In another embodiment the hinge region is of CD8 alpha. In another embodiment the hinge region 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 a sequence selected from the group consisting of SEQ ID NO: 17 and 85, and in another embodiment the hinge region 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 a sequence selected from the group consisting of SEQ ID NO: 16 and 84.

[0029] In another embodiment the CAR or TCR further comprises a costimulatory region. In another embodiment the costimulatory region is a signaling region of CD2, CD3 delta, CD3 epsilon, CD3 gamma, CD4, CD7, CD8 α , CD8 β , CD11a (ITGAL), CD11b

(ITGAM), CD11c (ITGAX), CD11d (ITGAD), CD18 (ITGB2), CD19 (B4), CD27 (TNFRSF7), CD28, CD28T, CD29 (ITGB1), CD30 (TNFRSF8), CD40 (TNFRSF5), CD48 (SLAMF2), CD49a (ITGA1), CD49d (ITGA4), CD49f (ITGA6), CD66a (CEACAM1), CD66b (CEACAM8), CD66c (CEACAM6), CD66d (CEACAM3), CD66e (CEACAM5),
 5 CD69 (CLEC2), CD79A (B-cell antigen receptor complex-associated alpha chain), CD79B (B-cell antigen receptor complex-associated beta chain), CD84 (SLAMF5), CD96 (Tactile), CD100 (SEMA4D), CD103 (ITGAE), CD134 (OX40), CD137 (4-1BB), CD150 (SLAMF1), CD158A (KIR2DL1), CD158B1 (KIR2DL2), CD158B2 (KIR2DL3), CD158C (KIR3DP1), CD158D (KIRDL4), CD158F1 (KIR2DL5A), CD158F2 (KIR2DL5B),
 10 CD158K (KIR3DL2), CD160 (BY55), CD162 (SELPLG), CD226 (DNAM1), CD229 (SLAMF3), CD244 (SLAMF4), CD247 (CD3-zeta), CD258 (LIGHT), CD268 (BAFFR), CD270 (TNFSF14), CD272 (BTLA), CD276 (B7-H3), CD279 (PD-1), CD314 (NKG2D), CD319 (SLAMF7), CD335 (NK-p46), CD336 (NK-p44), CD337 (NK-p30), CD352 (SLAMF6), CD353 (SLAMF8), CD355 (CRTAM), CD357 (TNFRSF18), inducible T cell
 15 co-stimulator (ICOS), LFA-1 (CD11a/CD18), NKG2C, DAP-10, ICAM-1, NKp80 (KLRF1), IL-2R beta, IL-2R gamma, IL-7R alpha, LFA-1, SLAMF9, LAT, GADS (GrpL), SLP-76 (LCP2), PAG1/CBP, a CD83 ligand, Fc gamma receptor, MHC class 1 molecule, MHC class 2 molecule, a TNF receptor protein, an immunoglobulin protein, a cytokine receptor, an integrin, activating NK cell receptors, a Toll ligand receptor, and or fragments
 20 or combinations thereof.

[0030] In another embodiment the costimulatory region is a CD28 costimulatory region. In another embodiment the costimulatory region 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
 25 SEQ ID NO: 23, and in another embodiment the costimulatory region 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: 22.

[0031] In another embodiment the costimulatory region is a CD137 (4-1BB)
 30 costimulatory region. In another embodiment the costimulatory region 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: 25 and in another embodiment the costimulatory region 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: 24.

[0032] In another embodiment the CAR or TCR further comprises an activation domain. And in another embodiment the activation domain is a CD3 zeta domain. In another embodiment the activation domain comprises an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 27 or 92, and in another embodiment 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: 26.

[0033] In another embodiment the CAR or TCR further comprises a leader peptide. In another embodiment 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: 28, and in another embodiment 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: 95.

[0034] In another aspect a polynucleotide encoding a CAR or TCR is provided. In a specific embodiment the polynucleotide is selected from the group consisting of SEQ ID NOs: 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 and 51. In another aspect, a vector comprising any of the polynucleotides disclosed herein. In another embodiment the vector is a retroviral vector, a DNA vector, a plasmid, a RNA vector, an adenoviral vector, an adenovirus associated vector, a lentiviral vector, or any combination thereof.

[0035] In another aspect a CAR or TCR encoded by a polynucleotide disclosed herein or a vector disclosed herein. In another aspect a cell comprising a polynucleotide disclosed herein, a vector disclosed herein, a CAR or TCR disclosed herein, or any combination thereof provided. In another embodiment the cell comprises an immune cell, and in another embodiment the cell is a T cell. In another embodiment the T cell is a tumor-infiltrating lymphocyte (TIL), autologous T cell, engineered autologous T cell (eACT), an

allogeneic T cell, or any combination thereof, and in another embodiment the cell is an *in vitro* cell.

[0036] In another aspect a composition comprising a polynucleotide disclosed herein, a vector disclosed herein, a CAR or TCR disclosed herein, or a cell disclosed herein.

5 In another embodiment a composition is formulated to be delivered to a subject.

[0037] In another aspect a method of making a cell expressing a CAR or TCR comprising transducing a cell with a polynucleotide disclosed herein under suitable conditions. In another embodiment the method further comprises isolating the cell.

[0038] In another aspect a method of inducing an immunity against a tumor is
10 provided, and in an embodiment comprises administering to a subject an effective amount of a cell comprising a polynucleotide disclosed herein, a vector disclosed herein, or a CAR or TCR disclosed herein.

[0039] In another aspect a method of treating a cancer in a subject in need thereof is provided, and in an embodiment comprises administering to the subject a polynucleotide
15 disclosed herein, a vector disclosed herein, a CAR or TCR disclosed herein, a cell disclosed herein, or a composition of disclosed herein. In an embodiment the cancer is a hematologic cancer. In another embodiment the cancer is of the white blood cells. In a further embodiment the cancer is of the plasma cells. In another embodiment the cancer is leukemia, lymphoma, or myeloma. In a specific embodiment the cancer is multiple
20 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), chronic or acute leukemia, acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia (ALL) (including non T cell ALL), chronic lymphocytic leukemia (CLL), T-cell
25 lymphoma, one or more of B-cell acute lymphoid leukemia ("BALL"), T-cell acute lymphoid leukemia ("TALL"), acute lymphoid leukemia (ALL), chronic myelogenous leukemia (CML), B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant
30 lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, myelodysplasia and myelodysplastic syndrome, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, a plasma cell proliferative disorder (*e.g.*, asymptomatic myeloma (smoldering multiple myeloma or

indolent myeloma), monoclonal gammopathy of undetermined significance (MGUS), plasmacytomas (*e.g.*, plasma cell dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, POEMS syndrome (also known as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome), or a combination thereof. In a specific embodiment the cancer is multiple myeloma. Also disclosed is a CAR or TCR, wherein the CAR or TCR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52. In various embodiments the CAR or TCR comprises a leader sequence of SEQ ID NOs: 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52 is absent.

BRIEF DESCRIPTION OF THE FIGURES

[0040] FIGURES 1A-1H are cartoons depicting examples of the CAR constructs provided herein; the representative components and a preferred arrangement thereof, are shown.

[0041] FIGURE 2 is a series of plots demonstrating CD70 expression in various target cell lines, which correspond to a range of blood cancers; top row from left panel to right panel, the human lymphoblast cell line CEM (also referred to as CCRF-CEM), the human eosinophil cell line EoL-1, the human myeloid cell line HL-60, the human myeloid cell line KG-1a, and the human myeloid cell line MV4-11; bottom row, from left panel to right panel, the human B cell line Namalwa, B lymphocyte cell line Raji, human B lymphocyte cell line Toledo, and human myeloid cell line U-937.

[0042] FIGURES 3A and 3B are a series of plots demonstrating expression of various CARs directed against CD70 in lentivirus transduced T cells isolated from a first healthy human T cell donor (FIGURE 3A) and a second healthy human T cell donor (FIGURE 3B); clear histograms denote mock transduction and grey filled histograms denote cells expressing the transduced CAR, with the numbers in the panels indicating the percent of cells that were found to be CAR positive.

[0043] FIGURES 4A-4F are a series of bar graphs depicting IFN γ , TNF α , and IL-2 production by lentivirus transduced T cells from two healthy donors expressing four different CARs (28T-28z, 28T-4Bz, 8K-28z, 8K-4Bz), each comprising a different scFv (8G1, 1C8 and 6E9), following 16 hours of coculturing with KG-1a, Raji or Namalwa target cell lines; FIGURES. 4A and 4B show the IFN γ (pg/ml; y-axis) production in lentivirus

transduced CAR T cells from donor 1 (FIGURE 4A) and donor 2 (FIGURE 4B), FIGURES 4C and 4D show the TNF α (pg/ml; y-axis) production in lentivirus transduced CAR T cells from donor 1 (FIGURES 4C) and donor 2 (FIGURES 4D), and FIGURES 4E and 4F show the IL-2 production (pg/ml; y-axis) in lentivirus transduced CAR T cells obtained from a first donor (FIGURE 4E) and a second donor (FIGURE 4F).

[0044] FIGURES 5A-5D show the cytolytic activity (as a percentage of viable target cells remaining; y-axis) over time of lentivirus transduced T cell obtained from healthy donor 1 (FIGURES 5A and 5C) or healthy donor 2 (FIGURES 5B and 5D) expressing the indicated CARs cocultured for 112 hours with KG-1a (CD70-) (FIGURES 5A and 5B), Raji (CD70+) (FIGURE 5C), or Namalwa (CD70+) (FIGURE 5D) target cells.

[0045] FIGURE 6 is a table showing the complementarity determining regions (CDRs) of the antigen binding molecule disclosed herein, as numbered using the Kabat, Chothia and IGMT systems.

[0046] FIGURES 7A-7F are a series of tables showing the variable heavy (VH) and variable light (VL) sequences for each of the CARs or TCRs provided herein; the CDRs are also presented and are showing as numbered using the Kabat, Chothia and IGMT systems.

[0047] FIGURES 8A-8L depict nucleic acid sequences encoding the various CARs disclosed herein; corresponding amino acid sequences are also provided.

[0048] FIGURE 9 is bar graph demonstrating expression of CD70 CAR C3L directed against CD70 in lentivirus transduced T cells.

[0049] FIGURES 10A-10D shows the cytolytic activity (as a percentage of viable target cells remaining; y-axis) over time of lentivirus transduced T cell obtained from a healthy donor 3 (FIGURES 10A and 10B) or healthy donor 4 (FIGURES 10C and 10D) expressing the indicated CARs cocultured for 112 hours with KG-1a or Raji at an E:T ratio of 4:1 (Fig. 10A and 10C) or 1:1 (Fig. 10B and 10D).

[0050] FIGURES 11A-11D are a series of bar graphs depicting IFN γ production by lentivirus transduced T cells from two healthy donors expressing CD70 CAR C3L (28T-28z, comprising an 8G1 scFv), following 16 hours of coculturing with KG-1a or Raji target cell lines; Fig. 11A and 11B show the IFN γ (pg/ml; y-axis) production in lentivirus transduced CAR T cells from donor 3 at an E:T ratio of 4:1 and 1:1, respectively; Fig. 11C and 11D show the IFN γ (pg/ml; y-axis) production in lentivirus transduced CAR T cells from donor 4 at an E:T ratio of 4:1 and 1:1, respectively.

[0051] FIGURES 12A-12D are a series of bar graphs depicting IL2, production by lentivirus transduced T cells from two healthy donors expressing a CD70 CAR C3L (28T-28z, comprising an 8G1 scFv) following 16 hours of coculturing with KG-1a or Raji target cell lines; Fig. 12A and 12B show the IL2 (pg/ml; y-axis) production in lentivirus transduced CAR T cells from donor 3 at an E:T ratio of 4:1 and 1:1, respectively; Fig. 12C and 12D show the IL2 (pg/ml; y-axis) production in lentivirus transduced CAR T cells from donor 4 at an E:T ratio of 4:1 and 1:1, respectively.

[0052] FIGURES 13A-13D are a series of bar graphs depicting TNF α , production by lentivirus transduced T cells from two healthy donors expressing a CD70 CAR C3L (28T-28z, comprising an 8G1 scFv) following 16 hours of coculturing with KG-1a or Raji target cell lines; Fig. 13A and 13B show the IL2 (pg/ml; y-axis) production in lentivirus transduced CAR T cells from donor 3 at an E:T ratio of 4:1 and 1:1, respectively; Fig. 13C and 13D show the TNF α (pg/ml; y-axis) production in lentivirus transduced CAR T cells from donor 4 at an E:T ratio of 4:1 and 1:1, respectively.

DETAILED DESCRIPTION

[0053] The instant disclosure relates to antibodies, antigen binding molecules thereof, chimeric antigen receptors (CARs), and engineered T cell receptors (TCRs), which bind CD70, polynucleotides encoding the same, and *in vitro* cells comprising the same. The polynucleotides, polypeptides, and *in vitro* cells described herein can be used in an engineered CAR T cell therapy, *e.g.*, an autologous cell therapy (eACT™), for the treatment of a patient suffering from a cancer. In particular, the polynucleotides, polypeptides, and *in vitro* cells described herein can be used for the treatment of multiple myeloma.

Definitions

[0054] In order that the instant disclosure can be more readily understood, some terms are first defined. As used in this application, except as otherwise expressly provided herein, each of the following terms shall have the meaning set forth below. Additional definitions are set forth throughout the application. The headings provided herein are not limitations of the various aspects of the disclosure, which aspects can be understood by reference to the specification as a whole.

[0055] It is understood that wherever aspects are described herein with the language “comprising,” otherwise analogous aspects described in terms of “consisting of” and/or “consisting essentially of” are also provided.

[0056] The use of the alternative (*e.g.*, “or”) should be understood to mean either one, both, or any combination thereof of the alternatives. As used herein, the indefinite articles “a” or “an” should be understood to refer to “one or more” of any recited or enumerated component.

[0057] 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).

[0058] 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.

[0059] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, Juo, The Concise Dictionary of Biomedicine and Molecular Biology, 2nd ed., (2001), CRC Press; The Dictionary of Cell & Molecular Biology, 5th ed., (2013), Academic Press; and The Oxford Dictionary Of Biochemistry And Molecular Biology, Cammack *et al.* eds., 2nd ed, (2006), Oxford University Press, provide those of skill in the art with a general dictionary for many of the terms used in this disclosure.

[0060] As used herein, the twenty conventional (*e.g.*, naturally occurring) amino acids and their abbreviations follow conventional usage. *See, e.g.*, Immunology - A Synthesis (2nd Edition), Golub and Green, eds., Sinauer Assoc., Sunderland, Mass. (1991), which is incorporated herein by reference for any purpose. Stereoisomers (*e.g.*, D-amino acids) of the twenty conventional amino acids, unnatural amino acids such as alpha-, alpha-disubstituted amino acids, N-alkyl amino acids, lactic acid, and other unconventional amino acids can also be suitable components for polypeptides of the instant disclosure. Examples of unconventional amino acids include: 4-hydroxyproline, gamma-carboxyglutamate,

epsilon-N,N,N-trimethyllysine, e-N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, sigma-N-methylarginine, and other similar amino acids and imino acids (*e.g.*, 4-hydroxyproline). In the polypeptide notation used herein, the left-hand direction is the amino terminal direction and the right-hand direction is the carboxy-terminal direction, in accordance with standard usage and convention.

[0061] As used herein, the term “about” refers to a value or composition that is within an acceptable error range for the particular value or composition as determined by one of ordinary skill in the art, which will depend in part on how the value or composition is measured or determined, *i.e.*, the limitations of the measurement system. For example, “about” or “comprising essentially of” can mean within one or more than one standard deviation per the practice in the art. Alternatively, “about” or “comprising essentially of” can mean a range of up to 10% (*i.e.*, $\pm 10\%$). For example, about 5mg can include any number between 4.5 mg and 5.5 mg. Furthermore, particularly with respect to biological systems or processes, the terms can mean up to an order of magnitude or up to 5-fold of a value. When particular values or compositions are provided in the instant disclosure, unless otherwise stated, the meaning of “about” or “comprising essentially of” should be assumed to be within an acceptable error range for that particular value or composition.

[0062] 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.

[0063] “Administering” refers to the physical introduction of an agent to a subject, using any of the various methods and delivery systems known to those skilled in the art. Exemplary routes of administration for the formulations disclosed herein include intravenous, intramuscular, subcutaneous, intraperitoneal, spinal or other parenteral routes of administration, for example by injection or infusion. The phrase “parenteral administration” as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intralymphatic, intralesional, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion, as well as *in vivo* electroporation. In some embodiments, the

formulation is administered via a non-parenteral route, *e.g.*, orally. Other non-parenteral routes include a topical, epidermal or mucosal route of administration, for example, intranasally, vaginally, rectally, sublingually or topically. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

[0064] The term “antibody” (Ab) includes, without limitation, a glycoprotein immunoglobulin which binds specifically to an antigen. In general, an antibody can comprise at least two heavy (H) chains and two light (L) chains interconnected by disulfide bonds, or an antigen binding molecule thereof. Each H chain comprises a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region comprises three constant domains, CH1, CH2 and CH3. Each light chain comprises a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region 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, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the Abs can 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.

[0065] Antibodies can include, for example, both naturally occurring and non-naturally occurring (recombinantly-produced) antibodies, human and non-human antibodies, monospecific antibodies, multispecific antibodies (including bispecific 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 (*see, e.g.*, Stocks, (2004) *Drug Discovery Today* 9(22):960-66), antibody fusions (which term encompasses antibody-drug conjugates) and which are sometimes referred to herein as “antibody conjugates”), heteroconjugate antibodies, single domain antibodies, monovalent antibodies, single chain antibodies or single-chain Fvs (scFv), camelized antibodies, affibodies, 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 thereof. In some embodiments, antibodies described herein refer to polyclonal antibody populations.

[0066] An immunoglobulin is a tetrameric molecule, normally composed of two identical pairs of polypeptide chains, each pair having one “light” (about 25 kDa) and one “heavy” chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 130 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. Human light chains are classified as kappa and lambda light chains. Heavy chains are classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, or IgE, respectively. Within light and heavy chains, the variable and constant regions are joined by a “J” region of about 12 or more amino acids, with the heavy chain also including a “D” region of about 10 more amino acids. See generally, Berzofsky & Berkower, Ch. 7 in Fundamental Immunology (Paul, W., ed., Lippincott Williams & Wilkins (2012); which chapter and volume is incorporated by reference in its entirety for all purposes). The variable regions of each light/heavy chain pair form the antibody binding site such that an intact immunoglobulin has two primary binding sites.

[0067] An immunoglobulin can derive from any of the commonly known isotypes, including but not limited to IgA, secretory IgA, IgG 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 antibodies; monoclonal and polyclonal antibodies; chimeric and humanized antibodies; human or nonhuman antibodies; wholly synthetic antibodies; and single chain antibodies. A nonhuman antibody can 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 molecule of any of the aforementioned immunoglobulins, and includes a monovalent and a divalent fragment or portion, and a single chain antibody (i.e., a scFv).

[0068] As used herein, the terms “single-chain antibody” and “single chain fragment variable (scFv)” are used interchangeably and mean an antigen binding molecule in which a VL and a VH region are joined via a linker to form a continuous protein chain wherein the linker is long enough to allow the protein chain to fold back on itself and form a monovalent antigen binding site (*see, e.g., Bird et al., (1988) Science 242:423-26 and Huston et al., (1988) Proc. Natl. Acad. Sci. U.S.A. 85:5879-83 (1988).*

[0069] As used herein, the term “diabody” or dAB means bivalent antibodies comprising two polypeptide chains, wherein each polypeptide chain comprises VH and VL domains joined by a linker that is too short to allow for pairing between two domains on the same chain, thus allowing each domain to pair with a complementary domain on another polypeptide chain (*see, e.g., Holliger et al., (1993) Proc Natl Acad Sci U.S.A. 90:6444-48, Poljak et al., (1994) Structure 2: 1121-23, and Perisic et al., (1994) Structure 2(12): 1217-26*). If the two polypeptide chains of a diabody are identical, then a diabody resulting from their pairing will have two identical antigen binding sites. Polypeptide chains having different sequences can be used to make a diabody with two different antigen binding sites. Similarly, tribodies and tetrabodies are antibodies comprising three and four polypeptide chains, respectively, and forming three and four antigen binding sites, respectively, which can be the same or different.

[0070] As used herein, the term “Fab fragment” means is a monovalent fragment having the VL, VH, CL and CH domains; a “F(ab')₂ fragment” is a bivalent fragment having two Fab fragments linked by a disulfide bridge at the hinge region; a “Fv fragment” has the VH and VL domains of a single arm of an antibody; and a “dAb fragment” has a VH domain, a VL domain, or an antigen-binding fragment of a VH or VL domain.

[0071] 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 some embodiments, the antigen binding molecule binds to CD70. In further embodiments, the antigen binding molecule is an antibody or fragment thereof, including one or more of the complementarity determining regions (CDRs) thereof. In further embodiments, the antigen binding molecule is a single chain variable fragment (scFv). In some embodiments, the antigen binding molecule comprises or consists of avimers.

[0072] An antigen binding molecule can comprise, for example, an alternative protein scaffold or artificial scaffold with grafted complementarity determining regions (CDRs) or CDR derivatives. Such scaffolds include, but are not limited to, antibody-derived scaffolds comprising mutations introduced to, for example, stabilize the three-dimensional structure of the antigen binding molecule as well as wholly synthetic scaffolds comprising, for example, a biocompatible polymer. *See, e.g.,* Korndorfer et al., 2003, *Proteins: Structure, Function, and Bioinformatics*, 53(1):121-129 (2003); Roque et al., *Biotechnol. Prog.* 20:639-654 (2004). In addition, peptide antibody mimetics (“PAMs”) can be used, as well as scaffolds based on antibody mimetics utilizing various components (*e.g.*, fibronectin) as a scaffold. An antigen binding molecule can have, for example, the structure of a naturally occurring immunoglobulin.

[0073] An antigen binding molecule can form a component of a CAR or TCR, and can serve to direct the CAR or TCR to recognize a target of interest (*e.g.*, CD70). As used herein, in the context of a disclosed CAR or TCR, an antigen binding molecule means any component of a CAR or TCR that directs the CAR or TCR to a desired target and associates with that target. In specific embodiments, an antigen binding molecule component of a CAR or TCR comprises a scFv comprising a heavy and light chain variable region joined by a linker. The heavy and light variable regions can be derived from the same antibody or two different antibodies. Antigen binding molecules used in a CAR or TCR can be derived from an antibody known or suspected to bind to a target of interest. In specific embodiments, an antigen binding molecule used in a CAR or TCR include the pairs of sequences comprising the amino acid sequences of SEQ ID NOs: 3 and 5, SEQ ID NOs: 7 and 9, and SEQ ID NOs: 11 and 13, which are also presented in FIGURES 7A-7F.

[0074] As used herein, the terms “variable region” or “variable domain” are used interchangeably and mean a portion of an antibody, generally a portion of a light or heavy chain, typically about the amino-terminal end of the antibody and comprising about 100-130 amino acids in the heavy chain and about 90 to 115 amino acids in the 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). The CDRs of the light and heavy chains are primarily responsible for the interaction and specificity of the antibody with antigen.

[0075] In some embodiments, the variable region is a human variable region. In further embodiments, the variable region comprises rodent, human or murine CDRs and human framework regions (FRs). In further embodiments, the variable region is a primate (*e.g.*, a non-human primate) variable region. In yet further embodiments, the variable region is a rabbit variable region. In other embodiments, the variable region comprises human CDRs and non-human (*e.g.*, rabbit, murine, rat or non-human primate) framework regions (FRs). In other embodiments, the variable region comprises non-human (*e.g.*, rabbit, murine, rat or non-human primate) CDRs and human framework regions (FRs).

[0076] The terms “VL”, “VL chain” and “VL domain” are used interchangeably and mean the light chain variable region of an antigen binding molecule, antibody or an antigen binding fragment thereof. .

[0077] The terms “VH”, “VH chain” and “VH domain” are used interchangeably and mean the heavy chain variable region of an antigen binding molecule, antibody or an antigen binding fragment thereof. .

[0078] As used herein, the term “complementarity determining region” or “CDR” means an amino acid sequence that contributes to antigen binding specificity and affinity. Framework regions can aid in maintaining the proper confirmation of the CDRs to promote binding between the antigen binding molecule and an antigen. A number of definitions of CDRs are commonly in use: Kabat numbering, Chothia numbering, contact numbering, AbM numbering or IMGT 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. Table 1 summarizes the definitions of these systems of nomenclature.

[0079]

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

[0080] 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 some aspects, the CDRs of an antibody can be determined according to the Kabat numbering system (*see, e.g.*, Kabat et al. in *Sequences of Proteins of Immunological Interest*, 5th Ed., NIH Publication 91-3242, Bethesda MD 1991). Using the Kabat numbering system, CDRs within an antibody heavy chain molecule are typically present at amino acid positions 31 to 35, which optionally can include one or two additional amino acids, following 35 (referred to in the Kabat numbering scheme as 35A and 35B) (CDR1), amino acid positions 50 to 65 (CDR2), and amino acid positions 95 to 102 (CDR3). Using the Kabat numbering system, CDRs within an antibody light chain molecule are typically present at amino acid positions 24 to 34 (CDR1), amino acid positions 50 to 56 (CDR2), and amino acid positions 89 to 97 (CDR3).

[0081] In a specific embodiment, the CDRs of the antibodies described herein can be described according to the Kabat numbering scheme, as shown in Figure 6 (although they can readily be construed in other numbering systems using Table 1 above). Figure 6 also provides the CDRs using the Chothia and IMGT numbering schemes.

[0082] In some 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; 5 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 10 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). See Table 1.

[0083] In a specific embodiment, the CDRs of the antibodies described herein have been determined according to the Chothia numbering scheme, as shown in Figure 6.

[0084] As used herein, the terms “constant region” and “constant domain” are 20 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 25 an immunoglobulin variable domain.

[0085] 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.*, 30 IgG₁, IgG₂, IgG₃ and IgG₄.

[0086] 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.

[0087] As used herein, the term “binding affinity” means the strength of the sum total of non-covalent interactions between a single binding site of a molecule (*e.g.*, an antigen binding molecule such as 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 standard techniques known to one of ordinary skill in the art, such as BIAcore[®] or KinExA or surface plasmon resonance.

[0088] 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 some embodiments, one or more amino acid residues within a CDR(s) or within a framework region(s) of an antibody or antigen-binding fragment thereof can be replaced with an amino acid residue with a similar side chain.

[0089] Conservative amino acid substitutions, which are encompassed by the instant disclosure, can encompass non-naturally occurring amino acid residues, which are typically incorporated by chemical peptide synthesis rather than by synthesis in biological systems. These include peptidomimetics and other reversed or inverted forms of amino acid moieties. Naturally occurring residues can be divided into classes based on common side chain properties:

hydrophobic: norleucine, Met, Ala, Val, Leu, Ile;

neutral hydrophilic: Cys, Ser, Thr, Asn, Gln;

acidic: Asp, Glu;

basic: His, Lys, Arg;

residues that influence chain orientation: Gly, Pro; and

aromatic: Trp, Tyr, Phe.

[0090] Non-conservative substitutions can involve the exchange of a member of one of these classes for a member from another class. Such substituted residues can be introduced, for example, into regions of a human antibody that are homologous with non-human antibodies, or into the non-homologous regions of the molecule. Exemplary conservative amino acid substitutions are set forth in Table 2 below.

[0091]

Table 2 Amino Acid Substitutions

<u>Original Residues</u>	<u>Exemplary Substitutions</u>	<u>Preferred Substitutions</u>
Ala	Val, Leu, Ile	Val
Arg	Lys, Gln, Asn	Lys
Asn	Gln	Gln
Asp	Glu	Glu
Cys	Ser, Ala	Ser
Gln	Asn	Asn
Glu	Asp	Asp
Gly	Pro, Ala	Ala
His	Asn, Gln, Lys, Arg	Arg
Ile	Leu, Val, Met, Ala, Phe, Norleucine	Leu
Leu	Norleucine, Ile, Val, Met, Ala, Phe	Ile
Lys	Arg, 1,4 Diamino-butyric acid, Gln, Asn	Arg
Met	Leu, Phe, Ile	Leu

Phe	Leu, Val, Ile, Ala, Tyr	Leu
Pro	Ala	Gly
Ser	Thr, Ala, Cys	Thr
Thr	Ser	Ser
Trp	Tyr, Phe	Tyr
Tyr	Trp, Phe, Thr, Ser	Phe
Val	Ile, Met, Leu, Phe, Ala, Norleucine	Leu

[0092] 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 some 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 can be accomplished using any of the known methods in the art (*e.g.*, Giege *et al.*, (1994) *Acta Crystallogr D Biol Crystallogr* 50(Pt 4): 339-350; McPherson, (1990) *Eur J Biochem* 189: 1-23; Chayen, (1997) *Structure* 5: 1269-1274; McPherson, (1976) *J Biol Chem* 251: 6300-6303). Antibody:antigen crystals can be studied using well known X-ray diffraction techniques and can be refined using computer software such as X-PLOR (Yale University, 1992, distributed by Molecular Simulations, Inc.; *see, e.g.*, *Meth Enzymol* (1985) Vols 114 & 115, eds Wyckoff *et al.*), and BUSTER (Bricogne, (1993) *Acta Crystallogr D Biol Crystallogr* 49(Pt 1): 37-60; Bricogne, (1997) *Meth Enzymol* 276A: 361-423, ed. Carter; Roversi *et al.*, (2000) *Acta Crystallogr D Biol Crystallogr* 56(Pt 10): 1316-1323). Mutagenesis mapping studies can be accomplished using any method known to one of skill in the art. *See, e.g.*, Champe *et al.*, (1995) *J Biol Chem* 270: 1388-94 and Cunningham & Wells, (1989) *Science* 244: 1081-85 for a description of mutagenesis techniques, including alanine and arginine scanning mutagenesis techniques.

[0093] As used herein, the term “cross competes” means the situation in which the interaction between an antigen (*e.g.*, CD70) and a first antigen binding molecule or binding fragment thereof blocks, limits, inhibits, or otherwise reduces the ability of a reference antigen binding molecule or binding fragment thereof (such as the antigen binding molecules, CARs and TCRs provided herein) 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 some 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 than 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) *Method Enzymol* 9:242-53); solid phase direct biotin-avidin EIA (Kirkland *et al.*, (1986) *J Immunol* 137:3614-19); 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 I¹²⁵ label (Morel *et al.*, (1988) *Molec Immunol* 25:7-15); solid phase direct biotin-avidin EIA (Cheung *et al.*, (1990) *Virology* 176:546-52); and direct labeled RIA (Moldenhauer *et al.*, (1990) *Scand J Immunol* 32:77-82).

[0094] 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.

[0095] In another embodiment, molecules that specifically bind to an antigen (*e.g.*, CD70), as well as molecules comprising this sequence and cells presenting such molecules) bind with a dissociation constant (K_d) of about 1×10^{-7} M. In some embodiments, the antigen binding molecule specifically binds an antigen (*e.g.*, CD70) 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 (*e.g.*, CD70) with “very high affinity” when the K_d is 1×10^{-10} M to about 5×10^{-10} M.

[0096] In another specific embodiment, molecules that specifically bind to an antigen do not cross react with other proteins under similar binding conditions. In another specific embodiment, molecules that specifically bind to an antigen do not cross react with other non-CD70 proteins. In a specific embodiment, provided herein is an antibody or fragment thereof that binds to CD70 with higher affinity than to another unrelated antigen. In some embodiments, provided herein is an antibody or fragment thereof that binds to CD70 (*e.g.*, human CD70) with a 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or higher affinity than to another, unrelated antigen as measured by, *e.g.*, a radioimmunoassay, surface plasmon resonance, or kinetic exclusion assay. In a specific embodiment, the extent of binding of an anti-CD70 antibody or antigen-binding fragment thereof described herein to an unrelated, non-CD70 protein is less than 10%, 15%, or 20% of the binding of the antibody to CD70 protein as measured by, *e.g.*, a radioimmunoassay.

[0097] In a specific embodiment, provided herein is an antibody or fragment thereof that binds to human CD70 with higher affinity than to another species of CD70. In some embodiments, provided herein is an antibody or fragment thereof that binds to human CD70 with a 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70% or higher affinity than to another species of CD70 as measured by, *e.g.*, a radioimmunoassay, surface plasmon resonance, or kinetic exclusion assay. In a specific embodiment, an antibody or fragment thereof described herein, which binds to human CD70, will bind to another species of CD70 protein with less than 10%, 15%, or 20% of the binding of the antibody or fragment thereof to the human CD70 protein as measured by, *e.g.*, a radioimmunoassay, surface plasmon resonance, or kinetic exclusion assay.

[0098] 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 can involve either antibody production, or the activation of specific

immunologically-competent cells, or both. Those of skill in the art will readily understand that any macromolecule, including virtually all proteins or peptides, can serve as an antigen. Generally, an antigen can be endogenously expressed, *i.e.* expressed by genomic DNA, or it can be recombinantly expressed, or it can be chemically synthesized. An antigen can be specific to a some 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 some embodiments, the antigen is CD70, which can optionally be conjugated to an adjuvant such as keyhole limpet hemocyanin (KLH).

[0099] The term “neutralizing” refers to an antigen binding molecule, scFv, antibody, or a fragment thereof, which binds to a ligand (*e.g.*, CD70) 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.

[00100] As used herein, the term “CD70” means a molecule that belongs to the tumor necrosis factor (TNF) ligand family, and is also known as CD27LG and TNFSF7. CD70 is a ligand for CD27 (TNFRSF27). It is a surface antigen on activated, but not on resting, T and B lymphocytes. It induces proliferation of costimulated T cells, enhances the generation of cytolytic T cells, and contributes to T cell activation. CD70 also plays a role in regulating B-cell activation, cytotoxic function of natural killer cells, and immunoglobulin synthesis. *See, e.g.,* Goodwin *et al.*, (1993) *Cell* 73(3):447-56 and Bowman *et al.*, (1994) *J. Immunol.* 152(4):1756-61. The term CD70 can include, but is not limited to, native CD70, an isoform of CD70, or an interspecies CD70 homolog of CD70. CD70 (also known as CD27LG, CD27L and TNFSF7) is expressed on the surface of T and B cell lymphoma cells. The amino acid sequence of human CD70 (hCD70) is provided in NCBI Accession NP_001243.1 (GI:4507605) (SEQ ID NO: 1), and has the amino acid sequence:

MPEEGSGCSVRRRPYGCVLRAALVPLVAGLVICLVVCIQRFAQAQQ
QLPLESLGWDVAELQLNHTGPQQDPRLYWQGGPALGRSFLHGPELD
KGQLRIHRDGIYMVHIQVTLAICSSTTASRHHPTTLAVGICSPASRSIS

LLRLSFHQGCTIASQRLTPLARGDTLCTNLTGTLLPSRNTDEFFGVQ
WVRP

(SEQ ID NO: 1).

5 **[00101]** Residues 1-17 of SEQ ID NO: 1 correspond to the cytoplasmic region of hCD70, residues 18-38 correspond to the transmembrane region of hCD70, and residues 39-193 correspond to the extracellular region of hCD70. At least one other isoform of hCD70 is known and is identified by the UniProt identifier P32970-2.

[00102] As used herein, CD70 includes human CD70 and non-human CD70
10 homologs, as well as variants, fragments, or post-translationally modified forms thereof, including, but not limited to, N- and O-linked glycosylated forms of CD70. CD70 proteins can further include fragments comprising all or a portion of SEQ ID NO: 1 (*e.g.*, amino acids 39-193 of SEQ ID NO: 1, corresponding to an extracellular component of hCD70, amino acids 18-193, corresponding to a transmembrane and extracellular component of
15 hCD70).

[00103] As used herein, the term “autologous” mean any material derived from the same individual to which it is later to be re-introduced. For example, the engineered autologous cell therapy (eACT™) methods described herein involve collection of lymphocytes from a patient, which are then engineered to express a construct, *e.g.*, a CAR
20 construct, and then administered back to the same patient.

[00104] As used herein the term “allogeneic” means any material derived from one individual which is then introduced to another individual of the same species, *e.g.*, allogeneic T cell transplantation.

[00105] As used herein, the terms “transduction” and “transduced” means the process
25 whereby foreign DNA is introduced into a cell via viral vector (*see* Hartl and Jones (1997) Genetics: Principles and Analysis, 4th ed, Jones & Bartlett). 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
30 any combination thereof.

[00106] As used herein, the term “cancer” refers to a broad group of various diseases characterized by the uncontrolled growth of abnormal cells. Unregulated cell division and growth in the body 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 instant disclosure 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 instant disclosure 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 some embodiments, the cancer is multiple myeloma. The particular cancer can be responsive to chemo- or radiation therapy, or the cancer can be refractory. The term “refractory cancer” means a cancer that is not amenable to surgical intervention and the cancer is either initially unresponsive to chemo- or radiation therapy or the cancer becomes unresponsive over time.

[00107] As used herein, the term “anti-tumor effect” means 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.

[00108] As used herein, the term “cytokine” means 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 can 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 7 (IL-7) and interleukin 15 (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).

[00109] As used herein, the term “chemokine” means 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).

[00110] As used herein, the terms “therapeutically effective amount,” “effective dose,” “effective amount,” and “therapeutically effective dosage” of a therapeutic agent, *e.g.*, engineered CAR T cells or cells expressing a TCR comprising a desired alpha chain, beta chain or both alpha and beta chains, are used interchangeably and mean 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.

[00111] As used herein, the term “lymphocyte” means a white blood cell found in a vertebrate’s immune system. Lymphocytes include natural killer (NK) cells, T cells and 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 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.

[00112] T cells play a major role in cell-mediated-immunity (no antibody involvement). Types of T cells include:

- 1) helper T cells (*e.g.*, CD4⁺ cells);
- 2) cytotoxic T cells (also known as TC, cytotoxic T lymphocyte, CTL, T-killer cell, cytolytic T cell, CD8⁺ T-cells or killer T cell);
- 3) memory T-cells, including:
 - (i) stem memory T_{SCM} cells which, 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, which express L-selectin and the CCR7, they secrete IL-2, but not IFNγ or IL-4; and
 - (iii) effector memory T_{EM} cells, however, do not express L-selectin or CCR7 but produce effector cytokines like IFNγ and IL-4);
- 4) regulatory T-cells (Tregs, suppressor T cells, or CD4⁺CD25⁺ regulatory T cells);
- 5) natural killer T cells (NKTs);

- 6) $\gamma\delta$ (Gamma Delta) T cells; and
- 7) mucosal associated invariant T cells (MAITs).

[00113] B cells play a principal role in humoral immunity (with antibody involvement). B cells make antibodies and antigens, perform the role of antigen-presenting cells (APCs) and turn into memory B cells after activation by antigen interaction.

[00114] As used herein, the terms “genetic engineering” or “engineering” are used interchangeably and mean a method of modifying the genome of a cell, including, but not limited to, deleting a coding or non-coding region or a portion thereof or inserting a coding region or a portion thereof. In some embodiments, the cell that is modified is a lymphocyte, *e.g.*, a T cell, which can either be obtained from a patient or a donor. The cell can be modified to express an exogenous construct, such as, *e.g.*, a chimeric antigen receptor (CAR) or a T cell receptor (TCR), which is incorporated into the cell's genome.

[00115] As used herein, the term “immune response” means the action of a cell of the immune system (for example, T lymphocytes, B lymphocytes, natural killer (NK) cells, macrophages, eosinophils, mast cells, dendritic cells and neutrophils) and soluble macromolecules produced by any of these cells or the liver (including antibodies, cytokines, and complement) that results in selective targeting, binding to, damage to, destruction of, and/or elimination from a vertebrate's body of invading pathogens, cells or tissues infected with pathogens, cancerous or other abnormal cells, or, in cases of autoimmunity or pathological inflammation, normal human cells or tissues.

[00116] As used herein, the term “immunotherapy” means 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. Those of skill in the art will 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 No. 2014/0154228, U.S. Patent Nos. 5,728,388 and 6,406,699, and International Publication No. WO 2008/081035.

[00117] The T cells of an immunotherapy can come from any source. For example, T cells can be differentiated *in vitro* from a stem cell population, or T cells can be obtained from a subject. T cells can also 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, T cells can be derived from one or more available T cell lines. 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.

[00118] The term “engineered Autologous Cell Therapy,” 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 engineered 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, a chimeric antigen receptor (CAR) or a T cell receptor (TCR). CAR positive (CAR+) T cells are engineered to express a CAR. CARs can 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 can be arranged in any order. The costimulatory domain can be derived from, *e.g.*, CD28 or CD28T, and the activating domain can 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. A 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 such as NHL, CLL, and non-T cell ALL. 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, which are incorporated by reference in their entirety for any purpose.

[00119] As used herein, the term “*in vitro* cell” refers to any cell which is cultured *ex vivo*. An *in vitro* cell can include a human cell such as a T cell or dendritic cell, or it can

include CHO, sP2/0, rabbit and other non-human cells. In some embodiments, an *in vitro* cell can include a T cell.

[00120] As used herein, the term “patient” means any human who is being treated for an abnormal physiological condition, such as cancer or has been formally diagnosed with a disorder, those without formally recognized disorders, those receiving medical attention, those at risk of developing the disorders, etc. The terms “subject” and “patient” are used interchangeably herein and include both human and non-human animal subjects. As used herein, the terms “patient” and “subject” are used interchangeably. In some embodiments the terms “subject” or “patient” mean any human who is afflicted with a cancer (*e.g.*, a lymphoma or a leukemia).

[00121] As used herein, the terms “peptide,” “polypeptide,” and “protein” are used interchangeably, and mean a compound comprising two or more amino acid residues covalently linked by peptide bonds. A protein or peptide must contain at least two amino acids, but 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 terms encompass both short chains, which also commonly are referred to in the art as peptides, oligopeptides and oligomers, for example, and to longer chains, which generally are referred to in the art as proteins, of which there are many types. “Polypeptides” include, for example, biologically active fragments, substantially homologous polypeptides, oligopeptides, homodimers, heterodimers, variants of polypeptides, modified polypeptides, derivatives, analogs, fusion proteins, among others. The term “polypeptides” include natural peptides, recombinant peptides, synthetic peptides, or a combination thereof.

[00122] In some aspects, the polypeptides have deletions from, additions to, and/or substitutions of one or more amino acid of antigen-binding protein, and in some embodiments preferably no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid substitutions therein. Useful polypeptide fragments may include immunologically functional fragments of antigen binding molecules, including not limited to one or more CDR regions, variable domains of a heavy and/or light chain, a portion of other portions of an antibody chain, and the like. Moieties that can be substituted for one or more amino acids of an antigen binding molecule include, *e.g.*, D or L forms of amino acids, an amino acid different from the amino acid normally found in the same position of an antigen binding molecule, deletions, non-naturally occurring amino acids, and chemical analogs of amino acids. Additionally,

polypeptide fragments of activating and/or costimulatory molecules and the like are within the scope of the instant disclosure.

[00123] As used herein, the terms “activation” and “stimulation” and “stimulatory signal” mean a primary response induced by binding of an activating molecule with its cognate ligand, wherein the binding mediates a signal transduction event. Examples of activating molecules are provided herein. In one example, an “activating molecule” or “stimulating molecule” means a molecule on a T cell, *e.g.*, the TCR/CD3 complex, which specifically binds with a cognate stimulatory ligand present on an antigen present cell. This type of signaling is sometimes referred to as “Signal 1” in the context of T cell activation.

[00124] As used herein, a “stimulatory ligand” means 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 MHC Class I molecule loaded with a peptide, an anti-CD3 antibody, a superagonist anti-CD28 antibody, and a superagonist anti-CD2 antibody.

[00125] As used herein, the term “costimulatory signal,” means 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. In an example, a costimulatory signal is induced upon the association of CD28 on a T cell with its cognate ligand B7 on an antigen presenting cell. This type of signaling is sometimes referred to as “Signal 2” in the context of T cell activation.

[00126] As used herein, the terms “costimulatory molecule” and “costimulatory ligand” means 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, CD2, CD3 delta, CD3 epsilon, CD3 gamma, CD4, CD7, CD8 α , CD8 β , CD11a (ITGAL), CD11b (ITGAM), CD11c (ITGAX), CD11d (ITGAD), CD18 (ITGB2), CD19 (B4), CD27 (TNFRSF7), CD28, CD28T, CD29 (ITGB1), CD30 (TNFRSF8), CD40 (TNFRSF5), CD48 (SLAMF2), CD49a (ITGA1), CD49d (ITGA4), CD49f (ITGA6), CD66a (CEACAM1), CD66b (CEACAM8), CD66c (CEACAM6), CD66d (CEACAM3), CD66e (CEACAM5), CD69 (CLEC2), CD79A (B-cell antigen receptor complex-associated alpha chain), CD79B (B-cell antigen receptor complex-associated beta chain), CD84 (SLAMF5), CD96 (Tactile),

CD100 (SEMA4D), CD103 (ITGAE), CD134 (OX40), CD137 (4-1BB), CD150 (SLAMF1), CD158A (KIR2DL1), CD158B1 (KIR2DL2), CD158B2 (KIR2DL3), CD158C (KIR3DP1), CD158D (KIR2DL4), CD158F1 (KIR2DL5A), CD158F2 (KIR2DL5B), CD158K (KIR3DL2), CD160 (BY55), CD162 (SELPLG), CD226 (DNAM1), CD229 (SLAMF3), CD244 (SLAMF4), CD247 (CD3-zeta), CD258 (LIGHT), CD268 (BAFFR), CD270 (TNFSF14), CD272 (BTLA), CD276 (B7-H3), CD279 (PD-1), CD314 (NKG2D), CD319 (SLAMF7), CD335 (NK-p46), CD336 (NK-p44), CD337 (NK-p30), CD352 (SLAMF6), CD353 (SLAMF8), CD355 (CRTAM), CD357 (TNFRSF18), inducible T cell co-stimulator (ICOS), LFA-1 (CD11a/CD18), NKG2C, DAP-10, ICAM-1, NKp80 (KLRF1), IL-2R beta, IL-2R gamma, IL-7R alpha, LFA-1, SLAMF9, LAT, GADS (GrpL), SLP-76 (LCP2), PAG1/CBP, PD-1, a CD83 ligand, Fc gamma receptor, MHC class 1 molecule, MHC class 2 molecule, a TNF receptor protein, an immunoglobulin protein, a cytokine receptor, an integrin, activating NK cell receptors, a Toll ligand receptor, and or fragments or combinations thereof.

[00127] 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. The terms “reducing” and “decreasing” include complete depletions.

[00128] As used herein, the terms “treatment” of a subject and “treating” a subject means any type of intervention or process performed on, or the administration of an active agent to, the subject with the objective of reversing, alleviating, ameliorating, inhibiting, slowing down or preventing the onset, progression, development, severity or recurrence of a symptom, complication or condition, or biochemical indicia associated with a disease. In one embodiment, “treatment” or “treating” includes a partial remission, as that term is defined in the context of a given therapeutic regimen. In another embodiment, “treatment” or “treating” includes a complete remission, as that term is defined in the context of a given therapeutic regimen.

[00129] As used herein, the term “percent identity” means the percent of identical residues between the amino acids or nucleotides in the compared molecules. For these calculations, gaps in alignments (if any) must be addressed by a particular mathematical model or computer program (*i.e.*, an “algorithm”). Methods that can be used to calculate the identity of the aligned nucleic acids or polypeptides include those described in Computational Molecular Biology, (Lesk, ed.), (1988) New York: Oxford University Press;

Biocomputing Informatics and Genome Projects, (Smith, ed.), 1993, New York: Academic Press; Computer Analysis of Sequence Data, Part I, (Griffin and Griffin, eds.), 1994, New Jersey: Humana Press; von Heinje, (1987) Sequence Analysis in Molecular Biology, New York: Academic Press; Sequence Analysis Primer, (Gribskov and Devereux, eds.), 1991, New York: M. Stockton Press; and Carillo et al., (1988) *J. Applied Math.* 48:1073.

[00130] In calculating percent identity, the sequences being compared are aligned in a way that gives the largest match between the sequences. The computer program used to determine percent identity can be, *e.g.*, MOE (Chemical Computing Group) or DNASTAR (University of Wisconsin, Madison, WI). The computer algorithm GAP can be used to align the two polypeptides or polynucleotides for which the percent sequence identity is to be determined. The sequences are aligned for optimal matching of their respective amino acid or nucleotide (the “matched span,” as determined by the algorithm). A gap opening penalty (which is calculated as 3x the average diagonal, wherein the “average diagonal” is the average of the diagonal of the comparison matrix being used; the “diagonal” is the score or number assigned to each perfect amino acid match by the particular comparison matrix) and a gap extension penalty (which is usually 1/10 times the gap opening penalty), as well as a comparison matrix such as PAM 250 or BLOSUM 62 are used in conjunction with the algorithm. In some embodiments, a standard comparison matrix (*see, e.g.*, 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.

[00131] Some alignment schemes for aligning two amino acid sequences can result in matching of only a short region of the two sequences, and this small aligned region can have very high sequence identity even though there is no significant relationship between the two full-length sequences. Accordingly, the selected alignment method (*e.g.*, the GAP program) can be adjusted if desired to result in an alignment that spans at least 50 contiguous amino acids of the target polypeptide.

[00132] Various aspects of the disclosure are described in further detail in the following subsections.

II. Antigen Binding Molecules and Polynucleotides Encoding the Same

[00133] The instant disclosure is directed to antigen binding molecules, including antibodies, that specifically bind CD70, molecules comprising this sequence (such as the

CARs and TCRs disclosed herein) and cells presenting such molecules, and/or antigen binding molecules which cross compete with one or more antigen binding molecules described herein (*i.e.*, one or more of those described in FIGURES 7A-7H and/or disclosed in the appended Sequence Listing). Polynucleotides encoding the antigen binding molecules are also provided, and form an aspect of the instant disclosure. The antigen binding molecules can form an antigen binding component of one or more of the CARs and TCRs disclosed herein.

[00134] An antibody or antigen binding molecule encoded of the instant disclosure can be single chained or double chained. In some embodiments, the antibody or antigen binding molecule is single chained. In some embodiments, the antigen binding molecule is selected from the group consisting of an scFv, a Fab, a Fab', a Fv, a F(ab')₂, a dAb, and any combination thereof. In some embodiments, the antibody or antigen binding molecule comprises an scFv. In some embodiments, an antigen binding molecule comprises a single chain, wherein the heavy chain variable region and the light chain variable region are connected by a linker to form an scFv (*e.g.*, an antigen binding molecule of instant disclosure). In some embodiments, the VH is located at the N terminus of the linker and the VL is located at the C terminus of the linker. In other embodiments, the VL is located at the N terminus of the linker and the VH is located at the C terminus of the linker. In some embodiments, the linker comprises at least about 5, at least about 8, at least about 10, at least about 13, at least about 15, at least about 18, at least about 20, at least about 25, at least about 30, at least about 35, at least about 40, at least about 45, at least about 50, at least about 60, at least about 70, at least about 80, at least about 90, or at least about 100 amino acids. In some embodiments, the linker comprises between about 8 amino acids and about 18 amino acids (*e.g.*, 10 amino acids). Examples of suitable linkers for joining a VH to a VL to form an scFv (*e.g.*, an antigen binding molecule of instant disclosure) include (Gly-Gly-Gly-Gly-Ser)₃ (SEQ ID NO: 80) and GSTSGSGKPGSGEGSTKG (SEQ ID NO: 81).

[00135] In some embodiments, the antigen binding molecules of the instant disclosure specifically bind to CD70, molecules comprising this sequence and cells presenting such molecules. In some embodiments, an antigen binding molecule of the instant disclosure specifically binds CD70, with a K_D of less than 1 x 10⁻⁶ M, less than 1 x 10⁻⁷ M, less than 1 x 10⁻⁸ M, or less than 1 x 10⁻⁹ M. In some embodiments, an antigen binding molecule specifically binds to CD70, with a K_D of less than 1 x 10⁻⁷ M. In another embodiment, an antigen binding molecule specifically binds SEQ ID NO: 1, as well as

molecules comprising this sequence and cells presenting such molecules, with a K_D of less than 1×10^{-8} M. In some embodiments, an antigen binding molecule binds CD70, 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. K_D can be calculated using standard methodologies, as described herein.

[00136] In specific embodiments, an antigen binding molecule of the instant disclosure is an antibody, or scFv formed therefrom, identified herein as Clone 8G1 or Clone 1C8 or 6E9. Each of the disclosed antigen binding molecules comprises one each of the following heavy and light chain amino acid, coding, variable, and CDR sequences, as provided and labeled:

Clone 8G1 VH DNA Coding Sequence

CAAGAGCAGCTGGTTGAGTCTGGGGGCGGCGTCGTCCAACCCGGC
CGGAGTCTGAGGTTGTCCTGCGCTGCAAGCGGATTTACATTTTCAT
CTTACGGCATGCACTGGGTTAGGCAGGCTCCTGGAAAAGGGCTGG
AGTGGGTCGCGGTGACTTGGTACGACGGCTCCAATAAGTATTATG
GGGATTCCGTGAAAGGTGCAATTCACAATTAGCAGGGATAACTCCA
AAAACACACTGTATCTCCAAATGAACTCCTTGAGGGCCGAGGACA
CGGCCGTCTATTATTGTGCAAGAGACCTCCTCCGGGGCGTAAAGG
GATATGcATGGACGTGTGGGGTCAGGGGACCACAGTTACTGTCA
GTTCA (SEQ ID NO: 2)

Clone 8G1 VH AA (CDRs underlined)

QEQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLE
WVAVTWYDGSNKYYGDSVKGRFTISRDN SKNTLYLQMNSLRAEDT
AVYYCARDLLRGVKGYAMDVWGQGTTVTVSS (SEQ ID NO: 3)

Clone 8G1 VH CDR1 AA

GFTFSSY

(SEQ ID NO: 71)

Clone 8G1 VH CDR2 AA

WYDGSN

(SEQ ID NO: 72)

Clone 8G1 VH CDR3 AA
 DLLRGVKGYAMDV
 (SEQ ID NO: 64)

5 Clone 8G1 VL DNA Coding Sequence
 GAAATCGTTCTCACTCAGTCTCCGGGCACACTGTCCCTCAGCCCC
 GGAGAGCGAGCCACTTTGAGCTGCCGGGCCAGCCAGTCACTTAGA
 CGCATTTATTTGGCCTGGTATCAGCAGAAACCAGGCCAGGCGCCC
 AGGCTGCTGATATACGATGTGTTCGATAGGGCCACGGGTATCCCC
 10 GATAGGTTCTCTGGCGGGGGGTCCGGGACTGACTTCACCCTCACT
 ATATCACGACTCGAGCCCGAAGACTTCGCAGTTTATTATTGCCAG
 CAGTACTCCGACTCCCCATTCACCTTCGGCCCTGGTACCAAAGTG
 GATATTAAACGG (SEQ ID NO: 4)

15 Clone 8G1 VL AA (CDRs underlined)
 EIVLTQSPGTLSPGERATLSCRASQSLRRIYLAWYQQKPGQAPRLLI
YDVFDRATGIPDRFSGGGSGTDFTLTISRLEPEDFAVYYCQQYSDSPF
TFGPGT
 KVDIKR (SEQ ID NO: 5)

20
 Clone 8G1 VL CDR1 AA
 RASQSLRRIYLA
 (SEQ ID NO: 53)

25 Clone 8G1 VL CDR2 AA
 DVFDRAT
 (SEQ ID NO: 54)

30 Clone 8G1 VL CDR3 AA
 QQYSDSPFT
 (SEQ ID NO: 55)

Clone 1C8 VH DNA Coding Sequence
 CAGGTGCAGCTCCAAGAATCTGGACCGGGTCTCGTCAAGCCATCA
 35 CAGACACTGTCCCTGACCTGCACCGTCTCCGGCGACTCTATCATTT
 CAGGCGGCTACTATTGGTCCTGGATTAGACAACATCCGGGAAAGG
 GTCTTGAATGGATCGGCTATATTTTCTACAGCGGGAGTACGGATT
 ACAATCCTAGTCTCAAGAGCCGCGTTACCATTTTCAGTGGATACTT
 CAAAAAACCAGTTTAGCCTGAAGCTGTCTTCTGTAACAGCTGCTG
 40 ACACAGCCGTGTACTATTGCGCCAGGAGCGGCTACAGCTATGCCC

TGTTTGACCACTGGGGGCAAGGCACTCTTGTGACGGTGTCAAGT
(SEQ ID NO: 6)

Clone 1C8 VH AA (CDRs underlined)

QVQLQESGPGLVKPSQTLSTCTVSGDSIISGGYYWSWIRQHPGKGL
EWIGYIFYSGSTDYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVY
YCARSSGYSYALFDHWGQGLVTVSS (SEQ ID NO: 7)

Clone 1C8 VH CDR1 AA

GDSIISGGY

(SEQ ID NO: 73)

Clone 1C8 VH CDR2 AA

FYSGS

(SEQ ID NO: 74)

Clone 1C8 VH CDR3 AA

SGYSYALFDH

(SEQ ID NO: 67)

Clone 1C8 VL DNA Coding Sequence

GACATTCAAATGACGCAGTCCCCAAGTTCTCTGTCCGCTAGCGTC
GGCGACCGAGTGACCATCAGCTGCCGAGCATCCCAGTTTATCGGT
AGATATTTCAATTGGTACCAGCAACAACCGGGCAAAGCGCCCAA
GGTCCTGATCTACGCTGAGAGCAGTCTGCAATCCGGCGTACCTAG
CAGGTTCTCCGGAAGTGGCAGCGGAACCGAGTTCACCCTGACAAT
TAGCTCCTTGCAGCCCGAGGATTTCGCTCGCTATTACTGTCAACAG
AGTTATTCAACCCCTTTTACATTCGGACAGGGAAGTAAAGTTGAA
ATTAAGAGG (SEQ ID NO: 8)

Clone 1C8 VL AA (CDRs underlined)

DIQMTQSPSSLSASVGDRVTISCRASQFIGRYFNWYQQQPGKAPKVL
YAESSLQSGVPSRFSGSGSGTEFTLTISSLQPEDFARYYCQQSYSTPFT
FGQGTVKVEIKR (SEQ ID NO: 9)

Clone 1C8 VL CDR1 AA

RASQFIGRYFN

(SEQ ID NO: 56)

Clone 1C8 VL CDR2 AA

AESSLQS

(SEQ ID NO: 57)

Clone 1C8 VL CDR3 AA

QQSYSTPFT

(SEQ ID NO: 58)

Clone 6E9 VH DNA Coding Sequence

CAGGTACACCTGGTGCAGAGCGGGGCGGAGGTCAAGAAACCGGG
CGCATCCGTACGCGTGAGCTGCAAGGCCTCCGGATACACTTTTAC
TTCTTACTATCTGCATTGGGTGAGGCAGGCACCGGGTCAGGGACT
GGAGTGGATGGGCATTGTGGACCCAAGCGGAGGGAGTACGTCAT
ATGATCAGAAGTTTCAAGGTAGGTTTACCATGACACGGGACACGT
CAACGAGTACCGTCTACATGGAGCTCAGTAGTCTGCGGAGCGAAG
ACACCGCAGTCTACTACTGCGCACGCGATTATGGAGACTATGTCT
TTGACTATTGGGGGCAGGGGACGCTCGTGACCGTTTCAAGC (SEQ
ID NO: 10)

Clone 6E9 VH AA (CDRs underlined)

QVHLVQSGAEVKKPGASVRVSCKASGYTFTSYYLHWVRQAPGQGL
EWMGIVDPSGGSTSVDQKFQGRFTMTRDTSTSTVYMESSLRSEDTA
VYYCARDYGDYVFDYWGQGLTVTVSS (SEQ ID NO: 11)

Clone 6E9 VH CDR1 AA

GYTFTSY

(SEQ ID NO: 75)

Clone 6E9 VH CDR2 AA

DPSGGS

(SEQ ID NO: 76)

Clone 6E9 VH CDR3 AA

DYGDYVFDY

(SEQ ID NO: 70)

Clone 6E9 VL DNA Coding Sequence

CAAAGCGTACTGACACAGCCCCGAGTGCATCCGGGACCCCCGGC
CAAAGGGTTACAATCAGCTGCTCTGGCAGCTCCAGTAACATAGGT
ACCAACACGGTGAAGTGGTACCAGCAGTTGCCTGGCACAGCGCCT
CAGCTGCTCATCTATATCAACAATCAGCGGCCAAGTGGCGTGCCC
GATAGATTCTCAGGCTCAAAGAGCGGAACCAGCGCTAGCTTGCA
ATCAGTGGCCTTCAATCCGAAGACGAAGCCGATTACTATTGTGCG

ACCTGGGACGATAGCCTGAACGGCCCCGTCGTGGGCGGCGGGAC
GAAACTGACAGTGTGGGC (SEQ ID NO: 12)

Clone 6E9 VL AA (CDRs underlined)

QSVLTQPPSASGTPGQRVTISCSGSSSNIGTNTVNWYQQLPGTAPQLL
IYINNQRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYCATWDDSL
NGPVVGGGTKLTVLG (SEQ ID NO: 13)

Clone 6E9 VL CDR1 AA

SGSSSNIGTNTVN
(SEQ ID NO: 59)

Clone 6E9 VL CDR2 AA

INNQRPS
(SEQ ID NO: 60)

Clone 6E9 VL CDR3 AA

ATWDDSLNGPVV
(SEQ ID NO: 61)

[00137] In one embodiment, the antigen binding molecules of the instant disclosure are antibodies and antigen binding fragments thereof (*e.g.*, scFvs). In one embodiment, the antibodies and antigen binding molecules of the instant disclosure comprise at least one CDR set forth in Figure 6. In another aspect, the instant disclosure provides hybridomas capable of producing the antibodies and antigen binding molecules disclosed herein, and also methods of producing antibodies from hybridomas, as described herein and as known in the art.

[00138] An antigen binding molecule of the instant disclosure can also be a humanized monoclonal antibody, from which an scFv can be generated, which can then form a component of a CAR or TCR provided herein. In one embodiment, a humanized monoclonal antibody comprises the variable domain of a murine or rabbit antibody (or all or part of the antigen binding site thereof) and a constant domain derived from a human antibody. Alternatively, a humanized antibody fragment can comprise an antigen binding site of a murine or rabbit monoclonal antibody and a variable domain fragment (lacking the antigen binding site) derived from a human antibody. Procedures for the production of engineered monoclonal antibodies include those described in Riechmann *et al.*, (1988) *Nature* 332:323, Liu *et al.*, (1987) *Proc. Nat. Acad. Sci. USA* 84:3439, Larrick *et al.*, (1989)

Bio/Technology 7:934, and Winter *et al.*, (1993) *TIPS* 14:139. In one embodiment, the chimeric antibody is a CDR grafted antibody. Techniques for humanizing antibodies are discussed in, *e.g.*, U.S. Pat. Nos. 5,869,619; 5,225,539; 5,821,337; 5,859,205; 6,881,557; Padlan *et al.*, (1995) *FASEB J.* 9:133-39; Tamura *et al.*, (2000) *J. Immunol.* 164:1432-41; Zhang *et al.*, (2005) *Mol. Immunol.* 42(12):1445-1451; Hwang *et al.*, *Methods.* (2005) 36(1):35-42; Dall'Acqua *et al.*, (2005) *Methods* 36(1):43-60; and Clark, (2000) *Immunology Today* 21(8):397-402.

[00139] An antigen binding molecule of the instant disclosure can also be a fully human monoclonal antibody, from which an scFv can be generated, which can then form a component of a CAR or TCR provided herein. Fully human monoclonal antibodies can be generated by any number of techniques with which those having ordinary skill in the art will be familiar. Such methods include, but are not limited to, Epstein Barr Virus (EBV) transformation of human peripheral blood cells (*e.g.*, containing B lymphocytes), *in vitro* immunization of human B-cells, fusion of spleen cells from immunized transgenic mice carrying inserted human immunoglobulin genes, isolation from human immunoglobulin V region phage libraries, or other procedures as known in the art and based on the disclosure herein.

[00140] Procedures have been developed for generating human monoclonal antibodies in non-human animals. For example, mice in which one or more endogenous immunoglobulin genes have been inactivated by various means have been prepared. Human immunoglobulin genes have been introduced into the mice to replace the inactivated mouse genes. In this technique, elements of the human heavy and light chain locus are introduced into strains of mice derived from embryonic stem cell lines that contain targeted disruptions of the endogenous heavy chain and light chain loci (see also Bruggemann *et al.*, (1997) *Curr. Opin. Biotechnol.* 8:455-58).

[00141] Examples of techniques for production and use of transgenic animals for the production of human or partially human antibodies are described in U.S. Pat. Nos. 5,814,318, 5,569,825, and 5,545,806; Davis *et al.*, Antibody Engineering: Methods and Protocols, (Lo, ed) Humana Press, NJ, 191-200 (2003); Kellermann *et al.*, (2002) *Curr Opin Biotechnol.* 13:593-97; Russel *et al.*, (2000) *Infect Immun.* 68:1820-26; Gallo *et al.*, (2000) *Eur J. Immun.* 30:534-40; Davis *et al.*, (1999) *Cancer Metastasis Rev.* 18:421-25; Green, (1999) *J Immunol Methods* 231:11-23; Jakobovits, (1998) *Advanced Drug Delivery Reviews* 31:33-42; Green *et al.*, (1998) *J Exp Med.* 188:483-95; Jakobovits, (1998) *Exp. Opin.*

Invest. Drugs. 7:607-14; Tsuda *et al.*, (1997) *Genomics*, 42:413-21; Mendez *et al.*, (1997) *Nat. Genet.* 15:146-56; Jakobovits, (1994) *Curr Biol.* 4:761-63; Arbones *et al.*, (1994) *Immunity* 1:247-60; Green *et al.*, (1994) *Nat. Genet.* 7:13-21; Jakobovits *et al.*, (1993) *Nature* 362:255-58; Jakobovits *et al.*, (1993) *Proc Natl Acad Sci USA* 90:2551-55; Chen *et al.*, (1993) *Intl Immunol* 5:647-656; Choi *et al.*, (1993) *Nature Genetics* 4:117-23; Fishwild *et al.*, (1996) *Nature Biotechnology* 14:845-51; Lonberg *et al.*, (1994) *Nature* 368: 856-59; Lonberg, (1994) Handbook of Experimental Pharmacology 113: 49-101; Neuberger, (1996) *Nature Biotech* 14:826; Taylor *et al.*, (1992) *Nucleic Acids Research* 20:6287-95; Taylor *et al.*, (1994) *Intl Immunol* 6:579-91; Tomizuka *et al.*, (1997) *Nature Genetics* 16:133-43; Tomizuka *et al.*, (2000) *Proc Nat Acad Sci USA* 97:722-27; Tuaillon *et al.*, (1993) *Proc Nat Acad Sci USA* 90:3720-24; Tuaillon *et al.*, (1994) *J Immunol* 152:2912-20.; Lonberg *et al.*, (1994) *Nature* 368:856; Taylor *et al.*, (1994) *Intl Immunol* 6:579; U.S. Pat. No. 5,877,397; Bruggemann *et al.*, (1997) *Curr. Opin. Biotechnol.* 8:455-58; Jakobovits *et al.*, (1995) *Ann. N.Y. Acad. Sci.* 764:525-35.

[00142] An additional method for obtaining antigen binding molecules of the instant disclosure is by the use of phage display, which is well-established for this purpose. *See, e.g.*, Winter *et al.*, (1994) *Ann. Rev. Immunol.* 12:433-55; Burton *et al.*, (1994) *Adv. Immunol* 57:191-280. Human or murine immunoglobulin variable region gene combinatorial libraries can be created in phage vectors that can be screened to select Ig fragments (Fab, Fv, sFv, or multimers thereof) that bind the scFv FMC63, as well as molecules comprising this sequence and cells presenting such molecules. *See, e.g.*, U.S. Pat. No. 5,223,409; Huse *et al.*, (1989) *Science* 246:1275-81; Sastry *et al.*, (1989) *Proc. Natl. Acad. Sci. USA* 86:5728-32; Alting-Mees *et al.*, (1990) *Strategies in Molecular Biology* 3:1-9; Kang *et al.*, (1991) *Proc. Natl. Acad. Sci. USA* 88:4363-66; Hoogenboom *et al.*, (1992) *J. Mol. Biol.* 227:381-388; Schlebusch *et al.*, (1997) *Hybridoma* 16:47-52 and references cited therein. For example, a library containing a plurality of polynucleotide sequences encoding Ig variable region fragments can be inserted into the genome of a filamentous bacteriophage, such as M13 or lambda phage (λ ImmunoZapTM(H) and λ ImmunoZapTM(L) vectors (Stratagene, La Jolla, Calif) can also be used in this approach) or a variant thereof, in frame with the sequence encoding a phage coat protein.

[00143] Briefly, mRNA is isolated from a B-cell population, and used to create heavy and light chain immunoglobulin cDNA expression libraries in the λ ImmunoZapTM(H) and λ ImmunoZapTM(L) vectors. These vectors can be screened individually or co-expressed to

form Fab fragments or antibodies. Positive plaques can subsequently be converted to a non-lytic plasmid that allows high level expression of monoclonal antibody fragments from *E. coli*.

[00144] In one embodiment, in a hybridoma the variable regions of a gene expressing a monoclonal antibody of interest are amplified using nucleotide primers. These primers can be synthesized by one of ordinary skill in the art, or can be purchased from commercial sources, which also sell primers for mouse and human variable regions including, among others, primers for V_H, V_L, C_H and C_L regions). These primers can be used to amplify heavy or light chain variable regions, which can then be inserted into vectors. These vectors can then be introduced into *E. coli*, yeast, or mammalian-based systems for expression. Large amounts of a single-chain protein containing a fusion of the V_H and V_L domains can be produced using these methods.

[00145] Once cells producing the antigen binding molecules provided herein have been obtained using any of the above-described immunization and other techniques, the specific antibody genes can be cloned by isolating and amplifying DNA or mRNA therefrom according to standard procedures as described herein. The antibodies produced therefrom can be sequenced and the CDRs identified and the DNA coding for the CDRs can be manipulated as described so as to generate other antibodies according to the instant disclosure.

[00146] It will be understood by those of skill in the art that some proteins, such as antibodies, can undergo a variety of posttranslational modifications. The type and extent of these modifications often depends on the host cell line used to express the protein as well as the culture conditions. Such modifications can include variations in glycosylation, methionine oxidation, diketopiperazine formation, aspartate isomerization and asparagine deamidation. A frequent modification is the loss of a carboxy-terminal basic residue (such as lysine or arginine) due to the action of carboxypeptidases (as described in, *e.g.*, Harris, (1995) *J Chromatog* 705:129-34).

[00147] An alternative method for production of a murine monoclonal antibody is to inject the hybridoma cells into the peritoneal cavity of a syngeneic mouse, for example, a mouse that has been treated (*e.g.*, pristane-primed) to promote formation of ascites fluid containing the monoclonal antibody. Monoclonal antibodies can be isolated and purified by a variety of well-established techniques. Such isolation techniques include affinity chromatography with Protein-A Sepharose, size-exclusion chromatography, and ion-

exchange chromatography (see, *e.g.*, Baines and Thorpe, (1992) in Methods in Molecular Biology, 10:79-104 (The Humana Press). Monoclonal antibodies can be purified by affinity chromatography using an appropriate ligand selected based on particular properties of the antibody (*e.g.*, heavy or light chain isotype, binding specificity, etc.). Examples of a
5 suitable ligand, immobilized on a solid support, include Protein A, Protein G, an anti-constant region (light chain or heavy chain) antibody, and an anti-idiotypic antibody.

[00148] The instant disclosure provides antigen binding molecules (*e.g.*, scFv's) that specifically bind to CD70, molecules comprising this sequence and cells presenting such molecules. Antigen binding molecules that cross compete with the antigen binding
10 molecules disclosed herein form another aspect of the instant disclosure.

[00149] In some embodiments, an antigen binding molecule cross competes with a reference antibody comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 5, 7, 9, 11 or 13. In some embodiments, the antigen binding molecule cross competes with a reference antibody, wherein the reference antibody comprises a VH
15 CDR1 comprising an amino acid sequence of SEQ ID NOs: 62, 65, 68, 71, 73, 75, 77, 78 and 79.

[00150] In some embodiments, an antigen binding molecule cross competes with a reference antibody comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 5, 7, 9, 11 or 13, wherein the reference antibody comprises a VH CDR2
20 comprising an amino acid sequence of SEQ ID NOs: 63, 66, 69, 72, 74, 76, 63, 66 and 69.

[00151] In some embodiments, an antigen binding molecule cross competes with a reference antibody comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 5, 7, 9, 11 or 13, wherein the reference antibody comprises a VH CDR3
comprising an amino acid sequence of SEQ ID NOs: 64, 67, and 70.

[00152] In some embodiments, an antigen binding molecule cross competes with a reference antibody comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 5, 7, 9, 11 or 13, wherein the reference antibody comprises a VL CDR1
25 comprising an amino acid sequence of SEQ ID NOs: 53, 56 and 59.

[00153] In some embodiments, an antigen binding molecule cross competes with a reference antibody comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 5, 7, 9, 11 or 13, wherein the reference antibody comprises a VL CDR2
30 comprising an amino acid sequence of SEQ ID NOs: 54, 57 and 60.

[00154] In some embodiments, an antigen binding molecule cross competes with a reference antibody comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 5, 7, 9, 11 or 13, wherein the reference antibody comprises a VL CDR3 comprising an amino acid sequence of SEQ ID NOs: 55, 58 and 61.

5 [00155] In some embodiments, an antibody or antigen binding molecule that specifically binds CD70, molecules comprising this sequence and cells presenting such molecules, binds the same or an overlapping epitope as a reference antibody disclosed herein (*e.g.*, those comprising sequences presented herein, which can comprise a CDR presented in Figure 6).

10 [00156] In some embodiments, the antibody or antigen binding molecule binds the same or an overlapping epitope as a reference antibody.

II.A. Clone 8G1

In some embodiments, an antigen binding molecule, such as an scFv, or antibody
15 that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a VH CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence GFTFSSY (SEQ ID NO: 71).

[00157] In some embodiments, an antigen binding molecule, such as an scFv, or antibody that specifically binds to CD70, molecules comprising this sequence and cells
20 presenting such molecules, comprises a VH CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence WYDGSN (SEQ ID NO: 72).

[00158] In some embodiments, an antigen binding molecule, such as an scFv, or antibody that specifically binds to CD70, molecules comprising this sequence and cells
25 presenting such molecules, comprises a VH CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence DLLRGVKGYAMDV (SEQ ID NO: 64).

[00159] In some embodiments, an antigen binding molecule, such as an scFv, or antibody that specifically binds to CD70, molecules comprising this sequence and cells
30 presenting such molecules, comprises a heavy chain VH comprising: (a) a VH CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence GFTFSSY (SEQ ID NO: 71); and/or (b) a VH CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence WYDGSN (SEQ ID NO: 72); and/or (c) a VH CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence DLLRGVKGYAMDV (SEQ ID NO: 64).

[00160] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a VH CDR1, a VH CDR2, and VH CDR3, wherein the VH CDR1, VH CDR2, and VH CDR3 comprise an amino acid sequence of a VH CDR1, VH CDR2, and VH CDR3 presented in FIGURE 6.

[00161] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a VH CDR1, a VH CDR2, and VH CDR3, wherein the VH CDR1, VH CDR2, and VH CDR3 comprise the amino acid sequence of the VH CDR1, VH CDR2, and VH CDR3 of an antigen binding molecule presented in FIGURES 6 and 7A (SEQ ID NOs: 71, 72 and 64, respectively).

[00162] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a heavy chain variable region sequence comprising an amino acid sequence of FIGURE 7A. In some embodiments, the antibody or antigen binding molecule comprises a heavy chain variable region sequence comprising SEQ ID NO: 3.

[00163] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises one or more of any of the VH CDRs listed above or described in FIGURE 6. In some embodiments, the antibody or antigen binding molecule comprises the VH framework regions (FRs) described herein. In specific embodiments, the antibody or antigen binding molecule comprises a VH FR as set forth in, or derivable from, the sequences presented in FIGURE 7A (*e.g.*, one, two, three, or four of the FRs in one sequence of FIGURE 7A).

[00164] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a heavy chain sequence disclosed herein (*e.g.*, in FIGURE 7A). In one embodiment, the antibody or antigen binding molecule comprises a heavy chain variable region comprising the amino acid sequence

QEQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVTWYD
GSNKYYGDSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDLLRGVKGYA
MDVWGQGTTVTVSS (SEQ ID NO: 3), encoded by the nucleic acid

CAAGAGCAGCTGGTTGAGTCTGGGGGCGGCGTCGTCCAACCCGGCCGGAGTCT
 GAGGTTGTCCTGCGCTGCAAGCGGATTTACATTTTCATCTTACGGCATGCACTG
 GGTTAGGCAGGCTCCTGGAAAAGGGCTGGAGTGGGTCGCGGTGACTTGGTACG
 ACGGCTCCAATAAGTATTATGGGGATTCCGTGAAAGGTCGATTCACAATTAGCA
 5 GGGATAACTCCAAAAACACACTGTATCTCCAAATGAACTCCTTGAGGGCCGAG
 GACACGGCCGTCTATTATTGTGCAAGAGACCTCCTCCGGGGCGTAAAGGGATAT
 GCtATGGACGTGTGGGGTCAGGGGACCACAGTTACTGTCAGTTCA (SEQ ID NO:
 2).

[00165] In various embodiments, the heavy chain variable region is 80%, 85%, 90%,
 10 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the heavy chain variable
 region sequence of SEQ ID NO: 3.

[00166] In some embodiments, an antigen binding molecule, such as an scFv, or
 antibody that specifically binds to CD70, molecules comprising this sequence and cells
 presenting such molecules, comprises a VL CDR1 comprising, consisting of, or consisting
 15 essentially of the amino acid sequence RASQSLRRIYLA (SEQ ID NO: 53).

[00167] In some embodiments, an antigen binding molecule, such as an scFv, or
 antibody that specifically binds to CD70, molecules comprising this sequence and cells
 presenting such molecules, comprises a VL CDR2 comprising, consisting of, or consisting
 essentially of the amino acid sequence DVFDRAT (SEQ ID NO: 54).

[00168] In some embodiments, an antigen binding molecule, such as an scFv, or
 20 antibody that specifically binds to CD70, molecules comprising this sequence and cells
 presenting such molecules, comprises a VL CDR3 comprising, consisting of, or consisting
 essentially of the amino acid sequence QQYSDSPFT (SEQ ID NO: 55).

[00169] In some embodiments, an antigen binding molecule, such as an scFv, or
 25 antibody that specifically binds to CD70, molecules comprising this sequence and cells
 presenting such molecules, comprises a heavy chain VL comprising: (a) a VL CDR1
 comprising, consisting of, or consisting essentially of the amino acid sequence
 RASQSLRRIYLA (SEQ ID NO: 53); and/or (b) a VL CDR2 comprising, consisting of, or
 consisting essentially of the amino acid sequence DVFDRAT (SEQ ID NO: 54); and/or (c)
 30 a VL CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence
 QQYSDSPFT (SEQ ID NO: 55).

[00170] In some embodiments, the antibody or antigen binding molecule, such as an
 scFv, that specifically binds to CD70, molecules comprising this sequence and cells

presenting such molecules, wherein the antibody or antigen binding molecule comprises a VL CDR1, a VL CDR2, and VL CDR3, wherein the VL CDR1, VL CDR2, and VL CDR3 comprise the amino acid sequence of a VL CDR1, VL CDR2, and VL CDR3 presented in FIGURE 6.

[00171] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a light chain variable region sequence comprising an amino acid sequence of FIGURE 7B. In some embodiments, the antibody or antigen binding molecule comprises a light chain variable region sequence comprises SEQ ID NO:

5. 10

[00172] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, wherein the antibody or antigen binding molecule comprises the VL framework regions (FRs) described herein. In specific embodiments, the antibody or antigen binding molecule comprises the VL FRs of an amino acid sequence as set forth in, or derivable from, the sequences presented in FIGURE 7B (*e.g.*, one, two, three, or four of the FRs in one sequence of FIGURE 7B).

[00173] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a light chain sequence disclosed herein (*e.g.*, in FIGURE 7B). In one embodiment, the antibody or antigen binding molecule comprises a light chain variable region comprising the amino acid sequence of

EIVLTQSPGTLSPGERATLSCRASQSLRRIYLAWYQQKPGQAPRLLIYDVFDRA
T
GIPDRFSGGGSGTDFTLTISRLEPEDFAVYYCQQYSDSPFTFGPGTKVDIKR (SEQ ID

NO: 5), encoded by the nucleic acid

GAAATCGTTCTCACTCAGTCTCCGGGCACACTGTCCCTCAGCCCCGGAGAGCGA
GCCACTTTGAGCTGCCGGGCCAGCCAGTCACTTAGACGCATTTATTTGGCCTGG
TATCAGCAGAAACCAGGCCAGGCGCCCAGGCTGCTGATATACGATGTGTTCGAT
AGGGCCACGGGTATCCCCGATAGGTTCTCTGGCGGGGGTCCGGGACTGACTTC
ACCCTCACTATATCACGACTCGAGCCCGAAGACTTCGCAGTTTATTATTGCCAG
CAGTACTCCGACTCCCCATTACCTTCGGCCCTGGTACCAAAGTGGATATTAAA
CGG (SEQ ID NO:4).

[00174] In various embodiments, the light chain variable region is 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the light chain variable region sequence of SEQ ID NO: 4.

[00175] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises any one, two, and/or three VH CDR sequences disclosed herein. In some embodiments, the antibody or antigen binding molecule comprises a VH CDR1, a VH CDR2, and a VH CDR3 having the amino acid sequence of any VH CDR1, VH CDR2, and VH CDR3 disclosed herein, respectively. In some
10 embodiments, the antibody or antigen binding molecule comprises any one, two, and/or three VL CDR sequences disclosed herein. In some embodiments, the antibody or antigen binding molecule comprises a VL CDR1, a VL CDR2, and a VL CDR3 having the amino acid sequence of any VL CDR1, VL CDR2, and VL CDR3 disclosed herein, respectively.

[00176] In one embodiment, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises: (a) a VH CDR1 region comprising the amino acid sequence of SEQ ID NO: 71; (b) a VH CDR2 region comprising the amino acid sequence of SEQ ID NO: 72; (c) a VH CDR3 region comprising the amino acid sequence of SEQ ID NO: 64; (d) a VL CDR1 region comprising the amino acid sequence of SEQ ID NO: 53; (e)
20 a VL CDR2 region comprising the amino acid sequence of SEQ ID NO: 54; and (f) a VL CDR3 region comprising the amino acid sequence of SEQ ID NO: 55.

[00177] In one embodiment, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises: (a) a VH CDR1 region; (b) a VH CDR2 region; (c) a
25 VH CDR3 region; (d) a VL CDR1 region comprising; (e) a VL CDR2 region; and (f) a VL CDR3 region, wherein the VH and VL CDRs are shown in FIGURES 7A and 7B, respectively, and in FIGURE 6.

[00178] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells
30 presenting such molecules, comprises a heavy chain variable region sequence disclosed herein (*e.g.*, in FIGURE 7A) and a light chain variable region sequence disclosed herein (*e.g.*, in FIGURE 7B).

[00179] In one embodiment, the antibody or antigen binding molecule, such as an scFv, comprises: (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 3; and (b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 5. Nucleotide sequences encoding the heavy chain variable region and the light chain variable regions are provided herein and in FIGURES 7A and 7B, respectively

[00180] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a heavy chain sequence disclosed herein (*e.g.*, in FIGURE 7A) and a light chain sequence disclosed herein (*e.g.*, in FIGURE 7B).

[00181] In one embodiment, the antibody or antigen binding molecule, such as an scFv, comprises: (a) a heavy chain variable region comprising the amino acid sequence of QEQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVTWYD GSNKYYGDSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDLLRGVKGYA MDVWGQGTTVTVSS (SEQ ID NO: 3); and (b) a light chain variable region comprising the amino acid sequence of EIVLTQSPGTLSPGERATLSCRASQSLRRIYLA WYQQKPGQAPRLLIYDVFD RAT GIPDRFSGGGSGTDFTLTISRLEPEDFAVYYCQQYSDSPFTFGPGTKVDIKR (SEQ ID NO: 5).

[00182] In one embodiment, the antibody or antigen binding molecule comprises: (a) a heavy chain comprising an amino acid sequence that is 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of SEQ ID NO: 3; and (b) a light chain comprising an amino acid sequence that is 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of SEQ ID NO: 5.

II.B. Clone 1C8

In some embodiments, an antigen binding molecule, such as an scFv, or antibody that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a VH CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence GDSIISGGY (SEQ ID NO: 73).

[00183] In some embodiments, an antigen binding molecule, such as an scFv, or antibody that specifically binds to CD70, molecules comprising this sequence and cells

presenting such molecules, comprises a VH CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence FYSGS (SEQ ID NO: 74).

[00184] In some embodiments, an antigen binding molecule, such as an scFv, or antibody that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a VH CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence SGYSYALFDH (SEQ ID NO: 67).

[00185] In some embodiments, an antigen binding molecule, such as an scFv, or antibody that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a heavy chain VH comprising: (a) a VH CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence GDSIISGGY (SEQ ID NO: 73); and/or (b) a VH CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence FYSGS (SEQ ID NO: 74); and/or (c) a VH CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence SGYSYALFDH (SEQ ID NO: 67).

[00186] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a VH CDR1, a VH CDR2, and VH CDR3, wherein the VH CDR1, VH CDR2, and VH CDR3 comprise an amino acid sequence of a VH CDR1, VH CDR2, and VH CDR3 presented in FIGURES 6 and 7C.

[00187] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a VH CDR1, a VH CDR2, and VH CDR3, wherein the VH CDR1, VH CDR2, and VH CDR3 comprise the amino acid sequence of the VH CDR1, VH CDR2, and VH CDR3 of an antigen binding molecule presented in FIGURES 7C (SEQ ID NOs: 73, 74 and 67, respectively).

[00188] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a heavy chain variable region sequence comprising an amino acid sequence of FIGURE 7C. In some embodiments, the antibody or antigen binding molecule comprises a heavy chain variable region sequence comprising SEQ ID NO: 7.

[00189] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells

presenting such molecules, comprises one or more of any of the VH CDRs listed above or described in FIGURE 6. In some embodiments, the antibody or antigen binding molecule comprises the VH framework regions (FRs) described herein. In specific embodiments, the antibody or antigen binding molecule comprises a VH FR as set forth in, or derivable from, the sequences presented in FIGURE 7C (*e.g.*, one, two, three, or four of the FRs in one sequence of FIGURE 7C).

[00190] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a heavy chain sequence disclosed herein (*e.g.*, in FIGURE 7C). In one embodiment, the antibody or antigen binding molecule comprises a heavy chain variable region comprising the amino acid sequence

QVQLQESGPGLVKPSQTLSTCTVSGDSIISGGYYWSWIRQHPGKGLEWIGYIFYSG
STDYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARSGYSYALFDHWGQG
TLVTVSS (SEQ ID NO: 7), encoded by the nucleic acid

CAGGTGCAGCTCCAAGAATCTGGACCGGGTCTCGTCAAGCCATCACAGACACT
GTCCCTGACCTGCACCGTCTCCGGCGACTCTATCATTTCAGGCGGCTACTATTGG
TCCTGGATTAGACAACATCCGGGAAAGGGTCTTGAATGGATCGGCTATATTTTC
TACAGCGGGAGTACGGATTACAATCCTAGTCTCAAGAGCCGCGTTACCATTTC
GTGGATACTTCAAAAAACCAGTTTAGCCTGAAGCTGTCTTCTGTAACAGCTGCT
GACACAGCCGTGTACTATTGCGCCAGGAGCGGCTACAGCTATGCCCTGTTTGAC
CACTGGGGGCAAGGCACTCTTGTGACGGTGTCAAGT (SEQ ID NO: 6).

[00191] In various embodiments, the heavy chain variable region is 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the heavy chain variable region sequence of SEQ ID NO: 7C.

[00192] In some embodiments, an antigen binding molecule, such as an scFv, or antibody that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a VL CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence RASQFIGRYFN (SEQ ID NO: 56).

[00193] In some embodiments, an antigen binding molecule, such as an scFv, or antibody that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a VL CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence AESSLQS (SEQ ID NO: 57).

[00194] In some embodiments, an antigen binding molecule, such as an scFv, or antibody that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a VL CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence QQSYSTPFT (SEQ ID NO: 58).

5 [00195] In some embodiments, an antigen binding molecule, such as an scFv, or antibody that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a heavy chain VL comprising: (a) a VL CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence RASQFIGRYFN (SEQ ID NO: 56); and/or (b) a VL CDR2 comprising, consisting of, or
10 consisting essentially of the amino acid sequence AESSLQS (SEQ ID NO: 57); and/or (c) a VL CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence QQSYSTPFT (SEQ ID NO: 58).

[00196] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells
15 presenting such molecules, wherein the antibody or antigen binding molecule comprises a VL CDR1, a VL CDR2, and VL CDR3, wherein the VL CDR1, VL CDR2, and VL CDR3 comprise the amino acid sequence of a VL CDR1, VL CDR2, and VL CDR3 presented in FIGURE 6 and 7D.

[00197] In some embodiments, the antibody or antigen binding molecule, such as an
20 scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a light chain variable region sequence comprising an amino acid sequence of FIGURE 7D. In some embodiments, the antibody or antigen binding molecule comprises a light chain variable region sequence comprises SEQ ID NO: 9.

25 [00198] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, wherein the antibody or antigen binding molecule comprises the VL framework regions (FRs) described herein. In specific embodiments, the antibody or antigen binding molecule comprises the VL FRs of an amino acid sequence as set forth in,
30 or derivable from, the sequences presented in FIGURE 7D (*e.g.*, one, two, three, or four of the FRs in one sequence of FIGURE 7D).

[00199] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells

presenting such molecules, comprises a light chain sequence disclosed herein (*e.g.*, in FIGURE 7D). In one embodiment, the antibody or antigen binding molecule comprises a light chain variable region comprising the amino acid sequence of

DIQMTQSPSSLSASVGDRVTISCRASQFIGRYFNWYQQQPGKAPKVLIIYAESSLQSG
 5 VPSRFSGSGSGTEFTLTISLQPEDFARYYCQQSYSTPFTFGQGTKVEIKR (SEQ ID
 NO: 9), encoded by the nucleic acid
 GACATTCAAATGACGCAGTCCCCAAGTTCTCTGTCCGCTAGCGTCGGCGACCGA
 GTGACCATCAGCTGCCGAGCATCCCAGTTTATCGGTAGATATTTCAATTGGTAC
 CAGCAACAACCGGGCAAAGCGCCCAAGGTCCTGATCTACGCTGAGAGCAGTCT
 10 GCAATCCGGCGTACCTAGCAGGTTCTCCGGAAGTGGCAGCGGAACCGAGTTCA
 CCCTGACAATTAGCTCCTTGCAGCCCGAGGATTTGCTCGCTATTACTGTCAAC
 AGAGTTATTCAACCCCTTTTACATTCGGACAGGGAAGTAAAGTTGAAATTAAGA
 GG (SEQ ID NO:8).

[00200] In various embodiments, the light chain variable region is 80%, 85%, 90%,
 15 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the light chain variable
 region sequence of SEQ ID NO: 9.

[00201] In some embodiments, the antibody or antigen binding molecule, such as an
 scFv, that specifically binds to CD70, molecules comprising this sequence and cells
 presenting such molecules, comprises any one, two, and/or three VH CDR sequences
 20 disclosed herein. In some embodiments, the antibody or antigen binding molecule
 comprises a VH CDR1, a VH CDR2, and a VH CDR3 having the amino acid sequence of
 any VH CDR1, VH CDR2, and VH CDR3 disclosed herein, respectively. In some
 embodiments, the antibody or antigen binding molecule comprises any one, two, and/or
 three VL CDR sequences disclosed herein. In some embodiments, the antibody or antigen
 25 binding molecule comprises a VL CDR1, a VL CDR2, and a VL CDR3 having the amino
 acid sequence of any VL CDR1, VL CDR2, and VL CDR3 disclosed herein, respectively.

[00202] In one embodiment, the antibody or antigen binding molecule, such as an
 scFv, that specifically binds to CD70, molecules comprising this sequence and cells
 presenting such molecules, comprises: (a) a VH CDR1 region comprising the amino acid
 30 sequence of SEQ ID NO: 73; (b) a VH CDR2 region comprising the amino acid sequence of
 SEQ ID NO: 74; (c) a VH CDR3 region comprising the amino acid sequence of SEQ ID
 NO: 67; (d) a VL CDR1 region comprising the amino acid sequence of SEQ ID NO: 56; (e)

a VL CDR2 region comprising the amino acid sequence of SEQ ID NO: 57; and (f) a VL CDR3 region comprising the amino acid sequence of SEQ ID NO: 58.

[00203] In one embodiment, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises: (a) a VH CDR1 region; (b) a VH CDR2 region; (c) a VH CDR3 region; (d) a VL CDR1 region comprising; (e) a VL CDR2 region; and (f) a VL CDR3 region, wherein the VH and VL CDRs are shown in FIGURES 7C and 7D, respectively, and in FIGURE 6.

[00204] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a heavy chain variable region sequence disclosed herein (*e.g.*, in FIGURE 7C) and a light chain variable region sequence disclosed herein (*e.g.*, in FIGURE 7D).

[00205] In one embodiment, the antibody or antigen binding molecule, such as an scFv, comprises: (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 7; and (b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 9. Nucleotide sequences encoding the heavy chain variable region and the light chain variable regions are provided herein and in FIGURES 7C and 7D, respectively.

[00206] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a heavy chain sequence disclosed herein (*e.g.*, in FIGURE 7C) and a light chain sequence disclosed herein (*e.g.*, in FIGURE 7D).

[00207] In one embodiment, the antibody or antigen binding molecule, such as an scFv, comprises: (a) a heavy chain variable region comprising the amino acid sequence of QVQLQESGPGLVKPSQTLSTCTVSGDSIISGGYYWSWIRQHPGKGLEWIGYIFYSG STDYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARSGYSYALFDHWGQG TLVTVSS (SEQ ID NO: 7); and (b) a light chain variable region comprising the amino acid sequence of

DIQMTQSPSSLSASVGDRVTISCRASQFIGRYFNWYQQQPGKAPKVLIAESSLQSG VPSRFGSGSGSTEFTLTISLQPEDFARYYCQQSYSTPFTFGQGTKVEIKR (SEQ ID NO: 9).

[00208] In one embodiment, the antibody or antigen binding molecule comprises: (a) a heavy chain comprising an amino acid sequence that is 80%, 85%, 90%, 91%, 92%, 93%,

94%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of SEQ ID NO: 7; and (b) a light chain comprising an amino acid sequence that is 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of SEQ ID NO: 9.

5

II.C. Clone 6E9

[00209] In some embodiments, an antigen binding molecule, such as an scFv, or antibody that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a VH CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence GYTFTSY (SEQ ID NO: 75).

10

[00210] In some embodiments, an antigen binding molecule, such as an scFv, or antibody that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a VH CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence DPSGGS (SEQ ID NO: 76).

15

[00211] In some embodiments, an antigen binding molecule, such as an scFv, or antibody that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a VH CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence DYGDYVFDY (SEQ ID NO: 70).

[00212] In some embodiments, an antigen binding molecule, such as an scFv, or antibody that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a heavy chain VH comprising: (a) a VH CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence GYTFTSY (SEQ ID NO: 75); and/or (b) a VH CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence DPSGGS (SEQ ID NO: 76); and/or (c) a VH CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence DYGDYVFDY (SEQ ID NO: 70).

20

25

[00213] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a VH CDR1, a VH CDR2, and VH CDR3, wherein the VH CDR1, VH CDR2, and VH CDR3 comprise an amino acid sequence of a VH CDR1, VH CDR2, and VH CDR3 presented in FIGURES 6 and 7E.

30

[00214] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells

presenting such molecules, comprises a VH CDR1, a VH CDR2, and VH CDR3, wherein the VH CDR1, VH CDR2, and VH CDR3 comprise the amino acid sequence of the VH CDR1, VH CDR2, and VH CDR3 of an antigen binding molecule presented in FIGURE 7E (SEQ ID NOs: 75, 76 and 70, respectively).

5 [00215] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a heavy chain variable region sequence comprising an amino acid sequence of FIGURE 7E. In some embodiments, the antibody or antigen binding molecule comprises a heavy chain variable region sequence comprising SEQ ID
10 NO: 11.

[00216] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises one or more of any of the VH CDRs listed above or described in FIGURE 6. In some embodiments, the antibody or antigen binding molecule
15 comprises the VH framework regions (FRs) described herein. In specific embodiments, the antibody or antigen binding molecule comprises a VH FR as set forth in, or derivable from, the sequences presented in FIGURE 7E (*e.g.*, one, two, three, or four of the FRs in one sequence of FIGURE 7E).

[00217] In some embodiments, the antibody or antigen binding molecule, such as an
20 scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a heavy chain sequence disclosed herein (*e.g.*, in FIGURE 7E). In one embodiment, the antibody or antigen binding molecule comprises a heavy chain variable region comprising the amino acid sequence
25 QVHLVQSGAEVKKPGASVRVSCKASGYTFTSYLHWVRQAPGQGLEWMGIVDPS
GGSTSYDQKFQGRFTMTRDTSTSTVYMELSSLRSEDVAVYYCARDYGDYVFDYW
GQGTLLVTVSS (SEQ ID NO: 11), encoded by the nucleic acid
CAGGTACACCTGGTGCAGAGCGGGGCGGAGGTCAAGAAACCGGGCGCATCCGT
ACGCGTGAGCTGCAAGGCCTCCGGATACACTTTTACTTCTTACTATCTGCATTGG
GTCAGGCAGGCACCGGGTCAGGGACTGGAGTGGATGGGCATTGTGGACCCAAG
30 CGGAGGGAGTACGTCATATGATCAGAAGTTTCAAGGTAGGTTTACCATGACAC
GGGACACGTCAACGAGTACCGTCTACATGGAGCTCAGTAGTCTGCGGAGCGAA
GACACCGCAGTCTACTACTGCGCACGCGATTATGGAGACTATGTCTTTGACTAT
TGGGGGCAGGGGACGCTCGTGACCGTTTCAAGC (SEQ ID NO: 10).

[00218] In various embodiments, the heavy chain variable region is 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the heavy chain variable region sequence of SEQ ID NO: 7E.

[00219] In some embodiments, an antigen binding molecule, such as an scFv, or antibody that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a VL CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence SGSSSNIGTNTVN (SEQ ID NO: 59).

[00220] In some embodiments, an antigen binding molecule, such as an scFv, or antibody that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a VL CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence INNQRPS (SEQ ID NO: 60).

[00221] In some embodiments, an antigen binding molecule, such as an scFv, or antibody that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a VL CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence ATWDDSLNGPVV (SEQ ID NO: 61).

[00222] In some embodiments, an antigen binding molecule, such as an scFv, or antibody that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a heavy chain VL comprising: (a) a VL CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence SGSSSNIGTNTVN (SEQ ID NO: 59); and/or (b) a VL CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence INNQRPS (SEQ ID NO: 60); and/or (c) a VL CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence ATWDDSLNGPVV (SEQ ID NO: 61).

[00223] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, wherein the antibody or antigen binding molecule comprises a VL CDR1, a VL CDR2, and VL CDR3, wherein the VL CDR1, VL CDR2, and VL CDR3 comprise the amino acid sequence of a VL CDR1, VL CDR2, and VL CDR3 presented in FIGURE 6 and 7F.

[00224] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a light chain variable region sequence comprising an amino acid sequence of FIGURE 7F. In some embodiments, the antibody or antigen

binding molecule comprises a light chain variable region sequence comprises SEQ ID NO: 13.

[00225] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, wherein the antibody or antigen binding molecule comprises the VL framework regions (FRs) described herein. In specific embodiments, the antibody or antigen binding molecule comprises the VL FRs of an amino acid sequence as set forth in, or derivable from, the sequences presented in FIGURE 7F (*e.g.*, one, two, three, or four of the FRs in one sequence of FIGURE 7F).

[00226] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a light chain sequence disclosed herein (*e.g.*, in FIGURE 7F). In one embodiment, the antibody or antigen binding molecule comprises a light chain variable region comprising the amino acid sequence of

QSVLTQPPSASGTPGQRVTISCSGSSSNIGTNTVNWYQQLPGTAPQLLIYINNQRPSG
VPDRFSGSKSGTSASLAISGLQSEDEADYYCATWDDSLNGPVGGGTKLTVLG

(SEQ ID NO: 13), encoded by the nucleic acid

CAAAGCGTACTGACACAGCCCCCGAGTGCATCCGGGACCCCCGGCCAAAGGGT
TACAATCAGCTGCTCTGGCAGCTCCAGTAACATAGGTACCAACACGGTGAAGT
GTACCAGCAGTTGCCTGGCACAGCGCCTCAGCTGCTCATCTATATCAACAATCA
GCGGCCAAGTGGCGTGCCCGATAGATTCTCAGGCTCAAAGAGCGGAACCAGCG
CTAGCTTGGCAATCAGTGGCCTTCAATCCGAAGACGAAGCCGATTACTATTGTG
CGACCTGGGACGATAGCCTGAACGGCCCCGTCGTGGGCGGCGGGACGAAACTG
ACAGTGTTGGGC (SEQ ID NO: 12).

[00227] In various embodiments, the light chain variable region is 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the light chain variable region sequence of SEQ ID NO:13.

[00228] In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises any one, two, and/or three VH CDR sequences disclosed herein. In some embodiments, the antibody or antigen binding molecule comprises a VH CDR1, a VH CDR2, and a VH CDR3 having the amino acid sequence of any VH CDR1, VH CDR2, and VH CDR3 disclosed herein, respectively. In some

embodiments, the antibody or antigen binding molecule comprises any one, two, and/or three VL CDR sequences disclosed herein. In some embodiments, the antibody or antigen binding molecule comprises a VL CDR1, a VL CDR2, and a VL CDR3 having the amino acid sequence of any VL CDR1, VL CDR2, and VL CDR3 disclosed herein, respectively.

5 **[00229]** In one embodiment, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises: (a) a VH CDR1 region comprising the amino acid sequence of SEQ ID NO: 75; (b) a VH CDR2 region comprising the amino acid sequence of SEQ ID NO: 76; (c) a VH CDR3 region comprising the amino acid sequence of SEQ ID NO: 70; (d) a VL CDR1 region comprising the amino acid sequence of SEQ ID NO: 59; (e) 10 a VL CDR2 region comprising the amino acid sequence of SEQ ID NO: 60; and (f) a VL CDR3 region comprising the amino acid sequence of SEQ ID NO: 61.

15 **[00230]** In one embodiment, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises: (a) a VH CDR1 region; (b) a VH CDR2 region; (c) a VH CDR3 region; (d) a VL CDR1 region comprising; (e) a VL CDR2 region; and (f) a VL CDR3 region, wherein the VH and VL CDRs are shown in FIGURES 7E and 7F, respectively, and in FIGURE 6.

20 **[00231]** In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a heavy chain variable region sequence disclosed herein (*e.g.*, in FIGURE 7E) and a light chain variable region sequence disclosed herein (*e.g.*, in FIGURE 7F).

25 **[00232]** In one embodiment, the antibody or antigen binding molecule, such as an scFv, comprises: (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 11; and (b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 13. Nucleotide sequences encoding the heavy chain variable region and the light chain variable regions are provided herein and in FIGURES 7E and 7F, respectively

30 **[00233]** In some embodiments, the antibody or antigen binding molecule, such as an scFv, that specifically binds to CD70, molecules comprising this sequence and cells presenting such molecules, comprises a heavy chain sequence disclosed herein (*e.g.*, in FIGURE 7E) and a light chain sequence disclosed herein (*e.g.*, in FIGURE 7F).

[00234] In one embodiment, the antibody or antigen binding molecule, such as an scFv, comprises: (a) a heavy chain variable region comprising the amino acid sequence of QVHLVQSGAEVKKPGASVRVSCKASGYTFTSYLHWVRQAPGQGLEWMGIVDPS GGSTSYDQKFQGRFTMTRDTSTSTVYMELSSLRSEDVAVYYCARDYGDYVFDYW
 5 GQGTLLTVSS (SEQ ID NO: 11); and (b) a light chain variable region comprising the amino acid sequence of QSVLTQPPSASGTPGQRVTISCSGSSSNIGTNTVNWYQQLPGTAPQLLIYINNQRPSG VPDRFSGSKSGTSASLAISGLQSEDEADYYCATWDDSLNGPVVGGGTKLTVLG (SEQ ID NO: 13).

10 [00235] In one embodiment, the antibody or antigen binding molecule, such as an scFv, comprises: (a) a heavy chain comprising an amino acid sequence that is 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of SEQ ID NO: 11; and (b) a light chain comprising an amino acid sequence that is 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the
 15 amino acid sequence of SEQ ID NO: 13.

III Polynucleotides Encoding Antigen Binding Molecules, Chimeric Antigen Receptors and T Cell Receptors Comprising Such Antigen Binding Molecules

[00236] The instant disclosure is also directed to polynucleotides encoding antibodies
 20 and antigen binding molecules, such as an scFv, that specifically bind to CD70, molecules comprising this sequence and cells presenting such molecules.

[00237] In some embodiments, a polynucleotide of the instant disclosure encodes an antigen binding molecule, such as an scFv, wherein the antigen binding molecule comprises a heavy chain variable region amino acid sequence that is at least about 75%, at least about
 25 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 a heavy chain variable region amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7, and 11.

[00238] In some embodiments, a polynucleotide of the instant disclosure encodes
 30 antigen binding molecule, such as an scFv, wherein the antigen binding molecule comprises a light chain variable 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 a light chain variable region amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 9 and 13.

[00239] In some embodiments, the polynucleotide comprises a heavy chain coding sequence selected from the group consisting of SEQ ID NOs: 2, 6 and 10.

5 [00240] In another embodiment, the polynucleotide comprises a light chain coding sequence selected from the group consisting of SEQ ID NOs: 4, 8 and 12.

[00241] In another embodiment, the polynucleotide comprises a heavy chain coding sequence comprising SEQ ID NO: 2 and a light chain coding sequence comprising SEQ ID NO: 4.

10 [00242] In another embodiment, the polynucleotide comprises a heavy chain coding sequence comprising SEQ ID NO: 6 and a light chain coding sequence comprising SEQ ID NO: 8.

[00243] In another embodiment, the polynucleotide comprises a heavy chain coding sequence comprising SEQ ID NO: 10 and a light chain coding sequence comprising SEQ ID NO: 12.

15 [00244] As will be appreciated by those of skill in the art, variations of the disclosed polynucleotide sequences are possible due to the degeneracy of the genetic code. Such variants of the disclosed polynucleotide sequences thus form an aspect of the instant disclosure.

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IV. Chimeric Antigen Receptors and T Cell Receptors

[00245] The instant disclosure is also directed to chimeric antigen receptors (CARs) or T cell receptors (TCRs) comprising an antigen binding molecule, such as an scFv, that specifically binds to CD70 described herein, and engineered T cells comprising an antigen binding molecule that specifically binds to CD70 described herein. In some embodiments, an anti-CD70 CAR or TCR of the instant disclosure comprises an antigen binding molecule that specifically binds to CD70. In some embodiments, the anti-CD70 CAR or TCR further comprises a costimulatory domain, and/or an extracellular domain (*i.e.*, a “hinge” or “spacer” region), and/or a transmembrane domain, and/or an intracellular (signaling) domain, and/or a CD3 zeta activating domain. In some embodiments, the anti-CD70 CAR or TCR comprises an scFv antigen binding molecule that specifically binds CD70 (*e.g.*, hCD70) disclosed herein, a costimulatory domain, an extracellular domain, a transmembrane domain, and a CD3 zeta activating domain.

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[00246] In some embodiments, a TCR of the instant disclosure comprises an antigen binding molecule that specifically binds to CD70, and wherein the TCR further comprises a fourth complementarity determining region (CDR4). In some embodiments, the TCR comprises an antigen binding molecule that specifically binds to CD70, and 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. CAR and TCR design is discussed further below.

[00247] It will further be appreciated that where desired, the various domains and regions described herein can be expressed in a separate chain from the antigen binding molecule (*e.g.*, scFv) and activating domains, in so-called “trans” configuration. Thus, in one embodiment an activating domain can be expressed on one chain, while the antigen binding molecule, and/or an extracellular domain, and/or a transmembrane domain and/or a costimulatory domain (depending on the desired construction of the CAR or TCR) can be expressed on a separate chain.

[00248] As described more fully herein, it will be further appreciated that the N to C-terminal, or extracellular to intracellular, order of the components of a CAR of the instant disclosure can be varied as desired. The antigen binding molecule (the scFv) will be extracellular in order to associated with the target antigen, and can include a leader or signal peptide at the N terminal end the scFv that is most distal to the cell membrane. A preferred orientation and ordering for a CAR of the instant disclosure is: optional leader sequence (*e.g.*, the leader sequence of CD8a)--anti-CD70 scFv--optional mini-linker, such as GSG or AAA--hinge--optional mini-linker, such as GSG or AAA—transmembrane region (*e.g.*, CD8a transmembrane region)-- optional mini-linker, such as GSG or AAA—costimulatory region (*e.g.*, CD28T or a subsequence of 4-1BB)-- optional mini-linker, such as GSG or AAA—activation domain (*e.g.*, a CD3 zeta domain, such as one of those provided herein).

[00249] Another preferred orientation and ordering for a CAR of the instant disclosure comprises two costimulatory domains and is: optional leader sequence (*e.g.*, the leader sequence of CD8a)--anti-CD70 scFv--optional mini-linker, such as GSG or AAA--hinge--optional mini-linker, such as GSG or AAA—transmembrane region (*e.g.*, CD8a transmembrane region)-- optional mini-linker, such as GSG or AAA—costimulatory region (*e.g.*, CD28T or a subsequence of 4-1BB)-- costimulatory region (*e.g.*, CD28T or a subsequence of 4-1BB)-- optional mini-linker, such as GSG or AAA—activation domain (*e.g.*, a CD3 zeta domain, such as one of those provided herein).

[00250] A more detailed description of the components of a CAR are provided below.

IV.A. Extracellular or “Hinge” Domain

[00251] In one embodiment, a CAR or TCR of the instant disclosure comprises an “extracellular” or “hinge” or “spacer” domain or region, which terms are used interchangeably herein. In another embodiment, an extracellular domain is from or derived from (*e.g.*, comprises all or a fragment of) CD2, CD3 delta, CD3 epsilon, CD3 gamma, CD4, CD7, CD8 α , CD8 β , CD11a (ITGAL), CD11b (ITGAM), CD11c (ITGAX), CD11d (ITGAD), CD18 (ITGB2), CD19 (B4), CD27 (TNFRSF7), CD28, CD28T, CD29 (ITGB1), CD30 (TNFRSF8), CD40 (TNFRSF5), CD48 (SLAMF2), CD49a (ITGA1), CD49d (ITGA4), CD49f (ITGA6), CD66a (CEACAM1), CD66b (CEACAM8), CD66c (CEACAM6), CD66d (CEACAM3), CD66e (CEACAM5), CD69 (CLEC2), CD79A (B-cell antigen receptor complex-associated alpha chain), CD79B (B-cell antigen receptor complex-associated beta chain), CD84 (SLAMF5), CD96 (Tactile), CD100 (SEMA4D), CD103 (ITGAE), CD134 (OX40), CD137 (4-1BB), CD150 (SLAMF1), CD158A (KIR2DL1), CD158B1 (KIR2DL2), CD158B2 (KIR2DL3), CD158C (KIR3DP1), CD158D (KIR2DL4), CD158F1 (KIR2DL5A), CD158F2 (KIR2DL5B), CD158K (KIR3DL2), CD160 (BY55), CD162 (SELPLG), CD226 (DNAM1), CD229 (SLAMF3), CD244 (SLAMF4), CD247 (CD3-zeta), CD258 (LIGHT), CD268 (BAFFR), CD270 (TNFSF14), CD272 (BTLA), CD276 (B7-H3), CD279 (PD-1), CD314 (NKG2D), CD319 (SLAMF7), CD335 (NK-p46), CD336 (NK-p44), CD337 (NK-p30), CD352 (SLAMF6), CD353 (SLAMF8), CD355 (CRTAM), CD357 (TNFRSF18), inducible T cell co-stimulator (ICOS), LFA-1 (CD11a/CD18), NKG2C, DAP-10, ICAM-1, NKp80 (KLRF1), IL-2R beta, IL-2R gamma, IL-7R alpha, LFA-1, SLAMF9, LAT, GADS (GrpL), SLP-76 (LCP2), PAG1/CBP, a CD83 ligand, Fc gamma receptor, MHC class 1 molecule, MHC class 2 molecule, a TNF receptor protein, an immunoglobulin protein, a cytokine receptor, an integrin, activating NK cell receptors, a Toll ligand receptor, and fragments or combinations thereof. An “extracellular” or “hinge” or “spacer” domain or region can be derived either from a natural or from a synthetic source.

[00252] In some embodiments, an “extracellular” or “hinge” or “spacer” domain or region is positioned between an antigen binding molecule (*e.g.*, an scFv) and a transmembrane domain. In this orientation the hinge domain provides distance between the antigen binding molecule and the surface of a cell membrane on which the CAR or TCR is

expressed. In some embodiments, an “extracellular” or “hinge” or “spacer” domain or region is from or derived from an immunoglobulin. In some embodiments, an “extracellular” or “hinge” or “spacer” domain or region is selected from the hinge regions of IgG1, IgG2, IgG3, IgG4, IgA, IgD, IgE, and IgM, or a fragment thereof. In other
 5 embodiments, an “extracellular” or “hinge” or “spacer” domain or region comprises, is from, or is derived from the hinge region of CD8 alpha. In some embodiments, an “extracellular” or “hinge” or “spacer” domain or region comprises, is from, or is derived from the hinge region of CD28T. In some embodiments, an “extracellular” or “hinge” or “spacer” domain or region comprises a fragment of the hinge region of CD8 alpha or a
 10 fragment of the hinge region of CD28T, wherein the fragment is anything less than the whole hinge region. In some embodiments, the fragment of the CD8 alpha hinge region or the fragment of the CD28 hinge region comprises an amino acid sequence that excludes at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at
 15 least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 amino acids at the N-terminus or C-Terminus, or both, of the CD8 alpha hinge region, or of the CD28T hinge region.

[00253] In some embodiments, an “extracellular” or “hinge” or “spacer” domain or region 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
 20 97%, at least about 98%, at least about 99%, or 100% identical to the amino acid sequence LDNEKSNGTIIHVKGKHLCPSPFPGPSKPFVVLVVVGGVLACYSLVTVAFIIFWV (SEQ ID NO: 15) or a fragment thereof. In some embodiments, an “extracellular” or “hinge” or “spacer” domain or region comprises the amino acid sequence of SEQ ID NO: 15 or a fragment thereof.

[00254] In some embodiments, an “extracellular” or “hinge” or “spacer” domain or region 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
 25 97%, at least about 98%, at least about 99%, or 100% identical to the amino acid sequence LDNEKSNGTIIHVKGKHLCPSPFPGPSK (SEQ ID NO: 15) or a fragment thereof. In
 30 some embodiments, an “extracellular” or “hinge” or “spacer” domain or region comprises the amino acid sequence of SEQ ID NO: 83, or a fragment thereof.

[00255] In some embodiments, an “extracellular” or “hinge” or “spacer” domain or region is encoded by a nucleotide sequence 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 nucleotide sequence

CTTGATAATGAAAAGTCAAACGGAACAATCATTACGTGAAGGGCAAGCACCT
CTGTCCGTCACCCTTGTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTA
5 GTGGGTGGAGTCCTCGCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCT
TCTGGGTT (SEQ ID NO: 14) or a fragment thereof. In some embodiments, an

“extracellular” or “hinge” or “spacer” domain or region is encoded by a nucleotide sequence that comprises the nucleotide sequence of SEQ ID NO: 14 or a fragment thereof.

[00256] In some embodiments, an “extracellular” or “hinge” or “spacer” domain or
10 region is encoded by a nucleotide sequence 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 nucleotide sequence

CTTGATAATGAAAAGTCAAACGGAACAATCATTACGTGAAGGGCAAGCACCT
CTGTCCGTCACCCTTGTTCCCTGGTCCATCCAAGCCA (SEQ ID NO: 82) or a
15 fragment thereof. In some embodiments, an “extracellular” or “hinge” or “spacer” domain or region is encoded by a nucleotide sequence that comprises the nucleotide sequence of SEQ ID NO: 82 or a fragment thereof.

[00257] In some embodiments, an “extracellular” or “hinge” or “spacer” domain or
20 region 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

FVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI
WAPLAGTCGVLLLSLVITLYCNHRN (SEQ ID NO: 17) or a fragment thereof. In some
25 embodiments, an “extracellular” or “hinge” or “spacer” domain or region comprises the amino acid sequence of SEQ ID NO: 17 or a fragment thereof.

[00258] In some embodiments, an “extracellular” or “hinge” or “spacer” domain or
region is encoded by a nucleotide sequence 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 nucleotide sequence

30 TTCGTGCCTGTTTTTCTGCCCCGCGAAACCCACAACCTACCCCCGCCCCCTCGGCCCC
CAACTCCTGCACCAACTATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCAT
GCCGCCCCGCGGCAGGCGGCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGC
GATATTTATATCTGGGCCCCCCTTGCCGGGACATGCGGGGTACTGCTGCTGTCT

CTGGTGATTACCCTCTACTGCAACCACAGAAAC (SEQ ID NO: 16) or a fragment thereof. In some embodiments, an “extracellular” or “hinge” or “spacer” domain or region is encoded by a nucleotide sequence that comprises the nucleotide sequence of SEQ ID NO: 16 or a fragment thereof.

5 **[00259]** In some embodiments, an “extracellular” or “hinge” or “spacer” domain or region 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 FVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD
10 (SEQ ID NO: 85) or a fragment thereof. In some embodiments, an “extracellular” or “hinge” or “spacer” domain or region comprises the amino acid sequence of SEQ ID NO: 85 or a fragment thereof.

[00260] In some embodiments, an “extracellular” or “hinge” or “spacer” domain or region 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 TTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIY (SEQ ID NO: 93) or a fragment thereof. In some embodiments, an “extracellular” or “hinge” or “spacer” domain or region comprises the amino acid sequence of SEQ ID NO: 85 or a fragment
20 thereof.

[00261] In some embodiments, an “extracellular” or “hinge” or “spacer” domain or region is encoded by a nucleotide sequence 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 nucleotide sequence
25 TTCGTGCCTGTTTTTCTGCCCCGCGAAACCCACAACCTACCCCCGCCCCCTCGGCCCC
CAACTCCTGCACCAACTATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCAT
GCCGCCCCGCGGCAGGCGGCCGTGCACACTAGAGGCCTGGACTTCGCCTGC
GAT (SEQ ID NO: 84) or a fragment thereof. In some embodiments, an “extracellular” or “hinge” or “spacer” domain or region is encoded by a nucleotide sequence that comprises
30 the nucleotide sequence of SEQ ID NO: 84 or a fragment thereof.

[00262] In some embodiments, the CD28T domain is derived from a human CD28T hinge region, and can comprise SEQ ID NO: 15. In other embodiments, the CD28T domain is derived from a rodent, murine, or primate (*e.g.*, non-human primate) CD28T hinge

region. In some embodiments, the CD28T domain is derived from a chimeric CD28T hinge region.

[00263] In some embodiments, the CD28T domain is derived from a human CD28T hinge region, and can comprise SEQ ID NO: 83. In other embodiments, the CD28T domain is derived from a rodent, murine, or primate (*e.g.*, non-human primate) CD28T hinge region. In some embodiments, the CD28T domain is derived from a chimeric CD28T hinge region.

[00264] In some embodiments, the CD8 domain is derived from a human CD8 hinge region, and can comprise SEQ ID NO: 17. In other embodiments, the CD8 domain is derived from a rodent, murine, or primate (*e.g.*, non-human primate) CD8 hinge region. In some embodiments, the CD8 domain is derived from a chimeric CD8 hinge region.

[00265] In some embodiments, the CD8 domain is derived from a human CD8 hinge region, and can comprise SEQ ID NO: 85. In other embodiments, the CD8 domain is derived from a rodent, murine, or primate (*e.g.*, non-human primate) CD8 hinge region. In some embodiments, the CD8 domain is derived from a chimeric CD8 hinge region.

[00266] In some embodiments, an extracellular domain comprises some or all of a member of the immunoglobulin family such as IgG1, IgG2, IgG3, IgG4, IgA, IgD, IgE, IgM, or fragment thereof.

[00267] Optionally, a short peptide or polypeptide linker, preferably between 2 and 10 amino acids in length can form the linkage between the hinge domain and the antigen binding domain, or between the hinge domain and a transmembrane domain of a CAR. Optionally, a short oligo- or polypeptide linker, preferably between 2 and 10 amino acids in length can form the linkage. A glycine-serine doublet (GS), glycine-serine-glycine triplet (GSG), or alanine-alanine-alanine triplet (AAA) provides a particularly suitable linker.

IV.B. Transmembrane Domain

[00268] A CAR or TCR of the instant disclosure can further comprise a transmembrane domain. A transmembrane domain can be designed to be fused to the hinge domain. It can similarly be fused to an intracellular domain, such as a costimulatory domain. In one embodiment, a transmembrane domain that naturally is associated with one of the domains in a CAR can be used. For example, a transmembrane domain can comprise the natural transmembrane region of a costimulatory domain (*e.g.*, the TM region of a CD28T or 4-1BB employed as a costimulatory domain) or the natural transmembrane

domain of a hinge region (*e.g.*, the TM region of a CD8 alpha or CD28T employed as a hinge domain).

[00269] 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. A transmembrane domain can be derived either from a natural or from a synthetic source. When the transmembrane domain is derived from a naturally-occurring source, the domain can be derived from any membrane-bound or transmembrane protein. In some embodiments, a transmembrane domain is derived from CD2, CD3 delta, CD3 epsilon, CD3 gamma, CD4, CD7, CD8 α , CD8 β , CD11a (ITGAL), CD11b (ITGAM), CD11c (ITGAX), CD11d (ITGAD), CD18 (ITGB2), CD19 (B4), CD27 (TNFRSF7), CD28, CD28T, CD29 (ITGB1), CD30 (TNFRSF8), CD40 (TNFRSF5), CD48 (SLAMF2), CD49a (ITGA1), CD49d (ITGA4), CD49f (ITGA6), CD66a (CEACAM1), CD66b (CEACAM8), CD66c (CEACAM6), CD66d (CEACAM3), CD66e (CEACAM5), CD69 (CLEC2), CD79A (B-cell antigen receptor complex-associated alpha chain), CD79B (B-cell antigen receptor complex-associated beta chain), CD84 (SLAMF5), CD96 (Tactile), CD100 (SEMA4D), CD103 (ITGAE), CD134 (OX40), CD137 (4-1BB), CD150 (SLAMF1), CD158A (KIR2DL1), CD158B1 (KIR2DL2), CD158B2 (KIR2DL3), CD158C (KIR3DP1), CD158D (KIR2DL4), CD158F1 (KIR2DL5A), CD158F2 (KIR2DL5B), CD158K (KIR3DL2), CD160 (BY55), CD162 (SELPLG), CD226 (DNAM1), CD229 (SLAMF3), CD244 (SLAMF4), CD247 (CD3-zeta), CD258 (LIGHT), CD268 (BAFFR), CD270 (TNFRSF14), CD272 (BTLA), CD276 (B7-H3), CD279 (PD-1), CD314 (NKG2D), CD319 (SLAMF7), CD335 (NK-p46), CD336 (NK-p44), CD337 (NK-p30), CD352 (SLAMF6), CD353 (SLAMF8), CD355 (CRTAM), CD357 (TNFRSF18), inducible T cell co-stimulator (ICOS), LFA-1 (CD11a/CD18), NKG2C, DAP-10, ICAM-1, NKp80 (KLRP1), IL-2R beta, IL-2R gamma, IL-7R alpha, LFA-1, SLAMF9, LAT, GADS (GrpL), SLP-76 (LCP2), PAG1/CBP, a CD83 ligand, Fc gamma receptor, MHC class 1 molecule, MHC class 2 molecule, a TNF receptor protein, an immunoglobulin protein, a cytokine receptor, an integrin, activating NK cell receptors, a Toll ligand receptor, and combinations thereof.

[00270] In some embodiments, a transmembrane domain can comprise a sequence that spans a cell membrane, but extends into the cytoplasm of a cell and/or into the extracellular space. For example, a transmembrane can comprise a membrane-spanning

sequence which itself can further comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more amino acids that extend into the cytoplasm of a cell, and/or the extracellular space. Thus, a transmembrane domain comprises a membrane-spanning region, yet can further comprise an amino acid(s) that extend beyond the internal or external surface of the membrane itself; such sequences can still be considered to be a “transmembrane domain.”

[00271] In one embodiment, a transmembrane domain of a CAR of the instant disclosure comprises the CD28T transmembrane domain. In one embodiment, the CD28T transmembrane domain comprises the transmembrane portion of the protein encoded by the nucleic acid sequence:

CTTGATAATGAAAAGTCAAACGGAACAATCATTACGTGAAGGGCAAGCACCT
CTGTCCGTCACCCTTGTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGTA
GTGGGTGGAGTCCTCGCTTGTTACTCTCTGCTCGTCACCGTGGCTTTTATAATCT
TCTGGGTT (SEQ ID NO: 14).

[00272] For example, a transmembrane domain can be encoded by a nucleic acid sequence comprising the nucleic acid sequence

TTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCGCTTGTTACTCTCTGCTCGTCA
CCGTGGCTTTTATAATCTTCTGGGTT (SEQ ID NO: 18).

[00273] In another embodiment, the CD28T transmembrane domain comprises the transmembrane amino acid sequence contained within the amino acid sequence:

LDNEKSNGTIIHVKGKHLCPSPFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWV
(SEQ ID NO: 15).

[00274] For example, a transmembrane domain can comprise the amino acid sequence FWVLVVVGGVLACYSLLVTVAFIIFWV (SEQ ID NO: 19).

[00275] In one embodiment, a transmembrane domain of a CAR of the instant disclosure comprises the CD8 transmembrane domain. In one embodiment, the CD8 transmembrane domain comprises the transmembrane portion of the protein encoded by the nucleic acid sequence:

TTCGTGCCTGTTTTTCTGCCCCGCGAAACCCACAACCTACCCCCGCCCTCGGCCCC
CAACTCCTGCACCAACTATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCAT
GCCGCCCCGCGGCAGGCGGCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGC
GATATTTATATCTGGGCCCCCCTTGCCGGGACATGCGGGGTACTGCTGCTGTCT
CTGGTGATTACCCTCTACTGCAACCACAGAAAC (SEQ ID NO: 16).

[00276] For example, a transmembrane domain can be encoded by a nucleic acid sequence comprising the nucleic acid sequence
 ATTTATATCTGGGCCCCCCTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTG
 GTGATTACC (SEQ ID NO: 20).

5 **[00277]** In another embodiment, the CD8 transmembrane domain comprises the transmembrane amino acid sequence contained within the amino acid sequence:
 FVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI
 WAPLAGTCGVLLLSLVITLYCNHRN (SEQ ID NO: 17).

[00278] For example, a transmembrane domain can comprise the amino acid
 10 sequence IYIWAPLAGTCGVLLLSLVIT (SEQ ID NO: 21).

[00279] In some embodiments, a transmembrane domain is a CD28T transmembrane domain. In some embodiments, the transmembrane domain 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
 15 about 99%, or 100% identical to the amino acid sequence
 FWVLVVVGVLACYSLLVTVAFIIFWV (SEQ ID NO: 19).

[00280] In some embodiments, the transmembrane domain comprises the amino acid sequence of SEQ ID NO: 19.

[00281] In some embodiments, the CD28T transmembrane domain is encoded by a
 20 nucleotide sequence 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 nucleotide sequence
 TTCTGGGTGTTGGTCGTAGTGGGTGGAGTCCTCGCTTGTTACTCTCTGCTCGTCA
 CCGTGGCTTTTATAATCTTCTGGGTT (SEQ ID NO: 18).

25 **[00282]** In some embodiments, the transmembrane domain is encoded by a nucleic acid sequence comprising the nucleic acid sequence of SEQ ID NO: 18.

[00283] In another embodiment, a transmembrane domain is a CD8 transmembrane domain. In some embodiments, the transmembrane domain comprises an amino acid sequence that is at least about 75%, at least about 80%, at least about 85%, at least about
 30 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 IYIWAPLAGTCGVLLLSLVIT
 (SEQ ID NO: 21).

[00284] In some embodiments, the transmembrane domain comprises the amino acid sequence of SEQ ID NO: 21.

[00285] In another embodiment, a transmembrane domain is a CD8 transmembrane domain. In some embodiments, the transmembrane domain 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 IWAPLAGTCGVLLLSLVITLYC (SEQ ID NO: 94).

[00286] In some embodiments, the transmembrane domain comprises the amino acid sequence of SEQ ID NO: 94.

[00287] In some embodiments, the CD8 transmembrane domain is encoded by a nucleotide sequence 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 nucleotide sequence ATTTATATCTGGGCCCCCCTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTG GTGATTACC (SEQ ID NO: 20).

[00288] In some embodiments, the transmembrane domain is encoded by a nucleotide sequence that comprises the nucleotide sequence of SEQ ID NO: 20.

[00289] As noted herein, the various domains of a CAR of the instant disclosure can optionally comprise amino acids in addition to those sequences provided herein. For example, a transmembrane domain can comprise amino acids that extend the domain into the cytoplasm and/or extracellular space, which can be naturally occurring in the molecule from which the transmembrane domain was derived. Accordingly, in some embodiments, a CD8 transmembrane domain further comprises the contiguous amino acid sequence LYCNHRN (SEQ ID NO: 87), encoded by the nucleic acid sequence CTCTACTGCAACCACAGAAAC (SEQ ID NO: 86), and which extend the transmembrane domain into the cytoplasm or intracellular space.

[00290] Optionally, a short peptide or polypeptide linker, preferably between 2 and 10 amino acids in length can form the linkage between the transmembrane domain and a proximal cytoplasmic signaling domain of the CAR, such as a costimulatory or activation domain, or to an antigen binding molecule (e.g., an anti-CD70 scFv). Optionally, a short oligo- or polypeptide linker, preferably between 2 and 10 amino acids in length can form

the linkage. A glycine-serine doublet (GS), glycine-serine-glycine triplet (GSG), or alanine-alanine-alanine triplet (AAA) provides a particularly suitable linker.

IV.C. Costimulatory Domain

[00291] In some embodiments, the instant disclosure comprises a CAR, wherein the CAR comprises an antigen binding molecule that specifically binds to CD70 (one or more antigen binding molecules provided herein, in the Figures and in the attached Sequence Listing), and wherein the CAR further comprises a costimulatory domain. In some embodiments, a costimulatory domain is positioned between an antigen binding molecule (*e.g.*, an scFv), and an activating domain. In some embodiments, a costimulatory domain can, but need not, comprise an extracellular domain, and/or a transmembrane domain, in addition to an intracellular signaling domain. In some embodiments, a costimulatory domain can comprise a transmembrane domain and an intracellular signaling domain. In some embodiments, a costimulatory domain can comprise an extracellular domain and a transmembrane domain. In some embodiments a costimulatory domain can comprise an intracellular signaling domain. A CAR, TCR or engineered T cell of the instant disclosure can comprise one, two or three costimulatory domains, which can be configured in series or flanking one or more other components of the CAR.

[00292] A costimulatory domain of the CARs, TCRs and engineered T cells disclosed herein can provide signaling to an activating domain, which then activates at least one of the normal effector functions of the immune cell. Effector function of a T cell, for example, can be cytolytic activity or helper activity including the secretion of cytokines.

[00293] In some embodiments, suitable costimulatory domains include (*i.e.*, comprise), but are not limited to CD2, CD3 delta, CD3 epsilon, CD3 gamma, CD4, CD7, CD8 α , CD8 β , CD11a (ITGAL), CD11b (ITGAM), CD11c (ITGAX), CD11d (ITGAD), CD18 (ITGB2), CD19 (B4), CD27 (TNFRSF7), CD28, CD28T, CD29 (ITGB1), CD30 (TNFRSF8), CD40 (TNFRSF5), CD48 (SLAMF2), CD49a (ITGA1), CD49d (ITGA4), CD49f (ITGA6), CD66a (CEACAM1), CD66b (CEACAM8), CD66c (CEACAM6), CD66d (CEACAM3), CD66e (CEACAM5), CD69 (CLEC2), CD79A (B-cell antigen receptor complex-associated alpha chain), CD79B (B-cell antigen receptor complex-associated beta chain), CD84 (SLAMF5), CD96 (Tactile), CD100 (SEMA4D), CD103 (ITGAE), CD134 (OX40), CD137 (4-1BB), CD150 (SLAMF1), CD158A (KIR2DL1), CD158B1 (KIR2DL2), CD158B2 (KIR2DL3), CD158C (KIR3DP1), CD158D (KIRDL4), CD158F1 (KIR2DL5A), CD158F2 (KIR2DL5B), CD158K (KIR3DL2), CD160 (BY55),

CD162 (SELPLG), CD226 (DNAM1), CD229 (SLAMF3), CD244 (SLAMF4), CD247 (CD3-zeta), CD258 (LIGHT), CD268 (BAFFR), CD270 (TNFSF14), CD272 (BTLA), CD276 (B7-H3), CD279 (PD-1), CD314 (NKG2D), CD319 (SLAMF7), CD335 (NK-p46), CD336 (NK-p44), CD337 (NK-p30), CD352 (SLAMF6), CD353 (SLAMF8), CD355 (CRTAM), CD357 (TNFRSF18), inducible T cell co-stimulator (ICOS), LFA-1 (CD11a/CD18), NKG2C, DAP-10, ICAM-1, NKp80 (KLRF1), IL-2R beta, IL-2R gamma, IL-7R alpha, LFA-1, SLAMF9, LAT, GADS (GrpL), SLP-76 (LCP2), PAG1/CBP, a CD83 ligand, Fc gamma receptor, MHC class 1 molecule, MHC class 2 molecule, a TNF receptor protein, an immunoglobulin protein, a cytokine receptor, an integrin, activating NK cell receptors, a Toll ligand receptor, and fragments or combinations thereof.

[00294] An example of a nucleotide sequence encoding a costimulatory domain is set forth in SEQ ID NO. 22:

AGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGAATATGACTCCACGC
CGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATTTC
GCTGCCTATCGGAGC

[00295] In one embodiment, the polynucleotide encoding costimulatory signaling 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 AGATCCAAAAGAAGCCGCCTGCTCCATAGCGATTACATGAATATGACTCCACGC CGCCCTGGCCCCACAAGGAAACACTACCAGCCTTACGCACCACCTAGAGATTTC GCTGCCTATCGGAGC (SEQ ID NO: 22).

[00296] An example of a costimulatory signaling domain is RSKRSRLHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRS (SEQ ID NO. 23).

[00297] In some embodiments, 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 RSKRSRLHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRS (SEQ ID NO: 23).

[00298] Another example of a nucleotide sequence encoding an intracellular signaling domain is CGCTTTTCCGTCGTTAAGCGGGGAGAAAAAAGCTGCTGTACATTTTCAAACAG

CCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAAGACGGCTGCTCCTGCCG
CTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTG (SEQ ID NO. 24).

[00299] In one embodiment, the polynucleotide encoding a costimulatory signaling 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

CGCTTTTCCGTCGTTAAGCGGGGAGAAAAAAGCTGCTGTACATTTTCAAACAG
CCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAAGACGGCTGCTCCTGCCG
CTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTG (SEQ ID NO: 24).

[00300] Another example of an intracellular signaling domain is set forth in SEQ ID NO. 25: RFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL.

[00301] In some embodiments, an intracellular signaling 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 RFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL (SEQ ID NO: 25).

[00302] A costimulatory signaling sequence of a CAR of the instant disclosure can be directly linked to another costimulatory domain, to an activating domain, to a transmembrane domain, or other component of the CAR in a random or specified order. Optionally, a short oligo- or polypeptide linker, preferably between 2 and 10 amino acids in length can form the linkage. A glycine-serine doublet (GS), glycine-serine-glycine triplet (GSG), or alanine-alanine-alanine triplet (AAA) provides a particularly suitable linker.

[00303] It is further noted that multiple costimulatory domains can be incorporated into a CAR or TCR of the instant disclosure. For example, a CD28T costimulatory domain and a 4-1BB costimulatory domain can both be incorporated into a CAR or TCR of the instant disclosure and, by virtue of the antigen binding component of the CAR or TCR, still be directed against CD70 and cells expressing CD70 on their surfaces.

IV.D Activating Domain

[00304] In some embodiments, intracellular domains for use in the engineered T cell of the disclosure include cytoplasmic sequences of the T cell receptor (TCR) and co-

receptors that act in concert to initiate signal transduction following antigen/receptor engagement, as well as any derivative or variant of these sequences and any synthetic sequence that has the same functional capability. 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
 5 CARs. In one embodiment, the activating domain is CD3, *e.g.*, CD3 zeta, the nucleotide sequence of which is set forth in SEQ ID NO: 26:

AGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAA
 CCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGG
 ACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAA
 10 CCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCT
 ATTCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGG
 TTTGTACCAGGGACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACAT
 GCAAGCCCTGCCACCTAGG.

[00305] In some embodiments, the polynucleotide encoding an activating domain
 15 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

AGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAA
 20 CCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGG
 ACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAA
 CCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCT
 ATTCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGG
 TTTGTACCAGGGACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACAT
 25 GCAAGCCCTGCCACCTAGG (SEQ ID NO: 26).

[00306] The corresponding amino acid of intracellular CD3 zeta is
 RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPGEMGGKPRRKNP
 QEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQ
 ALPPR (SEQ ID NO: 27).

[00307] In some embodiments, the activating domain comprises an amino acid
 30 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:

RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNP
 QEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQ
 ALPPR (SEQ ID NO: 27).

[00308] In some embodiments, the activating domain comprises an amino acid
 5 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:

RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNP
 QEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQ
 10 ALPPR (SEQ ID NO: 92).

IV.E. Leader Peptide

[00309] In some embodiments, a polynucleotide of the instant disclosure encodes a
 CAR or a TCR, wherein the CAR or the TCR comprises an antigen binding molecule that
 15 specifically binds to CD70, and wherein the CAR or the TCR further comprises a leader
 peptide (also referred to herein as a “signal peptide” or “signal sequence”). The inclusion of
 a signal sequence in a CAR or TCR of the instant disclosure is optional. If a leader
 sequence is included in a CAR or TCR of the instant disclosure, it can be expressed on the
 N terminus of the CAR or TCR. Thus, a leader sequence can be associated with the VH or
 20 VL component of an antigen binding molecule of a CAR or TCR of the instant disclosure,
 depending on which domain is at the N terminus of the CAR or TCR.

[00310] If it is desired to include a leader sequence, such a leader sequence can be
 synthesized or it can be derived from a naturally occurring molecule. For example, the
 naturally occurring 21 residue leader sequence of CD8 (*see, e.g.,* Littman *et al.*, (1985) *Cell*
 25 40:237-46) can be employed as a leader sequence in the disclosed CAR and TCR
 constructs.

[00311] Thus, in some 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
 30 about 99%, or 100% identical to the amino acid sequence MALPVTALLLPLALLLHAARP
 (SEQ ID NO: 28).

[00312] In some embodiments, the signal peptide comprises the amino acid sequence
 of SEQ ID NO: 28. In some embodiments, the leader peptide is encoded by 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 ATGGCACTCCCCGTAAGTCTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCG
 5 CACGC (SEQ ID NO: 95).

[00313] In some embodiments, the polynucleotide of the instant disclosure encodes a CAR, wherein the CAR comprises a leader peptide (P), an antigen binding molecule such as an scFv that associates with human CD70 (B), a hinge domain (H), a transmembrane domain (T), one or more costimulatory regions (C), and an activation domain (A), wherein
 10 the CAR is configured according to the following: P-B-H-T-C-A. In some embodiments the components of the CAR are optionally joined through a linker sequence, such as AAA or GSG. In some embodiments, the antigen binding molecule comprises a VH and a VL, wherein the CAR is configured according to the following: P-VH-VL-H-T-C-A or P-VL-VH-H-T-C-A. In some embodiments, the VH and the VL are connected by a linker (L)
 15 such as SEQ ID NO: 80 or 81, wherein the CAR is configured according to the following, from N-terminus to C-terminus: P-VH-L-VL-H-T-C-A or P-VH-L-VL-H-T-C-A.

[00314] In some embodiments, a polynucleotide of the instant disclosure 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
 20 about 97%, at least about 98%, at least about 99%, or 100% identical to an amino acid sequence shown in FIGURES 8A-8L and in Table 2. In some embodiments, a polynucleotide of the instant disclosure encodes a CAR, wherein the CAR comprises an amino acid sequence shown in FIGURES 8A-8L and in Table 2.

[00315]

Table 2. Example CAR Sequences

Anti- CD70 CAR		SEQ ID NO:		SEQ ID NO:
8G1.1_C 28T_28z	ATGGCACTCCCCGTAAGTCTGCTCTGCTGCC GTTGGCATTGCTCCTGCACGCCGCACGCCGC AAGAGCAGCTGGTTGAGTCTGGGGGCGGCGTC GTCCAACCCGGCCGGAGTCTGAGGTTGTCTG CGCTGCAAGCGGATTTACATTTTCATCTTACG GCATGCACTGGGTTAGGCAGGCTCCTGAAAAA GGGCTGGAGTGGGTCGCGGTGACTTGGTACGA CGGCTCCAATAAGTATTATGGGGATTCCGTGA AAGGTCGATTACAAATTAGCAGGGATAACTCC AAAAACACACTGTATCTCCAAATGAACCTCTT GAGGGCCGAGGACACGGCCGTCTATTATTGTG CAAGAGACCTCTCCGGGGCGTAAAGGGATAT GCTATGGACGTGTGGGGTCAGGGGACCACAGT TACTGTCAGTTCAGGTGGCGGTGGCAGTGGCG GCGGGGGAAGTGGAGGCGGGGGCTCTGAAATC GTTCTCACTCAGTCTCCGGGCACACTGTCCCT CAGCCCCGAGAGCGAGCCACTTTGAGCTGCC GGGCCAGCCAGTCACTTAGACGCATTTATTTG GCCTGGTATCAGCAGAAACCAGGCCAGGCGCC CAGGCTGCTGATATACGATGTGTTTCGATAGAG CCACGGGTATCCCCGATAGGTTCTCTGGCGGG GGGTCCGGGACTGACTTCACCCTCACTATATC ACGACTCGAGCCCGAAGACTTCGCAGTTTATT ATTGCCAGCAGTACTCCGACTCCCCATTCACC TTCGGCCCTGGTACCAAAGTGGATATTAAACG GGCCGCTGCCCTTGATAATGAAAAGTCAAACG GAACAATCATTACGTGAAGGGCAAGCACCTC TGTCCGTCACCCTTGTTCCTGGTCCATCCAA GCCATTCTGGGTGTTGGTCGTAGTGGGTGGAG TCTTCGCTTGTTACTCTCTGCTCGTCACCGTG GCTTTTATAATCTTCTGGGTTAGATCCAAAAG AAGCCGCTGCTCCATAGCGATTACATGAATA TGACTCCACGCCGCCCTGGCCCCACAAGGAAA CACTACCAGCCTTACGCACCACCTAGAGATTT CGCTGCCTATCGGAGCAGGGTGAAGTTTTCCA GATCTGCAGATGCACCAGCGTATCAGCAGGGC CAGAACCAACTGTATAACGAGCTCAACCTGGG ACGCAGGGAAGAGTATGACGTTTTGGACAAGC GCAGAGGACGGGACCCTGAGATGGGTGGCAAA CCAAGACGAAAAAACCCCCAGGAGGGTCTCTA TAATGAGCTGCAGAAGGATAAGATGGCTGAAG CCTATTCTGAAATAGGCATGAAAGGAGAGCGG AGAAGGGGAAAAGGGCACGACGGTTTGTACCA GGGACTCAGCACTGCTACGAAGGATACTTATG ACGCTCTCCACATGCAAGCCCTGCCACCTAGG	29	MALPVTALLLPLALLLHAARP QEQLVESGGGVVQPGRSLRLS CAASGFTFSSYGMHWVRQAPG KGLEWVAVTWYDGSNKYYGDS VKGRFTISRDN SKNTLYLQMN SLRAEDTAVYYCARDLLRGVK GYAMDVWGQGT TVTVSSGGGG SGGGSGGGGSEIVLTQSPGT LSLSPGERATLSCRASQSLRR IYLAWYQQKPGQAPRLLIYDV FDRATGIPDRFSGGSGTDFT LTISRLEPEDFAVYYCQQYSD SPFTFGPGTKVDIKRAALDN EKSNGTIIHVKGKHLCPSPLF PGPSKPFVWL VVVGGVLACYS LLVTVAFIIFWVRSKRSRLH SDYMNMTPRRPGPTRKHYPY APPRDFAAYRSRVKFSRSADA PAYQQGQNQLYNELNLGRREE YDVLDKRRGRDP EMGGKPRRK NPQEGLYNELQKDKMAEAYSE IGMKGERRRGKGHDGLYQGLS TATKDTYDALHMQALPPR	30
8G1.1_C 28T_4Bz	ATGGCACTCCCCGTAAGTCTGCTCTGCTGCC GTTGGCATTGCTCCTGCACGCCGCACGCCGC AAGAGCAGCTGGTTGAGTCTGGGGGCGGCGTC GTCCAACCCGGCCGGAGTCTGAGGTTGTCTG CGCTGCAAGCGGATTTACATTTTCATCTTACG GCATGCACTGGGTTAGGCAGGCTCCTGAAAAA GGGCTGGAGTGGGTCGCGGTGACTTGGTACGA CGGCTCCAATAAGTATTATGGGGATTCCGTGA AAGGTCGATTACAAATTAGCAGGGATAACTCC	31	MALPVTALLLPLALLLHAARP QEQLVESGGGVVQPGRSLRLS CAASGFTFSSYGMHWVRQAPG KGLEWVAVTWYDGSNKYYGDS VKGRFTISRDN SKNTLYLQMN SLRAEDTAVYYCARDLLRGVK GYAMDVWGQGT TVTVSSGGGG SGGGSGGGGSEIVLTQSPGT LSLSPGERATLSCRASQSLRR	32

	AAAAACACACTGTATCTCCAAATGAACTCCTT GAGGGCCGAGGACACGGCCGTCTATTATTGTG CAAGAGACCTCCTCCGGGGCGTAAAGGGATAT GcTATGGACGTGTGGGGTCAGGGGACCACAGT TACTGTCAGTTCAGGTGGCGGTGGCAGTGGCG GCGGGGGAAGTGGAGGCGGGGGCTCTGAAATC GTTCTCACTCAGTCTCCGGGCACACTGTCCCT CAGCCCCGGAGAGCGAGCCACTTTGAGCTGCC GGGCCAGCCAGTCACCTTAGACGCATTTATTTG GCCTGGTATCAGCAGAAACCAGGCCAGGCGCC CAGGCTGCTGATATACGATGTGTTCGATAGGG CCACGGGTATCCCCGATAGGTTCTCTGGCGGG GGGTCCGGGACTGACTTCACCCCTCACTATATC ACGACTCGAGCCCCGAAGACTTCGCAGTTTATT ATTGCCAGCAGTACTCCGACTCCCCATTACCC TTCGGCCCTGGTACCAAAGTGGATATTAAACG GGCCGCTGCCCTTGATAATGAAAAGTCAAACG GAACAATCATTACAGTGAAGGGCAAGCACCTC TGTCCGTCACCCCTTGTTCCCTGGTCCATCCAA GCCATTCTGGGTGTTGGTCGTAGTGGGTGGAG TCCTCGCTTGTTACTCTCTGCTCGTCACCGTG GCTTTTATAATCTTCTGGGTTTCGCTTTTCCGT CGTTAAGCGGGGGAGAAAAAAGCTGCTGTACA TTTTCAAACAGCCGTTTATGAGGCCGGTCCAA ACGACTCAGGAAGAAGACGGCTGCTCCTGCCG CTTTCCTGAGGAGGAGGAGGGCGGGTGCGAAC TGAGGGTGAAGTTTTCCAGATCTGCAGATGCA CCAGCGTATCAGCAGGGCCAGAACCAACTGTA TAACGAGCTCAACCTGGGACGCAGGGAAGAGT ATGACGTTTTGGACAAGCGCAGAGGACGGGAC CCTGAGATGGGTGGCAAACCAAGACGAAAAAA CCCCCAGGAGGGTCTCTATAATGAGCTGCAGA AGGATAAGATGGCTGAAGCCTATTCTGAAATA GGCATGAAAGGAGAGCGGAGAAGGGGAAAAGG GCACGACGGTTTGTACCAGGGACTCAGCACTG CTACGAAGGATACTTATGACGCTCTCCACATG CAAGCCCTGCCACCTAGG		IYLAWYQQKPGQAPRLLIYDV FDRATGIPDRFSGGSGTDFT LTISRLEPEDFAVYYCQQYSD SPFTFGPGTKVDIKRAAALDN EKSNGTIIHVKGKHLCPSPLF PGPSKPFWVLVVVGGVLACYS LLVTVAFIIFWVRFVSVKRGR KKLLYIFKQPFMRPVQTTQEE DGCSCRFPEEEEGGCELRVKF SRADAPAYQQGQNQLYNELN LGRREEYDVLDKRRGRDPMEG GKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHG LYQGLSTATKDTYDALHMQAL PPR	
8G1.1 C 8K_28z	ATGGCACTCCCCGTAAGTCTGCTGCTGCC GTTGGCATTGCTCCTGCACGCCGCACGCCGC AAGAGCAGCTGGTTGAGTCTGGGGGCGGCGTC GTCCAACCCGGCCGAGTCTGAGGTTGCTCTG CGCTGCAAGCGGATTTACATTTTCATCTTACG GCATGCACTGGGTTAGGCAGGCTCCTGGAAAA GGGCTGGAGTGGGTGCGGGTGAATTGGTACGA CGGCTCCAATAAGTATTATGGGGATTCCGTGA AAGGTCGATTACAAATTAGCAGGGATAACTCC AAAAACACACTGTATCTCCAAATGAACTCCTT GAGGGCCGAGGACACGGCCGTCTATTATTGTG CAAGAGACCTCCTCCGGGGCGTAAAGGGATAT GcTATGGACGTGTGGGGTCAGGGGACCACAGT TACTGTCAGTTCAGGTGGCGGTGGCAGTGGCG GCGGGGGAAGTGGAGGCGGGGGCTCTGAAATC GTTCTCACTCAGTCTCCGGGCACACTGTCCCT CAGCCCCGGAGAGCGAGCCACTTTGAGCTGCC GGGCCAGCCAGTCACCTTAGACGCATTTATTTG GCCTGGTATCAGCAGAAACCAGGCCAGGCGCC CAGGCTGCTGATATACGATGTGTTCGATAGGG CCACGGGTATCCCCGATAGGTTCTCTGGCGGG GGGTCCGGGACTGACTTCACCCCTCACTATATC ACGACTCGAGCCCCGAAGACTTCGCAGTTTATT	33	MALPVTALLLPLALLLHAARP QEQLVESGGGVVQPGSRSLRLS CAASGFTFSSYGMHWVRQAPG KLEWVAVTWYDGSNKYYGDS VKGRFTISRDN SKNTLYLQMN SLRAEDTAVYYCARDLLRGVK GYAMDVWQGTTVTVS SGGGG SGGGSGGGGSEIVLTQSPGT LSLSPGERATLSCRASQSLRR IYLAWYQQKPGQAPRLLIYDV FDRATGIPDRFSGGSGTDFT LTISRLEPEDFAVYYCQQYSD SPFTFGPGTKVDIKRAAAFVP VFLPAKPTTTPAPRPPTPAPT IASQPLSLRPEACRPAAGGAV HTRGLDFACDIYIWAPLAGTC GVLLLSLVITLYCNHRNRSKR SRLHSDYMNMTPRRPGPTRK HYQPYAPPRDFAAYRSRVKFS RSADAPAYQQGQNQLYNELNL GRREEYDVLDKRRGRDPMEGG KPRRKNPQEGLYNELQKDKMA EAYSEIGMKGERRRGKHDGL	34

	ATTGCCAGCAGTACTCCGACTCCCCATTTCACC TTCGGCCCTGGTACCAAAGTGGATATTAAACG GGCCGCTGCCTTCGTGCCTGTTTTTCTGCCCCG CGAAACCCACAACCTACCCCCGCCCCCTCGGCC CCAACTCCTGCACCAACTATCGCTTCCCAACC CCTGTCTCTGAGACCTGAGGCATGCCGCCCCG CGGCAGGCGGCGCCGTGCACACTAGAGGCCTG GACTTCGCCTGCGATATTTATATCTGGGCCCC CCTTGCCGGGACATGCGGGGTACTGCTGCTGT CTCTGGTGATTACCCCTCTACTGCAACCACAGA AACAGATCCAAAAGAAGCCGCTGCTCCATAG CGATTACATGAATATGACTCCACGCCGCCCTG GCCCCACAAGGAAACACTACCAGCCTTACGCA CCACCTAGAGATTTTCGCTGCCATATCGGAGCAG GGTGAAGTTTTCCAGATCTGCAGATGCACCAG CGTATCAGCAGGGCCAGAACCAACTGTATAAC GAGCTCAACCTGGGACGCAGGGAAGAGTATGA CGTTTTTGGACAAGCGCAGAGGACGGGACCCTG AGATGGGTGGCAAACCAAGACGAAAAAACCCC CAGGAGGGTCTCTATAATGAGCTGCAGAAGGA TAAGATGGCTGAAGCCTATTCTGAAATAGGCA TGAAAGGAGAGCGGAGAAGGGGAAAAGGGCAC GACGGTTTGTACCAGGGACTCAGCACTGCTAC GAAGGATACTTATGACGCTCTCCACATGCAAG CCCTGCCACCTAGG		YQGLSTATKDTYDALHMQALP PR	
8G1.1_C 8K_4Bz	ATGGCACTCCCCGTAACCTGCTCTGCTGCC GTTGGCATTTGCTCCTGCACGCCGCACGCCCGC AAGAGCAGCTGGTTGAGTCTGGGGGCGGCGTC GTCCAACCCGGCCGGAGTCTGAGGTTGTCTTG CGCTGCAAGCGGATTTACATTTTCTATCTTACG GCATGCACTGGGTTAGGCAGGCTCCTGAAAA GGGCTGGAGTGGGTCGCGGTGACTTGGTACGA CGGCTCCAATAAGTATTATGGGGATTCCGTGA AAGGTCGATTACAAATTAGCAGGGATAACTCC AAAAACACACTGTATCTCCAAATGAACTCCTT GAGGGCCGAGGACACGGCCGTCTATTATTGTG CAAGAGACCTCCTCCGGGGCGTAAAGGGATAT GCTATGGACGTGTGGGGTCAGGGGACCACAGT TACTGTCAGTTTCAAGTGGCGGTGGCAGTGGCG GCGGGGGAAGTGGAGGCGGGGCTCTGAAATC GTTCTCACTCAGTCTCCGGGCACACTGTCCCT CAGCCCCGAGAGCGAGCCACTTTGAGCTGCC GGGCCAGCCAGTCACCTAGACGCATTTATTTG GCTGGTATCAGCAGAAACCAGGCCAGGCGCC CAGGCTGCTGATATACGATGTGTTTCGATAGGG CCACGGGTATCCCCGATAGGTTCTCTGGCGGG GGGTCCGGGACTGACTTCACCCCTCACTATATC ACGACTCGAGCCCCGAAGACTTCGCAGTTTATT ATTGCCAGCAGTACTCCGACTCCCCATTTCACC TTCGGCCCTGGTACCAAAGTGGATATTAAACG GGCCGCTGCCTTCGTGCCTGTTTTTCTGCCCCG CGAAACCCACAACCTACCCCCGCCCCCTCGGCC CCAACTCCTGCACCAACTATCGCTTCCCAACC CCTGTCTCTGAGACCTGAGGCATGCCGCCCCG CGGCAGGCGGCGCCGTGCACACTAGAGGCCTG GACTTCGCCTGCGATATTTATATCTGGGCCCC CCTTGCCGGGACATGCGGGGTACTGCTGCTGT CTCTGGTGATTACCCCTCTACTGCAACCACAGA AACCGCTTTTCCGTCGTTAAGCGGGGGAGAAA AAAGCTGCTGTACATTTTCAAACAGCCGTTTA	35	MALPVTALLLPLALLLHAARP QEQLVESGGGVVQPGSLRLS CAASGFTFSSYGMHWVRQAPG KGLEWVAVTWYDGSNKYYGDS VKGRFTISRDNKNTLYLQMN SLRAEDTAVYYCARDLLRGVK GYAMDVWQGTTVTVSSGGGG SGGGSGGGGSEIVLTQSPGT LSLSPGERATLSCRASQSLRR IYLAWYQQKPGQAPRLLIYDV FDRATGIPDRFSGGSGTDFT LTISRLEPEDFAVYYCQQYSD SPFTFGPGTKVDIKRAAFVP VFLPAKPTTTPAPRPPTPAPT IASQPLSLRPEACRPAAGGAV HTRGLDFACDIYIWAPLAGTC GVLLLSLVITLYCNHRNRFVS VKRGRKLLYIFKQPFMRPVQ TTQEEDGCSRFPPEEEGGCE LRVKFSRSADAPAYQQGQNQL YNELNLGRREEYDVLDRRGR DPEMGKPRRKNPQEGLYNEL QKDKMAEAYSEIGMKGERRRG KGDGLYQGLSTATKDTYDAL HMQALPPR	36

	TGAGGCCGGTCCAAACGACTCAGGAAGAAGAC GGCTGCTCCTGCCGCTTTCCTGAGGAGGAGGA GGGCGGGTGCGAACTGAGGGTGAAGTTTTCCA GATCTGCAGATGCACCAGCGTATCAGCAGGGC CAGAACCAACTGTATAACGAGCTCAACCTGGG ACGCAGGGAAGAGTATGACGTTTTTGGACAAGC GCAGAGGACGGGACCCTGAGATGGGTGGCAAA CCAAGACGAAAAAACCCCAAGGAGGTCTCTA TAATGAGCTGCAGAAGGATAAGATGGCTGAAG CCTATTCTGAAATAGGCATGAAAGGAGAGCGG AGAAGGGGAAAAGGGCACGACGGTTTGTACCA GGGACTCAGCACTGCTACGAAGGATACTTATG ACGCTCTCCACATGCAAGCCCTGCCACCTAGG			
1C8.1.0 01_C28T _28z	ATGGCACTCCCCGTAACGTCTGCTGCTGCC GTTGGCATTGCTCCTGCACGCCGCACGCCCGC AGGTGCAGCTCCAAGAATCTGGACCGGGTCTC GTCAAGCCATCACAGACACTGTCCCTGACCTG CACCGTCTCCGGCGACTCTATCATTTTCAGGCG GCTACTATTGGTCTGGATTAGACAACATCCG GGAAAGGGTCTTGAATGGATCGGCTATATTTT CTACAGCGGGAGTACGGATTACAATCCTAGTC TCAAGAGCCGCTTACCATTTTCAGTGGATACT TCAAAAAACCAGTTTAGCCTGAAGCTGTCTTC TGTAACAGCTGCTGACACAGCCGTGTACTATT GCGCCAGGAGCGGCTACAGCTATGCCCTGTTT GACCACTGGGGGCAAGGCACTCTTGTGACGGT GTCAAGTGGAGGGGAGGATCAGGCGGCGGGG GATCCGGCGGCGGGGGTAGTGACATTCAAATG ACGCAGTCCCCAAGTTCTCTGTCCGCTAGCGT CGGCGACCGAGTGACCATCAGCTGCCGAGCAT CCCAGTTTATCGGTAGATATTTCAATTGGTAC CAGCAACAACCGGGCAAAGCGCCCAAGGTCCT GATCTACGCTGAGAGCAGTCTGCAATCCGGCG TACCTAGCAGGTTCTCCGGAAGTGGCAGCGGA ACCGAGTTCAACCCTGACAATTAGCTCCTTGCA GCCCAGGATTTTCGCTCGCTATTACTGTCAAC AGAGTTATTCAACCCCTTTTACATTCCGACAG GGAACATAAGTTGAAATTAAGAGGGCCGCTGC CCTTGATAATGAAAAGTCAAACGGAACAATCA TTCACGTGAAGGGCAAGCACCTCTGTCCGTCA CCCTTGTTCCCTGGTCCATCCAAGCCATTCTG GGTGTGGTTCGTAGTGGGTGGAGTCCCTCGCTT GTTACTCTCTGCTCGTCACCGTGGCTTTTATA ATCTTCTGGGTTAGATCCAAAAGAAGCCGCCT GCTCCATAGCGATTACATGAATATGACTCCAC GCCGCCCTGGCCCCACAAGGAAACACTACCAG CCTTACGCACCACCTAGAGATTTTCGCTGCCTA TCGGAGCAGGGTGAAGTTTTCCAGATCTGCAG ATGCACCAGCGTATCAGCAGGGCCAGAACC CTGTATAACGAGCTCAACCTGGGACGCAGGGA AGAGTATGACGTTTTTGGACAAGCGCAGAGGAC GGGACCCTGAGATGGGTGGCAAACCAAGACGA AAAAACCCCAAGGAGGTCTCTATAATGAGCT GCAGAAGGATAAGATGGCTGAAGCCTATTCTG AAATAGGCATGAAAGGAGAGCGGAGAAGGGGA AAAGGGCACGACGGTTTGTACCAGGGACTCAG CACTGCTACGAAGGATACTTATGACGCTCTCC ACATGCAAGCCCTGCCACCTAGG	37	MALPVTALLLPLALLLHAARP QVQLQESGPGLVKPSQTLST CTVSGDSIIISGGYYWSWIRQH PGKLEWIGYIFYSGSTDYNP SLKSRVTISVDTSKNQFSLKL SSVTAADTAVYYCARSGYSYA LFDHWGQGLTVTVSSGGGGSG GGSGGGGSDIQMTQSPSSLS ASVGDRTVISCRAQFIGRYF NWYQQQPGKAPKVLIIYAESSL QSGVPSRFSGSGSGTEFTLTI SSLQPEDFARYYCQQSYSTPF TFGQGTKEIKRAALDNEKS NGTIIHVKGKHLCPSPFP SKPFWVLVVVGVLACYSLLV TVAFIIFWVRSKRSRLHSDY MNMTPRRPGPTRKHYPYAPP RDFAAYSRVKFSRSADAPAY QQGQNQLYNELNLGRREEYDV LDKRRGRDPEMGGKPRRKNPQ EGLYNELQKDKMAEAYSEIGM KGERRRGKHDGLYQGLSTAT KDTYDALHMQALPPR	38
1C8.1.0 01_C28T	ATGGCACTCCCCGTAACGTCTGCTGCTGCC GTTGGCATTGCTCCTGCACGCCGCACGCCCGC	39	MALPVTALLLPLALLLHAARP QVQLQESGPGLVKPSQTLST	40

4Bz	AGGTGCAGCTCCAAGAATCTGGACCGGGTCTC GTCAAGCCATCACAGACACTGTCCCTGACCTG CACCGTCTCCGGCGACTCTATCATTTTCAGGCG GCTACTATTGGTCCTGGATTAGACAACATCCG GGAAAGGGTCTTGAATGGATCGGCTATATTTT CTACAGCGGGAGTACGGATTACAATCCTAGTC TCAAGAGCCGCGTTACCATTTTCAGTGGATACT TCAAAAAACCAGTTTAGCCTGAAGCTGTCTTC TGTAACAGCTGCTGACACAGCCGTGTACTATT GCGCCAGGAGCGGTACAGCTATGCCCTGTTT GACCACTGGGGGCAAGGCACTCTTGTGACGGT GTCAAGTGGAGGGGGAGGATCAGGCGGCGGGG GATCCGGCGGCGGGGGTAGTGACATTCAAATG ACGCAGTCCCCAAGTTCTCTGTCCGCTAGCGT CGGCGACCGAGTGACCATCAGCTGCCGAGCAT CCCAGTTTATCGGTAGATATTTCAATTGGTAC CAGCAACAACCGGGCAAAGCGCCCAAGTCTCCT GATCTACGCTGAGAGCAGTCTGCAATCCGGCG TACCTAGCAGGTTCTCCGGAAGTGGCAGCGGA ACCGAGTTCACCCCTGACAATTAGCTCCTTGCA GCCCGAGGATTTCTGCTCGCTATTACTGTCAAC AGAGTTATTCAACCCCTTTTACATTCCGACAG GGAATAAAAGTTGAAATTAAGAGGGCCGCTGC CCTTGATAATGAAAAGTCAAACGGAACAATCA TTCACGTGAAGGGCAAGCACCTCTGTCCGTCA CCCTTGTTCCCTGGTCCATCCAAGCCATTCTG GGTGTGGTCTGCTAGTGGGTGGAGTCTCTGCTT GTTACTCTCTGCTCGTCACCGTGGCTTTTATA ATCTTCTGGGTTCGCTTTTCCGTCGTTAAGCG GGGGAGAAAAAAGCTGCTGTACATTTTCAAAC AGCCGTTTATGAGGCCGGTCCAAACGACTCAG GAAGAAGACGGCTGCTCCTGCCGCTTTCTGA GGAGGAGGAGGGCGGGTGCGAACTGAGGGTGA AGTTTTCCAGATCTGCAGATGCACCAGCGTAT CAGCAGGGCCAGAACCCTGTATAACGAGCT CAACCTGGGACGCAGGGAAGAGTATGACGTTT TGGACAAGCGCAGAGGACGGGACCCCTGAGATG GGTGGCAAACCAAGACGAAAAAACCCCGAGGA GGGTCTCTATAATGAGCTGCAGAAGGATAAGA TGGCTGAAGCCTATTCTGAAATAGGCATGAAA GGAGAGCGGAGAAGGGGAAAAGGGCACGACGG TTTGTACCAGGGACTCAGCACTGCTACGAAGG ATACTTATGACGCTCTCCACATGCAAGCCCTG CCACCTAGG		CTVSGDSIISGGYYWSWIRQH PGKLEWIGYIFYSGSTDYNP SLKSRVTISVDTSKNQFSLKL SSVTAADTAVYYCARSGYSYA LFDHWGQGTLLTVSSGGGGSG GGSGGGGSDIQMTQSPSSLS ASVGDRTVISCASQFIGRYF NWYQQQPGKAPKVLIIYAESSL QSGVPSRFSGSGSGTEFTLTI SSLQPEDFARYYCQSYSTPF TFGQGTKEIKRAALDNEKS NGTIIHVKGKHLCPSPFP SKPFWVLVVVGVLACYSLLV TVAFIIFWVRFSVVKRGRKKL LYIFKQPFMRPVQTTQEEDGC SCRFPSEEEEGGCELVRKFSRS ADAPAYQQGQNQLYNELNLGR REEYDVLDRRRGRDPEMGGKP RRKNPQEGLYNELQDKMAEA YSEIGMKGERRRGKHDGLYQ GLSTATKDTYDALHMQALPPR	
1C8.1.0 01_C8K_ 28z	ATGGCACTCCCCGTAAGTCTGCTGCTGCC GTTGGCATTTGCTCCTGCACGCCGCACGCCCGC AGGTGCAGCTCCAAGAATCTGGACCGGGTCTC GTCAAGCCATCACAGACACTGTCCCTGACCTG CACCGTCTCCGGCGACTCTATCATTTTCAGGCG GCTACTATTGGTCCTGGATTAGACAACATCCG GGAAAGGGTCTTGAATGGATCGGCTATATTTT CTACAGCGGGAGTACGGATTACAATCCTAGTC TCAAGAGCCGCGTTACCATTTTCAGTGGATACT TCAAAAAACCAGTTTAGCCTGAAGCTGTCTTC TGTAACAGCTGCTGACACAGCCGTGTACTATT GCGCCAGGAGCGGTACAGCTATGCCCTGTTT GACCACTGGGGGCAAGGCACTCTTGTGACGGT GTCAAGTGGAGGGGGAGGATCAGGCGGCGGGG GATCCGGCGGCGGGGGTAGTGACATTCAAATG ACGCAGTCCCCAAGTTCTCTGTCCGCTAGCGT	41	MALPVTALLLPLALLLHAARP QVQLQESGPGLVKPSQTLST CTVSGDSIISGGYYWSWIRQH PGKLEWIGYIFYSGSTDYNP SLKSRVTISVDTSKNQFSLKL SSVTAADTAVYYCARSGYSYA LFDHWGQGTLLTVSSGGGGSG GGSGGGGSDIQMTQSPSSLS ASVGDRTVISCASQFIGRYF NWYQQQPGKAPKVLIIYAESSL QSGVPSRFSGSGSGTEFTLTI SSLQPEDFARYYCQSYSTPF TFGQGTKEIKRAAFVPVFL PAKPTTTPAPRPPTPAPTIAS QPLSLRPEACRPAAGGAVHTR GLDFACDIYIWAPLAGTCGVL	42

	CGGCGACCGAGTGACCATCAGCTGCCGAGCAT CCCAGTTTATCGGTAGATATTTCAATTGGTAC CAGCAACAACCGGGCAAAGCGCCCCAAGGTCCT GATCTACGCTGAGAGCAGTCTGCAATCCGGCG TACCTAGCAGGTTCTCCGGAAGTGGCAGCGGA ACCGAGTTCACCCTGACAATTAGCTCCTTGCA GCCCCGAGGATTTGCTCGCTATTACTGTCAAC AGAGTTATTCAACCCCTTTTACATTCCGACAG GGAACATAAGTTGAAATTAAGAGGGCCGCTGC CTTCGTGCCTGTTTTTCTGCCCGCGAAACCCA CAACTACCCCCGCCCCCTCGGCCCCCAACTCCT GCACCAACTATCGCTTCCCAACCCCTGTCTCT GAGACCTGAGGCATGCCGCCCCGCGGCAGGCG GCGCCGTGCACACTAGAGGCCCTGGACTTCGCC TGCGATATTTATATCTGGGCCCCCTTGCCGG GACATGCGGGGTACTGCTGCTGTCTCTGGTGA TTACCCCTCTACTGCAACCACAGAAACAGATCC AAAAGAAGCCGCCTGCTCCATAGCGATTACAT GAATATGACTCCACGCCGCCCTGGCCCCACAA GGAAACACTACCAGCCTTACGCACCACCTAGA GATTTGCTGCCTATCGGAGCAGGGTGAAGTT TTCCAGATCTGCAGATGCACCAGCGTATCAGC AGGGCCAGAACCAACTGTATAACGAGCTCAAC CTGGGACGCAGGGAAGAGTATGACGTTTTTGA CAAGCGCAGAGGACGGGACCCCTGAGATGGGTG GCAAACCAAGACGAAAAACCCCCAGGAGGGT CTCTATAATGAGCTGCAGAAGGATAAGATGGC TGAAGCCTATTCTGAAATAGGCATGAAAGGAG AGCGGAGAAGGGGAAAAGGGCACGACGGTTTG TACCAGGGA CT CAGCACTGCTACGAAGGATAC TTATGACGCTCTCCACATGCAAGCCCTGCCAC CTAGG		LLSLVITLYCNHRNRSKRSRL LHSDYMNMTPRRPGPTRKHYQ PYAPPRDFAAYRSRVKFSRSA DAPAYQQGQNQLYNELNLGRR EEYDVLDKRRGRDPPEMGGKPR RKNPQEGLYNELQKDKMAEAY SEIGMKGERRRGKGHDGLYQG LSTATKDTYDALHMQALPPR	
1C8.1.0 01_C8K_ 4Bz	ATGGCACTCCCCGTAAGTCTGCTGCTGCC GTTGGCATTGCTCCTGCACGCCGCACGCCCG AGGTGCAGCTCCAAGAATCTGGACCGGTCTC GTCAAGCCATCACAGACACTGTCCCTGACCTG CACCGTCTCCGGCGACTCTATCATTTAGGCG GCTACTATTGGTCTGGATTAGACAACATCCG GGAAAGGGTCTTGAATGGATCGGCTATATTTT CTACAGCGGGAGTACGGATTACAATCCTAGTC TCAAGAGCCGCGTTACCATTTAGTGGATACT TCAAAAAACAGTTTAGCCTGAAGCTGTCTTC TGTAACAGCTGCTGACACAGCCGTGTACTATT GCGCCAGGAGCGGCTACAGCTATGCCCTGTTT GACCACTGGGGGCAAGGCACTCTTGTGACGGT GTCAAGTGGAGGGGGAGGATCAGGCGGCGGGG GATCCGGCGGCGGGGGTAGTGACATTCAAATG ACGCAGTCCCCAAGTTCTCTGTCCGCTAGCGT CGGCGACCGAGTGACCATCAGCTGCCGAGCAT CCCAGTTTATCGGTAGATATTTCAATTGGTAC CAGCAACAACCGGGCAAAGCGCCCCAAGGTCCT GATCTACGCTGAGAGCAGTCTGCAATCCGGCG TACCTAGCAGGTTCTCCGGAAGTGGCAGCGGA ACCGAGTTCACCCTGACAATTAGCTCCTTGCA GCCCCGAGGATTTGCTCGCTATTACTGTCAAC AGAGTTATTCAACCCCTTTTACATTCCGACAG GGAACATAAGTTGAAATTAAGAGGGCCGCTGC CTTCGTGCCTGTTTTTCTGCCCGCGAAACCCA CAACTACCCCCGCCCCCTCGGCCCCCAACTCCT GCACCAACTATCGCTTCCCAACCCCTGTCTCT	43	MALPVTALLPLALLHAARP QVQLQESGPGLVKPSQTLST CTVSGDSIISGGYWSWIRQH PGKLEWIGYIFYSGSTDYNP SLKSRVTISVDTSKNQFSLKL SSVTAADTAVYYCARGSYSA LFDHWGQGLTVTVSSGGGGSG GGSGGGGSDIQTQSPSSLS ASVGDRTVISCRAQFIGRYF NWYQQQPGKAPKVLIIYAESSL QSGVPSRFSGSGSGTEFTLTI SSLQPEDFARYYCQQSYSTPF TFGQGTKVEIKRAAFVPVFL PAKPTTTPAPRPPTPAPTIAS QPLSLRPEACRPAAGGAVHTR GLDFACDIYIWAPLAGTCGVL LLSLVITLYCNHRNRFVVKR GRKKLLYIFKQPFMRPVQTTQ EEDGCSCRFPEEEEGGCELRV KFSRSADAPAYQQGQNQLYNE LNLGRREEYDVLDKRRGRDPE MGGKPRRKNPQEGLYNELQKD KMAEAYSEIGMKGERRRGKGH DGLYQGLSTATKDTYDALHMQ ALPPR	44

	GAGACCTGAGGCATGCCGCCCCGCGGCAGGCG GCGCCGTGCACACTAGAGGCTTGGACTTCGCC TGCGATATTTATATCTGGGCCCCCTTGCCGG GACATGCGGGGTACTGCTGCTGTCTCTGGTGA TTACCCTCTACTGCAACCACAGAAACCGCTTT TCCGTCTGTTAAGCGGGGGAGAAAAAGCTGCT GTACATTTTCAAACAGCCGTTTATGAGGCCGG TCCAAACGACTCAGGAAGAAGACGGCTGCTCC TGCCGCTTTCCTGAGGAGGAGGAGGGCGGGTG CGAACTGAGGGTGAAGTTTTCAGATCTGCAG ATGCACCAGCGTATCAGCAGGGCCAGAACCAA CTGTATAACGAGCTCAACCTGGGACGCAGGGA AGAGTATGACGTTTTGGACAAGCGCAGAGGAC GGGACCCTGAGATGGGTGGCAAACCAAGACGA AAAAACCCCGAGGAGGGTCTCTATAATGAGCT CGAGAAGGATAAGATGGCTGAAGCCTATTCTG AAATAGGCATGAAAGGAGAGCGGAGAAGGGGA AAAGGGCACGACGGTTTGTACCAGGGACTCAG CACTGCTACGAAGGATACTTATGACGCTCTCC ACATGCAAGCCCTGCCACCTAGG			
6E9.1 C 28T_28z	ATGGCACTCCCCGTAACCTGCTCTGCTGCTGCC GTTGGCATTGCTCCTGCACGCCGCACGCCCGC AGGTACACCTGGTGCAGAGCGGGGCGGAGGTC AAGAAACCGGGCGCATCCGTACGCGTGAGCTG CAAGGCTCCGGATACACTTTTACTTCTTACT ATCTGCATTGGGTGAGGACGGCACC GGTCAG GGACTGGAGTGGATGGGCATTGTGGACCCAAG CGGAGGGAGTACGT CATATGATCAGAAGTTTC AAGGTAGGTTTACCATGACACGGGACACGTCA ACGAGTACCGTCTACATGGAGCTCAGTAGTCT GCGGAGCGAAGACACCGCAGTCTACTACTGCG CACGCGATTATGGAGACTATGTCTTTGACTAT TGGGGGCGAGGGACGCTCGTGACCGTTTCAAG CGGGGGGGGCGGATCCGGTGGGGGAGGTTCCG GCGGTGGGGGTTTCACAAAGCGTACTGACACAG CCCCCGAGTGCATCCGGGACCCCGGCCAAAG GGTTACAATCAGCTGCTCTGGCAGCTCCAGTA ACATAGGTACCAACACGGTGAACCTGGTACCAG CAGTTGCCCTGGCACAGCGCTCAGCTGCTCAT CTATATCAACAATCAGCGGCCAAGTGGCGTGC CCGATAGATTCTCAGGCTCAAAGAGCGGAACC AGCGCTAGCTTGGCAATCAGTGGCCTTCAATC CGAAGACGAAGCCGATTACTATTGTGCGACCT GGGACGATAGCCTGAACGGCCCCGTCTGGGGC GGCGGGACGAACTGACAGTGTGGGCGCCGC TGCCCTTGATAATGAAAAGTCAAACGGAACAA TCATTCACGTGAAGGGCAAGCACCTCTGTCCG TCACCCTTGTTCCTGGTCCATCCAAGCCATT CTGGGTGTTGGTCCGTAGTGGGTGGAGTCCCTCG CTTGTTACTCTCTGCTCGTCACCGTGGCTTTT ATAATCTTCTGGGTTAGATCCAAAAGAAGCCG CCTGCTCCATAGCGATTACATGAATATGACTC CACGCCGCCCTGGCCCCACAAGGAAACACTAC CAGCCTTACGCACCACCTAGAGATTTCTGCTGC CTATCGGAGCAGGGTGAAGTTTTCCAGATCTG CAGATGCACCAGCGTATCAGCAGGGCCAGAAC CAACTGTATAACGAGCTCAACCTGGGACGCAG GGAAGAGTATGACGTTTTTGGACAAGCGCAGAG GACGGGACCCTGAGATGGGTGGCAAACCAAGA CGAAAAACCCCGAGGAGGTCTCTATAATGA	45	MALPVTALLLPLALLLHAARP QVHLVQSGAEVKKPGASVRVS CKASGYTFTSYLHWVRQAPG QGLEWMGIVDPSSGSTSYDQK FQGRFTMTRDTSTSTVYMELS SLRSED TAVYYCARDYGDYVF DYWGQGT LVTVSSGGGGSGGG GSGGGGSQSVLTQPPSASGTP GQRV TISCSGSSSNIGTNTVN WYQQLPGTAPQLLIYINNQR SGVPDRFSGSKSGTSASLAIS GLQSEDEADYYCATWDDSLNG PVVGGGKLTVLGAAALDNEK SNGTIIHVKGKHLCPSP LFP PSKPFWVLVVGGVLACYSLL VTVAFIIFWVRSKRSRLHSD YMNMTPRRPGPTRKHYQPYAP PRDFAAYRSRVKFSRSADAPA YQQGQNQLYNELNLGRREEYD VLDKRRGRDPEMGGKPRRKNP QEGLYNELQKDKMAEAYSEIG MKGERRRGKGDGLYQGLSTA TKDTYDALHMQALPPR	46

	GCTGCAGAAGGATAAGATGGCTGAAGCCTATT CTGAAATAGGCATGAAAGGAGAGCGGAGAAGG GGAAAAGGGCACGACGGTTTGTACCAGGGACT CAGCACTGCTACGAAGGATACTTATGACGCTC TCCACATGCAAGCCCTGCCACCTAGG			
6E9.1_C 28T_4Bz	ATGGCACTCCCCGTAAGTCTGCTGCTGCC GTTGGCATTGCTCCTGCACGCCGCACGCCGC AGGTACACCTGGTGCAGAGCGGGCGGAGGTC AAGAAACCGGGCGCATCCGTACGCGTGAGCTG CAAGGCCCTCCGGATACACTTTTACTTCTTACT ATCTGCATTGGGTGAGGCAGGCACCGGGTCAG GGACTGGAGTGGATGGGCATTGTGGACCCAAG CGGAGGGAGTACGTCATATGATCAGAAGTTTC AAGGTAGGTTTACCATGACACGGGACACGTCA ACGAGTACCGTCTACATGGAGCTCAGTAGTCT GCGGAGCGAAGACACCGCAGTCTACTACTCG CACGCGATTATGGAGACTATGTCTTTGACTAT TGGGGGCGAGGGACGCTCGTGACCGTTTCAAG CGGGGGGGCGGATCCGGTGGGGGAGGTTCCG GCGGTGGGGGTTCAAAAGCGTACTGACACAG CCCCCGAGTGCATCCGGGACCCCGGCCAAAG GGTTACAATCAGCTGCTCTGGCAGCTCCAGTA ACATAGGTACCAACACGGTGAAGTGGTACCAG CAGTTGCCTGGCACAGCGCCTCAGCTGCTCAT CTATATCAACAATCAGCGGCCAAGTGGCGTGC CCGATAGATTCTCAGGCTCAAAGAGCGGAACC AGCGCTAGCTTGGCAATCAGTGGCCTTCAATC CGAAGACGAAGCCGATTACTATTGTGCGACCT GGGACGATAGCCTGAACGGCCCCGTCGTGGGC GGCGGGACGAAACTGACAGTGTGGGCGCCGC TGCCCTTGATAATGAAAAGTCAAACGGAACAA TCATTCACGTGAAGGGCAAGCACCTCTGTCCG TCACCTTGTTCCTGGTCCATCCAAGCCATT CTGGGTGTTGGTCTAGTGGGTGGAGTCCCTCG CTGTTACTCTCTGCTCGTCACCGTGGCTTTT ATAATCTTCTGGGTTTCGCTTTTCCGTCGTTAA GCGGGGGAGAAAAAGCTGCTGTACATTTTCA AACAGCCGTTTATGAGGCCGGTCCAAACGACT CAGGAAGAAGACGGCTGCTCCTGCCGCTTTCC TGAGGAGGAGGAGGGCGGGTGCAGACTGAGGG TGAAGTTTTCCAGATCTGCAGATGCACCAGCG TATCAGCAGGGCCAGAACCAACTGTATAACGA GCTCAACCTGGGACGCAGGGAAGAGTATGACG TTTTGGACAAGCGCAGAGGACGGGACCCCTGAG ATGGGTGGCAAACCAAGACGAAAAAACCCCA GGAGGGTCTCTATAATGAGCTGCAGAAGGATA AGATGGCTGAAGCCTATTCTGAAATAGGCATG AAAGGAGAGCGGAGAAGGGGAAAAGGGCACGA CGGTTTGTACCAGGGACTCAGCACTGCTACGA AGGATACTTATGACGCTCTCCACATGCAAGCC CTGCCACCTAGG	47	MALPVTALLLPLALLLHAARP QVHLVQSGAEVKKPGASVRVS CKASGYTFTSYLHWVRQAPG QGLEWMGIVDPSGGSTSVDQK FQGRFTMTRDTSTSTVYMELS SLRSEDVAVYYCARDYGDYVF DYWGQGTLLTVSSGGGGSGGG GSGGGGSQSVLTQPPSASGTP GQRTVISCSSSSNIGTNTVN WYQQLPGTAPQLLIYINNORP SGVPDRFSGSKSGTSASLAIS GLQSEADYYCATWDDSLNG PVVGGGKLTVLGAAALDNEK SNGTIIHVKGKHLCPSPFP PSKPFVVLVVVGGVLACYSLL VTVAFIIFWVRFVVKRGRKK LLYIFKQPFMRPVQTTQEDG CSCRFEEEEEGGCELRVKFSR SADAPAYQQGNQLYNELNLG RREEYDVLDKRRGRDP PEMGGK PRRKNPQEGLYNELQKDKMAE AYSEIGMKGERRRGKHDGLY QGLSTATKDTYDALHMQALPP R	48
6E9.1_C 8K_28z	ATGGCACTCCCCGTAAGTCTGCTGCTGCC GTTGGCATTGCTCCTGCACGCCGCACGCCGC AGGTACACCTGGTGCAGAGCGGGCGGAGGTC AAGAAACCGGGCGCATCCGTACGCGTGAGCTG CAAGGCCCTCCGGATACACTTTTACTTCTTACT ATCTGCATTGGGTGAGGCAGGCACCGGGTCAG GGACTGGAGTGGATGGGCATTGTGGACCCAAG CGGAGGGAGTACGTCATATGATCAGAAGTTTC AAGGTAGGTTTACCATGACACGGGACACGTCA	49	MALPVTALLLPLALLLHAARP QVHLVQSGAEVKKPGASVRVS CKASGYTFTSYLHWVRQAPG QGLEWMGIVDPSGGSTSVDQK FQGRFTMTRDTSTSTVYMELS SLRSEDVAVYYCARDYGDYVF DYWGQGTLLTVSSGGGGSGGG GSGGGGSQSVLTQPPSASGTP GQRTVISCSSSSNIGTNTVN	50

	ACGAGTACCGTCTACATGGAGCTCAGTAGTCT GCGGAGCGAAGACACCGCAGTCTACTACTGCG CACGCGATTATGGAGACTATGTCTTTGACTAT TGGGGGCGAGGGGACGCTCGTGACCGTTTCAAG CGGGGGGGGCGGATCCGGTGGGGGAGGTTCCG GCGGTGGGGGTTACAAAGCGTACTGACACAG CCCCCGAGTGCATCCGGGACCCCGGCCAAAG GGTTACAATCAGCTGCTCTGGCAGCTCCAGTA ACATAGGTACCAACACGGTGAACCTGGTACCAG CAGTTGCCTGGCACAGCGCCTCAGCTGCTCAT CTATATCAACAATCAGCGGCCAAGTGGCGTGC CCGATAGATTCTCAGGCTCAAAGAGCGGAACC AGCGCTAGCTTGGCAATCAGTGGCCTTCAATC CGAAGACGAAGCCGATTACTATTGTGCGACCT GGGACGATAGCCTGAACGGCCCCGTCGTGGG GGCGGGACGAAACTGACAGTGTGGGCGCCGC TGCCCTTCGTGCCTGTTTTCTGCCCGCGAAAC CCACAACCTACCCCGCCCCCTCGGCCCCCAACT CCTGCACCAACTATCGCTTCCCAACCCCTGTC TCTGAGACCTGAGGCATGCCGCCCCGCGGCAG GCGGCGCCGTGCACACTAGAGGCCTGGACTTC GCCTGCGATATTTATATCTGGGCCCCCTTGC CGGGACATGCGGGGTACTGCTGCTGTCTCTGG TGATTACCTCTACTGCAACCACAGAAACAGA TCCAAAAGAAGCCGCTGCTCCATAGCGATTA CATGAATATGACTCCACGCCGCCCTGGCCCCA CAAGGAAACACTACCAGCCTTACGCACCACCT AGAGATTTTCGCTGCCTATCGGAGCAGGGTGAA GTTTTCCAGATCTGCAGATGCACCAGCGTATC AGCAGGGCCAGAACCACCTGTATAACGAGCTC AACCTGGGACGCGAGGGAAGAGTATGACGTTTT GGACAAGCGCAGAGGACGGGACCCTGAGATGG GTGGCAAACCAAGACGAAAAAACCCCGAGGAG GGTCTCTATAATGAGCTGCAGAAGGATAAGAT GGCTGAAACCTATTCTGAAATAGGCATGAAAG GAGAGCGGAGAAGGGGAAAAGGGCACGACGGT TTGTACCAGGGACTCAGCACTGCTACGAAGGA TACTTATGACGCTCTCCACATGCAAGCCCTGC CACCTAGG		WYQQLPGTAPQLLIYINNQR SGVPDRFSGSKSGTSASLAIS GLQSEDEADYYCATWDDSLNG PVVGGGKLTVLGAAAFVPVF LPAKPTTTPAPRPPTPAPTIA SQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGV LLLSLVITLYCNHRNRSKR LLHSDYMNMTPRRPGPTRKHY QPYAPPRDFAAYRSRVKFSRS ADAPAYQQGQNQLYNELNLGR REEYDVLDKRRGRDP RRKNPQEGLYNELQDKMAEA YSEIGMKGERRRGKGDGLYQ GLSTATKDTYDALHMQALPPR	
6E9.1_C 8K_4Bz	ATGGCACTCCCCGTAACCTGCTCTGCTGCTGCC GTTGGCATTGCTCCTGCACGCCGCACGCCCGC AGGTACACCTGGTGCAGAGCGGGGCGGAGGTC AAGAAACCGGGCGCATCCGTACGCGTGAGCTG CAAGGCTCCGGATACACTTTTACTTCTTACT ATCTGCATTGGGTGAGGCAGGCACCGGGTCAG GGACTGGAGTGGATGGGCATTGTGGACCCAAG CGGAGGGAGTACGTATATGATCAGAAGTTTC AAGGTAGGTTTACCATGACACGGGACACGTCA ACGAGTACCGTCTACATGGAGCTCAGTAGTCT GCGGAGCGAAGACACCGCAGTCTACTACTGCG CACGCGATTATGGAGACTATGTCTTTGACTAT TGGGGGCGAGGGGACGCTCGTGACCGTTTCAAG CGGGGGGGGCGGATCCGGTGGGGGAGGTTCCG GCGGTGGGGGTTACAAAGCGTACTGACACAG CCCCCGAGTGCATCCGGGACCCCGGCCAAAG GGTTACAATCAGCTGCTCTGGCAGCTCCAGTA ACATAGGTACCAACACGGTGAACCTGGTACCAG CAGTTGCCTGGCACAGCGCCTCAGCTGCTCAT CTATATCAACAATCAGCGGCCAAGTGGCGTGC CCGATAGATTCTCAGGCTCAAAGAGCGGAACC	51	MALPVTALLLPLALLLHAARP QVHLVQSGAEVKKPGASVRVS CKASGYTFTSYLHWVRQAPG QGLEWMGIVDPSSGGSYSYDQK FQGRFTMTRDTSTSTVYMELS SLRSEDYAVYYCARDYGDYVF DYWGQGT LVTVSSGGGGSGGG GSGGGGSQSVLTQPPSASGTP GQRTVITSCGSSSNIGTNTVN WYQQLPGTAPQLLIYINNQR SGVPDRFSGSKSGTSASLAIS GLQSEDEADYYCATWDDSLNG PVVGGGKLTVLGAAAFVPVF LPAKPTTTPAPRPPTPAPTIA SQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGV LLLSLVITLYCNHRNRSVVK RGRKKLLYIFKQPFMRPVQTT QEEDGCSCRFP EEEEGGCELR VKFSRSADAPAYQQGQNQLYN ELNLGRREEYDVLDKRRGRDP	52

AGCGCTAGCTTGGCAATCAGTGGCCTTCAATC CGAAGACGAAGCCGATTACTATTGTGCGACCT GGGACGATAGCCTGAACGGCCCCGTCGTGGGC GGCGGGACGAACTGACAGTGTTGGGCGCCGC TGCCTTCGTGCCTGTTTTTCTGCCCCGAAAC CCACAAC TACCCCGCCCCCTCGGCCCAACT CCTGCACCAACTATCGCTTCCCAACCCCTGTC TCTGAGACCTGAGGCATGCCGCCCGCGGCAG GCGGCGCCGTGCACACTAGAGGCCTGGACTTC GCCTGCGATATTTATATCTGGGCCCCCTTGC CGGGACATGCGGGGTACTGCTGCTGTCTCTGG TGATTACCCCTCTACTGCAACCACAGAAACCGC TTTTCCGTCGTTAAGCGGGGGAGAAAAAGCT GCTGTACATTTTCAAACAGCCGTTTATGAGGC CGGTCCAAACGACTCAGGAAGAAGACGGCTGC TCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGG GTGCGAACTGAGGGTGAAGTTTTCCAGATCTG CAGATGCACCAGCGTATCAGCAGGGCCAGAAC CAACTGTATAACGAGCTCAACCTGGGACGCAG GGAAGAGTATGACGTTTTTGGACAAGCGCAGAG GACGGGACCCCTGAGATGGGTGGCAAACCAAGA CGAAAAAACCCCCAGGAGGGTCTCTATAATGA GCTGCAGAAGGATAAGATGGCTGAAGCCTATT CTGAAATAGGCATGAAAGGAGAGCGGAGAAGG GGAAGAGGGCACGACGGTTTGTACCAGGGACT CAGCACTGCTACGAAGGATACTTATGACGCTC TCCACATGCAAGCCCTGCCACCTAGG	EMGGKPRRKNPQEGLYNELQK DKMAEAYSEIGMKGERRRGKG HDGLYQGLSTATKDYDALHM QALPPR
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[00316] In some embodiments, a polynucleotide of the instant disclosure 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: 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52. In some embodiments, the CAR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52. In one embodiment, the CAR comprises the amino acid sequence of SEQ ID NO: 30. In another embodiment, the CAR comprises the amino acid sequence of SEQ ID NO: 32. In another embodiment, the CAR comprises the amino acid sequence of SEQ ID NO: 34. In another embodiment, the CAR comprises the amino acid sequence of SEQ ID NO: 36. In another embodiment, the CAR comprises the amino acid sequence of SEQ ID NO: 38. In another embodiment, the CAR comprises the amino acid sequence of SEQ ID NO: 40. In another embodiment, the CAR comprises the amino acid sequence of SEQ ID NO: 42. In another embodiment, the CAR comprises the amino acid sequence of SEQ ID NO: 44. In another embodiment, the CAR comprises the amino acid sequence of SEQ ID NO: 46.

48. In another embodiment, the CAR comprises the amino acid sequence of SEQ ID NO: 50. In another embodiment, the CAR comprises the amino acid sequence of SEQ ID NO: 52.

[00317] In some embodiments, a polynucleotide of the instant disclosure encoding a CAR comprises an nucleotide sequence at least about 50%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 85%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 and 51. In some embodiments, the polynucleotide comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 29. In one embodiment, the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 31. In another embodiment, the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 33. In another embodiment, the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 35. In another embodiment, the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 37. In another embodiment, the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 39. In another embodiment, the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 41. In another embodiment, the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 43. In another embodiment, the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 45. In another embodiment, the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 47. In another embodiment, the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 49. In another embodiment, the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 51.

IV. Vectors, Cells, and Pharmaceutical Compositions

[00318] In some aspects, provided herein are vectors comprising a polynucleotide of the instant disclosure. In some embodiments, the instant disclosure is directed to a vector or a set of vectors comprising a polynucleotide encoding a CAR or a TCR, as described herein. In other embodiments, the instant disclosure is directed to a vector or a set of vectors comprising a polynucleotide encoding an antibody or an antigen binding molecule thereof that specifically binds to CD70, as disclosed herein.

[00319] Any vector known in the art can be suitable for the instant disclosure. In some embodiments, the vector is a viral vector. In some embodiments, the vector is a

retroviral vector, a DNA vector, a murine leukemia virus vector, an SFG vector, a plasmid, a RNA vector, an adenoviral vector, a baculoviral vector, an Epstein Barr viral vector, a papovaviral vector, a vaccinia viral vector, a herpes simplex viral vector, an adenovirus associated vector (AAV), a lentiviral vector, or any combination thereof. In some
5 embodiments of the instant disclosure one, two or more vectors can be employed. For example, in one embodiment, one or more components of a CAR or TCR can be disposed on one vector, while one or more different components of a CAR or TCR can be disposed on a different vector.

[00320] In other aspects, provided herein are cells comprising a polynucleotide or a
10 vector of the instant disclosure. In some embodiments, the instant disclosure is directed to host cells, such as *in vitro* cells, comprising a polynucleotide encoding a CAR or a TCR, as described herein. In some embodiments, the instant disclosure is directed to host cells, *e.g.*, *in vitro* cells, comprising a polynucleotide encoding an antibody or an antigen binding molecule thereof that specifically binds to CD70, as disclosed herein.

[00321] In other embodiments, the instant disclosure is directed to *in vitro* cells
15 comprising a polypeptide encoded by a polynucleotide encoding a CAR or a TCR, as disclosed herein. In other embodiments, the instant disclosure is directed to cells, *in vitro* cells, comprising a polypeptide encoded by a polynucleotide encoding an antigen binding molecule that specifically binds to CD70, as disclosed herein.

[00322] Any cell can be used as a host cell for the polynucleotides, the vectors, or the
20 polypeptides of the instant disclosure. 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
25 embodiments, the host 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

some 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.

[00323] A cell of the instant disclosure can 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 some 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 some 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.

[00324] In some 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 CD28⁺, CD4⁺, CD8⁺, CD45RA⁺, and CD45RO⁺ T cells can be further isolated by positive or negative selection techniques known in the art. For example, enrichment of a T cell population by negative selection can be accomplished with a combination of antibodies directed to surface markers unique to the negatively selected cells. In some embodiments, cell sorting and/or selection via negative magnetic immunoadherence or flow cytometry that uses a cocktail of monoclonal antibodies directed to cell surface markers present on the cells negatively selected can be used. For example, to enrich for CD4⁺ cells by negative selection, a monoclonal antibody cocktail typically includes antibodies to CD14, CD20, CD11b, CD16, HLA-DR, and CD8. In some embodiments, flow cytometry and cell sorting

are used to isolate cell populations of interest for use in the instant disclosure. Using these standard techniques, the engineered T cells administered to a patient when performing the methods provided herein can comprise any desired proportion of cells. For example, it may be desirable to provide only engineered CD8⁺ cells to a patient, only engineered CD4⁺ cells to a patient, or a desired ratio of CD4⁺ to CD8⁺ cells, such as equal numbers of CD4⁺ and CD8⁺ cells.

[00325] 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 some 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.

[00326] In some embodiments, CD8⁺ cells are further sorted into naive, central memory, and effector cells by identifying cell surface antigens that are associated with each of these types of CD8⁺ cells. In some embodiments, the expression of phenotypic markers of central memory T cells includes CD3, CD28, CD44, CD45RO, CD45RA and CD127 and are negative for granzyme B. In some embodiments, central memory T cells are CD3⁺, CD28⁺, CD44^{hi}, CD45RO^{hi}, CD45RA^{low} and CD127^{hi} CD8⁺ T cells. In some embodiments, effector T cells are negative for CD62L, CCR7, CD28, and CD127 and positive for granzyme B and perforin. In some embodiments, CD4⁺ T cells are further sorted into subpopulations. For example, CD4⁺ T helper cells can be sorted into naive, central memory, and effector cells by identifying cell populations that have cell surface antigens.

[00327] In some embodiments, the immune cells, *e.g.*, T cells, are genetically modified following isolation using known methods, or the immune cells are activated and expanded (or differentiated in the case of progenitors) *in vitro* prior to being genetically modified. In another embodiment, the immune cells, *e.g.*, T cells, are genetically modified with the chimeric antigen receptors described herein (*e.g.*, transduced with a viral vector comprising one or more nucleotide sequences encoding a CAR) and then are activated and/or expanded *in vitro*. Methods for activating and expanding T cells are known in the art and are described, *e.g.*, in U.S. Patent Nos. 6,905,874; 6,867,041; and 6,797,514; and PCT Publication No. WO 2012/079000, the contents of which are hereby incorporated by reference in their entirety. Generally, such methods include contacting PBMC or isolated T cells with a stimulatory agent and costimulatory agent, such as anti-CD3 and anti-CD28 antibodies, generally attached to a bead or other surface, in a culture medium with

appropriate cytokines, such as IL-2. Anti-CD3 and anti-CD28 antibodies attached to the same bead serve as a “surrogate” antigen presenting cell (APC). One example is The Dynabeads® system, a CD3/CD28 activator/stimulator system for physiological activation of human T cells. In other embodiments, the T cells are activated and stimulated to proliferate with feeder cells and appropriate antibodies and cytokines using methods such as those described in U.S. Patent Nos. 6,040,177 and 5,827,642 and PCT Publication No. WO 2012/129514, the contents of which are hereby incorporated by reference in their entirety.

[00328] In some 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. In another embodiment, the T cells are derived from pluripotent stem cells maintained under conditions favorable to the differentiation of the stem cells to T cells.

[00329] Other aspects of the instant disclosure are directed to compositions comprising a polynucleotide provided herein, a vector provided herein, a polypeptide provided herein, or an *in vitro* cell provided 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, wherein the CAR or the TCR comprises an antigen binding molecule that specifically binds to CD70. In another embodiment, the composition comprises a CAR or a TCR encoded by a polynucleotide provided herein, wherein the CAR or the TCR comprises an antigen binding molecule that specifically binds to CD70. In another embodiment, the composition comprises a T cell comprising a polynucleotide encoding a CAR or a TCR, wherein the CAR or the TCR comprises an antigen binding molecule that specifically binds to CD70. In another embodiment, the composition comprises an antibody or an antigen binding molecule thereof encoded by a polynucleotide provided herein. In another embodiment, the composition comprises an *in vitro* cell comprising a polynucleotide encoding an antibody or an antigen binding molecule thereof encoded by a polynucleotide provided herein. In another embodiment, the composition comprises a CAR or a TCR provided herein, wherein the CAR or the TCR comprises a component comprising an antigen binding molecule that specifically binds to CD70.

[00330] In some embodiments, the composition includes more than one different CAR or the TCR comprising a component comprising an antigen binding molecule that specifically binds to CD70. In some embodiments, the composition included more than one CAR or the TCR comprising a component comprising an antigen binding molecule that specifically binds to CD70, wherein the antigen binding molecules to CD70 bind more than one epitope. In some embodiments, the CARs or the TCRs comprising a component comprising an antigen binding molecule that specifically binds to CD70 will not compete with one another for binding to CD70. In some embodiments, any of the CARs or the TCRs comprising a component comprising an antigen binding molecule that specifically binds to CD70 provided herein are combined together in a pharmaceutical composition.

[00331] In other embodiments, the composition is selected for parenteral delivery. The preparation of such pharmaceutically acceptable compositions is within the ability of one skilled in the art. In some 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 some embodiments, when parenteral administration is contemplated, the composition is in the form of a pyrogen-free, parenterally acceptable aqueous solution comprising a desired CAR or the TCR comprising a component comprising an antigen binding molecule that specifically binds to CD70, with or without additional therapeutic agents, in a pharmaceutically acceptable vehicle. In some embodiments the vehicle for parenteral injection is sterile distilled water in which a CAR or the TCR comprising a component comprising an antigen binding molecule that specifically binds to CD70, with or without at least one additional therapeutic agent, is formulated as a sterile, isotonic solution, properly preserved. In some embodiments, the preparation involves the formulation of the desired CAR or the TCR comprising a component comprising an antigen binding molecule that specifically binds to CD70 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 some embodiments, implantable drug delivery devices are used to introduce the desired molecule.

V. Methods of Using the Disclosed Antigen Binding Molecules, CARs and TCR

[00332] Another aspect of the instant disclosure 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, wherein the CAR or the TCR comprises an antigen binding molecule that specifically binds to CD70, as disclosed herein. In some embodiments, the method comprises transducing a cell with a vector comprising a polynucleotide encoding a CAR or a TCR, wherein the CAR or the TCR comprises an antigen binding molecule that specifically binds to CD70. In other embodiments, the method comprises transducing a cell with a polynucleotide encoding a CAR or TCR comprising an antigen binding molecule that specifically binds to CD70, as disclosed herein. In some embodiments, the method comprises transducing a cell with a vector comprising the polynucleotide encoding the CAR or the TCR comprises an antigen binding molecule that specifically binds to CD70, as described herein. In some embodiments, the method further comprises isolating the cell.

[00333] Another aspect of the instant disclosure is directed to a method of inducing an immunity against a tumor comprising administering to a subject an effective amount of a cell comprising a polynucleotide described herein, a vector described herein, or a CAR or a TCR described herein. In one embodiment, the method comprises administering to a subject an effective amount of a cell comprising a polynucleotide encoding a CAR or a TCR, wherein the CAR or TCR comprises an antigen binding molecule that specifically binds to CD70, as 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, wherein the CAR or the TCR comprises an antigen binding molecule that specifically binds to CD70, as disclosed herein. In another embodiment, the method comprises administering to a subject an effective amount of a cell comprising a CAR or a TCR encoded by a polynucleotide disclosed herein, wherein the CAR or the TCR comprises an antigen binding molecule that specifically binds to CD70.

[00334] In other embodiments, the method comprises administering to a subject an effective amount of a cell comprising a polynucleotide encoding a CAR or TCR comprises an antigen binding molecule that specifically binds to CD70, as 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 TCR comprising an antigen binding molecule that specifically binds to CD70, as disclosed herein. In another embodiment, the method comprises administering to a subject an effective amount of a cell comprising an antibody or antigen binding molecule thereof encoded by a polynucleotide

disclosed herein (*e.g.*, a CAR or TCR), wherein the antibody or antigen binding molecule thereof specifically binds to CD70.

[00335] Another aspect of the instant disclosure is directed to a method of inducing an immune response in a subject comprising administering an effective amount of the engineered immune cells of the present application. In some embodiments, the immune response is a T cell-mediated immune response. In some embodiments, the T cell-mediated immune response is directed against one or more target cells. In some embodiments, the engineered immune cell comprises a CAR or a TCR, such as those provided herein. In some embodiments, the target cell is a tumor cell.

[00336] Another aspect of the instant disclosure is directed to a method for treating or preventing a malignancy, said method comprising administering to a subject in need thereof an effective amount of at least one isolated antigen binding molecule described herein or at least one immune cell, wherein the immune cell comprises at least one CAR, TCR, and/or isolated antigen binding molecule as described herein.

[00337] Another aspect of the instant disclosure is directed to a method of treating a hyperproliferative disorder or an inflammatory disease in a subject in need thereof comprising administering to the subject a polynucleotide disclosed herein, a vector disclosed herein, a CAR or a TCR disclosed herein, a cell disclosed herein, or a composition disclosed herein. In some embodiments, the inflammatory disease is selected from the group consisting of rheumatoid arthritis, psoriasis, allergies, asthma, autoimmune diseases such as Crohn's, IBD, fibromyalgia, mastocytosis, Celiac disease, and any combination thereof.

[00338] Another aspect of the instant disclosure is directed to a method of treating a cancer in a subject in need thereof comprising administering to the subject a polynucleotide disclosed herein, a vector disclosed herein, a CAR or a TCR disclosed herein, a cell disclosed herein, or a composition disclosed herein. In one embodiment, the method comprises administering a polynucleotide encoding a CAR or a TCR, wherein the CAR or the TCR comprises an antigen binding molecule that specifically binds to CD70, as disclosed herein. In another embodiment, the method comprises administering a vector comprising a polynucleotide encoding a CAR or a TCR, wherein the CAR or the TCR comprises an antigen binding molecule that specifically binds to CD70, as disclosed herein. In another embodiment, the method comprises administering a CAR or a TCR encoded by a polynucleotide disclosed herein, wherein the CAR or the TCR comprises an antigen binding

molecule that specifically binds to CD70. In another embodiment, the method comprises administering a cell comprising the polynucleotide, or a vector comprising the polynucleotide, encoding a CAR or a TCR, wherein the CAR or the TCR comprises an antigen binding molecule that specifically binds to CD70, as disclosed herein. In other
5 embodiments, the method comprises administering a polynucleotide encoding a CAR or a TCR, wherein the CAR or the TCR comprises an antigen binding molecule that specifically binds to CD70, as disclosed herein. In another embodiment, the method comprises administering a vector comprising a polynucleotide encoding a CAR or a TCR, wherein the CAR or the TCR comprises an antigen binding molecule that specifically binds to CD70, as
10 disclosed herein. In another embodiment, the method comprises administering an antibody, CAR or TCR, wherein the CAR or the TCR comprises an antigen binding molecule that specifically binds to CD70, and is 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 an antibody, CAR or TCR, wherein the
15 CAR or the TCR comprises an antigen binding molecule that specifically binds to CD70, as disclosed herein.

[00339] In some embodiments, an antibody, CAR or TCR, wherein the CAR or the TCR comprises an antigen binding molecule that specifically binds to CD70, is administered alone. In such immune cells, the antibody, CAR or TCR, wherein the CAR or
20 the TCR comprises an antigen binding molecule that specifically binds to CD70, can be under the control of the same promoter region, or a separate promoter. In some embodiments, the genes encoding protein agents and/or an antibody, CAR or TCR, wherein the CAR or the TCR comprises an antigen binding molecule that specifically binds to CD70, can be in separate vectors.

[00340] 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 instant disclosure is engineered Autologous Cell Therapy (eACT™). According to this
25 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 an anti-CD70 CAR of the instant disclosure (“anti-CD70 CAR T cells”). In a particular embodiment, the anti-CD70 CAR T cells are administered to the patient. In some embodiments, the anti-CD70 CAR T cells treat a tumor or a cancer in the patient. In one embodiment the anti-CD70 CAR T cells
30 reduce the size of a tumor or a cancer.

[00341] 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 (*e.g.*, allogeneic T cell therapy).

5 [00342] 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 cells, at least about 10^{10} cells, or at least about 10^{11} cells. 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 some embodiments, the therapeutically effective amount of the anti-CD70 CAR T cells is about 1×10^5 cells/kg, 2×10^5 cells/kg, 3×10^5 cells/kg, 4×10^5 cells/kg, 5×10^5 cells/kg, 1×10^6 cells/kg, 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.

[00343] Another aspect of the instant disclosure is directed to methods of diagnosis, detection, or validation. In some embodiments, the antigen binding molecule is used as a diagnostic or validation tool. In some embodiments, the antigen binding molecules disclosed herein are used to assay the amount of CD70 present in a sample and/or subject. In some embodiments, the diagnostic antigen binding molecule is not neutralizing. In some embodiments, the antigen binding molecules disclosed herein are used or provided in an assay kit and/or method for the detection of CD70 in mammalian tissues or cells in order to screen/diagnose for a disease or disorder associated with changes in levels of CD70. In some embodiments, the kit comprises an antigen binding molecule that binds CD70, along with means for indicating the binding of the antigen binding molecule with CD70, if present, and optionally CD70 protein levels. Various means for indicating the presence of an antigen binding molecule can be used. For example, fluorophores, other molecular probes, or enzymes can be linked to the antigen binding molecule and the presence of the antigen binding molecule can be observed in a variety of ways. Examples of fluorophores include fluorescein, rhodamine, tetramethylrhodamine, eosin, erythrosin, coumarin, methyl-coumarins, pyrene, Malachite green, stilbene, Lucifer Yellow, Cascade Blue, Texas Red,

IAEDANS, EDANS, BODIPY FL, LC Red 640, Cy 5, Cy 5.5, LC Red 705, Oregon green, the Alexa-Fluor dyes (Alexa Fluor 350, Alexa Fluor 430, Alexa Fluor 488, Alexa Fluor 546, Alexa Fluor 568, Alexa Fluor 594, Alexa Fluor 633, Alexa Fluor 647, Alexa Fluor 660, Alexa Fluor 680), Cascade Blue, Cascade Yellow and R-phycoerythrin (PE) (Molecular Probes), FITC, Rhodamine, and Texas Red (Pierce), Cy5, Cy5.5, Cy7 (Amersham Life Science). As will be appreciated by one of skill in the art, the degree of antigen binding molecule binding can be used to determine how much CD70 is in a sample.

V.A. Cancer Treatment

[00344] The methods of the disclosure can be used to treat a cancer in a subject, reduce the size of a tumor, kill tumor cells, prevent tumor cell proliferation, prevent growth of a tumor, eliminate a tumor from a patient, prevent relapse of a tumor, prevent tumor metastasis, induce remission in a patient, or any combination thereof. In some embodiments, the methods induce a complete response. In other embodiments, the methods induce a partial response.

[00345] Cancers that can be treated using the CARs, YCR and antibodies provided herein include tumors that are not vascularized, not yet substantially vascularized, or vascularized. The cancer can also include solid or non-solid tumors. In some embodiments, the cancer is a hematologic cancer. In some embodiments, the cancer is of the white blood cells. In other embodiments, the cancer is of the plasma cells. In some embodiments, the cancer is leukemia, lymphoma, or myeloma. In some embodiments, the cancer is 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), chronic or acute leukemia, myeloid diseases including but not limited to acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL) (including non T cell ALL), chronic lymphocytic leukemia (CLL), T-cell lymphoma, one or more of B cell acute lymphoid leukemia ("BALL"), T-cell acute lymphoid leukemia ("TALL"), acute lymphoid leukemia (ALL), chronic myelogenous leukemia (CML), B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, marginal zone lymphoma, myelodysplasia and myelodysplastic syndrome (MDS), hemophagocytic syndrome

(Macrophage Activating Syndrome (MAS), and hemophagocytic lymphohistocytosis (HLH)), chronic or acute granulomatous disease, large cell granuloma, leukocyte adhesion deficiency, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, plasma cell proliferative disorders (*e.g.*, asymptomatic myeloma
5 (smoldering multiple myeloma or indolent myeloma), monoclonal gammopathy of undetermined significance (MGUS), plasmacytomas (*e.g.*, plasma cell dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, POEMS syndrome (Crow-Fukase syndrome, Takatsuki disease, PEP syndrome), or combinations thereof. In one
10 embodiment, the cancer is a myeloma. In some embodiments, the cancer is multiple myeloma. In another particular embodiment the cancer is T or B cell lymphoma.

[00346] In some embodiments, the methods further comprise administering a chemotherapeutic. In some embodiments, the chemotherapeutic selected is a lymphodepleting (preconditioning) chemotherapeutic. Beneficial preconditioning treatment
15 regimens, along with correlative beneficial biomarkers are described in U.S. Patent Application Serial Numbers 15/167,977 and 15/295,931 and published US Patent Application PCT/US2016/034885 which are hereby incorporated by reference in their entirety herein. These describe, *e.g.*, methods of conditioning a patient in need of a T cell therapy comprising administering to the patient specified beneficial doses of
20 cyclophosphamide (between about 100 mg/m²/day and about 2000 mg/m²/day; *e.g.*, about 100 mg/m²/day, about 200 mg/m²/day, about 300 mg/m²/day, about 400 mg/m²/day, about 500 mg/m²/day, about 600 mg/m²/day, about 700 mg/m²/day, about 800 mg/m²/day, about 900 mg/m²/day, about 1000 mg/m²/day, about 1500 mg/m²/day or about 2000 mg/m²/day) alone or in combination with specified doses of fludarabine (between about 10 mg/m²/day
25 and about 900 mg/m²/day; *e.g.*, about 10 mg/m²/day, about 20 mg/m²/day, about 30 mg/m²/day, about 40 mg/m²/day, about 40 mg/m²/day, about 50 mg/m²/day, about 60 mg/m²/day, about 70 mg/m²/day, about 80 mg/m²/day, about 90 mg/m²/day, about 100 mg/m²/day, about 500 mg/m²/day or about 900 mg/m²/day).

[00347] In some embodiments, the dose regimen involves treating a patient
30 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 administration of a therapeutically effective amount of engineered T cells to the patient.

[00348] In some embodiments, the dose regimen involves treating a patient comprising administering daily to the patient about 600 mg/m²/day of cyclophosphamide and about 30 mg/m²/day of fludarabine for three days prior to administration of a therapeutically effective amount of engineered T cells to the patient.

5 **[00349]** In some embodiments, the dose regimen involves treating a patient comprising administering daily to the patient about 500 mg/m²/day of cyclophosphamide for two days and about 30 mg/m²/day of fludarabine for four days prior to administration of a therapeutically effective amount of engineered T cells to the patient.

[00350] In some embodiments, the dose regimen involves treating a patient
10 comprising administering daily to the patient about 600 mg/m²/day of cyclophosphamide for three days and about 30 mg/m²/day of fludarabine for three days prior to administration of a therapeutically effective amount of engineered T cells to the patient.

[00351] In some embodiments, the dose regimen involves treating a patient comprising administering daily to the patient about 550 mg/m²/day of cyclophosphamide
15 for three days and about 30 mg/m²/day of fludarabine for three days prior to administration of a therapeutically effective amount of engineered T cells to the patient.

[00352] In some embodiments, the dose regimen involves treating a patient comprising administering daily to the patient about 500 mg/m²/day of cyclophosphamide
20 for three days and about 30 mg/m²/day of fludarabine for three days prior to administration of a therapeutically effective amount of engineered T cells to the patient.

[00353] In some embodiments, the dose regimen involves treating a patient comprising administering daily to the patient about 450 mg/m²/day of cyclophosphamide for three days and about 30 mg/m²/day of fludarabine for three days prior to administration of a therapeutically effective amount of engineered T cells to the patient.

25 **[00354]** In some embodiments, the dose regimen involves treating a patient comprising administering daily to the patient about 400 mg/m²/day of cyclophosphamide for three days and about 30 mg/m²/day of fludarabine for three days prior to administration of a therapeutically effective amount of engineered T cells to the patient.

[00355] In some embodiments, the dose regimen involves treating a patient
30 comprising administering daily to the patient about 440 mg/m²/day of cyclophosphamide for two days and about 100 mg/m²/day of etoposide for two days prior to administration of a therapeutically effective amount of engineered T cells to the patient.

[00356] In some embodiments, the dose regimen involves treating a patient comprising administering daily to the patient about 2-4 g/m²/day of cyclophosphamide for three days and about 200 mg/m²/day of etoposide for three days prior to administration of a therapeutically effective amount of engineered T cells to the patient.

5 [00357] In some embodiments, the dose regimen involves treating a patient comprising administering daily to the patient about 300 mg/m²/day of cyclophosphamide for three days and about 30 mg/m²/day of fludarabine for three days prior to administration of a therapeutically effective amount of engineered T cells to the patient.

[00358] In some embodiments, the dose regimen involves treating a patient
10 comprising administering daily to the patient about 30-60 mg/kg (about 1100 mg/m²-2200 mg/m²) of cyclophosphamide for three-five days and about 25 mg/m² of fludarabine for three-five days prior to administration of a therapeutically effective amount of engineered T cells to the patient.

[00359] In some embodiments, the dose regimen involves treating a patient
15 comprising administering daily to the patient about 1 g/m²) of cyclophosphamide prior to administration of a therapeutically effective amount of engineered T cells to the patient.

[00360] In some embodiments, the dose regimen involves treating a patient comprising administering daily to the patient about 1.2 g/m²) of cyclophosphamide for four days prior to administration of a therapeutically effective amount of engineered T cells to
20 the patient.

[00361] In some embodiments, the regimen involves treating a patient comprising administering daily to the patient about 2 g/m²) of cyclophosphamide prior to administration of a therapeutically effective amount of engineered T cells to the patient.

[00362] In some embodiments, the dose regimen involves treating a patient
25 comprising administering daily to the patient about 25 mg/m² of fludarabine for three days prior to administration of a therapeutically effective amount of engineered T cells to the patient.

[00363] In some embodiments, the dose regimen involves treating a patient comprising administering daily to the patient about 90 mg/m² of bendamustine for two days
30 prior to administration of a therapeutically effective amount of engineered T cells to the patient.

[00364] In some embodiments, the dose regimen involves treating a patient comprising administering daily to the patient about 500 mg/m²/day of cyclophosphamide

for two days and about 30 mg/m²/day of fludarabine for four days prior to administration of a therapeutically effective amount of engineered T cells to the patient.

[00365] In some embodiments, the dose regimen involves treating a patient comprising administering to the patient about 1000 mg/m² of methotrexate on day 1, about
5 1000 mg/m² every 12 hours on days 2 and 3 prior to administration of a therapeutically effective amount of engineered T cells to the patient.

[00366] Another preferred dose regimen involves treating a patient comprising administering to the patient about 300 mg/m² of cyclophosphamide every 12 hours on days one, two and three, 2 mg of vincristine on day three and 50 mg/m² of adriamycin on day
10 three prior to administration of a therapeutically effective amount of engineered T cells to the patient.

[00367] Another preferred dose regimen involves treating a patient comprising administering daily to the patient about 200 mg/m²/day of cyclophosphamide for three days and about 20 mg/m²/day of fludarabine for three days prior to administration of a
15 therapeutically effective amount of engineered T cells to the patient.

[00368] In some 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.

[00369] In some embodiments, compositions comprising CAR- and/or TCR-
20 expressing immune effector cells disclosed herein can be administered in conjunction with any number of chemotherapeutic agents. Examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclophosphamide (CYTOXANTM); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate and trimethylolomelamine resins; 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,
25 ranimustine; antibiotics such as aclacinomysins, actinomycin, anthramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabycin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic
30

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, epitiostanol, mepitiothane, 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 difitox); 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 can be administered in conjunction with an anti-hormonal agent that acts to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and toremifene (FARESTON[™]); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Combinations of chemotherapeutic agents are also administered where appropriate, including, but not limited to CHOP, *i.e.*,

Cyclophosphamide (CYTOXAN[®]), Doxorubicin (hydroxydoxorubicin), Vincristine (ONCOVIN[®]), and Prednisone; EPOCH (etoposide, prednisone, vincristine (ONCOVIN[®]) and doxorubicin hydrochloride (hydroxydaunorubicin hydrochloride)); and carboplatin and gemcitabine.

5 [00370] In some embodiments, the chemotherapeutic agent is administered at the same time or within one week after the administration of the engineered cell or nucleic acid. In other embodiments, the chemotherapeutic agent is administered from 1 to 4 weeks or from 1 week to 1 month, 1 week to 2 months, 1 week to 3 months, 1 week to 6 months, 1 week to 9 months, or 1 week to 12 months after the administration of the engineered cell or
10 nucleic acid. In some embodiments, the chemotherapeutic agent is administered at least 1 month before administering the cell or nucleic acid. In some embodiments, the methods further comprise administering two or more chemotherapeutic agents.

[00371] A variety of additional therapeutic agents can be used in conjunction with the compositions described herein. For example, potentially useful additional therapeutic
15 agents include PD-1 inhibitors such as nivolumab (OPDIVO[®]), pembrolizumab (KEYTRUDA[®]), pidilizumab (CureTech), and atezolizumab (TECENTRIQ[®]).

[00372] Additional therapeutic agents suitable for use in combination with the disclosure include, but are not limited to, ibrutinib (IMBRUVICA[®]), ofatumumab (ARZERRA[®]), rituximab (RITUXAN[®]), bevacizumab (AVASTIN[®]), trastuzumab
20 (HERCEPTIN[®]), trastuzumab emtansine (KADCYLA[®]), imatinib (GLEEVEC[®]), cetuximab (ERBITUX[®]), panitumumab (VECTIBIX[®]), catumaxomab (REMOVAB[®]), ibritumomab (ZEVALIN[®]), tositumomab, brentuximab (ADCETRIS[®]), alemtuzumab (LEMTRADA[®]), gemtuzumab, erlotinib (TARCEVA[®]), gefitinib (IRESSA[®]), vandetanib (CAPRELSA[®]), afatinib (GIOTRIF[®]), lapatinib (TYKERB[®]), neratinib, axitinib
25 (INLYTA[®]), masitinib (MASIVET[®]), pazopanib (VOTRIENT[®]), sunitinib (SUTENT[®]), sorafenib (NEXAVAR[®]), lestaurtinib, cediranib, lenvatinib (LENVIMA[®]), nintedanib (OFEV[®]), regorafenib (STIVARGA[®]), semaxanib, tivozanib, entrectinib, cabozantinib (CABOMETYX[®]), dasatinib (SPRYCEL[®]), nilotinib (TASIGNA[®]), ponatinib (ICLUSIG[®]), radotinib (SUPECT[®]), bosutinib (BOSULIF[®]), ruxolitinib (JAKAVI[®]),
30 pacritinib, cobimetinib (COTELLIC[®]), selumetinib, trametinib (MEKINIST[®]), binimetinib, alectinib (ALECENSA[®]), ceritinib (ZYKADIA[®]), crizotinib (XALKORI[®]), aflibercept (EYELEA[®]), adipotide, denileukin diftitox (ONTAK[®]), mTOR inhibitors such as everolimus (AFINITOR[®]) and temsirolimus (TORISEL[®]), hedgehog inhibitors such as

sonidegib (ODOZMO[®]) and vismodegib (ERIVEDGE[®]), CDK inhibitors such as CDK inhibitor (palbociclib; IBRANCE[®]).

[00373] In some embodiments, the composition comprising CAR- and/or TCR-containing immune are administered with an anti-inflammatory agent. Anti-inflammatory agents or drugs can include, but are not limited to, steroids and glucocorticoids (including betamethasone, budesonide, dexamethasone, hydrocortisone acetate, hydrocortisone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone), nonsteroidal anti-inflammatory drugs (NSAIDS) including aspirin, ibuprofen, naproxen, methotrexate, sulfasalazine, leflunomide, anti-TNF medications, cyclophosphamide and mycophenolate. Exemplary NSAIDs include ibuprofen, naproxen, naproxen sodium, Cox-2 inhibitors, and sialylates. Exemplary analgesics include acetaminophen, oxycodone, tramadol of propoxyphene hydrochloride. Exemplary glucocorticoids include cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, or prednisone. Exemplary biological response modifiers include molecules directed against cell surface markers (*e.g.*, CD4, CD5, etc.), cytokine inhibitors, such as the TNF antagonists, (*e.g.*, etanercept (ENBREL[®]), adalimumab (HUMIRA[®]) and infliximab (REMICADE[®]), chemokine inhibitors and adhesion molecule inhibitors. The biological response modifiers include monoclonal antibodies as well as recombinant forms of molecules. Exemplary DMARDs include azathioprine, cyclophosphamide, cyclosporine, methotrexate, penicillamine, leflunomide, sulfasalazine, hydroxychloroquine, Gold (oral (auranofin) and intramuscular), and minocycline.

[00374] In some embodiments, the compositions described herein are administered in conjunction with a cytokine. "Cytokine" as used herein is meant to refer to proteins released by one cell population that act on another cell as intercellular mediators. Examples of cytokines are lymphokines, monokines, and traditional polypeptide hormones. Included among the cytokines are growth hormones such as human growth hormone, N-methionyl human growth hormone, and bovine growth hormone; parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prorelaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH); hepatic growth factor (HGF); fibroblast growth factor (FGF); prolactin; placental lactogen; mullerian-inhibiting substance; mouse gonadotropin-associated peptide; inhibin; activin; vascular endothelial growth factor; integrin; thrombopoietin (TPO); nerve growth factors (NGFs) such as NGF-beta; platelet-growth factor; transforming growth factors (TGFs) such

as TGF-alpha and TGF-beta; insulin-like growth factor-I and -II; erythropoietin (EPO); osteoinductive factors; interferons such as interferon-alpha, beta, and -gamma; colony stimulating factors (CSFs) such as macrophage-CSF (M-CSF); granulocyte-macrophage-CSF (GM-CSF); and granulocyte-CSF (G-CSF); interleukins (ILs) such as IL-1, IL-1alpha, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12; IL-15, a tumor necrosis factor such as TNF-alpha or TNF-beta; and other polypeptide factors including LIF and kit ligand (KL). As used herein, the term cytokine includes proteins from natural sources or from recombinant cell culture, and biologically active equivalents of the native sequence cytokines.

[00375] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. However, the citation of a reference herein should not be construed as an acknowledgement that such reference is prior art to the instant disclosure. 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.

[00376] The instant disclosure is further illustrated by the following examples which should not be construed as further limiting. The contents of all references cited throughout this application are expressly incorporated herein by reference.

EXAMPLES

EXAMPLE 1

[00377] CD70 expression was measured in various cell lines. CD70 was found to be expressed, with a fragments/kilobase of exon/million reads mapped (FPKM) greater than 35, in 99% of the multiple myeloma tumor cell lines tested.

[00378] To further characterize the expression of CD70, CEM (ATCC), EoL-1 (Sigma), HL-60 (ATCC), KG-1a (ATCC), MV4;11 (ATCC), NAMALWA (ATCC), Raji (ATCC), Toledo (ATCC), and U-937 (ATCC) cells were stained with an anti-CD70 antibody conjugated to PE (BD Pharmingen) in stain buffer (BD Pharmingen) for 30 minutes at 4°C. Cells were then washed and resuspended in stain buffer with propidium iodide (BD Pharmingen) prior to data acquisition. Samples were then acquired by flow cytometry and data analyzed (FIGURE 2). CD70 expression was observed in the cell lines

EoL-1, MV4;11, NAMALWA, Raji, Toledo, and U-937 (FIGURE 2), but not in the cell lines CEM, HL-60, and KG-1a (FIGURE 2).

EXAMPLE 2

5 **[00379]** A third generation lentiviral transfer vector containing the CD70 CAR constructs shown schematically in FIGURES 1A-1H, having the sequences shown in FIGURES 8A-8L, and in the appended Sequence Listing (SEQ ID NOs: 29-52) were used along with the ViraPower Lentiviral Packaging Mix (Life Technologies) to generate the lentiviral supernatants. Briefly, a transfection mix was generated by mixing 15µg of DNA
10 and 22.5µl of polyethylenimine (Polysciences, 1mg/ml) in 600µl of OptiMEM media. The transfection mix was incubated for 5 minutes at room temperature. Simultaneously, 293T cells (ATCC) were trypsinized and counted. A total of 10×10^6 total 293T cells were then plated in a T75 flask with the transfection mix. Following culture for three days, supernatants were collected and filtered through a 0.45µm filter and stored at -80°C.

15 **[00380]** Peripheral blood mononuclear cells (PBMCs) were isolated from two different healthy donor leukopaks (Hemacare) using Ficoll[®]-Paque density centrifugation according to the manufacturer's instructions. PBMCs were stimulated using OKT3 (Muromonab-CD3, 50ng/ml, Miltenyi Biotec) in R10 media supplemented with IL-2 (300IU/ml, Proleukin[®], Prometheus[®] Therapeutics and Diagnostics). Forty-eight hours
20 post-stimulation, cells were transduced using lentivirus containing the different CD70 CAR constructs at a multiplicity of infection (MOI) of 10. Cells were maintained at 0.5×10^6 - 2.0×10^6 cells/ml prior to use in activity assays.

[00381] At day 14 post-stimulation, transduced T cells were stained with recombinant CD70-Fc (Sino Biological) in stain buffer (BD Pharmingen) for 30 minutes at 4°C. Cells
25 were then washed and stained with goat anti-human IgG Fc PE (Jackson ImmunoResearch) 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. All experiments were performed in two different donors. CD70 CAR expression was observed for each of the constructs in both Donor 1 (FIGURE 3A) and Donor 2(FIGURE 3B) transduced cells.

30 **[00382]** Effector cells, *e.g.*, anti-CD70 CAR T cells, were cultured with target cells at a 1:1 effector cell to target cell (E:T) ratio in R10 media 14 days after T cell stimulation. Cell lines tested included KG-1a, NAMALWA, and Raji. Sixteen hours post-coculture, supernatants were analyzed by Luminex (EMD Millipore), according to the manufacturer's

instructions, for production of the cytokines IFN γ (FIGURES 4A-4B), TNF α (FIGURES 4C-4D), and IL-2 (FIGURES 4E-4F). IFN γ (FIGURES 4A-4B), TNF α (FIGURES 4C-4D), and IL-2 (FIGURES 4E-4F) were observed in the supernatant of NAMALWA and Raji target cell cocultures for each anti-CD70 CAR T cell tested in both donors (FIGURES 4A-4F). However, IFN γ (FIGURES 4A-4B), TNF α (FIGURES 4C-4D), and IL-2 (FIGURES 4E-4F) were observed at much lower levels in the supernatant of KG-1a target cell cocultured with various CD70 CAR T cells (FIGURES 4A-4F).

[00383] Target cell viability was assessed by flow cytometric analysis of propidium iodide (PI) uptake of CD3 negative cells. The anti-CD70 CAR T cells were cocultured with KG-1a (FIGURES 5A-5B), Raji (FIGURE 5C), or NAMALWA (FIGURE 5D) target cells for 16 hours, 40 hours, 64 hours, 88 hours, or 112 hours. Little cytolytic activity was observed in the KG-1a cocultures at any time period for the anti-CD70 CAR T cells (FIGURES 5A-5B).

EXAMPLE 3

[00384] Donor CD4⁺ and CD8⁺ T cells were thawed and washed twice in OpTmizer media (Life Technologies) supplemented with 1X Penicillin-Streptomycin-L-Glutamine (PSQ)(Gibco). Cells were counted using a Vi-Cell cell analyzer, and cell density was adjusted to 1×10^6 cells/mL in OpTmizer media containing 1X PSQ and 300 IU/mL IL-2 (Proleukin®, Prometheus® Therapeutics and Diagnostics). After counting and resuspending T cells in medium, soluble anti-CD28 antibody was added at a final concentration of 1 μ g/mL. Cells were then transferred to T25 flasks coated with anti-CD3 antibody (Muromonab-CD3, 50ng/ml, Miltenyi Biotec) diluted in HBSS to a final concentration of 1.23 μ g/mL.

[00385] After 24 hours (day 1 post-stimulation), CD70 lentiviral vector comprising a CAR construct (*e.g.*, SEQ ID NOs: 29 and 30) was added to each T cell culture for an MOI of 10. For non-transduced T cells, cells were stimulated and expanded in the presence of 300 IU/mL IL-2 utilizing the same protocol, but without adding viral vector to the cells on day 1. Twenty four hours after transduction, T cells were washed with culture media containing the pre-specified components, counted, and reseeded at 0.5×10^6 cells/mL culture medium.

[00386] At day 14 post-stimulation, transduced T cells were stained with recombinant CD70-Fc (Sino Biological) in stain buffer (BD Pharmingen) for 30 minutes at 4°C. Cells

were then washed and stained with goat anti-human IgG Fc PE (Jackson ImmunoResearch) 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. All experiments were performed in two different donors. CD70 CAR expression was observed for each of the constructs in both Donor 3 and Donor 4 transduced cells (FIGURE 9).

[00387] Effector cells, *e.g.*, anti-CD70 CAR T cells, were cultured with target cells at a 1:1 or 4:1 effector cell to target cell (E:T) ratio in R10 media 14 days after T cell stimulation. Cell lines tested included KG-1a and Raji. Sixteen hours post-coculture, supernatants were analyzed by Luminex (EMD Millipore), according to the manufacturer's instructions, for production of the cytokines IFN γ (FIGURES 11A-11D), TNF α (FIGURES 13A-13D), and IL-2 (FIGURES 12A-12D). IFN γ (FIGURES 11A-11D), TNF α (FIGURES 13A-13D), and IL-2 (FIGURES 12A-12D) were observed in the supernatant of Raji target cell cocultures for each anti-CD70 CAR T cell tested in both donors (FIGURES 11A-12D, 12A-12D, and 13A-13D). However, IFN γ (FIGURES 11A-11D), TNF α (FIGURES 13A-13D), and IL-2 (FIGURES 12A-12D) were observed at much lower levels in the supernatant of KG-1a target cell cocultured with various CD70 CAR T cells (FIGURES 11A-12D, 12A-12D, and 13A-13D).

[00388] Target cell viability was assessed by flow cytometric analysis of propidium iodide (PI) uptake of CD3 negative cells. The anti-CD70 CAR T cells were cocultured with KG-1a or Raji target cells. Little cytolytic activity was observed in the KG-1a cocultures for the anti-CD70 CAR T cells (FIGURES 10A-10D).

CLAIMS

What is claimed is:

1. An isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to CD70, wherein the antigen binding molecule comprises:

(a) a heavy chain variable region (VH) complementarity determining region (CDR) 1 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of GFTFSSY (SEQ ID NO: 71), GDSIISGGY (SEQ ID NO: 73) and GYTFTSY (SEQ ID NO: 75);

(b) a heavy chain variable region (VH) complementarity determining region (CDR) 2 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of WYDGSN (SEQ ID NO: 72), FYSGS (SEQ ID NO: 74) and DPSGGG (SEQ ID NO: 76);

(c) a heavy chain variable region (VH) complementarity determining region (CDR) 3 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of DLLRGVKGYAMDV (SEQ ID NO: 64), SGYSYALFDH (SEQ ID NO: 67) and DYGDYVFDY (SEQ ID NO: 76);

(d) a light chain variable region (VL) complementarity determining region (CDR) 1 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of RASQSLRRIYLA (SEQ ID NO: 53), RASQFIGRYFN (SEQ ID NO: 56), and SGSSSNIGTNTVN (SEQ ID NO: 59);

(e) a light chain variable region (VL) complementarity determining region (CDR) 2 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of DVFDRAT (SEQ ID NO: 54), AESSLQS (SEQ ID NO: 57), and INNQRPS (SEQ ID NO: 60);

(f) a light chain variable region (VL) complementarity determining region (CDR) 3 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of QQYSDSPFT (SEQ ID NO: 55), QQSYSTPFT (SEQ ID NO: 58), and ATWDDSLNGPVV (SEQ ID NO: 61).

2. The polynucleotide of claim 1, wherein the VH CDR3 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 64, 67 and 70.
3. An isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to CD70,
5 wherein the antigen binding molecule comprises a VH CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 64, 67 and 70.
4. The polynucleotide of any one of claims 1 to 3, wherein the VH CDR1 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 71, 73 and 75.
5. The polynucleotide of any one of claims 1 to 4, wherein the VH CDR2 comprises an
10 amino acid sequence selected from the group consisting of SEQ ID NO: 72, 74 and 76.
6. The polynucleotide of any one of claims 1 to 5, wherein the VL CDR1 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 53, 56 and 59.
7. The polynucleotide of any one of claims 1 to 6, wherein the VL CDR2 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 54, 57 and 60.
- 15 8. The polynucleotide of any one of claims 1 to 7, wherein the VL CDR3 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 55, 58 and 61.
9. The polynucleotide of any one of claims 1, 2, and 4 to 5, wherein the VH CDR1, VH CDR2, and VH CDR3 each comprise the amino acid sequence of the VH CDR1, VH CDR2, and VH CDR3 of a variable light chain shown in FIGURES 7A, 7C or 7E.
- 20 10. The polynucleotide of any one of claims 1, 2, and 6 to 9, wherein the VL CDR1, VL CDR2, and VL CDR3 each comprise the amino acid sequence of the VL CDR1, VL CDR2, and VL CDR3 of an antibody in FIGURES 7B, 7D or 7F.
11. The polynucleotide of any one of claims 1 to 10, wherein the antigen binding molecule comprises a heavy chain variable region sequence comprising an amino acid
25 sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 11.

12. The polynucleotide of any one of claims 1 to 10, wherein the antigen binding molecule comprises a light chain variable region sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 9 and 13.

13. The polynucleotide of any one of claims 1 to 12, wherein the antigen binding molecule comprises one of:

(a) a VH CDR1 region comprising the amino acid sequence of SEQ ID NO: 71; a VH CDR2 region comprising the amino acid sequence of SEQ ID NO: 72; a VH CDR3 region comprising the amino acid sequence of SEQ ID NO: 64; a VL CDR1 region comprising the amino acid sequence of SEQ ID NO: 53; a VL CDR2 region comprising the amino acid sequence of SEQ ID NO: 54; and a VL CDR3 region comprising the amino acid sequence of SEQ ID NO: 55;

(b) a VH CDR1 region comprising the amino acid sequence of SEQ ID NO: 73; a VH CDR2 region comprising the amino acid sequence of SEQ ID NO: 74; a VH CDR3 region comprising the amino acid sequence of SEQ ID NO: 67; a VL CDR1 region comprising the amino acid sequence of SEQ ID NO: 56; a VL CDR2 region comprising the amino acid sequence of SEQ ID NO: 57; and a VL CDR3 region comprising the amino acid sequence of SEQ ID NO: 58; or

(c) a VH CDR1 region comprising the amino acid sequence of SEQ ID NO: 75; a VH CDR2 region comprising the amino acid sequence of SEQ ID NO: 76; a VH CDR3 region comprising the amino acid sequence of SEQ ID NO: 70; a VL CDR1 region comprising the amino acid sequence of SEQ ID NO: 59; a VL CDR2 region comprising the amino acid sequence of SEQ ID NO: 60; and a VL CDR3 region comprising the amino acid sequence of SEQ ID NO: 61.

14. The polynucleotide of any one of claims 1 to 13, wherein the antigen binding molecule comprises one of:

(a) a VH comprising the amino acid sequence of SEQ ID NO: 3; and a VL comprising the amino acid sequence of SEQ ID NO: 5;

(b) a VH comprising the amino acid sequence of SEQ ID NO: 7; and a VL comprising the amino acid sequence of SEQ ID NO: 9; or

(c) a VH comprising the amino acid sequence of SEQ ID NO: 11; and a VL comprising the amino acid sequence of SEQ ID NO: 13.

15. The polynucleotide of claim 14, which 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: 2 and 4.

16. The polynucleotide of claim 14, which 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: 6 and 8.

17. The polynucleotide of claim 14, which 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: 10 and 12.

18. The polynucleotide of any one of claims 1 to 17, wherein the antigen binding molecule is single chained.

19. The polynucleotide of any one of claims 1 to 18, wherein the antigen binding molecule is selected from the group consisting of scFv, Fab, Fab', Fv, F(ab')₂, dAb, and any combination thereof.

20. The polynucleotide of any one of claims 1 to 19, wherein the antigen binding molecule comprises an scFv.

21. The polynucleotide of any one of claims 1 to 19, wherein the VH and the VL are joined by a linker.

22. The polynucleotide of claim 21, wherein the VH is located at the N terminus of the linker and the VL is located at the C terminus of the linker.

23. The polynucleotide of claim 21, wherein the VL is located at the N terminus of the linker and the VH is located at the C terminus of the linker.

24. The polynucleotide of any one of claims 21 to 23, wherein 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.
25. The polynucleotide of any one of claims 21 to 24, wherein the linker comprises an amino acid sequence at least 75%, at least 85%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence of one of SEQ ID NOs: 80 and 81.
26. The polynucleotide of any one of claims 1 to 25, wherein the antigen binding molecule binds to CD70 with a K_D of less than about 1×10^{-6} M, less than about 1×10^{-7} M, less than about 1×10^{-8} M, or less than about 1×10^{-9} M.
27. The polynucleotide of any one of claims 1 to 25, wherein the CAR or TCR further comprises a constant region.
28. The polynucleotide of any one of claims 1 to 25, wherein the CAR or TCR further comprises a transmembrane domain.
29. The polynucleotide of claim 28, wherein the transmembrane domain is a transmembrane domain of CD28, 4-1BB/CD137, CD8 alpha, CD4, CD19, CD3 epsilon, CD45, CD5, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154, an alpha chain of a T cell receptor, a beta chain of a T cell receptor, a zeta chain of a T cell receptor, or any combination thereof.
30. The polynucleotide of claim 29, wherein the transmembrane domain is a CD28T transmembrane domain.
31. The polynucleotide of claim 30, wherein the CD28T 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: 15 or 19.
32. The polynucleotide of claim 30, wherein the CD28T 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: 16 or 18.

33. The polynucleotide of claim 29, wherein the transmembrane domain is a CD8 alpha transmembrane domain.

5 34. The polynucleotide of claim 33, wherein the CD8 alpha 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: 17, 21 or 94.

35. The polynucleotide of claim 33, wherein the CD8 alpha transmembrane domain is
10 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: 16 or 20.

36. The polynucleotide of any one of claims 28 to 35, wherein the CAR or TCR further
15 comprises a hinge region between the transmembrane domain and the antigen binding molecule.

37. The polynucleotide of claim 36, wherein the hinge region comprises all or a fragment of IgG1, IgG2, IgG3, IgG4, IgA, IgD, IgE, IgM, CD28, or CD8 alpha.

38. The polynucleotide of claim 37, wherein the hinge region is of CD28T.

39. The polynucleotide of claim 38, wherein the hinge region comprises an amino acid
20 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 a sequence selected from the group consisting of SEQ ID NOs: 15, and 83.

40. The polynucleotide of claim 38, wherein the hinge region is encoded by a nucleotide
25 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 a sequence selected from the group consisting of SEQ ID NOs: 14 and 82.

41. The polynucleotide of claim 37, wherein the hinge region is of CD8 alpha.

42. The polynucleotide of claim 41, wherein the hinge region 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 a sequence selected from the group consisting of SEQ ID NO: 17 and 85.

43. The polynucleotide of claim 41, wherein the hinge region 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 a sequence selected from the group consisting of SEQ ID NO: 16 and 84.

44. The polynucleotide of any one of claims 1 to 43, wherein the CAR or TCR further comprises a costimulatory region.

45. The polynucleotide of claim 44, wherein the costimulatory region is a signaling region of CD2, CD3 delta, CD3 epsilon, CD3 gamma, CD4, CD7, CD8 α , CD8 β , CD11a (ITGAL), CD11b (ITGAM), CD11c (ITGAX), CD11d (ITGAD), CD18 (ITGB2), CD19 (B4), CD27 (TNFRSF7), CD28, CD28T, CD29 (ITGB1), CD30 (TNFRSF8), CD40 (TNFRSF5), CD48 (SLAMF2), CD49a (ITGA1), CD49d (ITGA4), CD49f (ITGA6), CD66a (CEACAM1), CD66b (CEACAM8), CD66c (CEACAM6), CD66d (CEACAM3), CD66e (CEACAM5), CD69 (CLEC2), CD79A (B-cell antigen receptor complex-associated alpha chain), CD79B (B-cell antigen receptor complex-associated beta chain), CD84 (SLAMF5), CD96 (Tactile), CD100 (SEMA4D), CD103 (ITGAE), CD134 (OX40), CD137 (4-1BB), CD150 (SLAMF1), CD158A (KIR2DL1), CD158B1 (KIR2DL2), CD158B2 (KIR2DL3), CD158C (KIR3DP1), CD158D (KIRDL4), CD158F1 (KIR2DL5A), CD158F2 (KIR2DL5B), CD158K (KIR3DL2), CD160 (BY55), CD162 (SELPLG), CD226 (DNAM1), CD229 (SLAMF3), CD244 (SLAMF4), CD247 (CD3-zeta), CD258 (LIGHT), CD268 (BAFFR), CD270 (TNFSF14), CD272 (BTLA), CD276 (B7-H3), CD279 (PD-1), CD314 (NKG2D), CD319 (SLAMF7), CD335 (NK-p46), CD336 (NK-p44), CD337 (NK-p30), CD352 (SLAMF6), CD353 (SLAMF8), CD355 (CRTAM), CD357 (TNFRSF18), inducible T cell co-stimulator (ICOS), LFA-1 (CD11a/CD18), NKG2C, DAP-10, ICAM-1, NKp80 (KLRP1), IL-2R beta, IL-2R gamma, IL-7R alpha, LFA-1, SLAMF9, LAT, GADS (GrpL), SLP-76 (LCP2), PAG1/CBP, a CD83 ligand, Fc gamma receptor, MHC class 1 molecule, MHC class 2 molecule, a TNF receptor protein, an immunoglobulin protein, a

cytokine receptor, an integrin, activating NK cell receptors, a Toll ligand receptor, and or fragments or combinations thereof.

46. The polynucleotide of claim 45, wherein the costimulatory region is a CD28 costimulatory region.

5 47. The polynucleotide of claim 46, wherein the costimulatory region 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: 23.

10 48. The polynucleotide of claim 46, wherein the costimulatory region 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: 22.

49. The polynucleotide of claim 45, wherein the costimulatory region is a CD137 (4-1BB) costimulatory region.

15 50. The polynucleotide of claim 49, wherein the costimulatory region 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: 25.

20 51. The polynucleotide of claim 49, wherein the costimulatory region 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: 24.

52. The polynucleotide of any one of claims 1 to 51, wherein the CAR or TCR further comprises an activation domain.

25 53. The polynucleotide of claim 52, wherein the activation domain is a CD3 zeta domain.

54. The polynucleotide of claim 53, wherein the activation domain comprises an amino acid sequence at least about 80%, at least about 85%, at least about 90%, at least about 95%,

at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to SEQ ID NO: 27 or 92.

55. The polynucleotide of claim 53, wherein the activation domain is encoded by a nucleotide sequence at least about 80%, at least about 85%, at least about 90%, at least
5 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: 26.

56. The polynucleotide of any one of claims 1 to 55, wherein the CAR or TCR further comprises a leader peptide.

57. The polynucleotide of claim 56, wherein the leader peptide comprises an amino acid
10 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: 28.

58. The polynucleotide of claim 56, wherein the leader peptide is encoded by a nucleotide sequence at least about 80%, at least about 85%, at least about 90%, at least
15 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: 95.

59. A polynucleotide encoding a CAR or TCR, wherein the polynucleotide is selected from the group consisting of SEQ ID NOs: 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 and 51.

60. A vector comprising the polynucleotide of any one of claims 1 to 59.

20 61. The vector of claim 59, which is a retroviral vector, a DNA vector, a plasmid, a RNA vector, an adenoviral vector, an adenovirus associated vector, a lentiviral vector, or any combination thereof.

62. A CAR or TCR encoded by the polynucleotide of any one of claims 1 to 59 or the vector of claim 60 or 61.

25 63. A cell comprising the polynucleotide of any one of claims 1 to 59, the vector of claim 60 or 61, the CAR or TCR of claim 62, or any combination thereof.

64. The cell of claim 63, wherein the cell comprises an immune cell.

65. The cell of claim 64, wherein the cell is a T cell.

66. The cell of claim 65, wherein the T cell is a tumor-infiltrating lymphocyte (TIL), autologous T cell, engineered autologous T cell (eACT), an allogeneic T cell, or any combination thereof.

5 67. The cell of any one of claims 63 to 66, wherein the cell is an *in vitro* cell.

68. A composition comprising the polynucleotide of any one of claims 1 to 59, the vector of claim 60 or 61, the CAR or TCR of claim 62, or the cell of any one of claims 63 to 67.

69. The composition of claim 68, which is formulated to be delivered to a subject.

10 70. A method of making a cell expressing a CAR or TCR comprising transducing a cell with the polynucleotide of any one of claims 1 to 59 under suitable conditions.

71. The method of claim 70, further comprising isolating the cell.

72. A method of inducing an immunity against a tumor comprising administering to a subject an effective amount of a cell comprising the polynucleotide of any one of claims 1
15 to 59, the vector of claim 60 or 61, or the CAR or TCR of claim 62.

73. A method of treating a cancer in a subject in need thereof comprising administering to the subject the polynucleotide of any one of claims 1 to 59, the vector of claim 60 or 61, the CAR or TCR of claim 62, the cell of any one of claims 65 to 67, or the composition of claim 68 or 69.

20 74. The method of claim 73, wherein the cancer is a hematologic cancer.

75. The method of claim 74, wherein the cancer is of the white blood cells.

76. The method of claims 74, wherein the cancer is of the plasma cells.

77. The method of any one of claims 73 to 76, wherein the cancer is leukemia, lymphoma, or myeloma.

25 78. The method of anyone of claims 73 to 77, wherein the cancer is 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), chronic or acute leukemia, acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia (ALL) (including non T cell ALL), chronic lymphocytic leukemia (CLL), T-cell
 5 lymphoma, one or more of B-cell acute lymphoid leukemia ("BALL"), T-cell acute lymphoid leukemia ("TALL"), acute lymphoid leukemia (ALL), chronic myelogenous leukemia (CML), B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant
 10 lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, myelodysplasia and myelodysplastic syndrome, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, a plasma cell proliferative disorder (*e.g.*, asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), monoclonal gammopathy of undetermined significance (MGUS),
 15 plasmacytomas (*e.g.*, plasma cell dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, POEMS syndrome (also known as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome), or a combination thereof.

79. The method of any one of claims 73 to 78, wherein the cancer is multiple myeloma.

20 80. A CAR or TCR, wherein the CAR or TCR comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52.

81. The CAR or TCR of claim 80, wherein the leader sequence of SEQ ID NOs: 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52 is absent.

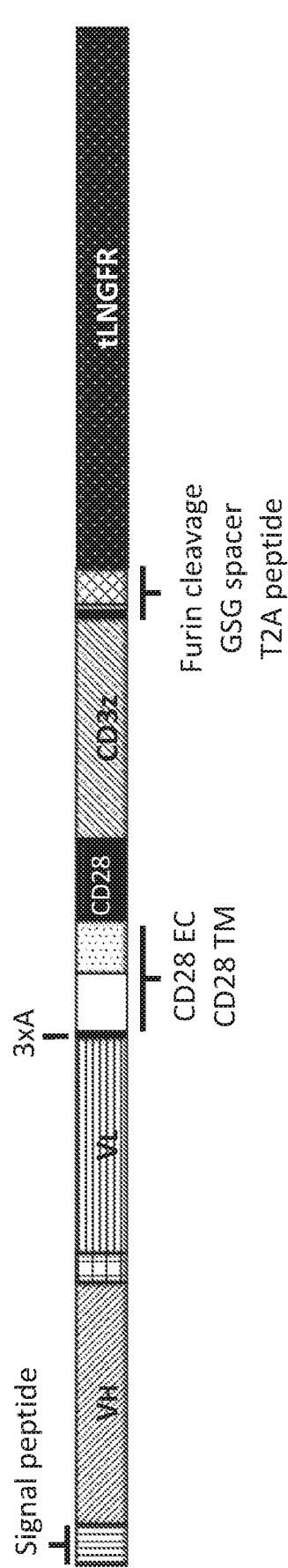


Figure 1A

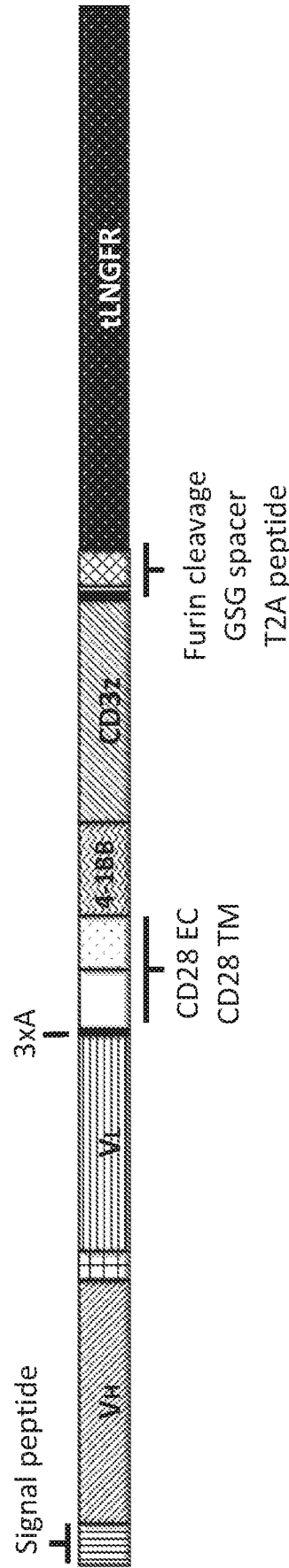


Figure 1B

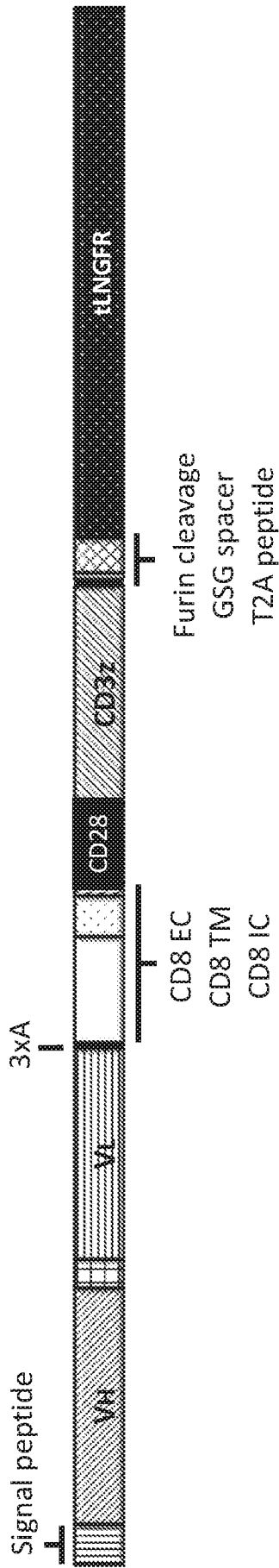


Figure 1C

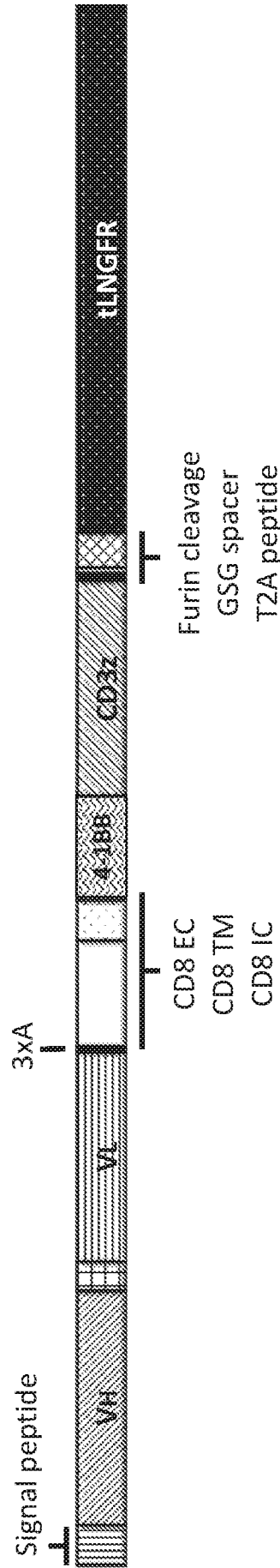


Figure 1D

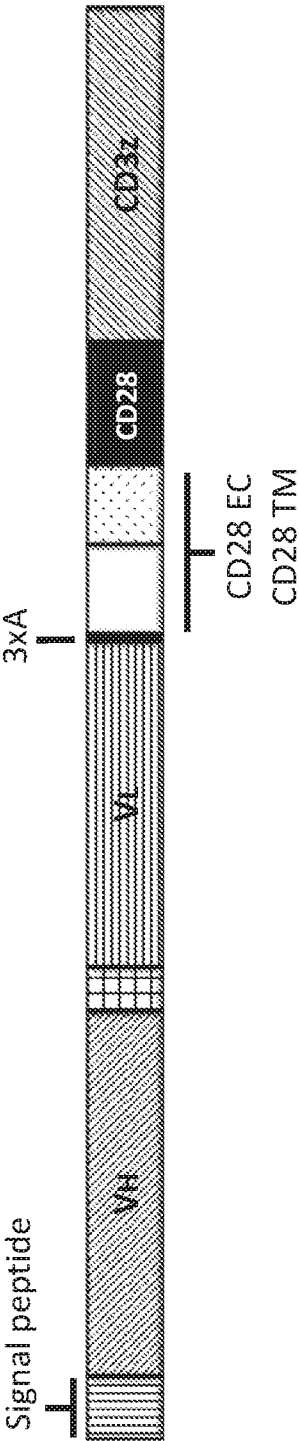


Figure 1E

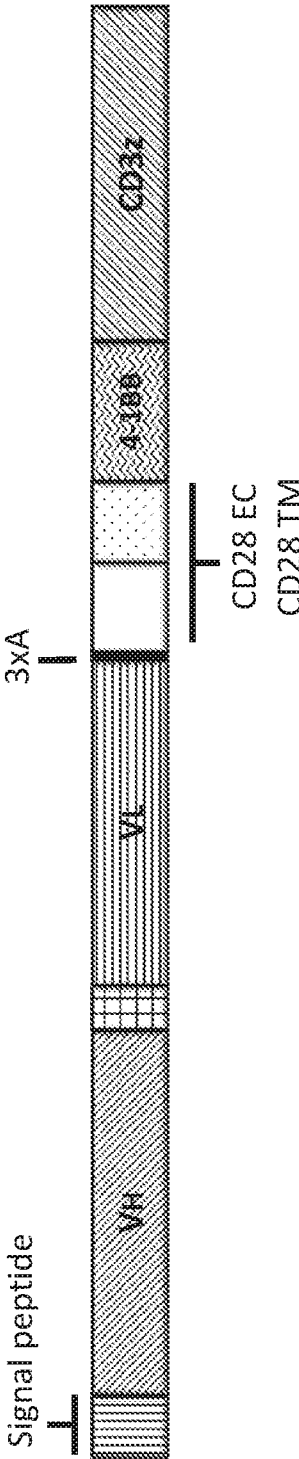


Figure 1F

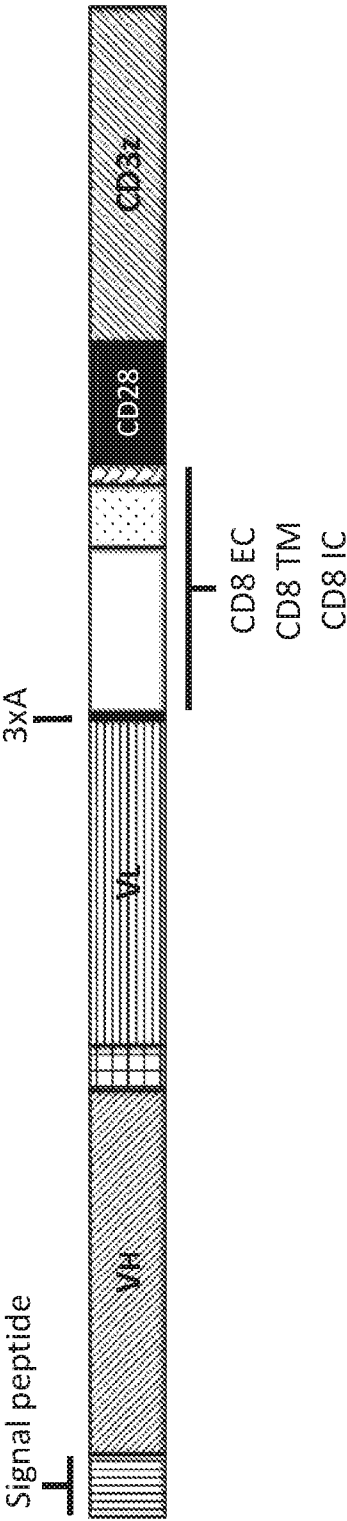


Figure 1G

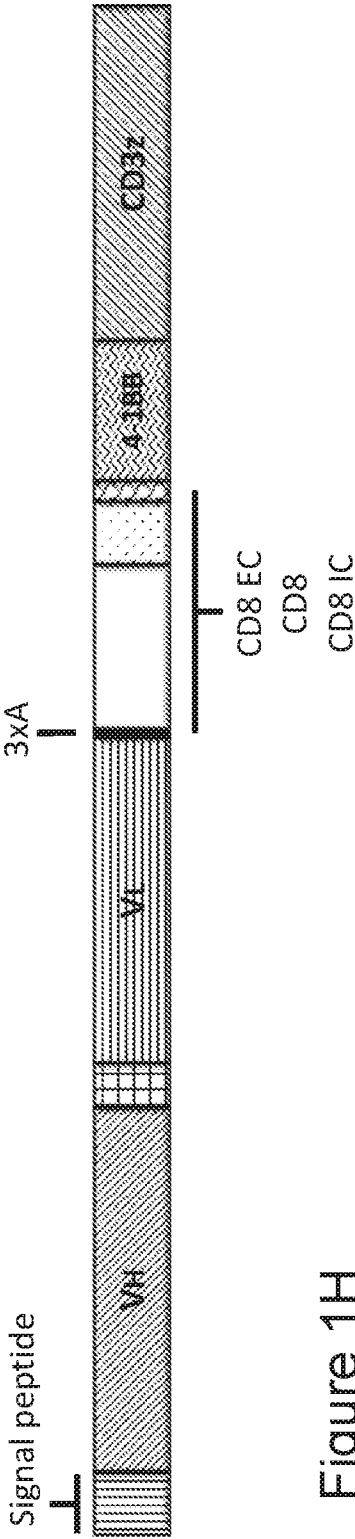


Figure 1H

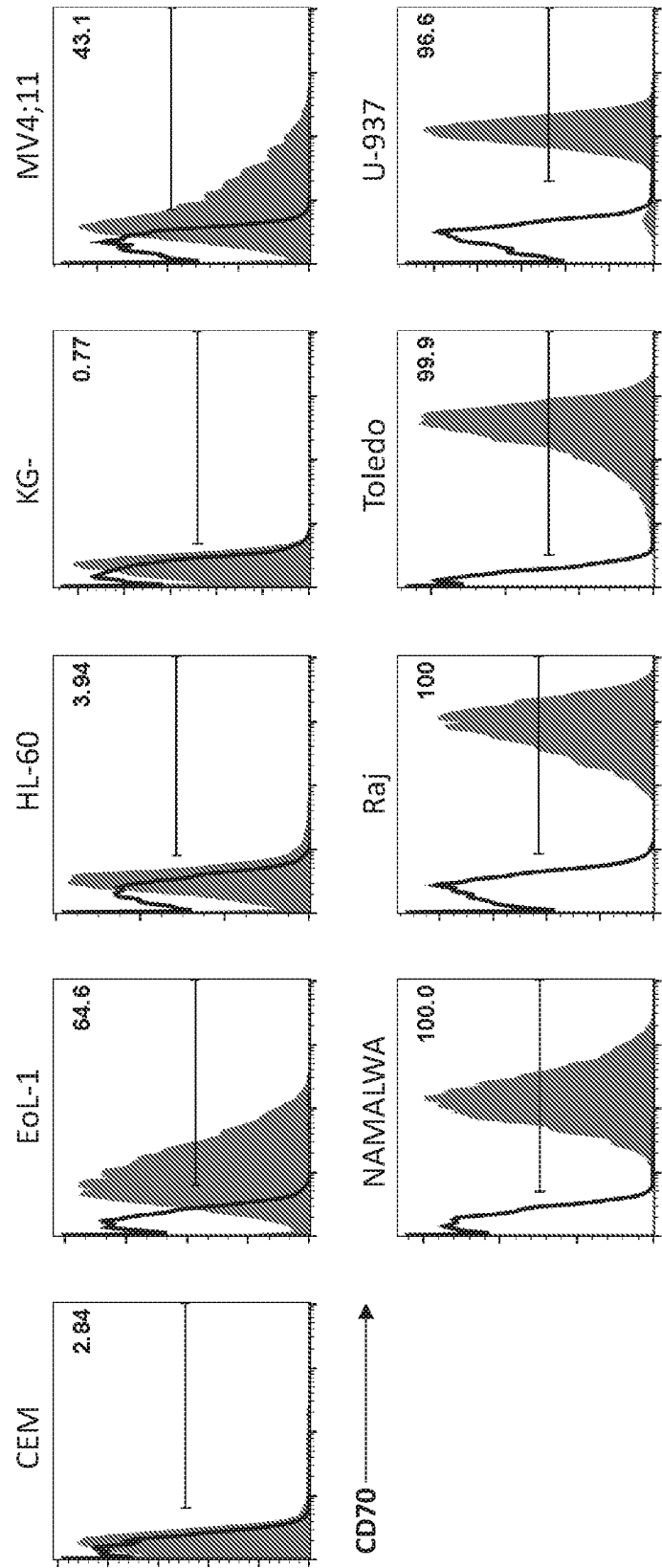


Figure 2

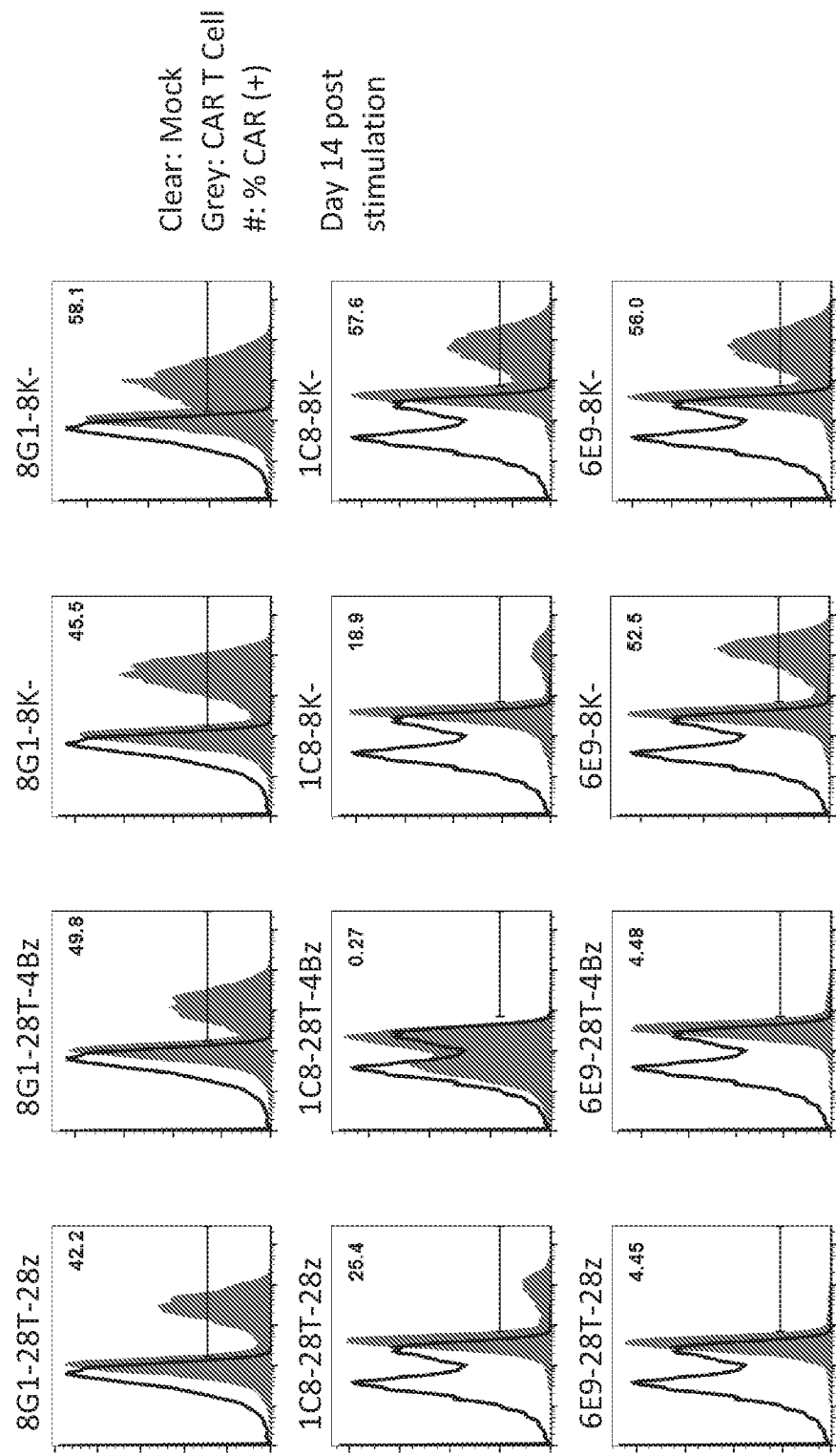


Figure 3A

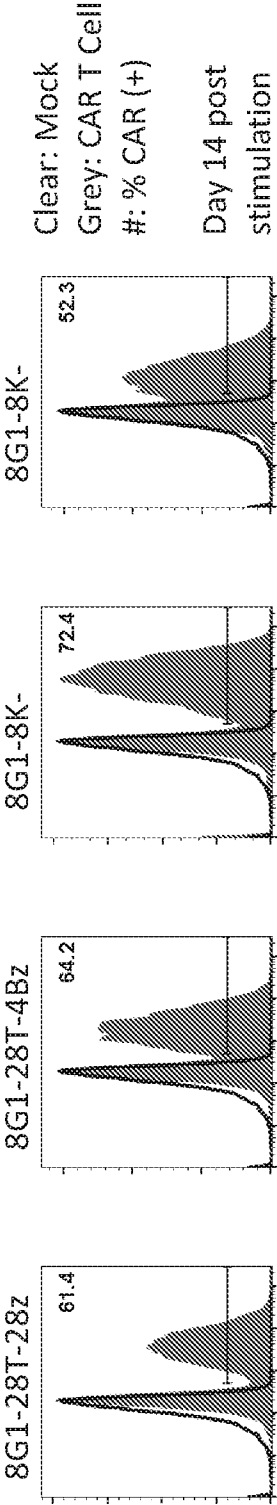


Figure 3B

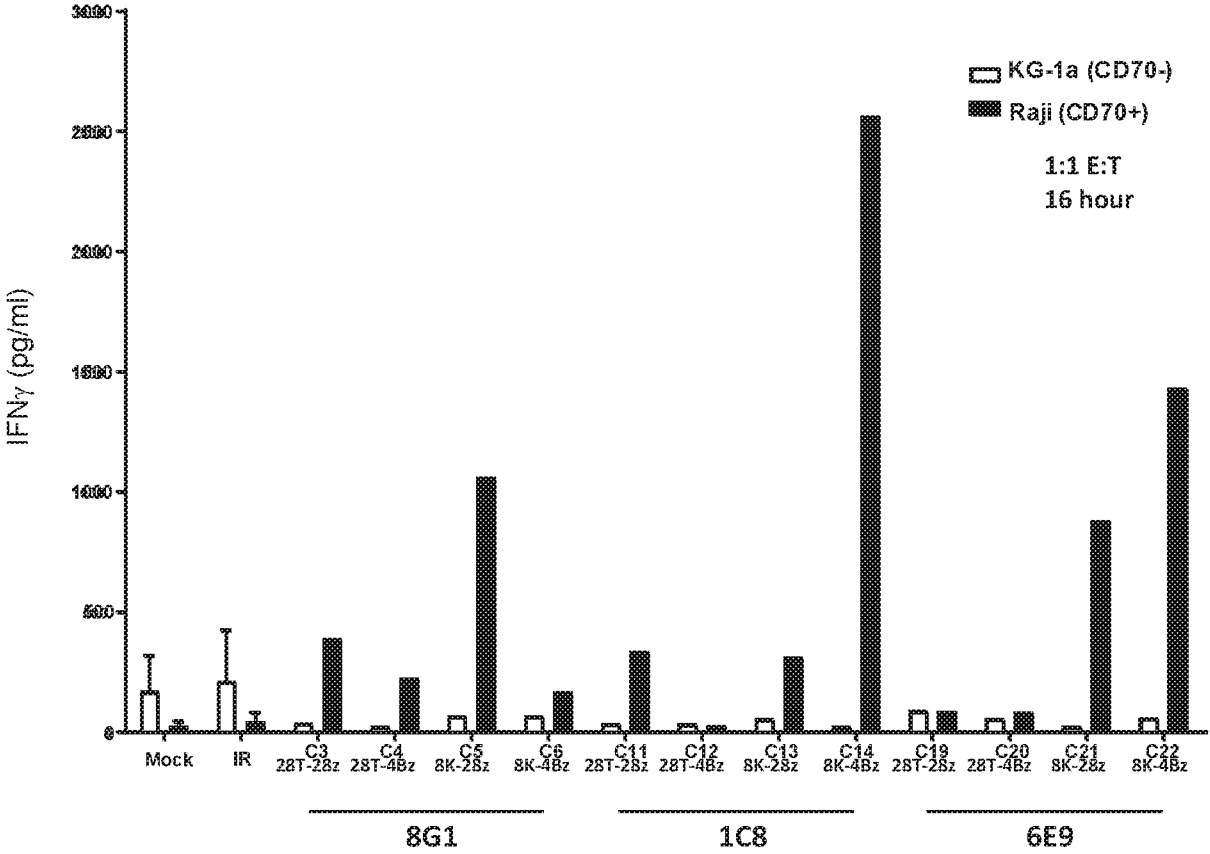
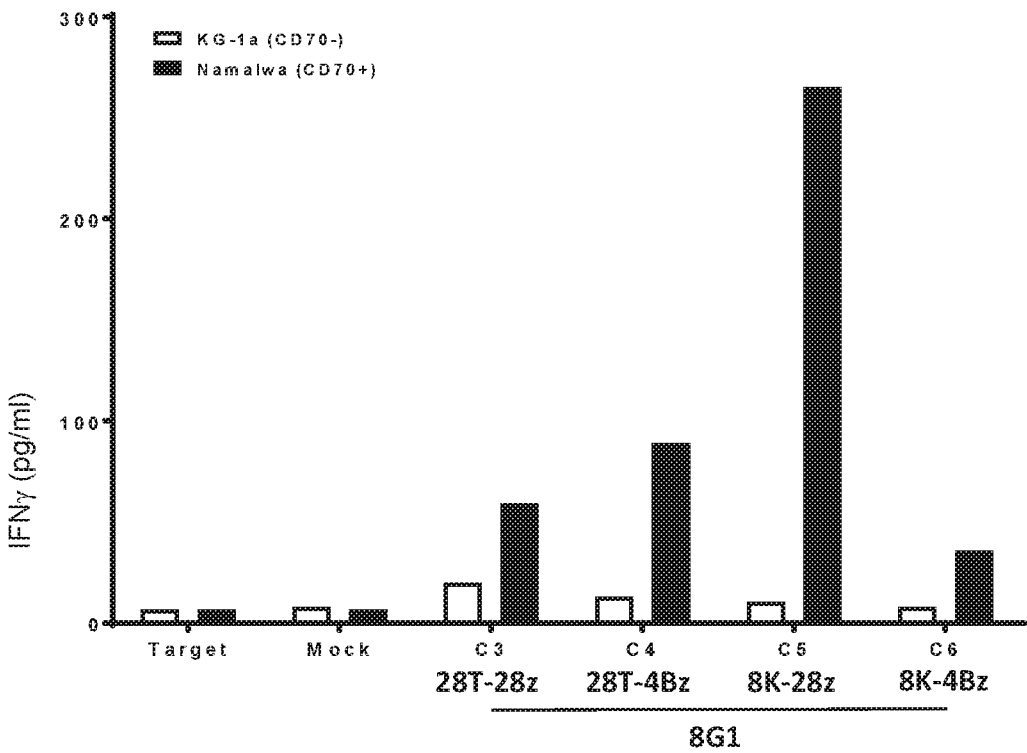


Figure 4A



1:1 E:T
16 hour

Figure 4B

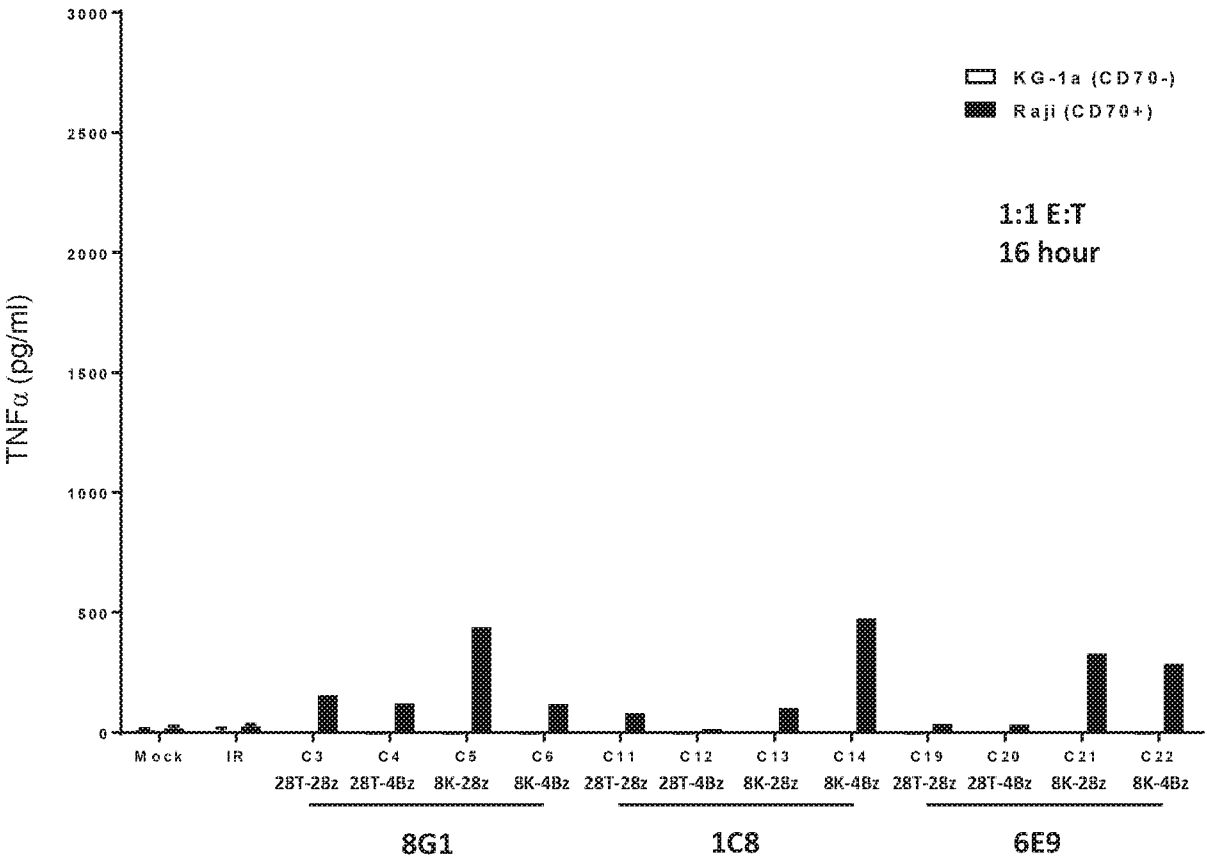


Figure 4C

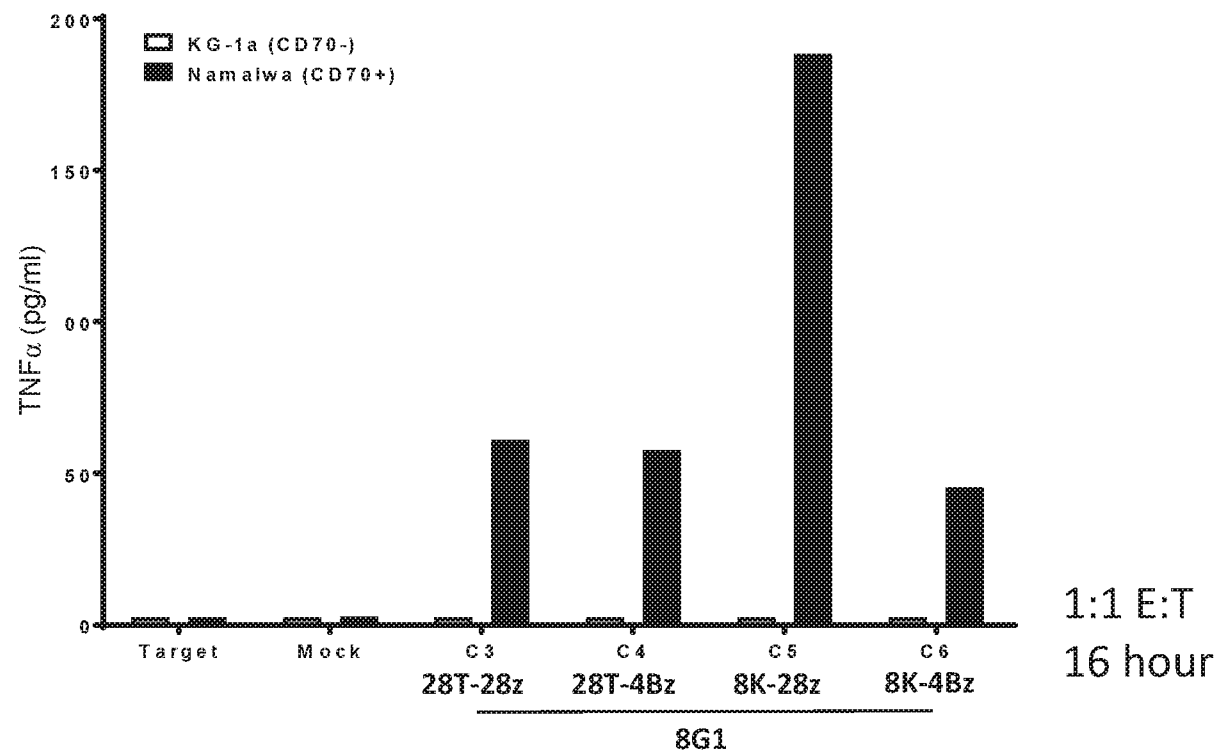


Figure 4D

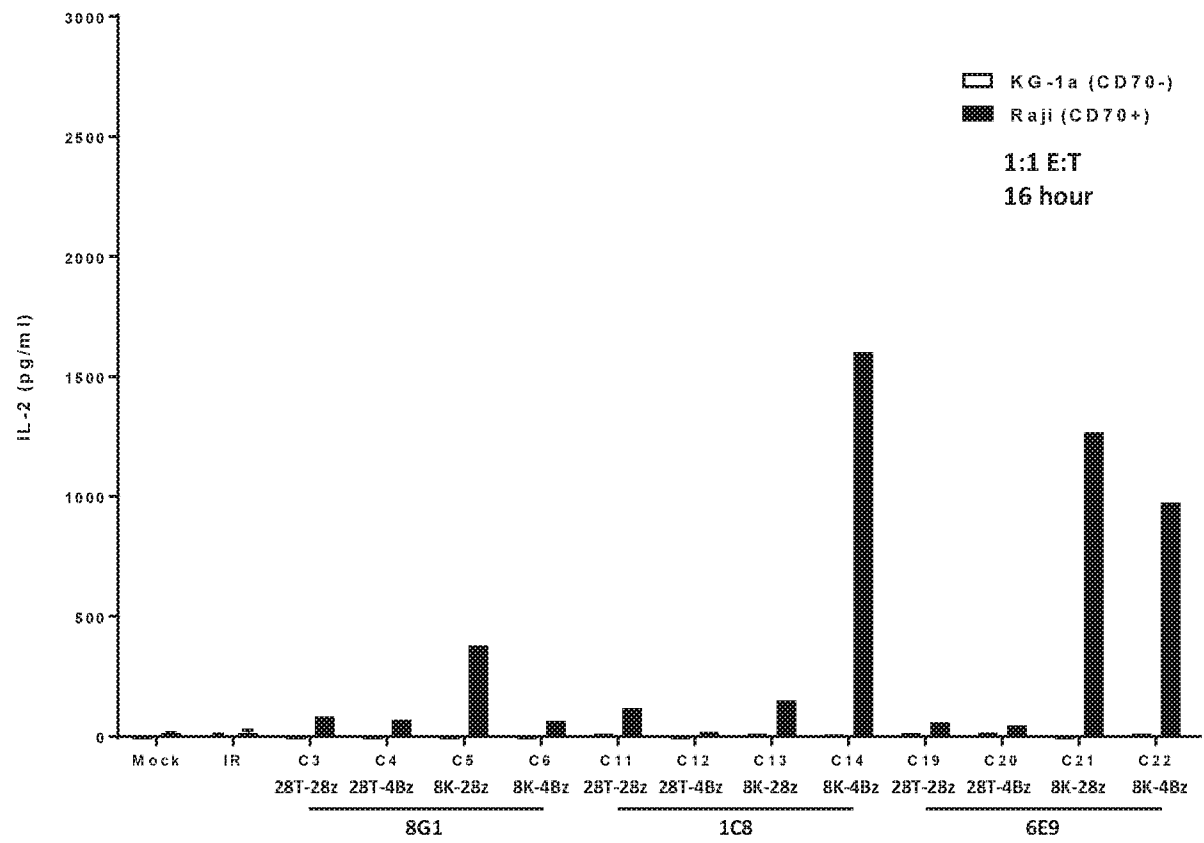


Figure 4E

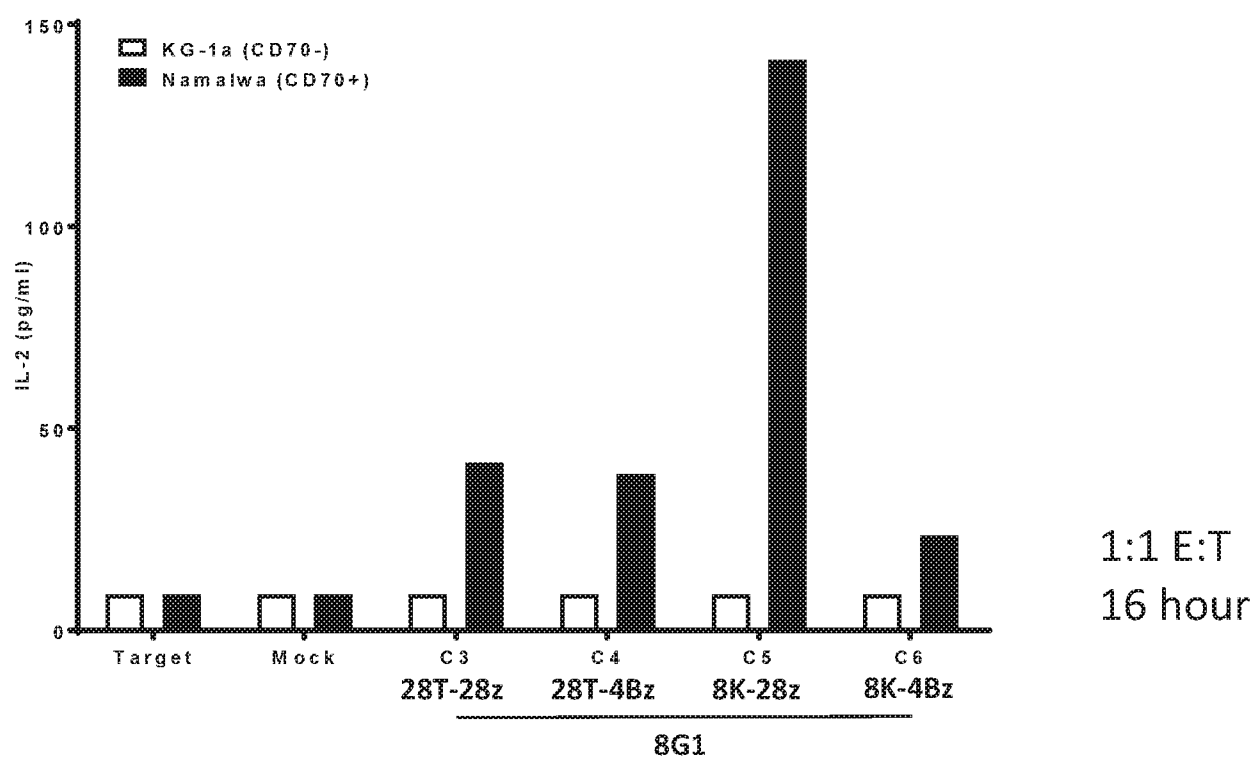


Figure 4F

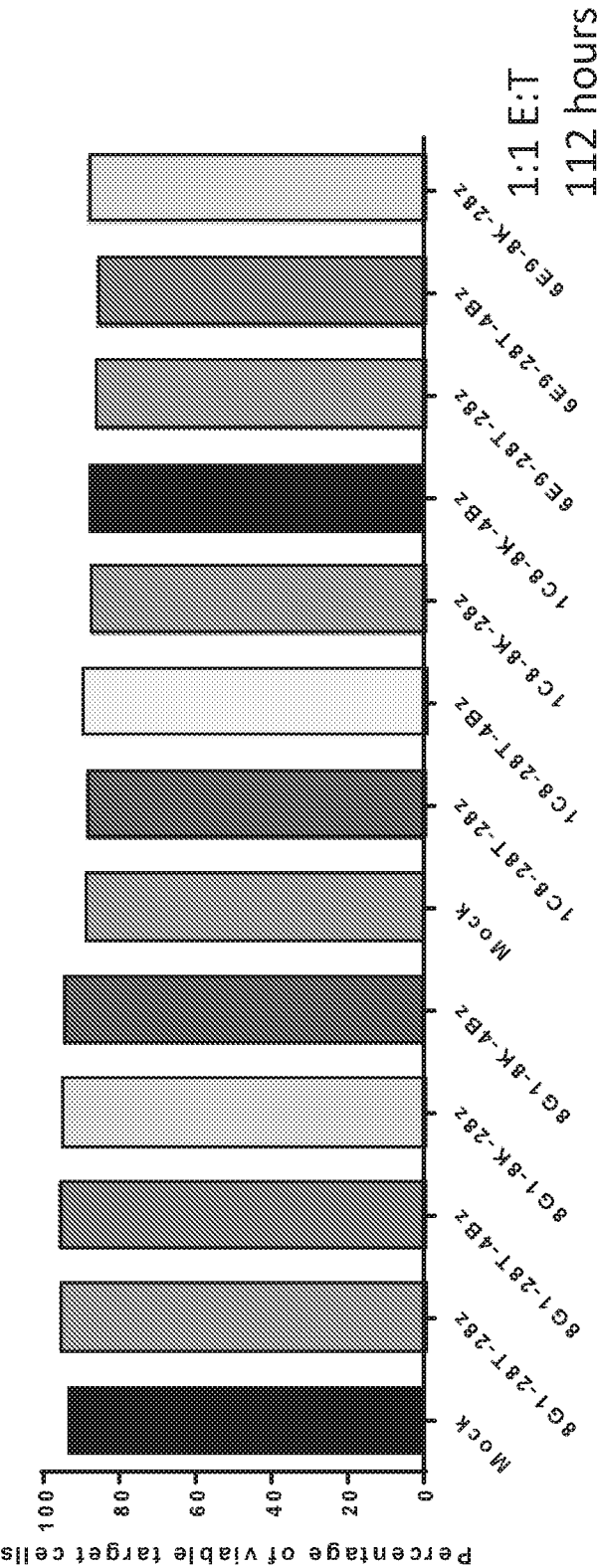


Figure 5A

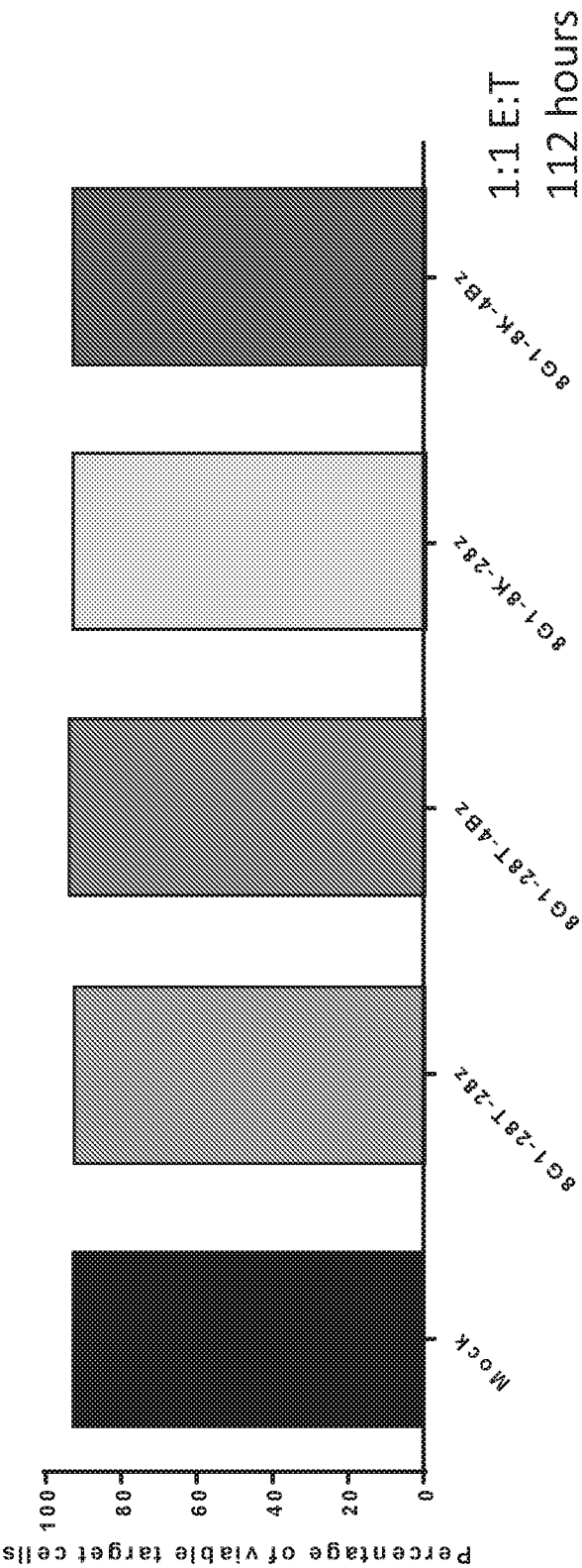


Figure 5B

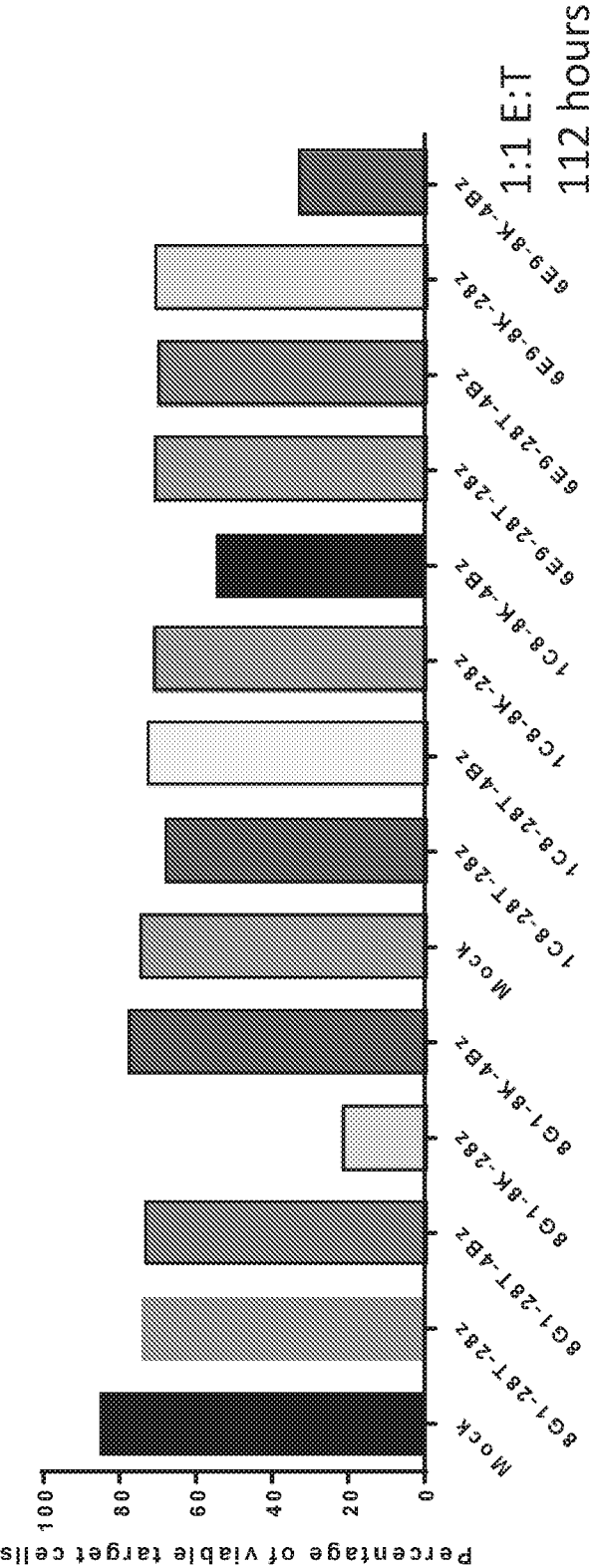


Figure 5C

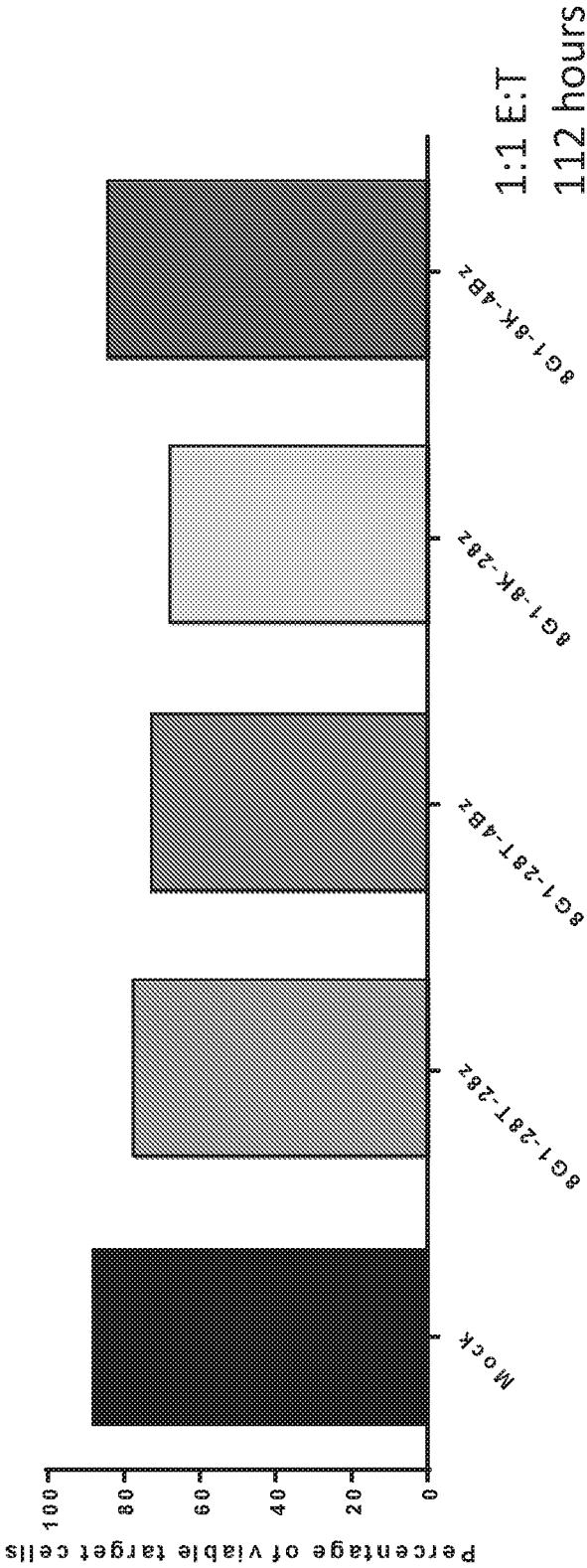


Figure 5D

Sequence	CDR1	Seq ID	CDR2	Seq ID	CDR3	Seq ID
8G1_VL	RASQSLRRIYLA	53	DVFDRAT	54	QQYSDSPFT	55
1C8_VL	RASQFIGRYFN	56	AESSLQS	57	QQSYSTPFT	58
6E9_VL	SGSSSNIGTNTVN	59	INNQRPS	60	ATWDDSLNGPVV	61
8G1_VH	SYGMH	62	VTWYDGSNKYYGDSVKG	63	DLLRGVKGYAMDV	64
1C8_VH	SGGYWS	65	YIFYSGSTDYNPSLKS	66	SGYSYALFDH	67
6E9_VH	SYLH	68	IVDPSGGSTSYDQKFQG	69	DYGDYVFDY	70

Table 1. CDR Table (Kabat)

Sequence	CDR1	Seq ID	CDR2	Seq ID	CDR3	Seq ID
8G1_VL	RASQSLRRIYLA	53	DVFDRAT	54	QQYSDSPFT	55
1C8_VL	RASQFIGRYFN	56	AESSLQS	57	QQSYSTPFT	58
6E9_VL	SGSSSNIGTNTVN	59	INNQRPS	60	ATWDDSLNGPVV	61
8G1_VH	GFTFSSY	71	WYDGSN	72	DLLRGVKGYAMDV	64
1C8_VH	GDSIISGGY	73	FYSGS	74	SGYSYALFDH	67
6E9_VH	GYTFTSY	75	DPSGGS	76	DYGDYVFDY	70

Table 2. CDR Table (Chothia)

Sequence	CDR1	Seq ID	CDR2	Seq ID	CDR3	Seq ID
8G1_VL	RASQSLRRIYLA	53	DVFDRAT	54	QQYSDSPFT	55
1C8_VL	RASQFIGRYFN	56	AESSLQS	57	QQSYSTPFT	58
6E9_VL	SGSSSNIGTNTVN	59	INNQRPS	60	ATWDDSLNGPVV	61
8G1_VH	GFTFSSYGMH	77	VTWYDGSNKYYGDSVKG	63	DLLRGVKGYAMDV	64
1C8_VH	GDSIISGGYYWS	78	YIFYSGSTDYNPSLKS	66	SGYSYALFDH	67
6E9_VH	GYTFTSYLH	79	IVDPSGGSTSYDQKFQG	69	DYGDYVFDY	70

Table 3. CDR Table (IMGT)**Figure 6**

SEQ ID NO	Description	Sequence
2	8G1 VH	CAAGAGCAGCTGGTTGAGTCTGGGGGGCGGCTGTCCAACCCGGCGGAGTCTGAGGTTGTCTCTG CGCTGCAAGCGGATTACATTTTCATCTTACGGCATGCACCTGGGTTAGGCAGGCTCCTGGAAAAGG GCTGGAGTGGTCCGGTGACTTGGTACGACGGCTCCAATAAGTATTATGGGGATTCCGTGAAAG GTCGATTACAAATTAGCAGGGATAAAGTCCAAAACACACTGTATCTCAAATGAACCTCCTTGAGGGC CGAGGACACGGCCGCTCTATTATTGTGCAAGAGACCTCCTCGGGGGCGTAAAGGGATATGCTATGGA CGTGTGGGGTCAGGGGACCACAGTTACTGTCAATTCA
3	8G1 VH	QEQLVESGGGVVQPRSLRLSCAASGFTSSYGMHWVRQAPGKGLEWVAVTWYDGSNKYYGDSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLLRGVKGYAMDVWGQGTITVTVSS
62	8G1 VH CDR1 (Kabat)	SYGMH
63	8G1 VH CDR2 (Kabat)	VTWYDGSNKYYGDSVKG
64	8G1 VH CDR3 (Kabat)	DLLRGVKGYAMDV
71	8G1 VH CDR1 (Chothia)	GFTFSSY
72	8G1 VH CDR2 (Chothia)	WYDGSN
64	8G1 VH CDR3 (Chothia)	DLLRGVKGYAMDV
77	8G1 VH CDR1 (IGMT)	GFTFSSYGMH
63	8G1 VH CDR2 (IGMT)	VTWYDGSNKYYGDSVKG
64	8G1 VH CDR3 (IGMT)	DLLRGVKGYAMDV

Figure 7A

SEQ ID NO	Description	Sequence
4	8G1 VL	GAAATCGTTCTCACTCAGTCTCCGGGCACACTGTCCCTCAGCCCCGGAGAGCGAGCCACTTTGAGCT GCCGGCCAGCCAGTCACTTAGACGCATTATTTGGCCTGGTATCAGCAGAAACCAGGCCAGGCGC CCAGGCTGCTGATATACGATGTGTCGATAGGGCCACGGGTATCCCCGATAGGTTCTCTGGCGGGG GGTCCGGGACTGACTTCACTTCACTTCACTATATCAGACTCGAGCCGAAAGACTTCGACGTTTATTG CCAGCAGTACTCCGACTCCCACTTCACTTCCGCCCTGGTACCAAGTGGATATTAAACGG EIVLTQSPGTLSLSPGERATLSCRASQSLRRIYLAWYQQKPGQAPRLIYDVFDRAITGIPDRFSGGGSGTD FTLTISRLEPEDFAVYVYQQYSDSPFTFGPGTKVDIKR
5	8G1 VL	RASQSLRRIYLA
53	8G1 VL CDR1 (Kabat)	DVFDRAT
54	8G1 VL CDR2 (Kabat)	QQYSDSPFT
55	8G1 VL CDR3 (Kabat)	RASQSLRRIYLA
53	8G1 VL CDR1 (Chothia)	DVFDRAT
54	8G1 VL CDR2 (Chothia)	QQYSDSPFT
55	8G1 VL CDR3 (Chothia)	RASQSLRRIYLA
53	8G1 VL CDR1 (IGMT)	DVFDRAT
54	8G1 VL CDR2 (IGMT)	QQYSDSPFT
55	8G1 VL CDR3 (IGMT)	

Figure 7B

SEQ ID NO	Description	Sequence
6	1C8 VH	CAGGTGCAGCTCCAAGAACTGGACCGGGTCTCGTCAAGCCATCACAGACACTGTCCCTGACCTGC ACCGTCTCCGGCGACTCTATCATTTACGGCGGCTACTATTGGTCTCGGATTAGACAACATCCGGGAA AGGGTCTTGAATGGATCGGCTATATTTCTACAGCGGGAGTACGGATTACAATCCTAGTCTCAAGAG CCGGTTACCAATTCAGTGGATACTTCAAAAACCAGTTTAGCCTGAAGCTGTCTTCTGTAAACAGCTG CTGACACAGCCGTGTACTATTGGCCAGGAGCGGTACAGCTATGCCCTGTTTGACCACTGGGGGC AAGGCACTCTTGTGACGGGTGCAAGT
7	1C8 VH	QVQLQESGPGLVKPSQTLSTCTVSGDSIISGGYWSWIRQHPGKGLEWIGYIFYSGSTDYNPSLKSRTI SVDTSKNQFSLKLSVTAADTAVYYCARSGYSYALFDHWGQGLTVTVSS
65	1C8 VH CDR1 (Kabat)	SGGYWS
66	1C8 VH CDR2 (Kabat)	YIFYSGSTDYNPSLKS
67	1C8 VH CDR3 (Kabat)	SGYSYALFDH
73	1C8 VH CDR1 (Chothia)	GDSIISGGY
74	1C8 VH CDR2 (Chothia)	FYSGS
67	1C8 VH CDR3 (Chothia)	SGYSYALFDH
78	1C8 VH CDR1 (IGMT)	GDSIISGGYWS
66	1C8 VH CDR2 (IGMT)	YIFYSGSTDYNPSLKS
67	1C8 VH CDR3 (IGMT)	SGYSYALFDH

Figure 7C

SEQ ID NO	Description	Sequence
8	1C8 VL	GACATTCAAAATGACGCAGTCCCAAGTTCTCTGTCCGCTAGCGTCGGCGACCGAGTGACCATCAGCT GCCGAGCATCCCAGTTTATCGGTAGATAATTTCAATTGGTACCAGCAACAACCGGGCAAAGCGCCCA AGGTCCTGATCTACGCTGAGAGCAGTCTGCAATCCGGCGTACCTAGCAGGTTCTCCGGAAGTGCCA GGGAACCGAGTTCACCTGACAATTAGCTCCTTGACGCCGAGGATTCGCTCGCTATTACTGTCA ACAGAGTTATTCAACCCCTTTACATTCCGACAGGAACTAAAGTTGAAATTAAGAGG DIQMTQSPSSLSASVGDRTISCRASQFIGRYFNWYQQPGKAPKVLIAESSLQSGVPSRFSGSGSGTE FTLTISLQPEDFARYYCCQSYSTPFTFGQGTKVEIKR
9	1C8 VL	RASQFIGRYFN
56	1C8 VL CDR1 (Kabat)	AESSLQS
57	1C8 VL CDR2 (Kabat)	QQSYSTPFT
58	1C8 VL CDR3 (Kabat)	RASQFIGRYFN
56	1C8 VL CDR1 (Chothia)	AESSLQS
57	1C8 VL CDR2 (Chothia)	QQSYSTPFT
58	1C8 VL CDR3 (Chothia)	RASQFIGRYFN
56	1C8 VL CDR1 (IGMT)	AESSLQS
57	1C8 VL CDR2 (IGMT)	QQSYSTPFT
58	1C8 VL CDR3 (IGMT)	RASQFIGRYFN

Figure 7D

SEQ ID NO	Description	Sequence
10	6E9 VH	CAGGTACACCTGGTGACAGCGGGGGGAGGTCAAGAAACCGGGCGCATCCGTACGCGTGAGCT GCAAGGCCTCCGGATACACITTTACTTCTTACTATCTGCAATGGGTACGGCAGGCACCGGGTCAAGG ACTGGAGTGGATGGGCATTGTGGACCCCAAGCGGAGGAGTACGTATATGATCAGAAGTTTCAAG GTAGGTTTACCATGACACGGGACACGTCAACGAGTACCGTCTACATGGAGCTCAGTAGTCTGCGGA GCGAAGACACCGCAGTCTACTACTGCGCACGCGATTATGGAGACTATGTCTTTGACTATTGGGGGC AGGGGACGCTCGTGACCGTTTCAAGC
11	6E9 VH	QVHLVQSGAEVKKPGASVRVSKASGYTFTSYLHWVRQAPGQGLEWMGIVDPSGGSTSYDQKFQGR FTMTRDTSTSTVYMELSLRSEDYVYVCARDYGDYVFDYWGQGLTVTVSS
68	6E9 VH CDR1 (Kabat)	SYLH
69	6E9 VH CDR2 (Kabat)	IVDPSGGSTSYDQKFQG
70	6E9 VH CDR3 (Kabat)	DYGDYVFDY
75	6E9 VH CDR1 (Chothia)	GYFTSY
76	6E9 VH CDR2 (Chothia)	DPSGGS
70	6E9 VH CDR3 (Chothia)	DYGDYVFDY
79	6E9 VH CDR1 (IGMT)	GYFTSYLH
69	6E9 VH CDR2 (IGMT)	IVDPSGGSTSYDQKFQG
70	6E9 VH CDR3 (IGMT)	DYGDYVFDY

Figure 7E

SEQ ID NO	Description	Sequence
12	6E9 VL	CAAAAGCGTACTGACACAGCCCCCGAGTGCATCCGGGACCCCCCGCCAAAGGGTTACAATCAGCTGC TCTGGCAGCTCCAGTAACATAGGTACCAACACGGTGAACCTGGTACCAGCAGTTGCCTGGCACAGCG CCTCAGCTGCTCATCTATATCAACAATCAGCGGCCAAGTGGCGTCCCCGATAGATTCTCAGGCTCAA AGAGCGGAACCAAGCGTAGCTTGGCAATCAGTGGCCTTCAATCCGAAGACGAAAGCCGATTACTATT GTGCGACCTGGGACGATAGCTGAACGGCCCCCGTCTGGCGCGGGGACGAAACTGACAGTGTG GGC
13	6E9 VL	QSVLTQPPSASGTPGQRVITSCSGSSNIGTNTVNWYQQLPGTAPQLLIYINNQRPSGVPDRFSGSKSGT SASLAISGLOSEADYYCATWDDSLNGPVPVGGGTKLTVLG
59	6E9 VL CDR1 (Kabat)	SGSSSNIGTNTVN
60	6E9 VL CDR2 (Kabat)	INNQRPS
61	6E9 VL CDR3 (Kabat)	ATWDDSLNGPW
59	6E9 VL CDR1 (Chothia)	SGSSSNIGTNTVN
60	6E9 VL CDR2 (Chothia)	INNQRPS
61	6E9 VL CDR3 (Chothia)	ATWDDSLNGPW
59	6E9 VL CDR1 (IGMT)	SGSSSNIGTNTVN
60	6E9 VL CDR2 (IGMT)	INNQRPS
61	6E9 VL CDR3 (IGMT)	ATWDDSLNGPW

Figure 7F

8G1.1_C28T_28z Coding Sequence

ATGGCACTCCCCGTAAGTGTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCGCACGCCCCGAAGAGCAGCTGG
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8G1.1_C28T_28z Amino Acid Sequence

MALPVTALLPLALLHAARPQEQLVESGGGVVQPGRSLRLSCAASGFTFSYGMHWVRQAPGKGLEWVAVTWYDG
SNKYYGDSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDLLRGVKGYAMDVWGQGTITVSSGGGGSGGGG
SGGGGSEIVLTQSPGTLSPGERATLSCRASQSLRRIYLAWYQQKPGQAPRLLIYDVFD RATGIPDRFSGGGSGTDFTLT
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SLLVTVAFIIFWVRSKRSRLHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQLYNEL
NLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGH DGLYQGLSTATKDT
YDALHMQALPPR (Seq. ID No. 30)

Figure 8A

8G1.1_C28T_4Bz Coding Sequence

TGGCACTCCCCGTAAGTCTGCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCGCACGCCCCGAAGAGCAGCTGGT
TGAGTCTGGGGGCGGCGTCGTCCAACCCGGCCGGAGTCTGAGGTTGTCCTGCGCTGCAAGCGGATTTACATTTTC
ATCTTACGGCATGCACTGGGTTAGGCAGGCTCCTGGAAAAGGGCTGGAGTGGGTGCGGGTGACTTGGTACGACG
GCTCCAATAAGTATTATGGGGATTCCGTGAAAGGTCGATTACAAATTAGCAGGGATAACTCCAAAAACACACTGT
ATCTCAAATGAAGTCTTGAGGGCCGAGGACACGGCCGTCTATTATTGTGCAAGAGACCTCCTCCGGGGCGTAA
AGGGATATGCTATGGACGTGTGGGGTCAGGGGACCACAGTTACTGTCAAGTTCAGGTGGCGGTGGCAGTGGCGGC
GGGGGAAGTGGAGGCGGGGGCTCTGAAATCGTTCTCACTCAGTCTCCGGGCACACTGTCCCTCAGCCCCGGAGA
GCGAGCCACTTTGAGCTGCCGGGCCAGCCAGTCACTTAGACGCATTTATTTGGCCTGGTATCAGCAGAAACCAGG
CCAGGCGCCAGGCTGCTGATATACGATGTGTTGATAGGGCCACGGGTATCCCCGATAGGTTCTCTGGCGGGGG
GTCCGGGACTGACTTCACCCCTCACTATATCACGACTCGAGCCCGAAGACTTCGCAAGTTTATTATTGCCAGCAGTACT
CCGACTCCCCATTACCTTCGGCCCTGGTACCAAAGTGGATATTAACGGGGCCGCTGCCCTTGATAATGAAAAGTC
AAACGGAACAATCATTACGTGAAGGGCAAGCACCTCTGTCCGTCACCTTGTTCCCTGGTCCATCCAAGCCATTCT
GGGTGTTGGTTCGTAGTGGGTGGAGTCTCGCTTGTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTT
CGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAGCTGCTGTACATTTTCAAACAGCCGTTTATGAGGCCGGTCCAA
ACGACTCAGGAAGAAGACGGCTGCTCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGA
AGTTTTCCAGATCTGCAGATGCACAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGAC
GCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAA
AAACCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAA
AGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGAAGGATACTTAT
GACGCTCTCCACATGCAAGCCCTGCCACCTAGG (Seq. ID No. 31)

8G1.1_C28T_4Bz Amino Acid Sequence

MALPVTALLPLALLHAARPQEQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVTWYDG
SNKYYGDSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDLLRGVKGYAMDVWVGQTTVTVSSGGGSGGGG
SGGGGSEIVLTQSPGTLSPGERATLSCRASQSLRRIYLA WYQQKPGQAPRLIYDVFD RATGIPDRFSGGSGTDFTLT
ISRLEPEDFAVYYCQYSDSPFTFGPGTKVDIKRAAALDNEKSNGTIIHVKGKHLCP SPLFPGPSKPFVVLVVGGVLACY
SLLVTVAFIIFWVRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL RVKFSRSADAPAYQQGQNQ
LYNELNLGRREEYDLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLST
ATKDTYDALHMQALPPR (Seq ID No. 32)

Figure 8B

8G1.1_C8K_28z Coding Sequence

ATGGCACTCCCCGTAAGTGTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCGCACGCCCCGAAGAGCAGCTGG
TTGAGTCTGGGGGCGGCGTCGTCCAACCCGCGGAGTCTGAGGTTGCTCCTGCGCTGCAAGCGGATTTACATTTT
CATCTTACGGCATGCACTGGGTTAGGCAGGCTCCTGGAAAAGGGCTGGAGTGGGTCGCGGTGACTTGGTACGAC
GGCTCCAATAAGTATTATGGGGATTCCGTGAAAGGTCGATTACAATTAGCAGGGATAACTCCAAAAACACACTG
TATCTCAAATGAACTCCTTGAGGGCCGAGGACACGGCCGTCTATTATTGTGCAAGAGACCTCCTCCGGGGCGTA
AAGGGATATGCTATGGACGTGTGGGGTCAGGGGACCACAGTTACTGTGAGTTCAGGTGGCGGTGGCAGTGGCGG
CGGGGGAAGTGGAGGCGGGGGCTCTGAAATCGTTCTCACTCAGTCTCCGGGCACACTGTCCCTCAGCCCCGGAG
AGCGAGCCACTTTGAGCTGCCGGCCAGCCAGTCACTTAGACGCATTTATTTGGCCTGGTATCAGCAGAAACCAG
GCCAGGCGCCAGGCTGCTGATATACGATGTGTTGATAGGGCCACGGGTATCCCCGATAGGTTCTCTGGCGGGG
GGTCCGGGACTGACTTACCCTCACTATATCACGACTCGAGCCCGAAGACTTCGCAGTTTATTATTGCCAGCAGTA
CTCCGACTCCCCATTACCTTCGGCCCTGGTACCAAAGTGGATATTAACGGGGCCGCTGCCTTCGTGCCTGTTTTTC
TGCCCGCGAAACCCACAACCTACCCCGCCCTCGGCCCCCAACTCCTGCACCAACTATCGCTTCCCAACCCCTGTCT
CTGAGACCTGAGGCATGCCGCCCCGCGGCAGGCGGCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGATATT
TATATCTGGGCCCCCTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTGGTGATTACCCTCTACTGCAACCACA
GAAACAGATCCAAAAGAAGCCGCTGCTCCATAGCGATTACATGAATATGACTCCACGCCGCCCTGGCCCCACAA
GGAAACACTACCAGCCTTACGCACCACCTAGAGATTTGCTGCCTATCGGAGCAGGGTGAAGTTTTCCAGATCTGC
AGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATG
ACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCAAGGAGGG
TCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAGAA
GGGGAAAAGGGCACGACGTTTGTACCAGGGACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGC
AAGCCCTGCCACCTAGG (Seq. ID No. 33)

8G1.1_C8K_28z Amino Acid Sequence

MALPVTALLLPLALLHAARPQEQLVESGGGVVQPGRSLRLSCAASGFTFSYGMHWVRQAPGKGLEWVAVTWYDG
SNKYYGDSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARDLLRGVKGYAMDVWGQGTITVSSGGGGSGGGG
SGGGGSEIVLTQSPGTLSPGERATLSCRASQSLRRIYLAWYQQKPGQAPRLIYDVFDRTATGIPDRFSGGGSGTDFLT
ISRLEPEDFAVYYCQYSDSPFTFGPGTKVDIKRAAAFVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGA
VHTRGLDFACDIYWAPLAGTCGVLLSLVITLYCNHRNRSKRSRLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYR
SRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIG
MKGERRRGKGDGLYQGLSTATKDTYDALHMQALPPR (Seq. ID No. 34)

Figure 8C

8G1.1_C8K_4Bz Coding Sequence

GTTCTCACTCAGTCTCCGGGCACACTGTCCCTCAGCCCCGGAGAGCGAGCCACTTTGAGCTGCCGGGCCAGCCAGT
CACTTAGACGCATTTATTTGGCCTGGTATCAGCAGAAACCAGGCCAGGCGCCAGGCTGCTGATATACGATGTGTT
CGATAGGGCCACGGGTATCCCCGATAGGTTCTCTGGCGGGGGTCCGGGACTGACTTCACCCTCACTATATCACG
ACTCGAGCCCCAAGACTTCGCAGTTTATTATTGCCAGCAGTACTCCGACTCCCCATTACCTTCGGCCCTGGTACCA
AAGTGGATATTAAACGGGCGCTGCCTTCGTGCCTGTTTTCTGCCGCGAAACCCACAACCTACCCCCGCCCTCG
GCCCCCAACTCCTGCACCAACTATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCATGCCGCCCCGCGGCAGGC
GGCGCCGTGCACACTAGAGGCTGGACTTCGCCTGCGATATTTATATCTGGGCCCCCTTGCCGGGACATGCGGG
GTACTGCTGCTGTCTCTGGTGATTACCTCTACTGCAACCACAGAAACCGCTTTTCCGTCGTTAAGCGGGGGAGAA
AAAAGCTGCTGTACATTTTCAAACAGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAGAAGACGGCTGCTCCT
GCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGCG
TATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAA
GCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAG
CTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGC
ACGACGTTTTGTACCAGGGACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACC
TAGG (Seq ID No. 35)

8G1.1_C8K_4Bz Amino Acid Sequence

MALPVTALLLPLALLLHAARPQEQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVTWYDG
SNKYYGDSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDLLRGVKGYAMDVWGQGTTVTVSSGGGGSGGGG
SGGGGSEIVLTQSPGTLSPGERATLSCRASQSLRRIYLAWYQQKPGQAPRLIYDVFD RATGIPDRFSGGGSGTDFLT
ISRLEPEDFAVYYCQYSDSPFTFGPGTKVDIKRAAAFVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGA
VHTRGLDFACDIYWAPLAGTCGVLLSLVITLYCNHRNRF SVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEE
GGCEL RVKFSRSADAPAYQQGNQLYNELNLGRREEYDVLDRRGRDP EMGGKPRRKNPQEGLYNELQDKMAEAY
SEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR (Seq. ID No. 36)

Figure 8D

1C8.1.001_C28T_28z Coding Sequence

ATGGCACTCCCCGTAAGTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCGCACGCCCCGAGGTGCAGCTCC
AAGAATCTGGACCGGGTCTCGTCAAGCCATCACAGACACTGTCCCTGACCTGCACCGTCTCCGGCGACTCTATCAT
TTCAGGCGGCTACTATTGGTCTGGATTAGACAACATCCGGGAAAGGGTCTTGAATGGATCGGCTATATTTTCTAC
AGCGGGAGTACGGATTACAATCCTAGTCTCAAGAGCCGCGTTACCATTTCAGTGGATACTTCAAAAAACCAGTTTA
GCCTGAAGCTGTCTTCTGTAACAGCTGCTGACACAGCCGTGACTATTGCGCCAGGAGCGGCTACAGCTATGCCCT
GTTTGACCACTGGGGGGCAAGGCACTCTTGTGACGGTGTCAAGTGGAGGGGGGAGGATCAGGCGGCGGGGGATCC
GGCGGCGGGGGTAGTGACATTCAAATGACGCAGTCCCCAAGTTCTCTGTCCGCTAGCGTCGGCGACCGAGTGACC
ATCAGCTGCCGAGCATCCCAGTTTATCGGTAGATATTTCAATTGGTACCAGCAACAACCGGGCAAAGCGCCCCAAG
GTCCTGATCTACGCTGAGAGCAGTCTGCAATCCGGCGTACCTAGCAGGTTCTCCGGAAGTGGCAGCGGAACCGAG
TTCACCCTGACAATTAGCTCCTTGACGCCCCGAGGATTCGCTCGCTATTACTGTCAACAGAGTTATTCAACCCCTTTT
ACATTTCGGACAGGGAACTAAAGTTGAAATTAAGAGGGCCGCTGCCCTTGATAATGAAAAGTCAAACGGAACAATC
ATTCACGTGAAGGGCAAGCACCTCTGTCCGTACCCCTGTTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGT
AGTGGGTGGAGTCCTCGCTTGTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTAGATCCAAAAGAA
GCCGCTGCTCCATAGCGATTACATGAATATGACTCCACGCCGCCCTGGCCCCACAAGGAAACACTACCAGCCTTA
CGCACCACTAGAGATTCGCTGCCTATCGGAGCAGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGCGTATCA
GCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCA
GAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCAAGGAGGGTCTCTATAATGAGCTGCAG
AAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACG
GTTTGTACCAGGGAAGTCAAGCTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGG
(Seq. ID No. 37)

1C8.1.001_C28T_28z Amino Acid Sequence

MALPVTALLPLALLHAARPQVQLQESGPGLVKPSQTLSTCTVSGDSIISGGYYWSWIRQHPGKGLEWIGYIFYSGST
DYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARSGYSYALFDHWGQGLTVTVSSGGGGSGGGSGGGGSDI
QMTQSPSSLSASVGDRVTISCRASQFIGRYFNWYQQQPGKAPKVLIIAESSLQSGVPSRFSGSGSGTEFTLTISLQPEDF
ARYYCQQSYSTPFTFGQGTKVEIKRAAALDNEKSNGTIIHVKGKHLCPSPLPFGPSKPFVVLVVGGVLACYSLLVTVAFI
IFWVRSKRSRLLHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQLYNELNLGRREEY
DVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDLGYQLGLSTATKDTYDALHMQ
ALPPR (Seq. ID No. 38)

Figure 8E

1C8.1.001_C28T_4Bz Coding Sequence

ATGGCACTCCCCGTAAGTCTGCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCGCACGCCCCGAGGTGCAGCTCC
AAGAATCTGGACCGGGTCTCGTCAAGCCATCACAGACACTGTCCCTGACCTGCACCGTCTCCGGCGACTCTATCAT
TTCAGGCGGCTACTATTGGTCTGGATTAGACAACATCCGGGAAAGGGTCTTGAATGGATCGGCTATATTTTCTAC
AGCGGGAGTACGGATTACAATCCTAGTCTCAAGAGCCGCGTTACCATTTCAGTGGATACTTCAAAAAACCAGTTTA
GCCTGAAGCTGTCTTCTGTAACAGCTGCTGACACAGCCGTGACTATTGCGCCAGGAGCGGCTACAGCTATGCCCT
GTTTGACCACTGGGGGGCAAGGCACTCTTGTGACGGTGTCAAGTGGAGGGGGGAGGATCAGGCGGCGGGGGGATCC
GGCGGCGGGGGTAGTGACATTCAAATGACGCAGTCCCCAAGTTCTGTGTCGCTAGCGTCGGCGACCGAGTGACC
ATCAGCTGCCGAGCATCCCAGTTTATCGGTAGATATTTCAATTGGTACCAGCAACAACCGGGCAAGCGCCCCAAG
GTCCTGATCTACGCTGAGAGCAGTCTGCAATCCGGCGTACCTAGCAGGTTCTCCGGAAGTGGCAGCGGAACCGAG
TTCACCCTGACAATTAGCTCCTTGACGCCCCGAGGATTCGCTCGCTATTACTGTCAACAGAGTTATTCAACCCCTTTT
ACATTCCGACAGGGAACTAAAGTTGAAATTAAGAGGGCCGCTGCCCTTGATAATGAAAAGTCAAACGGAACAATC
ATTCACGTGAAGGGCAAGCACCTCTGTCCGTCAACCTTGTCCCTGGTCCATCCAAGCCATTCTGGGTGTTGGTCGT
AGTGGGTGGAGTCCTCGCTTGTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTTTCGCTTTTCCGTCGT
TAAGCGGGGGAGAAAAAAGCTGCTGTACATTTTCAAACAGCCGTTTATGAGGCCGGTCCAAACGACTCAGGAAG
AAGACGGCTGCTCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGAAGTTTCCAGATCT
GCAGATGCACCAGCGTATCAGCAGGGCCAGAACCACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTA
TGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCAAGGAG
GGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAG
AAGGGGAAAAGGGCACGACGTTTGTACCAGGGACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACAT
GCAAGCCCTGCCACCTAGG (Seq. ID 39)

1C8.1.001_C28T_4Bz Amino Acid Sequence

MALPVTALLPLALLHAARPOVQLQESGGLVKPSQTLSTCTVSGDSIISGGYYWSWIRQHPGKGLEWIGYIFYSGST
DYNPSLKSRVTISVDTSKNQFSLKSSVTAADTAVYYCARSGYSYALFDHWGQGLTVTVSSGGGGSGGGSGGGGSDI
QMTQSPSSLSASVGDRTISCRASQFIGRYFNWYQQQPGKAPKVLIIAESSLQSGVPSRFSGSGSGTEFTLTISLQPEDF
ARYYCQQSYSTPFTFGQGTKVEIKRAAALDNEKSNGTIIHVKGKHLCPSPLPFGPSKPFVVLVVGGVLACYSLLVTVAFI
IFWVRFVSVKRGKRLLYIFKQPFMRPVQTTQEEDGCSCRFEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLG
RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGGHDGLYQGLSTATKDTYDA
LHMQLPPR (Seq. ID 40)

Figure 8F

1C8.1.001_C8K_28z Coding Sequence

ATGGCACTCCCCGTAAGTCTGCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCGCACGCCCCGAGGTGCAGCTCC
AAGAATCTGGACCGGGTCTCGTCAAGCCATCACAGACACTGTCCCTGACCTGCACCGTCTCCGGCGACTCTATCAT
TTCAGGCGGCTACTATTGGTCTGGATTAGACAACATCCGGGAAAGGGTCTTGAATGGATCGGCTATATTTTCTAC
AGCGGGAGTACGGATTACAATCCTAGTCTCAAGAGCCGCGTTACCATTTCAGTGGATACTTCAAAAAACCAAGTTTA
GCCTGAAGCTGTCTTCTGTAACAGCTGCTGACACAGCCGTGTAATGCGCCAGGAGCGGCTACAGCTATGCCCT
GTTTGACCACTGGGGGCAAGGCACTCTTGACGGTGTCAAGTGGAGGGGGAGGATCAGGCGGCGGGGGATCC
GGCGGCGGGGGTAGTGACATTCAAATGACGCAGTCCCCAAGTTCTCTGTCCGCTAGCGTCGGCGACCGAGTGACC
ATCAGCTGCCGAGCATCCCAGTTTATCGGTAGATATTTCAATTGGTACCAGCAACAACCGGGCAAAGCGCCCCAAG
GTCCTGATCTACGCTGAGAGCAGTCTGCAATCCGGCGTACCTAGCAGGTTCTCCGGAAGTGGCAGCGGAACCGAG
TTCACCCTGACAATTAGCTCCTTGACGCCCCGAGGATTTGCTCGCTATTACTGTCAACAGAGTTATTCAACCCCTTTT
ACATTCCGACAGGGAACTAAAGTTGAAATTAAGAGGGCCGCTGCCTTCGTGCCTGTTTTTCTGCCCGCGAAACCCA
CAACTACCCCCGCCCCCTCGGCCCCCAACTCCTGCACCAACTATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCA
TGCCGCCCCGCGGCAGGCGGCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGATATTTATATCTGGGCCCCC
CTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTGGTGATTACCCTCTACTGCAACCACAGAAACAGATCCAAAA
GAAGCCGCTGCTCCATAGCGATTACATGAATATGACTCCACGCCGCCCTGGCCCCACAAGGAAACACTACCAGCC
TTACGCACCACCTAGAGATTTGCTGCCTATCGGAGCAGGGTGAAGTTTTCCAGATCTGCAGATGCACCAGCGTAT
CAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTTTTGGACAAGCG
CAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGGAGGGTCTCTATAATGAGCTGC
AGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGGAAAAGGGCACGA
CGGTTTGTACCAGGGAAGTCTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGCCCTGCCACCTAGG

(Seq. ID 41)

1C8.1.001_C8K_28z Amino Acid Sequence

MALPVTALLLPLALLHAARPQVQLQESGPGLVKPSQTLSTCTVSGDSIISGGYYWSWIRQHPGKGLEWIGYIFYSGST
DYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARSGYSYALFDHWGQGLTVTVSSGGGGSGGGSGGGGSDI
QMTQSPSSLSASVGDRTISCRASQFIGRYFNWYQQQPGKAPKVLIAESSLQSGVPSRFSGSGSGTEFTLTISLQPEDF
ARYYCQQSYSTPFTFGQGTKVEIKRAAAFVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDF
ACDIYIWAPLAGTCGVLLSLVITLYCNHRNRSKRSLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSA
DAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRG
KGHDGLYQGLSTATKDTYDALHMQALPPR (Seq. ID 42)

Figure 8G

1C8.1.001_C8K_4Bz Coding Sequence

ATGGCACTCCCCGTAAGTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCGCACGCCCCGAGGTGCAGCTCC
AAGAATCTGGACCGGGTCTCGTCAAGCCATCACAGACACTGTCCCTGACCTGCACCGTCTCCGGCGACTCTATCAT
TTCAGGCGGCTACTATTGGTCTGGATTAGACAACATCCGGGAAAGGGTCTTGAATGGATCGGCTATATTTTCTAC
AGCGGGAGTACGGATTACAATCCTAGTCTCAAGAGCCGCGTTACCATTTCAGTGGATACTTCAAAAAACAGTTTA
GCCTGAAGCTGTCTTCTGTAACAGCTGCTGACACAGCCGTGTAATGCGCCAGGAGCGGCTACAGCTATGCCCT
GTTTGACCACTGGGGGCAAGGCACTCTTGTGACGGTGTCAAGTGGAGGGGGAGGATCAGGCGGCGGGGGATCC
GGCGGCGGGGGTAGTGACATTCAAATGACGCAGTCCCCAAGTTCTGTCCGCTAGCGTCGGCGACCGAGTGACC
ATCAGCTGCCGAGCATCCCAGTTTATCGGTAGATATTTCAATTGGTACCAGCAACAACCGGGCAAAGCGCCCCAAG
GTCCTGATCTACGCTGAGAGCAGTCTGCAATCCGGCGTACCTAGCAGGTTCTCCGGAAGTGGCAGCGGAACCGAG
TTCACCCTGACAATTAGCTCCTTGACGCCCCGAGGATTCGCTCGCTATTACTGTCAACAGAGTTATTCACCCCTTTT
ACATTCCGACAGGGAACTAAAGTTGAAATTAAGAGGGCCGCTGCCTTCGTGCCTGTTTTTCTGCCCGCGAAACCCA
CAACTACCCCCGCCCCCTCGGCCCCCAACTCCTGCACCAACTATCGCTTCCCAACCCCTGTCTCTGAGACCTGAGGCA
TGCCGCCCCGCGGCAGGCGGCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGATATTTATATCTGGGCCCCC
CTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTGGTGATTACCCTCTACTGCAACCACAGAAACCGCTTTTCCG
TCGTTAAGCGGGGGAGAAAAAGCTGCTGTACATTTCAAACAGCCGTTTATGAGGCCGTCCAAACGACTCAGG
AAGAAGACGGCTGCTCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGAAGTTTTCCAGA
TCTGCAGATGCACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGA
GTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAAACCCCCAGG
AGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGG
AGAAGGGGAAAAGGGCACGACGTTTGTACCAGGGAAGTCTGCACTGCTACGAAGGATACTTATGACGCTCTCCA
CATGCAAGCCCTGCCACCTAGG (Seq. ID NO. 43)

1C8.1.001_C8K_4Bz Amino Acid Sequence

MALPVTALLLPLALLLHAARPQVQLQESGPGLVKPSQTLSTCTVSGDSIISGGYYW5WIRQHPGKGLEWIGYIFYSGST
DYNPSLKSRVTISVDTSKNQFSLKSSVTAADTAVYYCARSGYSYALFDHWGQGLTVTVSSGGGGSGGGSGGGGSDI
QMTQSPSSLSASVGDRTISCRASQFIGRYFNWYQQQPGKAPKVLIAESSLQSGVPSRFSGSGSGTEFTLTISLQPEDF
ARYYCQQSYSTPFTFGQGTKVEIKRAAAFVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDF
ACDIYIWAPLAGTCGVLLLSLVITLYCNHRNRFVSVKGRKKLLYIFKQPFMRPVQTTQEEDGCSRFPEEEEGGCELRVK
FSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPEMGGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGE
RRRGKGDGLYQLSTATKDTYDALHMQALPPR (Seq. ID NO. 44)

Figure 8H

6E9.1_C28T_28z Coding Sequence

ATGGCACTCCCCGTAAGTCTGCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCGCACGCCCCGAGGTACACCTGG
TGCAGAGCGGGGCGGAGGTCAAGAAACCGGGCGCATCCGTACGCGTGAGCTGCAAGGCCTCCGGATACACTTTT
ACTTCTTACTATCTGCATTGGGTCAAGCAGGCACCGGGTCAAGGACTGGAGTGGATGGGCATTGTGGACCAAGC
GGAGGGAGTACGTCATATGATCAGAAAGTTTCAAGGTAGGTTTACCATGACACGGGACACGTCAACGAGTACCGTC
TACATGGAGCTCAGTAGTCTGCGGAGCGAAGACACCGCAGTCTACTACTGCGCACGCGATTATGGAGACTATGTC
TTTGAATATTGGGGGCGAGGGGACGCTCGTGACCGTTTCAAGCGGGGGGGGGCGGATCCGGTGGGGGAGGTTCCG
GCGGTGGGGGTTCAAAAGCGTACTGACACAGCCCCGAGTGCATCCGGGACCCCCGGCCAAAGGGTTACAATC
AGCTGCTCTGGCAGCTCCAGTAACATAGGTACCAACACGGTGAAGTGGTACCAGCAGTTGCCTGGCACAGCGCCT
CAGCTGCTCATCTATATCAACAATCAGCGGCCAAGTGGCGTGCCCGATAGATTCTCAGGCTCAAAGAGCGGAACC
AGCGCTAGCTTGGCAATCAGTGGCCTTCAATCCGAAGACGAAGCCGATTACTATTGTGCGACCTGGGACGATAGC
CTGAACGGCCCCGTCGTGGGCGGGCGGGACGAACTGACAGTGTGGGCGCCGCTGCCCTTGATAATGAAAAGTC
AAACGGAACAATCATTACGTGAAGGGCAAGCACCTCTGTCCGTCACCCTTGTCCCTGGTCCATCCAAGCCATTCT
GGGTGTTGGTCGTAGTGGGTGGAGTCCTCGCTTGTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTT
AGATCCAAAAGAAGCCGCTGCTCCATAGCGATTACATGAATATGACTCCACGCCGCCCTGGCCCCACAAGGAAA
CACTACCAGCCTTACGCACCACTAGAGATTTGCTGCTATCGGAGCAGGGTGAAGTTTTCCAGATCTGCAGATG
CACCAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGACGCAGGGAAGAGTATGACGTT
TTGGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGAAAAACCCCCAGGAGGGTCTCT
ATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAAAGGAGAGCGGAGAAGGGG
AAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGAAGGATACTTATGACGCTCTCCACATGCAAGC
CCTGCCACCTAGG (Seq. ID NO. 45)

6E9.1_C28T_28z Amino Acid Sequence

MALPVTALLPLALLHAARPQVHLVQSGAEVKKPGASVRVSCASGYTFTSYLHWVRQAPGQGLEWMGIVDPSGG
STSYDQKFQGRFTMTRDTSTSTVYMELSSLRSEDVAVYCARDYGDYVFDYWGGQTLVTVSSGGGGSGGGGSGGGG
SQSVLTQPPSASGTPGQRTVISCSSSNIGTNTVNWYQQLPGTAPQLLIYINNQRPSGVPDRFSGSKSGTSASLAISGL
QSEDEADYYCATWDDSLNGPVVGGGKLTVLGAAALDNEKSNGTIIHVKGKHLCPSPFPGPSKPFVVLVVVGGVLAC
YSLLVTVAFIIFWVRSKRSRLHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQLYNE
LNLGRREEYDVLDRRGRDPEMGGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKD
TYDALHMQALPPR (Seq. ID NO. 46)

Figure 8I

6E9.1_C28T_4Bz Coding Sequence

ATGGCACTCCCCGTAAGTCTGCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCGCACGCCCCGAGGTACACCTGG
TGCAGAGCGGGGCGGAGGTCAAGAAACCGGGCGCATCCGTACGCGTGAGCTGCAAGGCCTCCGGATACACTTTT
ACTTCTTACTATCTGCATTGGGTGAGGCAGGCACCGGGTCAGGGACTGGAGTGGATGGGCATTGTGGACCCAAGC
GGAGGGAGTACGTCATATGATCAGAAAGTTTCAAGGTAGGTTTACCATGACACGGGACACGTCAACGAGTACCGTC
TACATGGAGCTCAGTAGTCTGCGGAGCGAAGACACCGCAGTCTACTACTGCGCACGCGATTATGGAGACTATGTC
TTTGAATATTGGGGGCGAGGGGACGCTCGTGACCGTTTCAAGCGGGGGGGGGCGGATCCGGTGGGGGAGGTTCCG
GCGGTGGGGGTTCAAAAGCGTACTGACACAGCCCCGAGTGCATCCGGGACCCCCGGCCAAAGGGTTACAATC
AGCTGCTCTGGCAGCTCCAGTAACATAGGTACCAACACGGTGAAGTGGTACCAGCAGTTGCCTGGCACAGCGCCT
CAGCTGCTCATCTATATCAACAATCAGCGGCCAAGTGGCGTGCCCGATAGATTCTCAGGCTCAAAGAGCGGAACC
AGCGCTAGCTTGGCAATCAGTGGCCTTCAATCCGAAGACGAAGCCGATTACTATTGTGCGACCTGGGACGATAGC
CTGAACGGCCCCGTCGTGGGCGGCGGGACGAAACTGACAGTGTGGGCGCCGCTGCCCTTGATAATGAAAAGTC
AAACGGAACAATCATTACGTGAAGGGCAAGCACCTCTGTCCGTACCCTTGTCCCTGGTCCATCCAAGCCATTCT
GGGTGTTGGTCTAGTGGGTGGAGTCTCGCTTGTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTT
CGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAGCTGCTGTACATTTTCAAACAGCCGTTTATGAGGCCGGTCCAA
ACGACTCAGGAAGAAGACGGCTGCTCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGA
AGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGAC
GCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCCTGAGATGGGTGGCAAACCAAGACGAAA
AAACCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAA
AGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGAAGGATACTTAT
GACGCTCTCCACATGCAAGCCCTGCCACCTAGG (Seq. ID NO. 47)

6E9.1_C28T_4Bz Amino Acid Sequence

MALPVTALLPLALLHAARPQVHLVQSGAEVKKPGASVRVSCASGYTFTSYLHWVRQAPGQGLEWMGIVDPSGG
STSYDQKFQGRFTMTRDTSTSTVYMESSLRSED TAVYYCARDYGDYVFDYWGQGLTVTVSSGGGGSGGGGSGGGG
SQSVLTQPPSASGTPGQRTVITSCSGSSNIGTNTVNWYQQLPGTAPQLLIYINNQRPSGVPDRFSGSKSGTSASLAISGL
QSEDEADYYCATWDDSLNGPVVGGGKLTVLGAAALDNEKSNGTIIHVKGKHLCPSPFPGPSKPFVVLVVVGGVLAC
YLLVTVAFIIFWVRFSVVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQN
QLYNELNLGRREEYDVLDRRGRDPEMGGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGERRRRGKGHDLGYQLS
TATKDTYDALHMQALPPR (Seq. ID NO. 48)

Figure 8J

6E9.1_C8K_28z Coding Sequence

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ACTTCTTACTATCTGCATTGGGTGAGGCAGGCACCGGGTCAGGGACTGGAGTGGATGGGCATTGTGGACCCAAGC
GGAGGGAGTACGTCATATGATCAGAAAGTTTCAAGGTAGGTTTACCATGACACGGGACACGTCAACGAGTACCGTC
TACATGGAGCTCAGTAGTCTGCGGAGCGAAGACACCGCAGTCTACTACTGCGCACGCGATTATGGAGACTATGTC
TTTGACTATTGGGGGCGAGGGGACGCTCGTGACCGTTTCAAGCGGGGGGGGGCGGATCCGGTGGGGGAGGTTCCG
GCGGTGGGGGTTCAAAAGCGTACTGACACAGCCCCGAGTGCATCCGGGACCCCCGGCCAAAGGGTTACAATC
AGCTGCTCTGGCAGCTCCAGTAACATAGGTACCAACACGGTGAAGTGGTACCAGCAGTTGCCTGGCACAGCGCCT
CAGCTGCTCATCTATATCAACAATCAGCGGCCAAGTGGCGTGCCCGATAGATTCTCAGGCTCAAAGAGCGGAACC
AGCGCTAGCTTGGCAATCAGTGGCCTTCAATCCGAAGACGAAGCCGATTACTATTGTGCGACCTGGGACGATAGC
CTGAACGGCCCCGTCGTGGGCGGGCGGGACGAAACTGACAGTGTGGGCGCCGCTGCCCTTGATAATGAAAAGTC
AAACGGAACAATCATTACGTGAAGGGCAAGCACCTCTGTCCGTCACCTTGTCCCTGGTCCATCCAAGCCATTCT
GGGTGTTGGTTCGTAGTGGGTGGAGTCCTCGCTTGTACTCTCTGCTCGTCACCGTGGCTTTTATAATCTTCTGGGTT
CGCTTTTCCGTCGTTAAGCGGGGGAGAAAAAGCTGCTGTACATTTTCAAACAGCCGTTTATGAGGCCGGTCCAA
ACGACTCAGGAAGAAGACGGCTGCTCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGTGA
AGTTTTCCAGATCTGCAGATGCACCAGCGTATCAGCAGGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGGAC
GCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCCTGAGATGGGTGGCAAACCAAGACGAAA
AAACCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATGAA
AGGAGAGCGGAGAAGGGGAAAAGGGCACGACGGTTTGTACCAGGGACTCAGCACTGCTACGAAGGATACTTAT
GACGCTCTCCACATGCAAGCCCTGCCACCTAGG (Seq ID NO. 49)

6E9.1_C8K_28z Amino Acid Sequence

MALPVTALLPLALLHAARPOVHLVQSGAEVKKPGASVRVSCASGYFTSYLHWVRQAPGQGLEWMGIVDPSGG
STSYDQKFQGRFTMTRDTSTSTVYMESSLRSEDTAIVYVCARDYGDYVFDYWGGTLTVSSGGGGSGGGGSGGGG
SQSVLTQPPSASGTPGQRTVISCSSSSNIGTNTVNWYQQLPGTAPQLLIYINNQRPSGVPDRFSGSKSGTSASLAISGL
QSEDEADYYCATWDDSLNPGVVGGGTKLTVLGAAAFVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGA
VHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCNHRNRSKRSRLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYR
SRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQDKMAEAYSEIG
MKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR (Seq. ID NO. 50)

Figure 8K

6E9.1_C8K_4Bz Coding Sequence

ATGGCACTCCCCGTAAGTCTGCTGCTGCCGTTGGCATTGCTCCTGCACGCCGCACGCCCCGAGGTACACCTGG
TGCAGAGCGGGGCGGAGGTCAAGAAACCGGGCGCATCCGTACGCGTGAGCTGCAAGGCCTCCGGATACACTTTT
ACTTCTTACTATCTGCATTGGGTCAAGCAGGCACCGGGTCAGGGACTGGAGTGGATGGGCATTGTGGACCCAAGC
GGAGGGAGTACGTCATATGATCAGAAAGTTTCAAGGTAGGTTTACCATGACACGGGACACGTCAACGAGTACCGTC
TACATGGAGCTCAGTAGTCTGCGGAGCGAAGACACCGCAGTCTACTACTGCGCACGCGATTATGGAGACTATGTC
TTTGACTATTGGGGGCAGGGGACGCTCGTGACCGTTTCAAGCGGGGGGGGGCGGATCCGGTGGGGGAGGTTCCG
GCGGTGGGGGTTCAAAAGCGTACTGACACAGCCCCGAGTGCATCCGGGACCCCCGGCCAAAGGGTTACAATC
AGCTGCTCTGGCAGCTCCAGTAACATAGGTACCAACACGGTGAAGTGGTACCAGCAGTTGCCCTGGCACAGCGCCT
CAGCTGCTCATCTATATCAACAATCAGCGGCCAAGTGGCGTGCCCGATAGATTCTCAGGCTCAAAGAGCGGAACC
AGCGCTAGCTTGGCAATCAGTGGCCTTCAATCCGAAGACGAAGCCGATTACTATTGTGCGACCTGGGACGATAGC
CTGAACGGCCCCGTCGTGGGCGGCGGGACGAAACTGACAGTGTGGGCGCCGCTGCCTTCGTGCCTGTTTTTCTG
CCCGCGAAACCCACAACCTACCCCCGCCCTCGGCCCCCAACTCCTGCACCAACTATCGCTTCCCAACCCCTGTCTCT
GAGACCTGAGGCATGCCGCCCCGCGGCAGGCGGCGCCGTGCACACTAGAGGCCTGGACTTCGCCTGCGATATTTA
TATCTGGGCCCCCTTGCCGGGACATGCGGGGTACTGCTGCTGTCTCTGGTGATTACCTCTACTGCAACCACAGA
AACCGCTTTTCCGTCGTAAAGCGGGGGAGAAAAAGCTGCTGTACATTTTCAAACAGCCGTTTATGAGGCCGGTCC
AAACGACTCAGGAAGAAGACGGCTGCTCCTGCCGCTTTCCTGAGGAGGAGGAGGGCGGGTGCGAACTGAGGGT
GAAGTTTTCCAGATCTGCAGATGCACAGCGTATCAGCAGGGCCAGAACCAACTGTATAACGAGCTCAACCTGGG
ACGCAGGGAAGAGTATGACGTTTTGGACAAGCGCAGAGGACGGGACCCTGAGATGGGTGGCAAACCAAGACGA
AAAAACCCCCAGGAGGGTCTCTATAATGAGCTGCAGAAGGATAAGATGGCTGAAGCCTATTCTGAAATAGGCATG
AAAGGAGAGCGGAGAAGGGGAAAAGGGCACGACGTTTGTACCAGGGACTCAGCACTGCTACGAAGGATACTT
ATGACGCTCTCCACATGCAAGCCCTGCCACCTAGG (Seq. ID NO. 51)

6E9.1_C8K_4Bz Amino Acid Sequence

MALPVTALLLPLALLLHAARPQVHLVQSGAEVKKPGASVRVSKASGYTFTSYLHWVRQAPGQGLEWMGIVDPSSG
STSYDQKFQGRFTMTRDTSTSTVYMESSLRSEDATVYYCARDYGDYVFDYWQQGTLTVSSGGGGSGGGGSGGGG
SQSVLTQPPSASGTPGQRTVISCSSSNIGTNTVNWYQLPGTAPQLLIYINNQRPSGVPDRFSGSKSGTSASLAISGL
QSEDEADYYCATWDDSLNGPVVGGGKLTVLGAAAFVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGA
VHTRGLDFACDIYWAPLAGTCGVLLSLVITLYCNHRNRFVVKRGRKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEE
GGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAY
SEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR (Seq. ID NO. 52)

Figure 8L

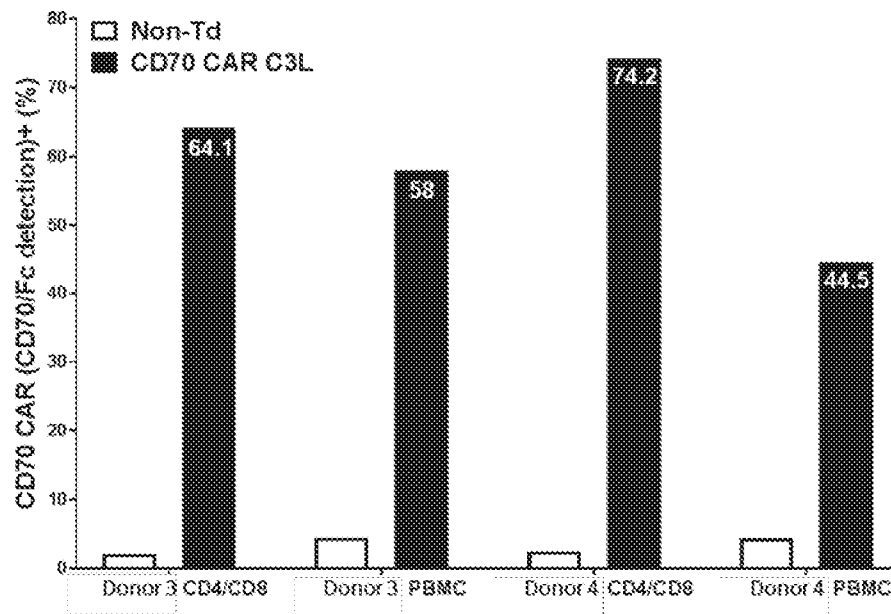


Figure 9

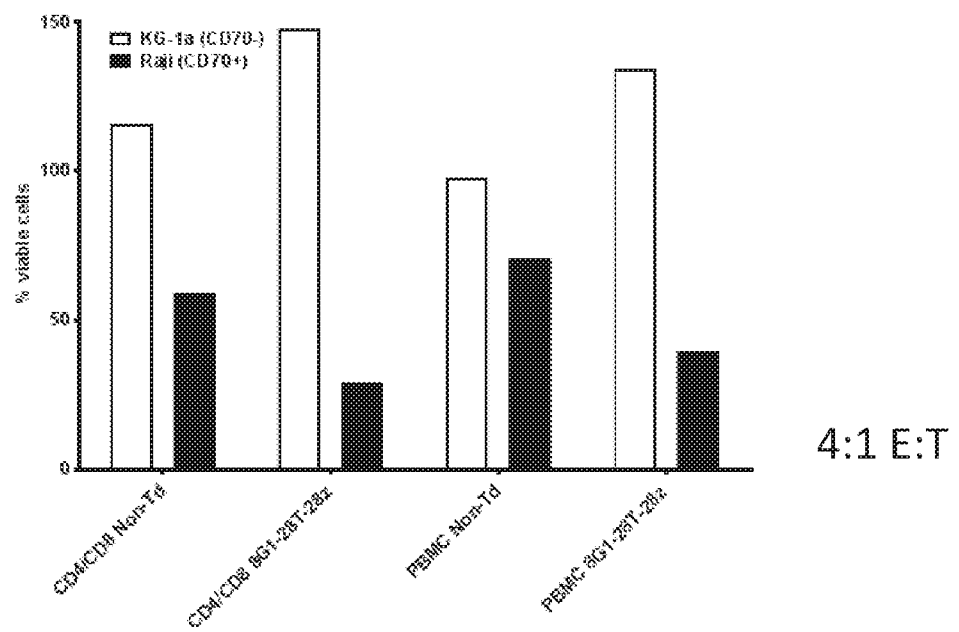


Figure 10A

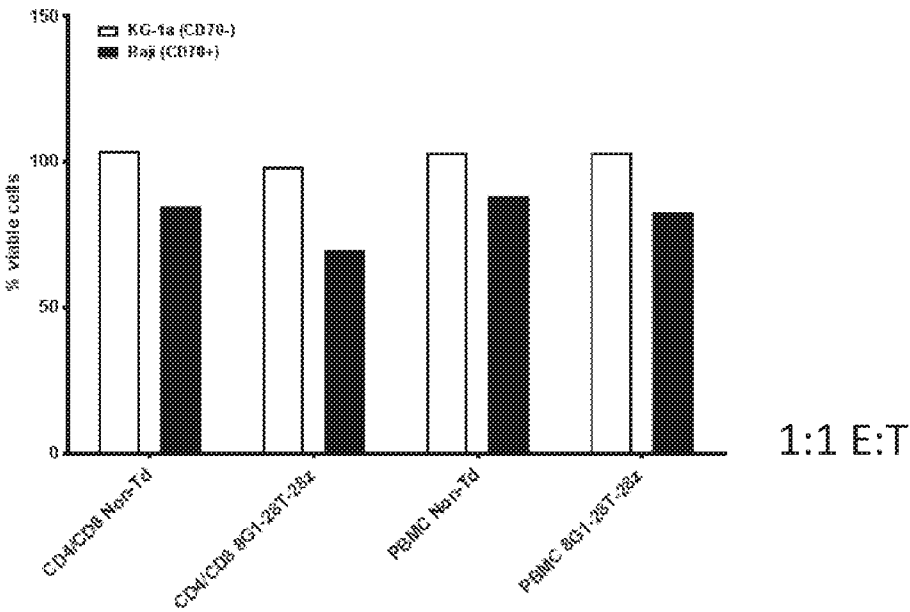


Figure 10B

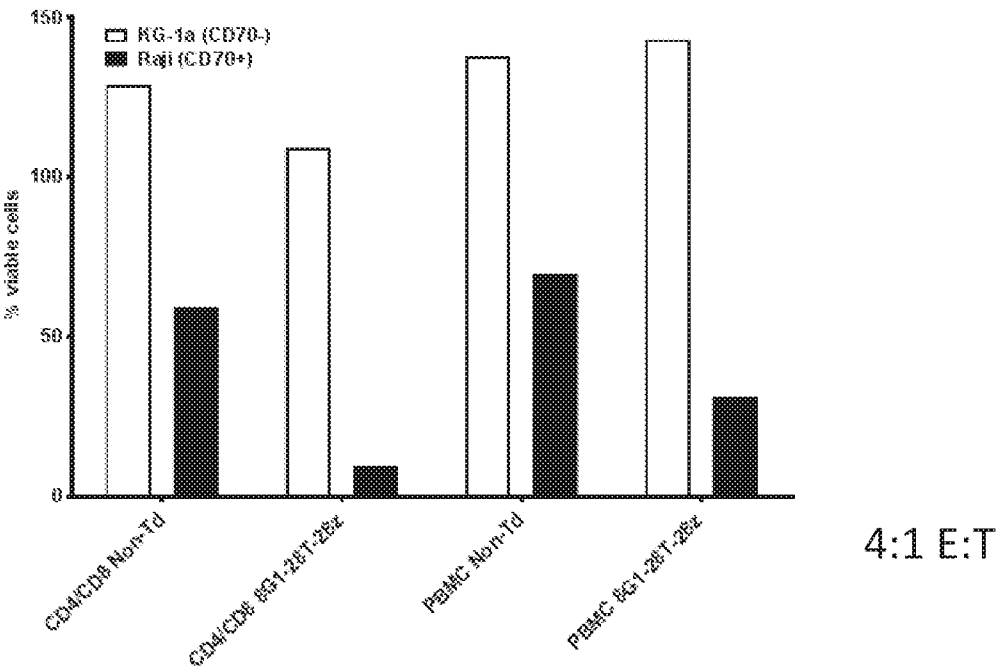


Figure 10C

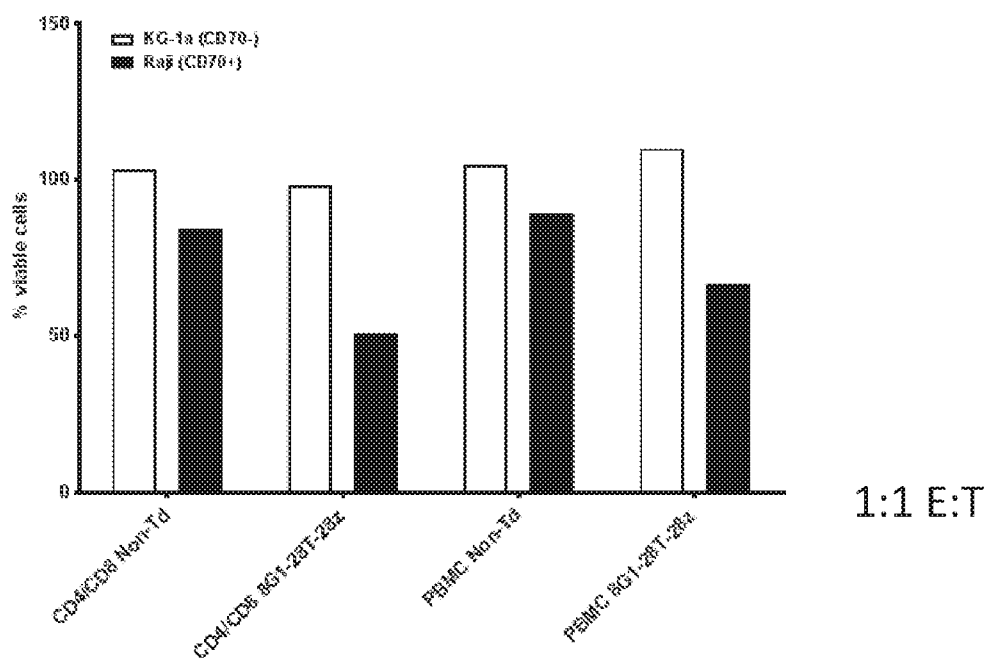


Figure 10D

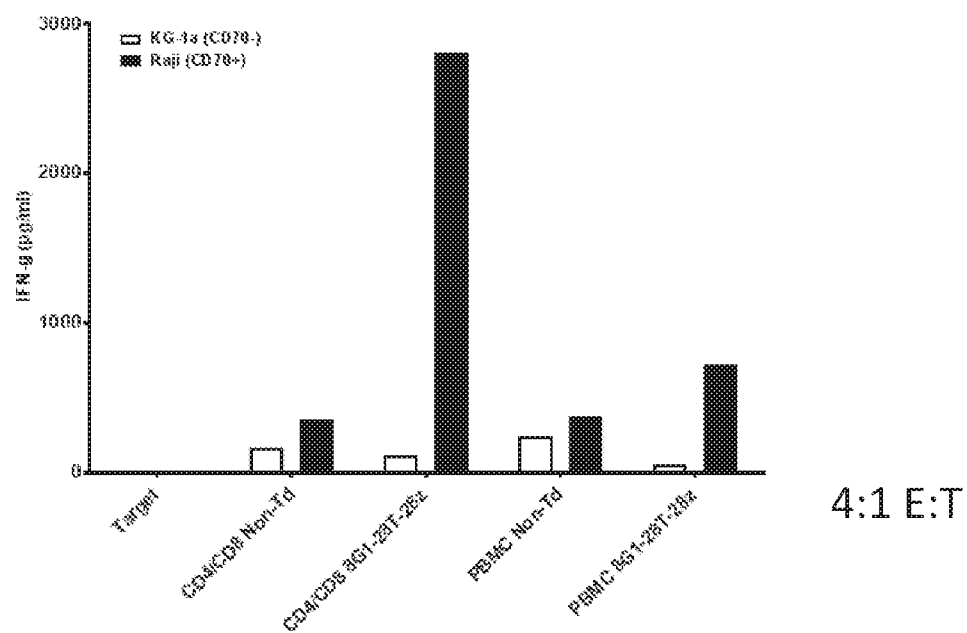


Figure 11A

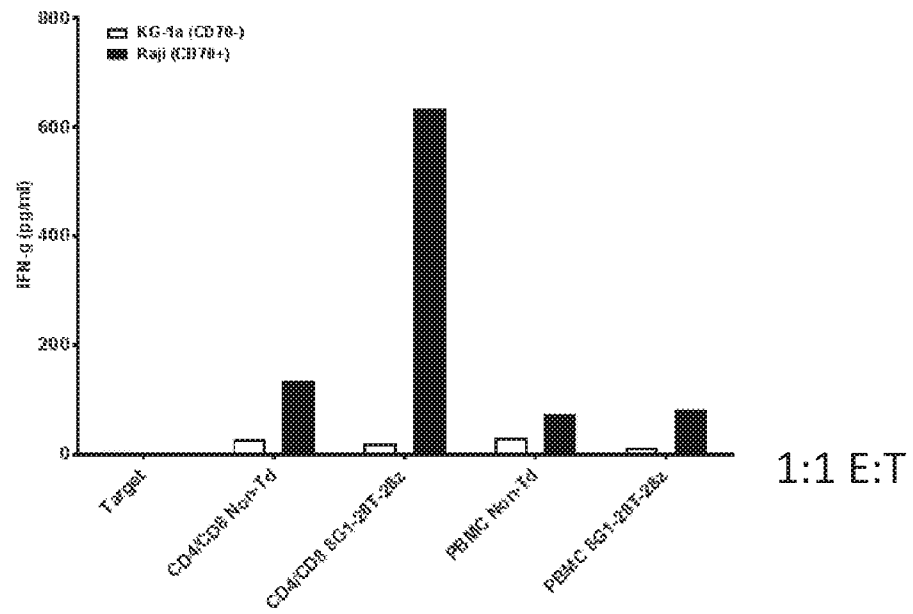


Figure 11B

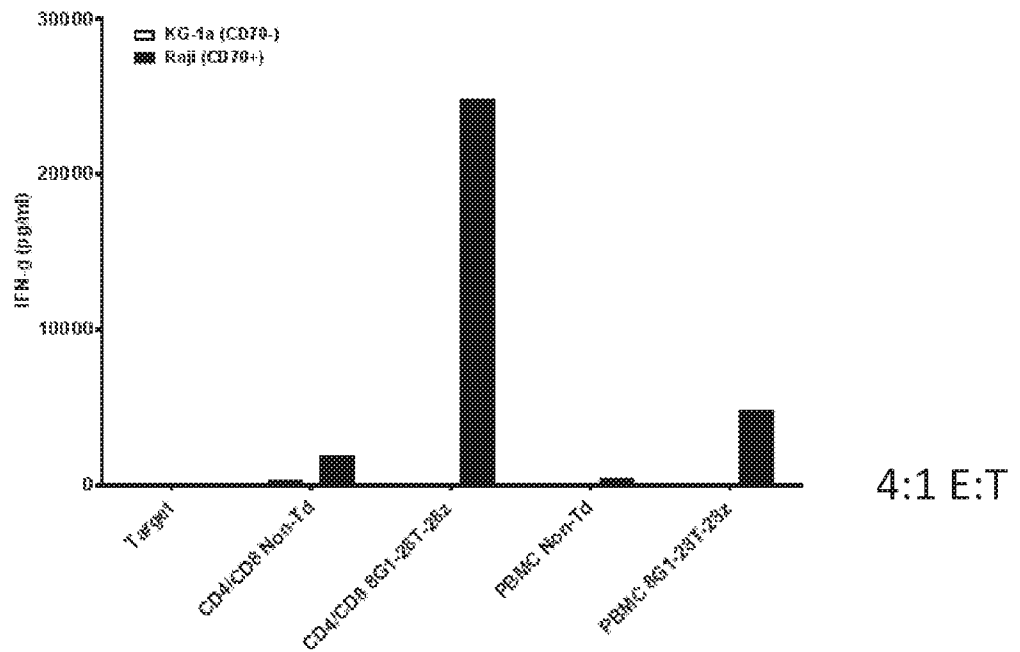


Figure 11C

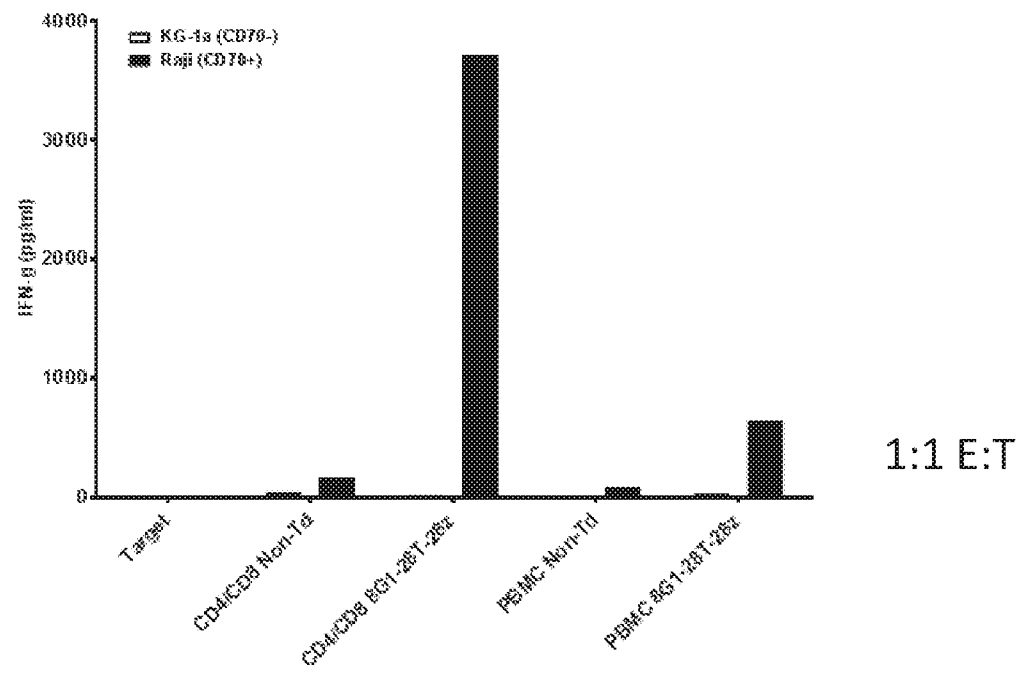


Figure 11D

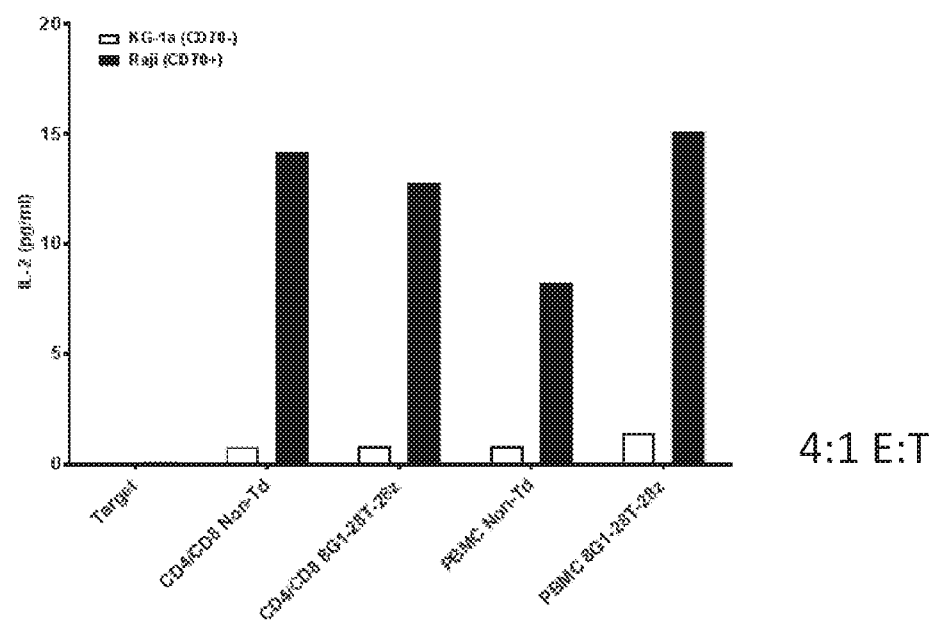


Figure 12A

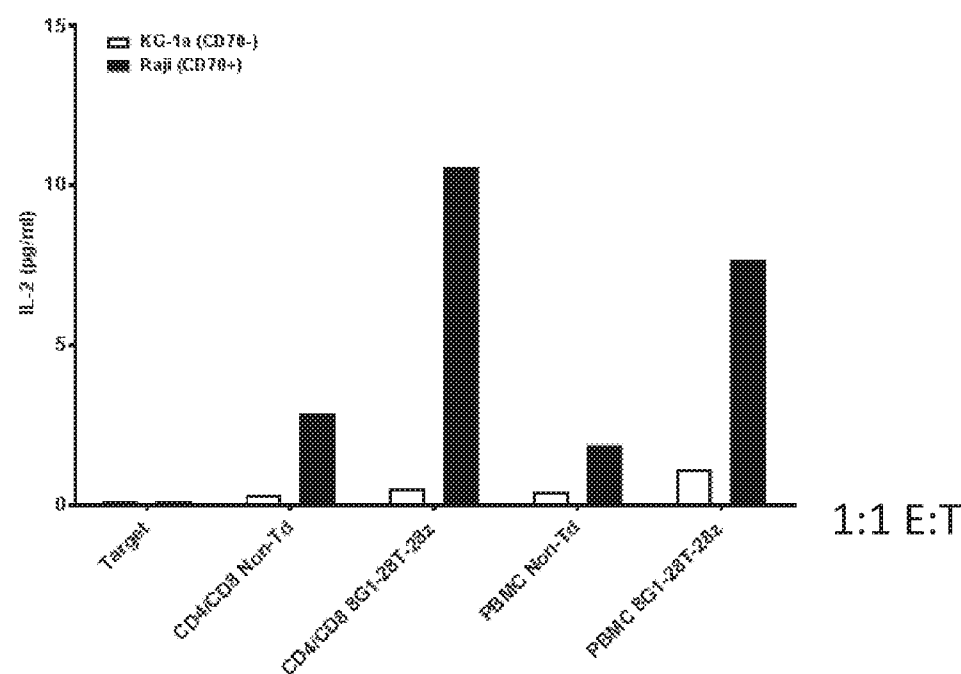


Figure 12B

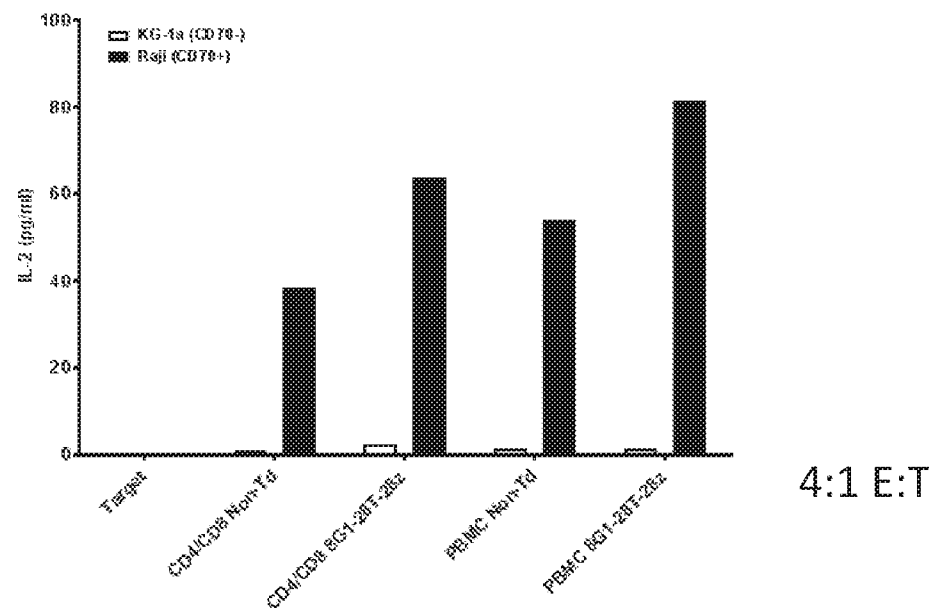


Figure 12C

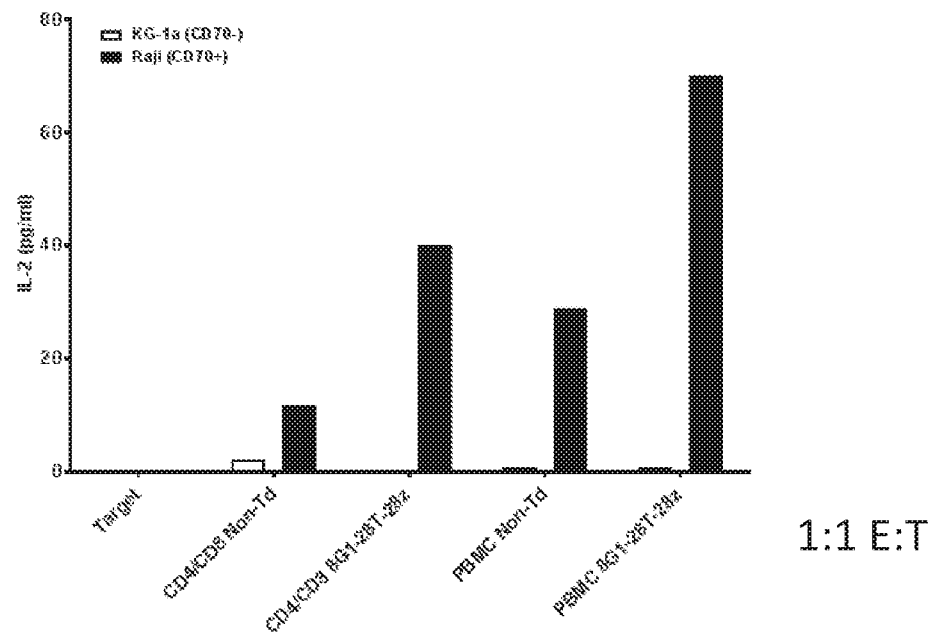


Figure 12D

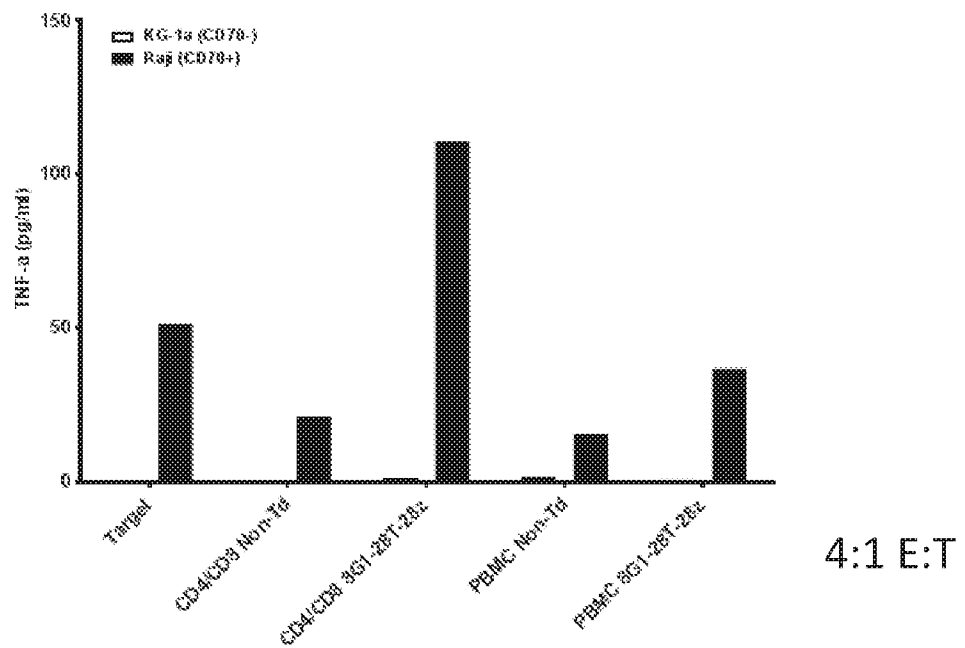


Figure 13A

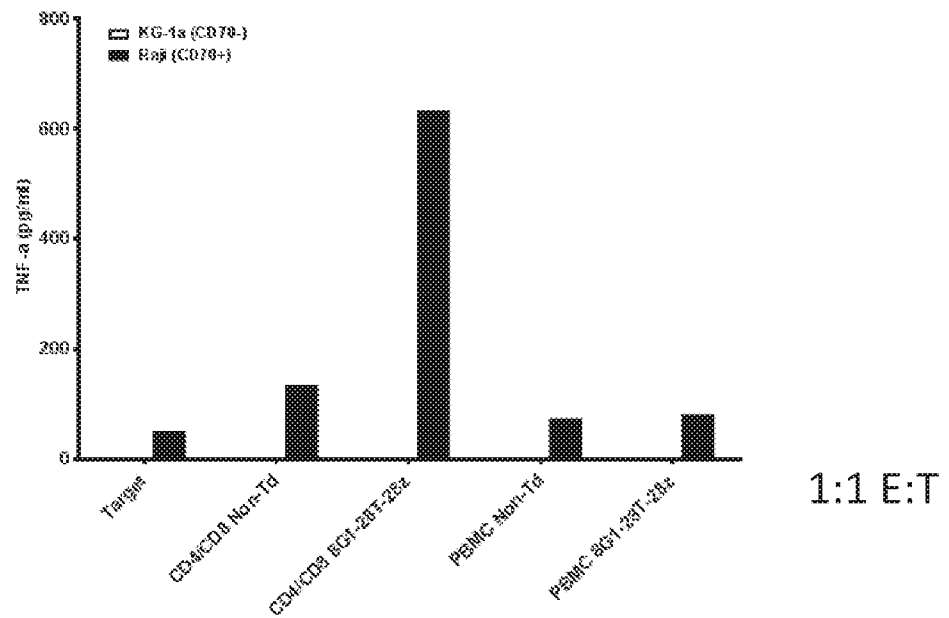


Figure 13B

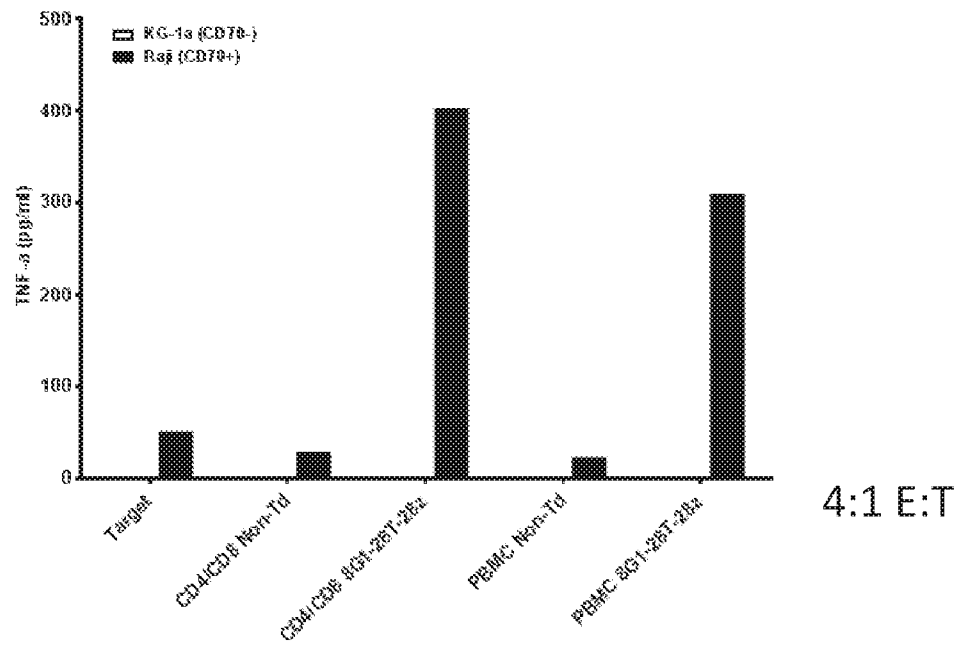


Figure 13C

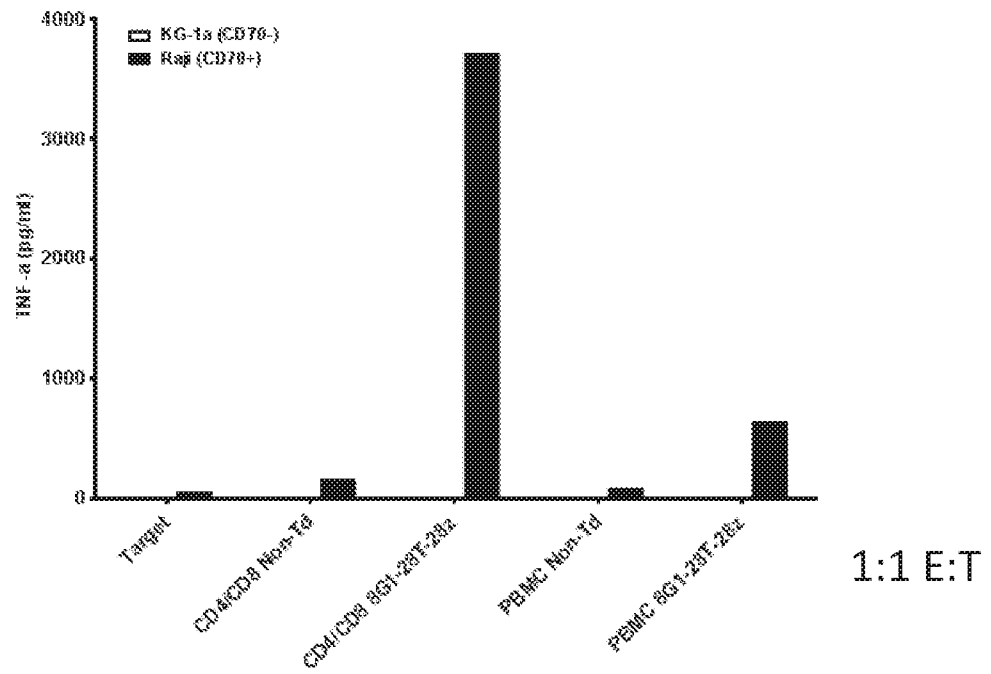


Figure 13D

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/018152

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/28
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WANG QIONG J ET AL: "Preclinical Evaluation of Chimeric Antigen Receptors Targeting CD70-Expressing Cancers.", CLINICAL CANCER RESEARCH : AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH 01 MAY 2017, vol. 23, no. 9, 1 November 2016 (2016-11-01), pages 2267-2276, XP055465432, ISSN: 1078-0432	1-12, 15-58, 60-79
Y	the whole document	13,14, 59,80,81
Y	----- WO 2016/016859 A1 (AMGEN RES MUNICH GMBH [DE]) 4 February 2016 (2016-02-04) claim 11 ----- -/-	13,14, 59,80,81



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

11 April 2018

Date of mailing of the international search report

18/04/2018

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Le Flao, Katell

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2018/018152

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHAFFER D R ET AL: "T cells redirected against CD70 for the immunotherapy of CD70-positive malignancies", BLOOD, AMERICAN SOCIETY OF HEMATOLOGY, US, vol. 117, no. 16, 21 April 2011 (2011-04-21), pages 4304-4314, XP002738263, ISSN: 0006-4971, DOI: 10.1182/BLOOD-2010-04-278218 [retrieved on 2011-02-08]	1-12, 15-58, 60-79
Y	the whole document	13,14, 59,80,81
Y	----- US 2013/078237 A1 (DELANEY JOHN M [US] ET AL) 28 March 2013 (2013-03-28) claim 1; sequences 18,57	13,14, 59,80,81
X,P	----- PARK YUK PHEEL ET AL: "CD70 as a target for chimeric antigen receptor T cells in head and neck squamous cell carcinoma.", ORAL ONCOLOGY MAR 2018, vol. 78, March 2018 (2018-03), pages 145-150, XP085353974, ISSN: 1879-0593 the whole document	1-81
X,P	----- LINCHUN JIN ET AL: "CD70, a novel target of CAR T-cell therapy for gliomas", NEURO-ONCOLOGY, vol. 20, no. 1, 10 January 2018 (2018-01-10), pages 55-65, XP055464384, US ISSN: 1522-8517, DOI: 10.1093/neuonc/nox116 the whole document -----	1-81

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2018/018152

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		CN 104136461 A 05-11-2014	
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		CR 20140169 A 18-08-2014	
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		US 2013078237 A1 28-03-2013	
		US 2015218284 A1 06-08-2015	
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