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(56) Related Art
ZHANG WEI ET AL, "Down-regulation of TET2 in CD3+ and CD34+ cells of myelodysplastic syndromes and enhances CD34+ cells proliferation.", INTERNATIONAL JOURNAL OF CLINICAL AND EXPERIMENTAL PATHOLOGY, (2015-09-01), vol. 8, no. 9, p10840-10846
WEI XU ET AL, "Oncometabolite 2-Hydroxyglutarate Is a Competitive Inhibitor of [alpha]-Ketoglutarate-Dependent Dioxygenases", CANCER CELL, US, (2011-01-01), vol. 19, no. 1, doi:10.1016/j.ccr.2010.12.014, ISSN 1535-6108, pages 17 - 30
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(54) **Title**: CAR T CELL THERAPIES WITH ENHANCED EFFICACY

(57) **Abstract**: The invention provides compositions and methods improved CAR T cell therapies. Specifically, the invention provides cells with reduced Tet, e.g., Tet2 function or expression, and methods of use therefore. The invention further provides Tet2 inhibitors and methods of use therefore in connection with CAR T cells.

CAR T CELL THERAPIES WITH ENHANCED EFFICACY

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Application Serial No. 62/220,196, filed September 17, 2015, the contents of which are incorporated herein by reference in their entireties.

SEQUENCE LISTING

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 September 14, 2016, is named N2067-7098WO_SL.txt and is 507,996 bytes in size.

FIELD OF THE INVENTION

The present invention relates generally to the use of immune effector cells (e.g., T cells, NK cells) engineered to express a Chimeric Antigen Receptor (CAR) to treat a disease associated with expression of a tumor antigen.

BACKGROUND OF THE INVENTION

Adoptive cell transfer (ACT) therapy with autologous T-cells, especially with T-cells transduced with Chimeric Antigen Receptors (CARs), has shown promise in hematologic cancer trials. There is a medical need for T cell therapies, especially CAR T cell therapies with improved efficacy.

SUMMARY OF THE INVENTION

The present invention provides compositions and methods that disrupt methylcytosine dioxygenase genes (e.g., Tet1, Tet2, Tet3), and uses of such compositions and methods for increasing the functional activities of engineered cells (e.g., gene-modified antigen-specific T cells, such as CAR T cells). In particular, the present invention provides methods and compositions for bolstering the therapeutic efficacy of chimeric antigen receptor (CAR) T cells. While not to be bound by the theory, disruption of a single allele of a Tet gene (e.g., a Tet1, Tet2,

or Tet3) leads to decreased total levels of 5-hydroxymethylcytosine in association with enhanced proliferation, regulation of effector cytokine production and degranulation, and thereby increases CAR T cell proliferation and/or function.

Accordingly, the present invention provides a cell (e.g., a population of cells, such as a population of immune effector cells) engineered to express a chimeric antigen receptor (CAR), wherein the CAR comprises an antigen-binding domain, a transmembrane domain, and an intracellular signaling domain, and wherein expression and/or function of Tet1, Tet2 and/or Tet3 in said cell has been reduced or eliminated. In one embodiment, the expression and/or function of Tet2 in said cell has been reduced or eliminated. In some embodiments, the antigen-binding domain binds to a tumor antigen is selected from a group consisting of: TSHR, CD19, CD123, CD22, CD30, CD171, CS-1, CLL-1, CD33, EGFRvIII , GD2, GD3, BCMA, Tn Ag, PSMA, ROR1, FLT3, FAP, TAG72, CD38, CD44v6, CEA, EPCAM, B7H3, KIT, IL-13Ra2, Mesothelin, IL-11Ra, PSCA, PRSS21, VEGFR2, LewisY, CD24, PDGFR-beta, SSEA-4, CD20, Folate receptor alpha, ERBB2 (Her2/neu), MUC1, EGFR, NCAM, Prostase, PAP, ELF2M, Ephrin B2, IGF-I receptor, CAIX, LMP2, gp100, bcr-abl, tyrosinase, EphA2, Fucosyl GM1, sLe, GM3, TGS5, HMWMAA, o-acetyl-GD2, Folate receptor beta, TEM1/CD248, TEM7R, CLDN6, GPRC5D, CXORF61, CD97, CD179a, ALK, Polysialic acid, PLAC1, GloboH, NY-BR-1, UPK2, HAVCR1, ADRB3, PANX3, GPR20, LY6K, OR51E2, TARP, WT1, NY-ESO-1, LAGE-1a, MAGE-A1, legumain, HPV E6,E7, MAGE A1, ETV6-AML, sperm protein 17, XAGE1, Tie 2, MAD-CT-1, MAD-CT-2, Fos-related antigen 1, p53, p53 mutant, prostein, survivin and telomerase, PCTA-1/Galectin 8, MelanA/MART1, Ras mutant, hTERT, sarcoma translocation breakpoints, ML-IAP, ERG (TMPRSS2 ETS fusion gene), NA17, PAX3, Androgen receptor, Cyclin B1, MYCN, RhoC, TRP-2, CYP1B1, BORIS, SART3, PAX5, OY-TES1, LCK, AKAP-4, SSX2, RAGE-1, human telomerase reverse transcriptase, RU1, RU2, intestinal carboxyl esterase, mut hsp70-2, CD79a, CD79b, CD72, LAIR1, FCAR, LILRA2, CD300LF, CLEC12A, BST2, EMR2, LY75, GPC3, FCRL5, and IGLL1. In one embodiment, the tumor antigen is CD19. In some embodiments, the antigen-binding domain is an antibody or antibody fragment as described in, e.g., WO2012/079000 or WO2014/153270.

In one aspect, the present invention provides a cell (e.g., a population of cells, such as a population of immune effector cells) engineered to express a CAR, and wherein expression and/or function of Tet1, Tet2 and/or Tet3 in said cell has been reduced or eliminated. In one

embodiment, the expression and/or function of Tet2 in said cell has been reduced or eliminated. In some embodiments, the transmembrane domain of said CAR comprises: (i) an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO: 12, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO: 12; or (ii) the sequence of SEQ ID NO: 12.

In one aspect, the present invention provides a cell (e.g., a population of cells, such as a population of immune effector cells) engineered to express a CAR, and wherein expression and/or function of Tet1, Tet2 and/or Tet3 in said cell has been reduced or eliminated. In one embodiment, the antigen binding domain of said CAR is connected to the transmembrane domain by a hinge region, wherein said hinge region comprises SEQ ID NO: 2 or SEQ ID NO: 6, or a sequence with 95-99% identity thereof. In some embodiments, the intracellular signaling domain of said CAR comprises a primary signaling domain and/or a costimulatory signaling domain, wherein the primary signaling domain comprises a functional signaling domain of a protein chosen from CD3 zeta, CD3 gamma, CD3 delta, CD3 epsilon, common FcR gamma (FCER1G), FcR beta (Fc Epsilon R1b), CD79a, CD79b, Fcgamma RIIa, DAP10, or DAP12.

In some embodiments, the primary signaling domain of said CAR comprises: (i) an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO: 18 or SEQ ID NO: 20, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO: 18 or SEQ ID NO: 20; or (ii) the amino acid sequence of SEQ ID NO:18 or SEQ ID NO: 20. In some embodiments, the intracellular signaling domain of said CAR comprises a costimulatory signaling domain, or a primary signaling domain and a costimulatory signaling domain, wherein the costimulatory signaling domain comprises a functional signaling domain of a protein selected from the group consisting of CD27, CD28, 4-1BB (CD137), OX40, CD30, CD40, PD-1, ICOS, lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, B7-H3, a ligand that specifically binds with CD83, CDS, ICAM-1, GITR, BAFFR, HVEM (LIGHTR), SLAMF7, NKp80 (KLRF1), CD160, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55),

PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, NKp44, NKp30, NKp46, and NKG2D.

In some embodiments, the costimulatory signaling domain of said CAR comprises an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO: 14 or SEQ ID NO: 16, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO: 14 or SEQ ID NO: 16. In some embodiments, the intracellular domain of said CAR comprises the sequence of SEQ ID NO: 14 or SEQ ID NO: 16, and the sequence of SEQ ID NO: 18 or SEQ ID NO: 20, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain. In some embodiments, the CAR of the present invention further comprises a leader sequence comprises the sequence of SEQ ID NO: 2.

In some embodiments, the immune effector cell of the present invention is a T cell or an NK cell. In some embodiments, the T cell is a CD4+ T cell, a CD8+ T cell, or a combination thereof. In one aspect, the cells of the present invention are human cells. In one aspect, the cells (e.g., engineered immune effector cells, e.g., CAR T cells) of the present invention comprise an inhibitor of Tet1, Tet2, and/or Tet3. In some embodiments, the cells of the present invention comprise a CAR, and an inhibitor of Tet1, Tet2 and/or Tet3, wherein said inhibitor is (1) a gene editing system targeted to one or more sites within the gene encoding Tet1, Tet2 and/or Tet3, or its regulatory elements, e.g., Tet2, or its regulatory elements; (2) nucleic acid encoding one or more components of said gene editing system; or (3) combinations thereof.

In some embodiments, the cells of the present invention comprise a CAR, and an inhibitor of Tet1, Tet2 and/or Tet3, wherein said inhibitor is a gene editing system targeted to one or more sites within the gene encoding Tet1, Tet2 and/or Tet3, or its regulatory elements, e.g., Tet2, or its regulatory elements, and wherein the gene editing system is selected from the group consisting of: a CRISPR/Cas9 system, a zinc finger nuclease system, a TALEN system and a meganuclease system.

In some embodiments, the cells of the present invention comprise a CAR, and an inhibitor of Tet1, Tet2 and/or Tet3, wherein said inhibitor is a gene editing system targeted to one or more sites within the gene encoding Tet1, Tet2 and/or Tet3, or its regulatory elements,

e.g., Tet2, or its regulatory elements, and wherein the gene editing system binds to a target sequence in an early exon or intron of a gene encoding Tet1, Tet2 and/or Tet3, e.g., Tet2.

In some embodiments, the cells of the present invention comprise a CAR, and an inhibitor of Tet1, Tet2 and/or Tet3, wherein said inhibitor is a gene editing system targeted to one or more sites within the gene encoding Tet1, Tet2 and/or Tet3, or its regulatory elements, e.g., Tet2, or its regulatory elements, and wherein the gene editing system binds a target sequence of a gene encoding tet2, and the target sequence is upstream of exon 4, e.g., in exon1, exon2, or exon3, e.g. in exon 3.

In some embodiments, the cells of the present invention comprise a CAR, and an inhibitor of Tet1, Tet2 and/or Tet3, wherein said inhibitor is a gene editing system targeted to one or more sites within the gene encoding Tet1, Tet2 and/or Tet3, or its regulatory elements, e.g., Tet2, or its regulatory elements, and wherein the gene editing system binds to a target sequence in a late exon or intron of a gene encoding Tet1, Tet2 and/or Tet3, e.g., Tet2.

In some embodiments, the cells of the present invention comprise a CAR, and an inhibitor of Tet1, Tet2 and/or Tet3, wherein said inhibitor is a gene editing system targeted to one or more sites within the gene encoding Tet1, Tet2 and/or Tet3, or its regulatory elements, e.g., Tet2, or its regulatory elements, and wherein the gene editing system binds a target sequence of a gene encoding tet2, and the target sequence is downstream of exon 8, e.g., is in exon9, exon10, or exon11, e.g. is in exon 9.

In some embodiments, the cells of the present invention comprise a CAR, and an inhibitor of Tet1, Tet2 and/or Tet3, wherein said inhibitor is a gene editing system targeted to one or more sites within the gene encoding Tet1, Tet2 and/or Tet3, or its regulatory elements, e.g., Tet2, or its regulatory elements, and wherein the gene editing system is a CRISPR/Cas system comprising a gRNA molecule comprising a targeting sequence which hybridize to a target sequence of a Tet2 gene. In some embodiments, the targeting sequence is a targeting sequence listed in Table 3. In some embodiments, the target sequence is a targeting sequence listed in Table 5.

In some embodiments, the cells of the present invention comprise a CAR, and an inhibitor of Tet1, Tet2 and/or Tet3, wherein said inhibitor is an siRNA or shRNA specific for Tet1, Tet2, Tet3, or nucleic acid encoding said siRNA or shRNA. In some embodiments, the

siRNA or shRNA comprises a sequence complementary to a sequence of a Tet2 mRNA, e.g., comprises a target sequence of shRNA listed in Table 4.

In some embodiments, the cells of the present invention comprise a CAR, and an inhibitor of Tet1, Tet2 and/or Tet3, wherein said inhibitor a small molecule.

In some embodiments, the cells of the present invention comprise a CAR, and an inhibitor of Tet1, Tet2 and/or Tet3, wherein the inhibitor is a protein, e.g., is a dominant negative binding partner of Tet1, Tet2, and/or Tet3 (e.g., a histone deacetylase (HDAC) that interacts with Tet1, Tet2, and/or Tet3), or nucleic acid encoding said dominant negative binding partner of Tet1, Tet2, and Tet3.

In some embodiments, the cells of the present invention comprise a CAR, and an inhibitor of Tet1, Tet2 and/or Tet3, wherein the inhibitor is a protein, e.g., is a dominant negative (e.g., catalytically inactive) Tet1, Tet2, or Tet3, or nucleic acid encoding said dominant negative Tet1, Tet2, or Tet3.

In one aspect, the present invention provides a method of increasing the therapeutic efficacy of a CAR-expressing cell, e.g., a cell of any of the previous claims, e.g., a CAR19-expressing cell (e.g., CTL019), comprising a step of decreasing the level of 5-hydroxymethylcytosine in said cell. In some embodiments, said step comprises contacting said cells with a Tet (e.g., Tet1, Tet2, and/or Tet3) inhibitor. In some embodiments, said Tet inhibitor is a Tet2 inhibitor. In some embodiments, a Tet (e.g., Tet1, Tet2, and/or Tet3) inhibitor of the present invention is selected from the group consisting of: (1) a gene editing system targeted to one or more sites within the gene encoding Tet1, Tet2, or Tet3, or its corresponding regulatory elements; (2) a nucleic acid (e.g., an siRNA or shRNA) that inhibits expression of Tet1, Tet2, or Tet3; (3) a protein (e.g., a dominant negative, e.g., catalytically inactive) Tet1, Tet2, or Tet3, or a binding partner of Tet1, Tet2, or Tet3; (4) a small molecule that inhibits expression and/or function of Tet1, Tet2, or Tet3; (5) a nucleic acid encoding any of (1)-(3); and (6) any combination of (1) –(5). In some embodiments, the Tet inhibitor of the present invention is a Tet2 inhibitor.

In one aspect, the present invention provides a method of increasing the therapeutic efficacy of a CAR-expressing cell, e.g., a cell of any of the previous claims, e.g., a CAR19-expressing cell (e.g., CTL019), comprising a step of decreasing the level of 5-hydroxymethylcytosine in said cell. In some embodiments, said step comprises contacting said

cells with a Tet (e.g., Tet1, Tet2, and/or Tet3) inhibitor. In some embodiments, said contacting occurs *ex vivo*. In some embodiments, said contacting occurs *in vivo*. In some embodiments, said contacting occurs *in vivo* prior to delivery of nucleic acid encoding a CAR into the cell. In some embodiments, said contacting occurs *in vivo* after the cells have been administered to a subject in need thereof.

In one aspet, the present invention provides a method of increasing the therapeutic efficacy of a CAR-expressed cell, e.g., a cell of any of the previous claims, e.g., a CAR19-expressing cell (e.g., CTL019), comprising a step of contacting said cell with a Tet inhibitor, e.g., a Tet1, Tet2 and/or Tet3 inhibitor. In some embodiments, said Tet inhibitor is a Tet2 inhibitor. In some embodiments, a Tet (e.g., Tet1, Tet2, and/or Tet3) inhibitor of the present invention is selected from the group consisting of: (1) a gene editing system targeted to one or more sites within the gene encoding Tet1, Tet2, or Tet3, or its corresponding regulatory elements; (2) a nucleic acid (e.g., an siRNA or shRNA) that inhibits expression of Tet1, Tet2, or Tet3; (3) a protein (e.g., a dominant negative, e.g., catalytically inactive) Tet1, Tet2, or Tet3, or a binding partner of Tet1, Tet2, or Tet3; (4) a small molecule that inhibits expression and/or function of Tet1, Tet2, or Tet3; (5) a nucleic acid encoding any of (1)-(3); and (6) any combination of (1) –(5). In some embodiments, the Tet inhibitor of the present invention is a Tet2 inhibitor.

In one aspet, the present invention provides a method of increasing the therapeutic efficacy of a CAR-expressed cell, e.g., a cell of any of the previous claims, e.g., a CAR19-expressing cell (e.g., CTL019), comprising a step of contacting said cell with a Tet inhibitor, e.g., a Tet1, Tet2 and/or Tet3 inhibitor. In some embodiments, said step comprises contacting said cells with a Tet (e.g., Tet1, Tet2, and/or Tet3) inhibitor. In some embodiments, said contacting occurs *ex vivo*. In some embodiments, said contacting occurs *in vivo*. In some embodiments, said contacting occurs *in vivo* prior to delivery of nucleic acid encoding a CAR into the cell. In some embodiments, said contacting occurs *in vivo* after the cells have been administered to a subject in need thereof.

In one aspects, the present invention provides a method of treating a subject in need thereof, comprising administering to said subject an effective amount of the cells as described herein, e.g., an immune effector cell (e.g., T cell or NK cell) comprising a CAR, and, optionally, administering to said subject a Tet1, Tet2, and/or Tet3 inhibitor. In some embodiments, the

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subject receives a pre-treatment of the Tetl, Tet2 and/or Tet3 inhibitor, and prior to the initiation of the CAR-expressing cell therapy. In some embodiments, the subject receives concurrent treatment with a Tetl, Tet2, and/or Tet3 inhibitor and the CAR expressing cell therapy. In some embodiments, the subject receives treatment with a Tetl, Tet2, and/or Tet3 inhibitor post-CAR-expressing cell therapy. In some embodiments, the subject has a disease associated with expression of a tumor antigen, e.g., a proliferative disease, a precancerous condition, a cancer, and a non-cancer related indication associated with expression of the tumor antigen. In some embodiments, the subject has a hematologic cancer chosen from one or more of chronic lymphocytic leukemia (CLL), acute leukemias, acute lymphocytic leukemia (ALL), B-cell acute lymphoblastic leukemia (B-ALL), T-cell acute lymphoblastic leukemia (T-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 lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, or preleukemia.

The present invention provides uses of the compositions and/or methods described here for treatment of cancer, wherein the cancer is selected from the group consisting of colon cancer, rectal cancer, renal-cell carcinoma, liver cancer, non-small cell carcinoma of the lung, cancer of the small intestine, cancer of the esophagus, melanoma, 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, Hodgkin's Disease, non-Hodgkin's lymphoma, 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, solid tumors of childhood, 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, combinations of said cancers, and metastatic lesions of said cancers.

The present invention provides Tet1, Tet2 and/or Tet3 inhibitors for use in the treatment of a subject, wherein said subject has received, is receiving, or is about to receive therapy comprising a CAR-expressing cell.

The present invention further provides a method of manufacturing a CAR-expressing cell, comprising introducing nucleic acid encoding a CAR into a cell such that said nucleic acid (or CAR-encoding portion thereof) integrates into the genome of the cell within a Tet1, Tet2 and/or Tet3 gene (e.g., within an intron or exon of a Tet1, Tet2 and/or Tet3 gene), such that Tet1, Tet2 and/or Tet3 expression and/or function is reduced or eliminated.

The present invention further provides a method of manufacturing a CAR-expressing cell, comprising contacting said CAR-expressing cell *ex vivo* with a Tet1, Tet2 and/or Tet3 inhibitor. In some embodiments, the inhibitor is a Tet2 inhibitor.

The present invention further provides a vector comprising sequence encoding a CAR and sequence encoding a Tet inhibitor, e.g., a Tet1, Tet2, and/or Tet3 inhibitor. In some embodiments, the Tet inhibitor is a (1) a gene editing system targeted to one or more sites within the gene encoding Tet1, Tet2, or Tet3, or its corresponding regulatory elements; (2) a nucleic acid (e.g., an siRNA or shRNA) that inhibits expression of Tet1, Tet2, or Tet3; (3) a protein (e.g., a dominant negative, e.g., catalytically inactive) Tet1, Tet2, or Tet3, or a binding partner of Tet1, Tet2, or Tet3; and (4) a nucleic acid encoding any of (1)-(3), or combinations thereof. In some embodiments, the sequence encoding a CAR and the sequence encoding a Tet inhibitor are separated by a 2A site.

The present invention further provides a gene editing system that is specific for a sequence of a Tet gene or its regulatory elements, e.g., a Tet1, Tet2 or Tet3 gene or its regulatory elements. In some embodiments, the gene editing system is specific for a sequence of a Tet2 gene. In some embodiments, the gene editing system is (1) a CRISPR/Cas gene editing system, (2) a zinc finger nuclease system, a TALEN system and a meganuclease system. In some embodiments, the gene editing system is a CRISPR/Cas gene editing system. In some embodiments, the gene editing system comprises: a gRNA molecule comprising a targeting sequence specific to a sequence of a Tet2 gene or its regulatory elements, and a Cas9 protein; a gRNA molecule comprising a targeting sequence specific to a sequence of a Tet2 gene or its

regulatory elements, and a nucleic acid encoding a Cas9 protein; a nucleic acid encoding a gRNA molecule comprising a targeting sequence specific to a sequence of a Tet2 gene or its regulatory elements, and a Cas9 protein; or a nucleic acid encoding a gRNA molecule comprising a targeting sequence specific to a sequence of a Tet2 gene or its regulatory elements, and a nucleic acid encoding a Cas9 protein. In some embodiments, the gene editing system further comprises a template DNA. In some embodiments, the template DNA comprises nucleic acid sequence encoding a CAR, e.g., a CAR as described herein.

The present invention further provides a composition for the *ex vivo* manufacture of a CAR-expressing cell, comprising a Tet inhibitor, e.g., a Tet1, Tet2, and/or Tet3 inhibitor, e.g., a Tet2 inhibitor. In some embodiments, the Tet inhibitor is selected from N-[3-[7-(2,5-dimethyl-2H-pyrazol-3-ylamino)-1-methyl-2-oxo-1,4-dihydro-2H-pyrimido[4,5-d]pyrimidin-3-yl]-4-methylphenyl]-3-trifluoromethyl-benzamide, 2-[(2,6-dichloro-3-methylphenyl)amino]benzoic acid and 2-hydroxyglutarate.

The present invention further provides a population of cells comprising one or more cells described herein, wherein the population of cells comprises a higher percentage of Tscm cells (e.g., CD45RA+CD62L+CCR7+CD27+CD95+ T cells) than a population of cells which does not comprise one or more cells in which expression and/or function of Tet1, Tet2 and/or Tet3 in said cell has been reduced or eliminated.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1: CD19-expressing CART cells were administered to a patient (UPCC04409-10) for the treatment of CLL. CART cells in patient UPCC04409-10 were monitored over time by sampling blood. The amount of BBZ expression in cells was determined (red). The number of copies of sequence from the Vbeta5.1 TCR family was determined (blue). Both measurements were made from samples collected on the indicated days after the second infusion of CART cells.

FIGS. 2A and 2B: The T-cell receptor repertoire from patient UPCC04409-10 was determined from a sample collected on day 28 (FIG. 2A) or day 51 (FIG. 2B) after CART infusion. This demonstrates the abundance of the TCRBV05-01 family of T-cell receptors at day 51 indicating clonal expansion over time.

FIG. 3: The T-cells isolated from patient UPCC04409-10 were analyzed for the simultaneous expression of CAR19 and 2 different TCR family genes over time (day 50 and day 51) and compared to the input dosed material (product): upper panel is TCR family Vb13.1; the lower panel shows TCR family Vb5.1. The data demonstrate that the CAR19 positive cells contain a single TCR family gene (Vb5.1) that becomes rapidly enriched between days 50 and 51.

FIG. 4: The T-cell receptor repertoire of CD8 positive cells from patient UPCC04409-10 was determined from a sample collected on day 51 after CART infusion. This demonstrates the abundance of the TCRBV05-01 family of T-cell receptors at day 51 indicating clonal expansion of CD8 positive cells over time.

FIG. 5: The T-cell receptor from patient UPCC04409-10 was sequenced and the sequence of the alpha and beta chains are shown (Amino Acid sequences disclosed as SEQ ID NOS: 1297-1298 and Nucleotide sequences disclosed as SEQ ID NOS: 1299-1301, all respectively, in order of appearance).

FIG. 6: Sonically fragmented DNA was generated from T-cells from Patient UPCC04409-10. This material was used to amplify genomic sequences adjacent to the CAR19 insertion. The genes indicated were identified as being enriched relative to the infused product (D0) adjacent to CAR19 in the genome. At the different time points after CART infusion indicated (d=day; m=month), a different relative abundance of adjacent genes was seen, with Tet2 abundance peaking in both peripheral blood (PBMC) and CAR+CD8+ T-cells samples at day 51.

FIG. 7: The site of insertion of the CAR19 gene was mapped to the Tet2 gene. More specifically, the insertion occurred between exons 9 and 10 of the Tet2 gene. The catalytic domain for Tet2 resides in exon 11. The insertion at this location may lead to expression of aberrant mRNA transcripts or decrease the expression of functional (wild-type) Tet2.

FIG. 8: Transcripts of the Tet2 gene from mRNA isolated from patient UPCC04409-10 were evaluated by RTPCR using primers spanning the indicated regions of Tet2 or CAR19 or both as indicated in the right hand side of the figure. Rxn 3 contains primers designed to amplify the region of the Tet2 transcript spanning exons 9 and 10. Rxn, 6, 7, 8, 9, and 10 are primers designed to amplify the indicated portions of the CAR19 lentivirus. Rxn 12-16 are pairs of primers that contain exon 9 sequence of the Tet2 transcript as well as sequence from the CAR19

lentiviral construct. These data show that transcripts are made from the Tet2 locus that contains both Tet2 sequence as well as CAR19 sequence.

FIG. 9: A schematic representation of the transcripts derived from the Tet2 locus discovered in FIGS. 10A and 10B is shown. This figure indicates splice variants of this Tet2/CAR19 fusion that were detected in the patient sample. This analysis has revealed that the CAR19 insertion into Tet2 has resulted in transcripts containing stop codons upstream of exon 11. Exon 11 has been demonstrated to be important for Tet2 function. This suggests Tet2 function has been disrupted by the insertion of the CAR19. This also suggests that the disruption of Tet2 function has resulted in favorable expansion of this individual CART clones.

FIGS. 10A and 10B: The enzymatic activity of Tet2 is schematized (FIG. 10A). Tet family protein convert 5-methylcytosine (5-mc) to 5-hydroxymethylcytosine (5-hmc) and then into 5-formylcytosine (5-fmc) resulting in demethylated cytosine. Methylated DNA is an epigenetic state that is known to affect transcriptional profiles. The methylation state of the T-cells from patient UPCC04409-10 was evaluated (FIG. 10B). The patient's T-cells were stained for TCRVb5.1 (which contain the CAR19 insertion at Tet2) and the 5-hmc and 5-fmc were evaluated in TCRVb5.1 positive (red) and TCRVb5.1 negative (blue) populations by flow cytometry. This data indicates that the cells containing the insertion of CAR19 in the Tet2 gene are defective in demethylation.

FIG.11: TET2 shRNAs reduce 5-hmc levels in normal human T cells. TET2 and scramble control shRNA constructs expressing mCherry were introduced into normal human T cells. 5-hmc levels were determined by intracellular staining by FACS on day 6 following expansion with anti-CD3/CD28 beads. Knockdown of TET2 reduced overall 5-hmc levels.

FIG. 12: TET2 shRNAs expand Tscm T cells. TET2 and scramble control shRNA constructs expressing mCherry were introduced into normal human T cells. CD45RA+CD62L+CCR7+CD27+CD95+ Tscm T cells were determined by FACS staining on day 11 following expansion with anti-CD3/CD28 beads. Knockdown of TET2 promoted the expansion of T cells with a Tscm phenotype.

FIG. 13A: Gating strategy for quantification of CAR+ cells.

FIG. 13B: CAR expression levels in cells electroporated with CRISPR/Cas systems targeting Tet2, as compared with untransfected cells.

FIG. 14: Quantitation of CD4+ and CD8+ cells after CAR transduction and Tet2 editing.

FIG. 15: Effect of Tet2 inhibition on CD3/CD28 bead expansion of CAR T cells.

FIG. 16: Effect of Tet2 inhibition on antigen-dependendent interleukin-2 (IL-2) production by CAR T cells.

FIG. 17: Effect of Tet2 inhibition on antigen-dependendent interferon gamma production by CAR T cells.

FIG. 18: Effect of Tet2 inhibition on antigen-driven CAR+ T cell proliferation.

FIG. 19: Effect of Tet2 inhibition on antigen-driven T cell proliferation.

FIG. 20: Effect of Tet2 inhibition on antigen-driven CD4+ T cell proliferation.

FIG. 21: Effect of Tet2 inhibition on antigen-driven CAR+ CD4+ T cell proliferation.

FIG. 22: Effect of Tet2 inhibition on antigen-driven CD8+ T cell proliferation.

FIG. 23: Effect of Tet2 inhibition on antigen-driven CAR+ CD8+ T cell proliferation.

FIG. 24: % editing, and % frameshift edit by introduction of CRISPR/Cas systems targeting Tet2 as measured by NGS.

FIG. 25: Top 5 most frequent indels observed in T cells after addition of RNP that included the indicated TET2 Exon 3-targeting gRNAs (SEQ ID NOS: 1302-1326, respectively, in order of appearance). Changes from the unmodified wt sequence are shown, with insertions represented with lowercase letters ("a". "t", "g" and "c") and deletions shown with a dash ("-"). Indel frequency is shown in the right-most column.

FIG. 26: Top 5 most frequent indels observed in T cells after addition of RNP that included the indicated TET2 Exon 9 -targeting gRNAs (SEQ ID NOS: 1327-1356, respectively, in order of appearance). Changes from the unmodified wt sequence are shown, with insertions represented with lowercase letters ("a," "t," "g," and "c") and deletions shown with a dash ("-"). Indel frequency is shown in the right-most column.

FIG. 27: Schematic experimental protocol for determination of TET2 knockdown in Jurkat cells in response to lentivirus encoding shRNA TET2 inhibitors.

FIG. 28: RFP expression in shRNA infected Jurkat cells. RFP expression was determined by FACS on day 6 after puromycin treatment. Based on RFP expression, greater than 99% shRNA introduced jurkat cells were selected by puromycin treatment.

FIG. 29: Knockdown efficiency of *tet2* in TET2 shRNAs infected Jurkat cells. qRT-PCR experiment was performed. The expression levels of tet1 and tet3 were also measured. β-actin serves as an internal control to quantify relative gene expression among samples tested. To

increase reliability of qRT-PCR, two β-actin primers and one RPLP1 primer were used in this experiment.

FIG. 30: Knockdown of TET2 protein in response to shRNAs in Jurkat cells. A western blot experiment was performed.

FIG. 31A: Venn diagrams of ATAC peaks in the CAR+CD8+ T cells from a patient with a Tet2 disruption compared to CAR-CD8+ T cells from the same patient at the matched time point without the Tet2 disruption. The box plots show differences in ATAC enrichment between the two cell populations.

FIG. 31B: GO terms associated with ATAC peaks more closed in the cell population with the Tet2 disruption, compared to its counterpart.

FIG. 32A: Silencing of Tet2 by shRNA in primary CD8+ T cells from healthy donors as measured by quantitative PCR. Expression (mean, SEM) normalized to GAPDH is presented as fold change relative to non-targeting control shRNA.

FIGS. 32B and 32C: Relative frequencies of central memory (FIG. 32B) and effector CD8+ T cells (FIG. 32C) at day 14 post-expansion via CD3/CD28 stimulation in the same healthy donors as presented in A.

DETAILED DESCRIPTION

Definitions

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 the invention pertains.

The term "a" and "an" refers to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

The term "about" when referring to a measurable value such as an amount, a temporal duration, and the like, is meant to encompass variations of ±20% or in some instances ±10%, or in some instances ±5%, or in some instances ±1%, or in some instances ±0.1% from the specified value, as such variations are appropriate to perform the disclosed methods.

The term "Chimeric Antigen Receptor" or alternatively a "CAR" refers to a set of polypeptides, typically two in the simplest embodiments, which when in an immune effector cell,

provides the cell with specificity for a target cell, typically a cancer cell, and with intracellular signal generation. In some embodiments, a CAR comprises at least an extracellular antigen binding domain, a transmembrane domain and a cytoplasmic signaling domain (also referred to herein as "an intracellular signaling domain") comprising a functional signaling domain derived from a stimulatory molecule and/or costimulatory molecule as defined below. In some aspects, the set of polypeptides are contiguous with eachother. In some embodiments, the set of polypeptides include a dimerization switch that, upon the presence of a dimerization molecule, can couple the polypeptides to one another, e.g., can couple an antigen binding domain to an intracellular signaling domain. In one aspect, the stimulatory molecule is the zeta chain associated with the T cell receptor complex. In one aspect, the cytoplasmic signaling domain further comprises one or more functional signaling domains derived from at least one costimulatory molecule as defined below. In one aspect, the costimulatory molecule is chosen from the costimulatory molecules described herein, e.g., 4-1BB (i.e., CD137), CD27 and/or CD28. In one aspect, the CAR comprises a chimeric fusion protein comprising an extracellular antigen binding domain, a transmembrane domain and an intracellular signaling domain comprising a functional signaling domain derived from a stimulatory molecule. In one aspect, the CAR comprises a chimeric fusion protein comprising an extracellular antigen binding domain, a transmembrane domain and an intracellular signaling domain comprising a functional signaling domain derived from a costimulatory molecule and a functional signaling domain derived from a stimulatory molecule. In one aspect, the CAR comprises a chimeric fusion protein comprising an extracellular antigen binding domain, a transmembrane domain and an intracellular signaling domain comprising two functional signaling domains derived from one or more costimulatory molecule(s) and a functional signaling domain derived from a stimulatory molecule. In one aspect, the CAR comprises a chimeric fusion protein comprising an extracellular antigen binding domain, a transmembrane domain and an intracellular signaling domain comprising at least two functional signaling domains derived from one or more costimulatory molecule(s) and a functional signaling domain derived from a stimulatory molecule. In one aspect, the CAR comprises an optional leader sequence at the amino-terminus (N-ter) of the CAR fusion protein. In one aspect, the CAR further comprises a leader sequence at the N-terminus of the extracellular antigen binding domain, wherein the leader sequence is

optionally cleaved from the antigen binding domain (e.g., a scFv) during cellular processing and localization of the CAR to the cellular membrane.

A CAR that comprises an antigen binding domain (e.g., a scFv, or TCR) that targets a specific tumor maker X, such as those described herein, is also referred to as XCAR. For example, a CAR that comprises an antigen binding domain that targets CD19 is referred to as CD19CAR.

The term "signaling domain" refers to the functional portion of a protein which acts by transmitting information within the cell to regulate cellular activity via defined signaling pathways by generating second messengers or functioning as effectors by responding to such messengers.

The term "antibody," as used herein, refers to a protein, or polypeptide sequence derived from an immunoglobulin molecule which specifically binds with an antigen. Antibodies can be polyclonal or monoclonal, multiple or single chain, or intact immunoglobulins, and may be derived from natural sources or from recombinant sources. Antibodies can be tetramers of immunoglobulin molecules.

The term "antibody fragment" refers to at least one portion of an antibody, that retains the ability to specifically interact with (e.g., by binding, steric hinderance, stabilizing/destabilizing, spatial distribution) an epitope of an antigen. Examples of antibody fragments include, but are not limited to, Fab, Fab', $F(ab')_2$, Fv fragments, scFv antibody fragments, disulfide-linked Fvs (sdFv), a Fd fragment consisting of the VH and CH1 domains, linear antibodies, single domain antibodies such as sdAb (either VL or VH), camelid VHH domains, multi-specific antibodies formed from antibody fragments such as a bivalent fragment comprising two Fab fragments linked by a disulfide brudge at the hinge region, and an isolated CDR or other epitope binding fragments of an antibody. An antigen binding fragment can also be incorporated into single domain antibodies, maxibodies, minibodies, nanobodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR and bis-scFv (see, e.g., Hollinger and Hudson, Nature Biotechnology 23:1126-1136, 2005). Antigen binding fragments can also be grafted into scaffolds based on polypeptides such as a fibronectin type III (Fn3)(see U.S. Patent No.: 6,703,199, which describes fibronectin polypeptide minibodies).

The term "scFv" refers to a fusion protein comprising at least one antibody fragment comprising a variable region of a light chain and at least one antibody fragment comprising a

variable region of a heavy chain, wherein the light and heavy chain variable regions are contiguously linked, e.g., via a synthetic linker, e.g., a short flexible polypeptide linker, and capable of being expressed as a single chain polypeptide, and wherein the scFv retains the specificity of the intact antibody from which it is derived. Unless specified, as used herein an scFv may have the VL and VH variable regions in either order, e.g., with respect to the N-terminal and C-terminal ends of the polypeptide, the scFv may comprise VL-linker-VH or may comprise VH-linker-VL.

The portion of the CAR of the invention comprising an antibody or antibody fragment thereof may exist in a variety of forms where the antigen binding domain is expressed as part of a contiguous polypeptide chain including, for example, a single domain antibody fragment (sdAb), a single chain antibody (scFv), a humanized antibody or bispecific antibody (Harlow et al., 1999, In: Using Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press, NY; Harlow et al., 1989, In: Antibodies: A Laboratory Manual, Cold Spring Harbor, New York; Houston et al., 1988, Proc. Natl. Acad. Sci. USA 85:5879-5883; Bird et al., 1988, Science 242:423-426). In one aspect, the antigen binding domain of a CAR composition of the invention comprises an antibody fragment. In a further aspect, the CAR comprises an antibody fragment that comprises a scFv. The precise amino acid sequence boundaries of a given CDR can be determined using any of a number of well-known schemes, including those described by Kabat et al. (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD ("Kabat" numbering scheme), Al-Lazikani et al., (1997) JMB 273,927-948 ("Chothia" numbering scheme), or a combination thereof.

As used herein, the term "binding domain" or "antibody molecule" refers to a protein, e.g., an immunoglobulin chain or fragment thereof, comprising at least one immunoglobulin variable domain sequence. The term "binding domain" or "antibody molecule" encompasses antibodies and antibody fragments. In an embodiment, an antibody molecule is a multispecific antibody molecule, e.g., it comprises a plurality of immunoglobulin variable domain sequences, wherein a first immunoglobulin variable domain sequence of the plurality has binding specificity for a first epitope and a second immunoglobulin variable domain sequence of the plurality has binding specificity for a second epitope. In an embodiment, a multispecific antibody molecule is a bispecific antibody molecule. A bispecific antibody has specificity for no more than two antigens. A bispecific antibody molecule is characterized by a first immunoglobulin variable

domain sequence which has binding specificity for a first epitope and a second immunoglobulin variable domain sequence that has binding specificity for a second epitope.

The portion of the CAR of the invention comprising an antibody or antibody fragment thereof may exist in a variety of forms where the antigen binding domain is expressed as part of a contiguous polypeptide chain including, for example, a single domain antibody fragment (sdAb), a single chain antibody (scFv), a humanized antibody, or bispecific antibody (Harlow et al., 1999, In: Using Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press, NY; Harlow et al., 1989, In: Antibodies: A Laboratory Manual, Cold Spring Harbor, New York; Houston et al., 1988, Proc. Natl. Acad. Sci. USA 85:5879-5883; Bird et al., 1988, Science 242:423-426). In one aspect, the antigen binding domain of a CAR composition of the invention comprises an antibody fragment. In a further aspect, the CAR comprises an antibody fragment that comprises a scFv.

The term "antibody heavy chain," refers to the larger of the two types of polypeptide chains present in antibody molecules in their naturally occurring conformations, and which normally determines the class to which the antibody belongs.

The term "antibody light chain," refers to the smaller of the two types of polypeptide chains present in antibody molecules in their naturally occurring conformations. Kappa (κ) and lambda (λ) light chains refer to the two major antibody light chain isotypes.

The term "recombinant antibody" refers to an antibody which is generated using recombinant DNA technology, such as, for example, an antibody expressed by a bacteriophage or yeast expression system. The term should also be construed to mean an antibody which has been generated by the synthesis of a DNA molecule encoding the antibody and which DNA molecule expresses an antibody protein, or an amino acid sequence specifying the antibody, wherein the DNA or amino acid sequence has been obtained using recombinant DNA or amino acid sequence technology which is available and well known in the art.

The term "antigen" or "Ag" refers to a molecule that provokes an immune response. This immune response may involve either antibody production, or the activation of specific immunologically-competent cells, or both. The skilled artisan will understand that any macromolecule, including virtually all proteins or peptides, can serve as an antigen. Furthermore, antigens can be derived from recombinant or genomic DNA. A skilled artisan will understand that any DNA, which comprises a nucleotide sequences or a partial nucleotide sequence

encoding a protein that elicits an immune response therefore encodes an "antigen" as that term is used herein. Furthermore, one skilled in the art will understand that an antigen need not be encoded solely by a full length nucleotide sequence of a gene. It is readily apparent that the present invention includes, but is not limited to, the use of partial nucleotide sequences of more than one gene and that these nucleotide sequences are arranged in various combinations to encode polypeptides that elicit the desired immune response. Moreover, a skilled artisan will understand that an antigen need not be encoded by a "gene" at all. It is readily apparent that an antigen can be generated synthesized or can be derived from a biological sample, or might be macromolecule besides a polypeptide. Such a biological sample can include, but is not limited to a tissue sample, a tumor sample, a cell or a fluid with other biological components.

The term "anti-cancer effect" refers to a biological effect which can be manifested by various means, including but not limited to, e.g., a decrease in tumor volume, a decrease in the number of cancer cells, a decrease in the number of metastases, an increase in life expectancy, decrease in cancer cell proliferation, decrease in cancer cell survival, or amelioration of various physiological symptoms associated with the cancerous condition. An "anti-cancer effect" can also be manifested by the ability of the peptides, polynucleotides, cells and antibodies in prevention of the occurrence of cancer in the first place. The term "anti-tumor effect" refers to a biological effect which can be manifested by various means, including but not limited to, e.g., a decrease in tumor volume, a decrease in the number of tumor cells, a decrease in tumor cell proliferation, or a decrease in tumor cell survival.

The term "autologous" refers to any material derived from the same individual to whom it is later to be re-introduced into the individual.

The term "allogeneic" refers to any material derived from a different animal of the same species as the individual to whom the material is introduced. Two or more individuals are said to be allogeneic to one another when the genes at one or more loci are not identical. In some aspects, allogeneic material from individuals of the same species may be sufficiently unlike genetically to interact antigenically

The term "xenogeneic" refers to a graft derived from an animal of a different species.

The term "cancer" refers to a disease characterized by the uncontrolled growth of aberrant cells. Cancer cells can spread locally or through the bloodstream and lymphatic system to other parts of the body. Examples of various cancers are described herein and include but are

not limited to, breast cancer, prostate cancer, ovarian cancer, cervical cancer, skin cancer, pancreatic cancer, colorectal cancer, renal cancer, liver cancer, brain cancer, lymphoma, leukemia, lung cancer and the like. The terms "tumor" and "cancer" are used interchangeably herein, e.g., both terms encompass solid and liquid, e.g., diffuse or circulating, tumors. As used herein, the term "cancer" or "tumor" includes premalignant, as well as malignant cancers and tumors.

"Derived from" as that term is used herein, indicates a relationship between a first and a second molecule. It generally refers to structural similarity between the first molecule and a second molecule and does not connotate or include a process or source limitation on a first molecule that is derived from a second molecule. For example, in the case of an intracellular signaling domain that is derived from a CD3zeta molecule, the intracellular signaling domain retains sufficient CD3zeta structure such that is has the required function, namely, the ability to generate a signal under the appropriate conditions. It does not connotate or include a limitation to a particular process of producing the intracellular signaling domain, e.g., it does not mean that, to provide the intracellular signaling domain, one must start with a CD3zeta sequence and delete unwanted sequence, or impose mutations, to arrive at the intracellular signaling domain.

The phrase "disease associated with expression of a tumor antigen as described herein" includes, but is not limited to, a disease associated with expression of a tumor antigen as described herein or condition associated with cells which express a tumor antigen as described herein including, e.g., proliferative diseases such as a cancer or malignancy or a precancerous condition such as a myelodysplasia, a myelodysplastic syndrome or a preleukemia; or a noncancer related indication associated with cells which express a tumor antigen as described herein. In one aspect, a cancer associated with expression of a tumor antigen as described herein is a hematological cancer. In one aspect, a cancer associated with expression of a tumor antigen as described herein is a solid cancer. Further diseases associated with expression of a tumor antigen described herein include, but not limited to, e.g., atypical and/or non-classical cancers, malignancies, precancerous conditions or proliferative diseases associated with expression of a tumor antigen as described herein. Non-cancer related indications associated with expression of a tumor antigen as described herein include, but are not limited to, e.g., autoimmune disease, (e.g., lupus), inflammatory disorders (allergy and asthma) and transplantation. In some embodiments, the tumor antigen-expressing cells express, or at any time expressed, mRNA

encoding the tumor antigen. In an embodiment, the tumor antigen -expressing cells produce the tumor antigen protein (e.g., wild-type or mutant), and the tumor antigen protein may be present at normal levels or reduced levels. In an embodiment, the tumor antigen -expressing cells produced detectable levels of a tumor antigen protein at one point, and subsequently produced substantially no detectable tumor antigen protein.

The term "conservative sequence modifications" refers to amino acid modifications that do not significantly affect or alter the binding characteristics of the antibody or antibody fragment containing the amino acid sequence. Such conservative modifications include amino acid substitutions, additions and deletions. Modifications can be introduced into an antibody or antibody fragment of the invention by standard techniques known in the art, such as site-directed mutagenesis and PCR-mediated mutagenesis. Conservative amino acid substitutions are ones in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar 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). Thus, one or more amino acid residues within a CAR of the invention can be replaced with other amino acid residues from the same side chain family and the altered CAR can be tested using the functional assays described herein.

The term "stimulation," refers to a primary response induced by binding of a stimulatory molecule (e.g., a TCR/CD3 complex or CAR) with its cognate ligand (or tumor antigen in the case of a CAR) thereby mediating a signal transduction event, such as, but not limited to, signal transduction via the TCR/CD3 complex or signal transduction via the appropriate NK receptor or signaling domains of the CAR. Stimulation can mediate altered expression of certain molecules.

The term "stimulatory molecule," refers to a molecule expressed by ~~a~~an immune cell (e.g., T cell, NK cell, B cell) that provides the cytoplasmic signaling sequence(s) that regulate activation of the immune cell in a stimulatory way for at least some aspect of the immune cell signaling pathway. In one aspect, the signal is a primary signal that is initiated by, for instance, binding of a TCR/CD3 complex with an MHC molecule loaded with peptide, and which leads to

mediation of a T cell response, including, but not limited to, proliferation, activation, differentiation, and the like. A primary cytoplasmic signaling sequence (also referred to as a "primary signaling domain") that acts in a stimulatory manner may contain a signaling motif which is known as immunoreceptor tyrosine-based activation motif or ITAM. Examples of an ITAM containing cytoplasmic signaling sequence that is of particular use in the invention includes, but is not limited to, those derived from CD3 zeta, common FcR gamma (FCER1G), Fc gamma RIIa, FcR beta (Fc Epsilon R1b), CD3 gamma, CD3 delta, CD3 epsilon, CD79a, CD79b, DAP10, and DAP12. In a specific CAR of the invention, the intracellular signaling domain in any one or more CARS of the invention comprises an intracellular signaling sequence, e.g., a primary signaling sequence of CD3-zeta. In a specific CAR of the invention, the primary signaling sequence of CD3-zeta is the sequence provided as SEQ ID NO:18, or the equivalent residues from a non-human species, e.g., mouse, rodent, monkey, ape and the like. In a specific CAR of the invention, the primary signaling sequence of CD3-zeta is the sequence as provided in SEQ ID NO: 20, or the equivalent residues from a non-human species, e.g., mouse, rodent, monkey, ape and the like.

The term "antigen presenting cell" or "APC" refers to an immune system cell such as an accessory cell (e.g., a B-cell, a dendritic cell, and the like) that displays a foreign antigen complexed with major histocompatibility complexes (MHC's) on its surface. T-cells may recognize these complexes using their T-cell receptors (TCRs). APCs process antigens and present them to T-cells.

An "intracellular signaling domain," as the term is used herein, refers to an intracellular portion of a molecule. The intracellular signaling domain generates a signal that promotes an immune effector function of the CAR containing cell, e.g., a CART cell. Examples of immune effector function, e.g., in a CART cell, include cytolytic activity and helper activity, including the secretion of cytokines.

In an embodiment, the intracellular signaling domain can comprise a primary intracellular signaling domain. Exemplary primary intracellular signaling domains include those derived from the molecules responsible for primary stimulation, or antigen dependent simulation. In an embodiment, the intracellular signaling domain can comprise a costimulatory intracellular domain. Exemplary costimulatory intracellular signaling domains include those derived from molecules responsible for costimulatory signals, or antigen independent stimulation. For

example, in the case of a CART, a primary intracellular signaling domain can comprise a cytoplasmic sequence of a T cell receptor, and a costimulatory intracellular signaling domain can comprise cytoplasmic sequence from co-receptor or costimulatory molecule.

A primary intracellular signaling domain can comprise a signaling motif which is known as an immunoreceptor tyrosine-based activation motif or ITAM. Examples of ITAM containing primary cytoplasmic signaling sequences include, but are not limited to, those derived from CD3 zeta, common FcR gamma (FCER1G), Fc gamma RIIa, FcR beta (Fc Epsilon R1b), CD3 gamma, CD3 delta, CD3 epsilon, CD79a, CD79b, DAP10, and DAP12.

The term "zeta" or alternatively "zeta chain", "CD3-zeta" or "TCR-zeta" is defined as the protein provided as GenBan Acc. No. BAG36664.1, or the equivalent residues from a non-human species, e.g., mouse, rodent, monkey, ape and the like, and a "zeta stimulatory domain" or alternatively a "CD3-zeta stimulatory domain" or a "TCR-zeta stimulatory domain" is defined as the amino acid residues from the cytoplasmic domain of the zeta chain, or functional derivatives thereof, that are sufficient to functionally transmit an initial signal necessary for T cell activation. In one aspect the cytoplasmic domain of zeta comprises residues 52 through 164 of GenBank Acc. No. BAG36664.1 or the equivalent residues from a non-human species, e.g., mouse, rodent, monkey, ape and the like, that are functional orthologs thereof. In one aspect, the "zeta stimulatory domain" or a "CD3-zeta stimulatory domain" is the sequence provided as SEQ ID NO: 18. In one aspect, the "zeta stimulatory domain" or a "CD3-zeta stimulatory domain" is the sequence provided as SEQ ID NO: 20.

The term a "costimulatory molecule" refers to 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 are cell surface molecules other than antigen receptors or their ligands that are contribute to an efficient immune response. Costimulatory molecules include, but are not limited to an MHC class I molecule, BTLA and a Toll ligand receptor, as well as OX40, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), and 4-1BB (CD137). Further examples of such costimulatory molecules include CDS, ICAM-1, GITR, BAFFR, HVEM (LIGHTR), SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD160, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c,

ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, and a ligand that specifically binds with CD83.

A costimulatory intracellular signaling domain can be the intracellular portion of a costimulatory molecule. A costimulatory molecule can be represented in the following protein families: TNF receptor proteins, Immunoglobulin-like proteins, cytokine receptors, integrins, signaling lymphocytic activation molecules (SLAM proteins), and activating NK cell receptors. Examples of such molecules include CD27, CD28, 4-1BB (CD137), OX40, GITR, CD30, CD40, ICOS, BAFFR, HVEM, ICAM-1, lymphocyte function-associated antigen-1 (LFA-1), CD2, CDS, CD7, CD287, LIGHT, NKG2C, NKG2D, SLAMF7, NKp80, NKp30, NKp44, NKp46, CD160, B7-H3, and a ligand that specifically binds with CD83, and the like.

The intracellular signaling domain can comprise the entire intracellular portion, or the entire native intracellular signaling domain, of the molecule from which it is derived, or a functional fragment or derivative thereof.

The term "4-1BB" refers to a member of the TNFR superfamily with an amino acid sequence provided as GenBank Acc. No. AAA62478.2, or the equivalent residues from a non-human species, e.g., mouse, rodent, monkey, ape and the like; and a "4-1BB costimulatory domain" is defined as amino acid residues 214-255 of GenBank Acc. No. AAA62478.2, or the equivalent residues from a non-human species, e.g., mouse, rodent, monkey, ape and the like. In one aspect, the "4-1BB costimulatory domain" is the sequence provided as SEQ ID NO: 14 or the equivalent residues from a non-human species, e.g., mouse, rodent, monkey, ape and the like.

"Immune effector cell," as that term is used herein, refers to a cell that is involved in an immune response, e.g., in the promotion of an immune effector response. Examples of immune effector cells include T cells, e.g., alpha/beta T cells and gamma/delta T cells, B cells, natural killer (NK) cells, natural killer T (NKT) cells, mast cells, and myeloic-derived phagocytes.

"Immune effector function or immune effector response," as that term is used herein, refers to function or response, e.g., of an immune effector cell, that enhances or promotes an immune attack of a target cell. E.g., an immune effector function or response refers a property of a T or NK cell that promotes killing or the inhibition of growth or proliferation, of a target cell.

In the case of a T cell, primary stimulation and co-stimulation are examples of immune effector function or response.

The term "encoding" refers to the inherent property of specific sequences of nucleotides in a polynucleotide, such as a gene, a cDNA, or an mRNA, to serve as templates for synthesis of other polymers and macromolecules in biological processes having either a defined sequence of nucleotides (e.g., rRNA, tRNA and mRNA) or a defined sequence of amino acids and the biological properties resulting therefrom. Thus, a gene, cDNA, or RNA, encodes a protein if transcription and translation of mRNA corresponding to that gene produces the protein in a cell or other biological system. Both the coding strand, the nucleotide sequence of which is identical to the mRNA sequence and is usually provided in sequence listings, and the non-coding strand, used as the template for transcription of a gene or cDNA, can be referred to as encoding the protein or other product of that gene or cDNA.

Unless otherwise specified, a "nucleotide sequence encoding an amino acid sequence" includes all nucleotide sequences that are degenerate versions of each other and that encode the same amino acid sequence. The phrase nucleotide sequence that encodes a protein or a RNA may also include introns to the extent that the nucleotide sequence encoding the protein may in some version contain an intron(s).

The term "effective amount" or "therapeutically effective amount" are used interchangeably herein, and refer to an amount of a compound, formulation, material, or composition, as described herein effective to achieve a particular biological result.

The term "endogenous" refers to any material from or produced inside an organism, cell, tissue or system.

The term "exogenous" refers to any material introduced from or produced outside an organism, cell, tissue or system.

The term "expression" refers to the transcription and/or translation of a particular nucleotide sequence driven by a promoter.

The term "transfer vector" refers to a composition of matter which comprises an isolated nucleic acid and which can be used to deliver the isolated nucleic acid to the interior of a cell. Numerous vectors are known in the art including, but not limited to, linear polynucleotides, polynucleotides associated with ionic or amphiphilic compounds, plasmids, and viruses. Thus, the term "transfer vector" includes an autonomously replicating plasmid or a virus. The term

should also be construed to further include non-plasmid and non-viral compounds which facilitate transfer of nucleic acid into cells, such as, for example, a polylysine compound, liposome, and the like. Examples of viral transfer vectors include, but are not limited to, adenoviral vectors, adeno-associated virus vectors, retroviral vectors, lentiviral vectors, and the like.

The term "expression vector" refers to a vector comprising a recombinant polynucleotide comprising expression control sequences operatively linked to a nucleotide sequence to be expressed. An expression vector comprises sufficient cis-acting elements for expression; other elements for expression can be supplied by the host cell or in an in vitro expression system. Expression vectors include all those known in the art, including cosmids, plasmids (e.g., naked or contained in liposomes) and viruses (e.g., lentiviruses, retroviruses, adenoviruses, and adeno-associated viruses) that incorporate the recombinant polynucleotide.

The term "lentivirus" refers to a genus of the Retroviridae family. Lentiviruses are unique among the retroviruses in being able to infect non-dividing cells; they can deliver a significant amount of genetic information into the DNA of the host cell, so they are one of the most efficient methods of a gene delivery vector. HIV, SIV, and FIV are all examples of lentiviruses.

The term "lentiviral vector" refers to a vector derived from at least a portion of a lentivirus genome, including especially a self-inactivating lentiviral vector as provided in Milone et al., Mol. Ther. 17(8): 1453–1464 (2009). Other examples of lentivirus vectors that may be used in the clinic, include but are not limited to, e.g., the LENTIVECTOR® gene delivery technology from Oxford BioMedica, the LENTIMAX™ vector system from Lentigen and the like. Nonclinical types of lentiviral vectors are also available and would be known to one skilled in the art.

The term "homologous" or "identity" refers to the subunit sequence identity between two polymeric molecules, e.g., between two nucleic acid molecules, such as, two DNA molecules or two RNA molecules, or between two polypeptide molecules. When a subunit position in both of the two molecules is occupied by the same monomeric subunit; e.g., if a position in each of two DNA molecules is occupied by adenine, then they are homologous or identical at that position. The homology between two sequences is a direct function of the number of matching or homologous positions; e.g., if half (e.g., five positions in a polymer ten subunits in length) of the positions in two sequences are homologous, the two sequences are 50% homologous; if 90% of

the positions (e.g., 9 of 10), are matched or homologous, the two sequences are 90% homologous.

"Humanized" forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')2 or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies and antibody fragments thereof are human immunoglobulins (recipient antibody or antibody fragment) in which residues from a complementary-determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, a humanized antibody/antibody fragment can comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. These modifications can further refine and optimize antibody or antibody fragment performance. In general, the humanized antibody or antibody fragment thereof will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or a significant portion of the FR regions are those of a human immunoglobulin sequence. The humanized antibody or antibody fragment can also comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones et al., Nature, 321: 522-525, 1986; Reichmann et al., Nature, 332: 323-329, 1988; Presta, Curr. Op. Struct. Biol., 2: 593-596, 1992.

"Fully human" refers to an immunoglobulin, such as an antibody or antibody fragment, where the whole molecule is of human origin or consists of an amino acid sequence identical to a human form of the antibody or immunoglobulin.

The term "isolated" means altered or removed from the natural state. For example, a nucleic acid or a peptide naturally present in a living animal is not "isolated," but the same nucleic acid or peptide partially or completely separated from the coexisting materials of its natural state is "isolated." An isolated nucleic acid or protein can exist in substantially purified form, or can exist in a non-native environment such as, for example, a host cell.

In the context of the present invention, the following abbreviations for the commonly occurring nucleic acid bases are used. "A" refers to adenosine, "C" refers to cytosine, "G" refers to guanosine, "T" refers to thymidine, and "U" refers to uridine.

The term "operably linked" or "transcriptional control" refers to functional linkage between a regulatory sequence and a heterologous nucleic acid sequence resulting in expression of the latter. For example, a first nucleic acid sequence is operably linked with a second nucleic acid sequence when the first nucleic acid sequence is placed in a functional relationship with the second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Operably linked DNA sequences can be contiguous with each other and, e.g., where necessary to join two protein coding regions, are in the same reading frame.

The term "parenteral" administration of an immunogenic composition includes, e.g., subcutaneous (s.c.), intravenous (i.v.), intramuscular (i.m.), or intrasternal injection, intratumoral, or infusion techniques.

The term "nucleic acid" or "polynucleotide" refers to deoxyribonucleic acids (DNA) or ribonucleic acids (RNA) and polymers thereof in either single- or double-stranded form. Unless specifically limited, the term encompasses nucleic acids containing known analogues of natural nucleotides that have similar binding properties as the reference nucleic acid and are metabolized in a manner similar to naturally occurring nucleotides. Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (e.g., degenerate codon substitutions), alleles, orthologs, SNPs, and complementary sequences as well as the sequence explicitly indicated. Specifically, degenerate codon substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzer et al., Nucleic Acid Res. 19:5081 (1991); Ohtsuka et al., J. Biol. Chem. 260:2605-2608 (1985); and Rossolini et al., Mol. Cell. Probes 8:91-98 (1994)).

The terms "peptide," "polypeptide," and "protein" are used interchangeably, and refer to a compound comprised of amino acid residues covalently linked by peptide bonds. A protein or peptide must contain at least two amino acids, and no limitation is placed on the maximum number of amino acids that can comprise a protein's or peptide's sequence. Polypeptides include any peptide or protein comprising two or more amino acids joined to each other by peptide

bonds. As used herein, the term refers to both short chains, which also commonly are referred to in the art as peptides, oligopeptides and oligomers, for example, and to longer chains, which generally are referred to in the art as proteins, of which there are many types. "Polypeptides" include, for example, biologically active fragments, substantially homologous polypeptides, oligopeptides, homodimers, heterodimers, variants of polypeptides, modified polypeptides, derivatives, analogs, fusion proteins, among others. A polypeptide includes a natural peptide, a recombinant peptide, or a combination thereof.

The term "promoter" refers to a DNA sequence recognized by the synthetic machinery of the cell, or introduced synthetic machinery, required to initiate the specific transcription of a polynucleotide sequence.

The term "promoter/regulatory sequence" refers to a nucleic acid sequence which is required for expression of a gene product operably linked to the promoter/regulatory sequence. In some instances, this sequence may be the core promoter sequence and in other instances, this sequence may also include an enhancer sequence and other regulatory elements which are required for expression of the gene product. The promoter/regulatory sequence may, for example, be one which expresses the gene product in a tissue specific manner.

The term "constitutive" promoter refers to a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a cell under most or all physiological conditions of the cell.

The term "inducible" promoter refers to a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a cell substantially only when an inducer which corresponds to the promoter is present in the cell.

The term "tissue-specific" promoter refers to a nucleotide sequence which, when operably linked with a polynucleotide encodes or specified by a gene, causes the gene product to be produced in a cell substantially only if the cell is a cell of the tissue type corresponding to the promoter.

The terms "cancer associated antigen" or "tumor antigen" interchangeably refers to a molecule (typically a protein, carbohydrate or lipid) that is expressed on the surface of a cancer cell, either entirely or as a fragment (e.g., MHC/peptide), and which is useful for the preferential targeting of a pharmacological agent to the cancer cell. In some embodiments, a tumor antigen is

a marker expressed by both normal cells and cancer cells, e.g., a lineage marker, e.g., CD19 on B cells. In some embodiments, a tumor antigen is a cell surface molecule that is overexpressed in a cancer cell in comparison to a normal cell, for instance, 1-fold over expression, 2-fold overexpression, 3-fold overexpression or more in comparison to a normal cell. In some enbodiments, a tumor antigen is a cell surface molecule that is inappropriately synthesized in the cancer cell, for instance, a molecule that contains deletions, additions or mutations in comparison to the molecule expressed on a normal cell. In some embodiments, a tumor antigen will be expressed exclusively on the cell surface of a cancer cell, entirely or as a fragment (e.g., MHC/peptide), and not synthesized or expressed on the surface of a normal cell. In some embodiments, the CARs of the present invention includes CARs comprising an antigen binding domain (e.g., antibody or antibody fragment) that binds to a MHC presented peptide. Normally, peptides derived from endogenous proteins fill the pockets of Major histocompatibility complex (MHC) class I molecules, and are recognized by T cell receptors (TCRs) on CD8 + T lymphocytes. The MHC class I complexes are constitutively expressed by all nucleated cells. In cancer, virus-specific and/or tumor-specific peptide/MHC complexes represent a unique class of cell surface targets for immunotherapy. TCR-like antibodies targeting peptides derived from viral or tumor antigens in the context of human leukocyte antigen (HLA)-A1 or HLA-A2 have been described (see, e.g., Sastry et al., J Virol. 2011 85(5):1935-1942; Sergeeva et al., Blood, 2011 117(16):4262-4272; Verma et al., J Immunol 2010 184(4):2156-2165; Willemsen et al., Gene Ther 2001 8(21) :1601-1608 ; Dao et al., Sci Transl Med 2013 5(176) :176ra33 ; Tassev et al., Cancer Gene Ther 2012 19(2):84-100). For example, TCR-like antibody can be identified from screening a library, such as a human scFv phage displayed library.

The term "tumor-supporting antigen" or "cancer-supporting antigen" interchangeably refer to a molecule (typically a protein, carbohydrate or lipid) that is expressed on the surface of a cell that is, itself, not cancerous, but supports the cancer cells, e.g., by promoting their growth or survival e.g., resistance to immune cells. Exemplary cells of this type include stromal cells and myeloid-derived suppressor cells (MDSCs). The tumor-supporting antigen itself need not play a role in supporting the tumor cells so long as the antigen is present on a cell that supports cancer cells.

The term "flexible polypeptide linker" or "linker" as used in the context of a scFv refers to a peptide linker that consists of amino acids such as glycine and/or serine residues used alone

or in combination, to link variable heavy and variable light chain regions together. In one embodiment, the flexible polypeptide linker is a Gly/Ser linker and comprises the amino acid sequence (Gly-Gly-Gly-Ser)n, where n is a positive integer equal to or greater than 1. For example, n=1, n=2, n=3. n=4, n=5 and n=6, n=7, n=8, n=9 and n=10 (SEQ ID NO:28). In one embodiment, the flexible polypeptide linkers include, but are not limited to, (Gly4 Ser)4 (SEQ ID NO:29) or (Gly4 Ser)3 (SEQ ID NO:30). In another embodiment, the linkers include multiple repeats of (Gly2Ser), (GlySer) or (Gly3Ser) (SEQ ID NO:31). Also included within the scope of the invention are linkers described in WO2012/138475, incorporated herein by reference).

As used herein, a 5' cap (also termed an RNA cap, an RNA 7-methylguanosine cap or an RNA m^7G cap) is a modified guanine nucleotide that has been added to the "front" or 5' end of a eukaryotic messenger RNA shortly after the start of transcription. The 5' cap consists of a terminal group which is linked to the first transcribed nucleotide. Its presence is critical for recognition by the ribosome and protection from RNases. Cap addition is coupled to transcription, and occurs co-transcriptionally, such that each influences the other. Shortly after the start of transcription, the 5' end of the mRNA being synthesized is bound by a cap-synthesizing complex associated with RNA polymerase. This enzymatic complex catalyzes the chemical reactions that are required for mRNA capping. Synthesis proceeds as a multi-step biochemical reaction. The capping moiety can be modified to modulate functionality of mRNA such as its stability or efficiency of translation.

As used herein, "in vitro transcribed RNA" refers to RNA, preferably mRNA, that has been synthesized in vitro. Generally, the in vitro transcribed RNA is generated from an in vitro transcription vector. The in vitro transcription vector comprises a template that is used to generate the in vitro transcribed RNA.

As used herein, a "poly(A)" is a series of adenosines attached by polyadenylation to the mRNA. In the preferred embodiment of a construct for transient expression, the polyA is between 50 and 5000 (SEQ ID NO: 34), preferably greater than 64, more preferably greater than 100, most preferably greater than 300 or 400. poly(A) sequences can be modified chemically or enzymatically to modulate mRNA functionality such as localization, stability or efficiency of translation.

As used herein, "polyadenylation" refers to the covalent linkage of a polyadenylyl moiety, or its modified variant, to a messenger RNA molecule. In eukaryotic organisms, most

messenger RNA (mRNA) molecules are polyadenylated at the 3' end. The 3' poly(A) tail is a long sequence of adenine nucleotides (often several hundred) added to the pre-mRNA through the action of an enzyme, polyadenylate polymerase. In higher eukaryotes, the poly(A) tail is added onto transcripts that contain a specific sequence, the polyadenylation signal. The poly(A) tail and the protein bound to it aid in protecting mRNA from degradation by exonucleases. Polyadenylation is also important for transcription termination, export of the mRNA from the nucleus, and translation. Polyadenylation occurs in the nucleus immediately after transcription of DNA into RNA, but additionally can also occur later in the cytoplasm. After transcription has been terminated, the mRNA chain is cleaved through the action of an endonuclease complex associated with RNA polymerase. The cleavage site is usually characterized by the presence of the base sequence AAUAAA near the cleavage site. After the mRNA has been cleaved, adenosine residues are added to the free 3' end at the cleavage site.

As used herein, "transient" refers to expression of a non-integrated transgene for a period of hours, days or weeks, wherein the period of time of expression is less than the period of time for expression of the gene if integrated into the genome or contained within a stable plasmid replicon in the host cell.

As used herein, the terms "treat", "treatment" and "treating" refer to the reduction or amelioration of the progression, severity and/or duration of a proliferative disorder, or the amelioration of one or more symptoms (preferably, one or more discernible symptoms) of a proliferative disorder resulting from the administration of one or more therapies (e.g., one or more therapeutic agents such as a CAR of the invention). In specific embodiments, the terms "treat", "treatment" and "treating" refer to the amelioration of at least one measurable physical parameter of a proliferative disorder, such as growth of a tumor, not necessarily discernible by the patient. In other embodiments the terms "treat", "treatment" and "treating" -refer to the inhibition of the progression of a proliferative disorder, either physically by, e.g., stabilization of a discernible symptom, physiologically by, e.g., stabilization of a physical parameter, or both. In other embodiments the terms "treat", "treatment" and "treating" refer to the reduction or stabilization of tumor size or cancerous cell count.

The term "signal transduction pathway" refers to the biochemical relationship between a variety of signal transduction molecules that play a role in the transmission of a signal from one portion of a cell to another portion of a cell. The phrase "cell surface receptor" includes

molecules and complexes of molecules capable of receiving a signal and transmitting signal across the membrane of a cell.

The term "subject" is intended to include living organisms in which an immune response can be elicited (e.g., mammals, human).

The term, a "substantially purified" cell refers to a cell that is essentially free of other cell types. A substantially purified cell also refers to a cell which has been separated from other cell types with which it is normally associated in its naturally occurring state. In some instances, a population of substantially purified cells refers to a homogenous population of cells. In other instances, this term refers simply to cell that have been separated from the cells with which they are naturally associated in their natural state. In some aspects, the cells are cultured in vitro. In other aspects, the cells are not cultured in vitro.

The term "therapeutic" as used herein means a treatment. A therapeutic effect is obtained by reduction, suppression, remission, or eradication of a disease state.

The term "prophylaxis" as used herein means the prevention of or protective treatment for a disease or disease state.

In the context of the present invention, "tumor antigen" or "hyperproliferative disorder antigen" or "antigen associated with a hyperproliferative disorder" refers to antigens that are common to specific hyperproliferative disorders. In certain aspects, the hyperproliferative disorder antigens of the present invention are derived from, cancers including but not limited to primary or metastatic melanoma, thymoma, lymphoma, sarcoma, lung cancer, liver cancer, non-Hodgkin lymphoma, Hodgkin lymphoma, leukemias, uterine cancer, cervical cancer, bladder cancer, kidney cancer and adenocarcinomas such as breast cancer, prostate cancer, ovarian cancer, pancreatic cancer, and the like.

The term "transfected" or "transformed" or "transduced" refers to a process by which exogenous nucleic acid is transferred or introduced into the host cell. A "transfected" or "transformed" or "transduced" cell is one which has been transfected, transformed or transduced with exogenous nucleic acid. The cell includes the primary subject cell and its progeny.

The term "specifically binds," refers to an antibody, or a ligand, which recognizes and binds with a binding partner (e.g., a tumor antigen) protein present in a sample, but which antibody or ligand does not substantially recognize or bind other molecules in the sample.

"Regulatable chimeric antigen receptor (RCAR),"as that term is used herein, refers to a set of polypeptides, typically two in the simplest embodiments, which when in a RCARX cell, provides the RCARX cell with specificity for a target cell, typically a cancer cell, and with regulatable intracellular signal generation or proliferation, which can optimize an immune effector property of the RCARX cell. An RCARX cell relies at least in part, on an antigen binding domain to provide specificity to a target cell that comprises the antigen bound by the antigen binding domain. In an embodiment, an RCAR includes a dimerization switch that, upon the presence of a dimerization molecule, can couple an intracellular signaling domain to the antigen binding domain.

"Membrane anchor" or "membrane tethering domain", as that term is used herein, refers to a polypeptide or moiety, e.g., a myristoyl group, sufficient to anchor an extracellular or intracellular domain to the plasma membrane.

"Switch domain," as that term is used herein, e.g., when referring to an RCAR, refers to an entity, typically a polypeptide-based entity, that, in the presence of a dimerization molecule, associates with another switch domain. The association results in a functional coupling of a first entity linked to, e.g., fused to, a first switch domain, and a second entity linked to, e.g., fused to, a second switch domain. A first and second switch domain are collectively referred to as a dimerization switch. In embodiments, the first and second switch domains are the same as one another, e.g., they are polypeptides having the same primary amino acid sequence, and are referred to collectively as a homodimerization switch. In embodiments, the first and second switch domains are different from one another, e.g., they are polypeptides having different primary amino acid sequences, and are referred to collectively as a heterodimerization switch. In embodiments, the switch is intracellular. In embodiments, the switch is extracellular. In embodiments, the switch domain is a polypeptide-based entity, e.g., FKBP or FRB-based, and the dimerization molecule is small molecule, e.g., a rapalogue. In embodiments, the switch domain is a polypeptide-based entity, e.g., an scFv that binds a myc peptide, and the dimerization molecule is a polypeptide, a fragment thereof, or a multimer of a polypeptide, e.g., a myc ligand or multimers of a myc ligand that bind to one or more myc scFvs. In embodiments, the switch domain is a polypeptide-based entity, e.g., myc receptor, and the dimerization molecule is an antibody or fragments thereof, e.g., myc antibody.

"Dimerization molecule," as that term is used herein, e.g., when referring to an RCAR, refers to a molecule that promotes the association of a first switch domain with a second switch domain. In embodiments, the dimerization molecule does not naturally occur in the subject, or does not occur in concentrations that would result in significant dimerization. In embodiments, the dimerization molecule is a small molecule, e.g., rapamycin or a rapalogue, e.g, RAD001.

The term "bioequivalent" refers to an amount of an agent other than the reference compound (e.g., RAD001), required to produce an effect equivalent to the effect produced by the reference dose or reference amount of the reference compound (e.g., RAD001). In an embodiment the effect is the level of mTOR inhibition, e.g., as measured by P70 S6 kinase inhibition, e.g., as evaluated in an in vivo or in vitro assay, e.g., as measured by an assay described herein, e.g., the Boulay assay. In an embodiment, the effect is alteration of the ratio of PD-1 positive/PD-1 negative T cells, as measured by cell sorting. In an embodiment a bioequivalent amount or dose of an mTOR inhibitor is the amount or dose that achieves the same level of P70 S6 kinase inhibition as does the reference dose or reference amount of a reference compound. In an embodiment, a bioequivalent amount or dose of an mTOR inhibitor is the amount or dose that achieves the same level of alteration in the ratio of PD-1 positive/PD-1 negative T cells as does the reference dose or reference amount of a reference compound.

The term "low, immune enhancing, dose" when used in conjunction with an mTOR inhibitor, e.g., an allosteric mTOR inhibitor, e.g., RAD001 or rapamycin, or a catalytic mTOR inhibitor, refers to a dose of mTOR inhibitor that partially, but not fully, inhibits mTOR activity, e.g., as measured by the inhibition of P70 S6 kinase activity. Methods for evaluating mTOR activity, e.g., by inhibition of P70 S6 kinase, are discussed herein. The dose is insufficient to result in complete immune suppression but is sufficient to enhance the immune response. In an embodiment, the low, immune enhancing, dose of mTOR inhibitor results in a decrease in the number of PD-1 positive T cells and/or an increase in the number of PD-1 negative T cells, or an increase in the ratio of PD-1 negative T cells/PD-1 positive T cells. In an embodiment, the low, immune enhancing, dose of mTOR inhibitor results in an increase in the number of naive T cells. In an embodiment, the low, immune enhancing, dose of mTOR inhibitor results in one or more of the following:

an increase in the expression of one or more of the following markers: $CD62L^{high}$, $CD127^{high}$, $CD27^{+}$, and BCL2, e.g., on memory T cells, e.g., memory T cell precursors;

a decrease in the expression of KLRG1, e.g., on memory T cells, e.g., memory T cell precursors; and

an increase in the number of memory T cell precursors, e.g., cells with any one or combination of the following characteristics: increased $CD62L^{high}$, increased $CD127^{high}$, increased $CD27^{+}$, decreased KLRG1, and increased BCL2;

wherein any of the changes described above occurs, e.g., at least transiently, e.g., as compared to a non-treated subject.

"Refractory" as used herein refers to a disease, e.g., cancer, that does not respond to a treatment. In embodiments, a refractory cancer can be resistant to a treatment before or at the beginning of the treatment. In other embodiments, the refractory cancer can become resistant during a treatment. A refractory cancer is also called a resistant cancer.

"Relapsed" as used herein refers to the return of a disease (e.g., cancer) or the signs and symptoms of a disease such as cancer after a period of improvement, e.g., after prior treatment of a therapy, e.g., cancer therapy

Ranges: throughout this disclosure, various aspects of the invention can be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 2.7, 3, 4, 5, 5.3, and 6. As another example, a range such as 95-99% identity, includes something with 95%, 96%, 97%, 98% or 99% identity, and includes subranges such as 96-99%, 96-98%, 96-97%, 97-99%, 97-98% and 98-99% identity. This applies regardless of the breadth of the range.

"Tet" as the term is used herein, refers to the family of genes, and the proteins encoded by said genes, of the ten-eleven translocation methlcytosine dioxygenase family. Tet includes, for example, Tet1, Tet2 and Tet3.

"Tet2" as the term is used herein, refers to gene, tet methylcytosine dioxygenase 2, and the protein encoded by said gene, the tet2 methylcytosine dioxygenase, which catalyzes the conversion of methylcytosine to 5-hydroxymethylcytosine. It is sometimes also referred to as

"KIAA1546," "FLJ20032" and "tet oncogene family member 2" The encoded protein is involved in myelopoiesis, and defects in this gene have been associated with several myeloproliferative disorders. In the human genome, TET2 is located on chromosome 4q24. Currently six TET2 isoforms have been described and their Genebank numbers are: NM_001127208.2; XM_005263082.1; XM_006714242.2; NM_017628.4; XM_011532044.1; and XM_011532043.1.

An example of the protein sequence of human Tet2 is provided as UniProt accession number Q6N021:

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         10         20         30         40         50
MEQDRTNHVE GNRLSPFLIP SPPICQTEPL ATKLQNGSPL PERAHPEVNG
         60         70         80         90        100
DTKWHSFKSY YGIPCMKGSQ NSRVSPDFTQ ESRGYSKCLQ NGGIKRTVSE
        110        120        130        140        150
PSLSGLLQIK KLKQDQKANG ERRNFGVSQE RNPGESSQPN VSDLSDKKES
        160        170        180        190        200
VSSVAQENAV KDFTSFSTHN CSGPENPELQ ILNEQEGKSA NYHDKNIVLL
        210        220        230        240        250
KNKAVLMPNG ATVSASSVEH THGELLEKTL SQYYPDCVSI AVQKTTSHIN
        260        270        280        290        300
AINSQATNEL SCEITHPSHT SGQINSAQTS NSELPPKPAA VVSEACDADD
        310        320        330        340        350
ADNASKLAAM LNTCSFQKPE QLQQQKSVFE ICPSPAENNI QGTTKLASGE
        360        370        380        390        400
EFCSGSSSNL QAPGGSSERY LKQNEMNGAY FKQSSVFTKD SFSATTTPPP
        410        420        430        440        450
PSQLLLSPPP PLPQVPQLPS EGKSTLNGGV LEEHHHYPNQ SNTTLLREVK
        460        470        480        490        500
IEGKPEAPPS QSPNPSTHVC SPSPMLSERP QNNCVNRNDI QTAGTMTVPL
        510        520        530        540        550
CSEKTRPMSE HLKHNPPIFG SSGELQDNCQ QLMRNKEQEI LKGRDKEQTR
        560        570        580        590        600
DLVPPTQHYL KPGWIELKAP RFHQAESHLK RNEASLPSIL QYQPNLSNQM
        610        620        630        640        650
TSKQYTGNSN MPGGLPRQAY TQKTTQLEHK SQMYQVEMNQ GQSQGTVDQH
        660        670        680        690        700
LQFQKPSHQV HFSKTDHLPK AHVQSLCGTR FHFQQRADSQ TEKLMSPVLK
        710        720        730        740        750
QHLNQQASET EPFSNSHLLQ HKPHKQAAQT QPSQSSHLPQ NQQQQQKLQI
        760        770        780        790        800
KNKEEILQTF PHPQSNNDQQ REGSFFGQTK VEECFHGENQ YSKSSEFETH
        810        820        830        840        850
NVQMGLEEVQ NINRRNSPYS QTMKSSACKI QVSCSNNTHL VSENKEQTTH
        860        870        880        890        900
PELFAGNKTQ NLHHMQYFPN NVIPKQDLLH RCFQEQEQKS QQASVLQGYK
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        910         920         930         940         950
NRNQDMSGQQ AAQLAQQRYL IHNHANVFPV PDQGGSHTQT PPQKDTQKHA
        960         970         980         990        1000
ALRWHLLQKQ EQQQTQQPQT ESCHSQMHRP IKVEPGCKPH ACMHTAPPEN
       1010        1020        1030        1040        1050
KTWKKVTKQE NPPASCDNVQ QKSIIETMEQ HLKQFHAKSL FDHKALTLKS
       1060        1070        1080        1090        1100
QKQVKVEMSG PVTVLTRQTT AAELDSHTPA LEQQTTSSEK TPTKRTAASV
       1110        1120        1130        1140        1150
LNNFIESPSK LLDTPIKNLL DTPVKTQYDF PSCRCVEQII EKDEGPFYTH
       1160        1170        1180        1190        1200
LGAGPNVAAI REIMEERFGQ KGKAIRIERV IYTGKEGKSS QGCPIAKWVV
       1210        1220        1230        1240        1250
RRSSSEEKLL CLVRERAGHT CEAAVIVILI LVWEGIPLSL ADKLYSELTE
       1260        1270        1280        1290        1300
TLRKYGTLTN RRCALNEERT CACQGLDPET CGASFSFGCS WSMYYNGCKF
       1310        1320        1330        1340        1350
ARSKIPRKFK LLGDDPKEEE KLESHLQNLS TLMAPTYKKL APDAYNNQIE
       1360        1370        1380        1390        1400
YEHRAPECRL GLKEGRPFSG VTACLDFCAH AHRDLHNMQN GSTLVCTLTR
       1410        1420        1430        1440        1450
EDNREFGGKP EDEQLHVLPL YKVSDVDEFG SVEAQEEKKR SGAIQVLSSF
       1460        1470        1480        1490        1500
RRKVRMLAEP VKTCRQRKLE AKKAAAEKLS SLENSSNKNE KEKSAPSRTK
       1510        1520        1530        1540        1550
QTENASQAKQ LAELLRLSGP VMQQSQQPQP LQKQPPQPQQ QQRPQQQQPH
       1560        1570        1580        1590        1600
HPQTESVNSY SASGSTNPYM RRPNPVSPYP NSSHTSDIYG STSPMNFYST
       1610        1620        1630        1640        1650
SSQAAGSYLN SSNPMNPYPG LLNQNTQYPS YQCNGNLSVD NCSPYLGSYS
       1660        1670        1680        1690        1700
PQSQPMDLYR YPSQDPLSKL SLPPIHTLYQ PRFGNSQSFT SKYLGYGNQN
       1710        1720        1730        1740        1750
MQGDGFSSCT IRPNVHHVGK LPPYPTHEMD GHFMGATSRL PPNLSNPNMD
       1760        1770        1780        1790        1800
YKNGEHHSPS HIIHNYSAAP GMFNSSLHAL HLQNKENDML SHTANGLSKM
       1810        1820        1830        1840        1850
LPALNHDRTA CVQGGLHKLS DANGQEKQPL ALVQGVASGA EDNDEVWSDS
       1860        1870        1880        1890        1900
EQSFLDPDIG GVAVAPTHGS ILIECAKREL HATTPLKNPN RNHPTRISLV
       1910        1920        1930        1940        1950
FYQHKSMNEP KHGLALWEAK MAEKAREKEE ECEKYGPDYV PQKSHGKKVK
       1960        1970        1980        1990        2000
REPAEPHETS EPTYLRFIKS LAERTMSVTT DSTVTTSPYA FTRVTGPYNR
 2002
YI
      [SEQ ID NO: 1357]
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The tet2 gene is located on chromosome 4, location GRCh38.p2 (GCF_000001405.28) (NC_000004.12 (105145875 to 105279803); Gene ID 54790.

Examples of nucleic acid sequences encoding Tet2 are provided below. There are 6 identified isoforms of human Tet2 have been identified. The mRNA sequences are provided below (In embodiments, in each sequence, T may be replaced with U). In embodiments, Tet2 includes the proteins encoded by each of the sequences below:

NName	**NCBI Reference Sequence**	**Sequence**
HHomo sapiens tet methylcytosine dioxygenase 2 (TET2), transcript variant 1, mRNA [SEQ ID NO: 1358]	NNM_001127208.2	GGCAGTGGCAGCGGCGAGAGCTTGGGCGGCCGCCGCCGCC TCCTCGCGAGCGCCGCGCGCCCGGGTCCCG CTCGCATGCAAGTCACGTCCGCCCCCTCGGCGCGGCCGCCC CGAGACGCCGGCCCCGCTGAGTGATGAGA ACAGACGTCAAACTGCCTTATGAATATTGATGCGGAGGCTA GGCTGCTTTCGTAGAGAAGCAGAAGGAAG CAAGATGGCTGCCCTTTAGGATTTGTTAGAAAGGAGACCCG ACTGCAACTGCTGGATTGCTGCAAGGCTG AGGGACGAGAACGAGGCTGGCAAACATTCAGCAGCACACC CTCTCAAGATTGTTTACTTGCCTTTGCTCC TGTTGAGTTACAACGCTTGGAAGCAGGAGATGGGCTCAGCA GCAGCCAATAGGACATGATCCAGGAAGAG CAGTAAGGGACTGAGCTGCTGAATTCAACTAGAGGGCAGC CTTGTGGATGGCCCCGAAGCAAGCCTGATG GAACAGGATAGAACCAACCATGTTGAGGGCAACAGACTAA GTCCATTCCTGATACCATCACCTCCCATTT GCCAGACAGAACCTCTGGCTACAAAGCTCCAGAATGGAAG CCCACTGCCTGAGAGAGCTCATCCAGAAGT AAATGGAGACACCAAGTGGCACTCTTTCAAAAGTTATTATG GAATACCCTGTATGAAGGGAAGCCAGAAT AGTCGTGTGAGTCCTGACTTTACACAAGAAAGTAGAGGGTA TTCCAAGTGTTTGCAAAATGGAGGAATAA AACGCACAGTTAGTGAACCTTCTCTCTCTGGGCTCCTTCAGA TCAAGAAATTGAAACAAGACCAAAAGGC TAATGGAGAAAGACGTAACTTCGGGGTAAGCCAAGAAAGA AATCCAGGTGAAAGCAGTCAACCAAATGTC TCCGATTTGAGTGATAAGAAAGAATCTGTGAGTTCTGTAGC CCAAGAAAATGCAGTTAAAGATTTCACCA GTTTTTCAACACATAACTGCAGTGGGCCTGAAAATCCAGAG CTTCAGATTCTGAATGAGCAGGAGGGGAA AAGTGCTAATTACCATGACAAGAACATTGTATTACTTAAAA ACAAGGCAGTGCTAATGCCTAATGGTGCT ACAGTTTCTGCCTCTTCCGTGGAACACACACATGGTGAACT CCTGGAAAAAACACTGTCTCAATATTATC CAGATTGTGTTTCCATTGCGGTGCAGAAAACCACATCTCAC ATAAATGCCATTAACAGTCAGGCTACTAA TGAGTTGTCCTGTGAGATCACTCACCCATCGCATACCTCAG GGCAGATCAATTCCGCACAGACCTCTAAC TCTGAGCTGCCTCCAAAGCCAGCTGCAGTGGTGAGTGAGGC CTGTGATGCTGATGATGCTGATAATGCCA GTAAACTAGCTGCAATGCTAAATACCTGTTCCTTTCAGAAA

		CCAGAACAACTACAACAACAAAAATCAGT TTTTGAGATATGCCCATCTCCTGCAGAAAATAACATCCAGG GAACCACAAAGCTAGCGTCTGGTGAAGAA TTCTGTTCAGGTTCCAGCAGCAATTTGCAAGCTCCTGGTGGC AGCTCTGAACGGTATTTAAAACAAAATG AAATGAATGGTGCTTACTTCAAGCAAAGCTCAGTGTTCACT AAGGATTCCTTTTCTGCCACTACCACACC ACCACCACCATCACAATTGCTTCTTTCTCCCCCTCCTCCTCT TCCACAGGTTCCTCAGCTTCCTTCAGAA GGAAAAAGCACTCTGAATGGTGGAGTTTTAGAAGAACACC ACCACTACCCCAACCAAAGTAACACAACAC TTTTAAGGGAAGTGAAAATAGAGGGTAAACCTGAGGCACC ACCTTCCCAGAGTCCTAATCCATCTACACA TGTATGCAGCCCTTCTCCGATGCTTTCTGAAAGGCCTCAGA ATAATTGTGTGAACAGGAATGACATACAG ACTGCAGGGACAATGACTGTTCCATTGTGTTCTGAGAAAAC AAGACCAATGTCAGAACACCTCAAGCATA ACCCACCAATTTTTGGTAGCAGTGGAGAGCTACAGGACAAC TGCCAGCAGTTGATGAGAAACAAAGAGCA AGAGATTCTGAAGGGTCGAGACAAGGAGCAAACACGAGAT CTTGTGCCCCCAACACAGCACTATCTGAAA CCAGGATGGATTGAATTGAAGGCCCCTCGTTTTCACCAAGC GGAATCCCATCTAAAACGTAATGAGGCAT CACTGCCATCAATTCTTCAGTATCAACCCAATCTCTCCAATC AAATGACCTCCAAACAATACACTGGAAA TTCCAACATGCCTGGGGGGCTCCCAAGGCAAGCTTACACCC AGAAAACAACACAGCTGGAGCACAAGTCA CAAATGTACCAAGTTGAAATGAATCAAGGGCAGTCCCAAG GTACAGTGGACCAACATCTCCAGTTCCAAA AACCCTCACACCAGGTGCACTTCTCCAAAACAGACCATTTA CCAAAAGCTCATGTGCAGTCACTGTGTGG CACTAGATTTCATTTTCAACAAAGAGCAGATTCCCAAACTG AAAAACTTATGTCCCCAGTGTTGAAACAG CACTTGAATCAACAGGCTTCAGAGACTGAGCCATTTTCAAA CTCACACCTTTTGCAACATAAGCCTCATA AACAGGCAGCACAAACACAACCATCCCAGAGTTCACATCTC CCTCAAAACCAGCAACAGCAGCAAAAATT ACAAATAAAGAATAAAGAGGAAATACTCCAGACTTTTCCTC ACCCCCAAAGCAACAATGATCAGCAAAGA GAAGGATCATTCTTTGGCCAGACTAAAGTGGAAGAATGTTT TCATGGTGAAAATCAGTATTCAAAATCAA GCGAGTTCGAGACTCATAATGTCCAAATGGGACTGGAGGA AGTACAGAATATAAATCGTAGAAATTCCCC TTATAGTCAGACCATGAAATCAAGTGCATGCAAAATACAGG TTTCTTGTTCAAACAATACACACCTAGTT TCAGAGAATAAAGAACAGACTACACATCCTGAACTTTTTGC AGGAAACAAGACCCAAAACTTGCATCACA TGCAATATTTTCCAAATAATGTGATCCCAAAGCAAGATCTT CTTCACAGGTGCTTTCAAGAACAGGAGCA GAAGTCACAACAAGCTTCAGTTCTACAGGGATATAAAAATA

		GAAACCAAGATATGTCTGGTCAACAAGCT GCGCAACTTGCTCAGCAAAGGTACTTGATACATAACCATGC AAATGTTTTTCCTGTGCCTGACCAGGGAG GAAGTCACACTCAGACCCCTCCCCAGAAGGACACTCAAAA GCATGCTGCTCTAAGGTGGCATCTCTTACA GAAGCAAGAACAGCAGCAAACACAGCAACCCCAAACTGAG TCTTGCCATAGTCAGATGCACAGGCCAATT AAGGTGGAACCTGGATGCAAGCCACATGCCTGTATGCACAC AGCACCACCAGAAAACAAAACATGGAAAA AGGTAACTAAGCAAGAGAATCCACCTGCAAGCTGTGATAAT GTGCAGCAAAAGAGCATCATTGAGACCAT GGAGCAGCATCTGAAGCAGTTTCACGCCAAGTCGTTATTTG ACCATAAGGCTCTTACTCTCAAATCACAG AAGCAAGTAAAAGTTGAAATGTCAGGGCCAGTCACAGTTTT GACTAGACAAACCACTGCTGCAGAACTTG ATAGCCACACCCCAGCTTTAGAGCAGCAAACAACTTCTTCA GAAAAGACACCAACCAAAAGAACAGCTGC TTCTGTTCTCAATAATTTTATAGAGTCACCTTCCAAATTACT AGATACTCCTATAAAAAATTTATTGGAT ACACCTGTCAAGACTCAATATGATTTCCCATCTTGCAGATGT GTAGAGCAAATTATTGAAAAAGATGAAG GTCCTTTTTATACCCATCTAGGAGCAGGTCCTAATGTGGCA GCTATTAGAGAAATCATGGAAGAAAGGTT TGGACAGAAGGGTAAAGCTATTAGGATTGAAAGAGTCATCT ATACTGGTAAAGAAGGCAAAAGTTCTCAG GGATGTCCTATTGCTAAGTGGGTGGTTCGCAGAAGCAGCAG TGAAGAGAAGCTACTGTGTTTGGTGCGGG AGCGAGCTGGCCACACCTGTGAGGCTGCAGTGATTGTGATT CTCATCCTGGTGTGGGAAGGAATCCCGCT GTCTCTGGCTGACAAACTCTACTCGGAGCTTACCGAGACGC TGAGGAAATACGGCACGCTCACCAATCGC CGGTGTGCCTTGAATGAAGAGAGAACTTGCGCCTGTCAGGG GCTGGATCCAGAAACCTGTGGTGCCTCCT TCTCTTTTGGTTGTTCATGGAGCATGTACTACAATGGATGTA AGTTTGCCAGAAGCAAGATCCCAAGGAA GTTTAAGCTGCTTGGGGATGACCCAAAAGAGGAAGAGAAA CTGGAGTCTCATTTGCAAAACCTGTCCACT CTTATGGCACCAACATATAAGAAACTTGCACCTGATGCATA TAATAATCAGATTGAATATGAACACAGAG CACCAGAGTGCCGTCTGGGTCTGAAGGAAGGCCGTCCATTC TCAGGGGTCACTGCATGTTTGGACTTCTG TGCTCATGCCCACAGAGACTTGCACAACATGCAGAATGGCA GCACATTGGTATGCACTCTCACTAGAGAA GACAATCGAGAATTTGGAGGAAAACCTGAGGATGAGCAGC TTCACGTTCTGCCTTTATACAAAGTCTCTG ACGTGGATGAGTTTGGGAGTGTGGAAGCTCAGGAGGAGAA AAAACGGAGTGGTGCCATTCAGGTACTGAG TTCTTTTCGGCGAAAAGTCAGGATGTTAGCAGAGCCAGTCA AGACTTGCCGACAAAGGAAACTAGAAGCC AAGAAAGCTGCAGCTGAAAAGCTTTCCTCCCTGGAGAACAG

		CTCAAATAAAAATGAAAAGGAAAAGTCAG CCCCATCACGTACAAAACAAACTGAAAACGCAAGCCAGGC TAAACAGTTGGCAGAACTTTTGCGACTTTC AGGACCAGTCATGCAGCAGTCCCAGCAGCCCCAGCCTCTAC AGAAGCAGCCACCACAGCCCCAGCAGCAG CAGAGACCCCAGCAGCAGCAGCCACATCACCCTCAGACAG AGTCTGTCAACTCTTATTCTGCTTCTGGAT CCACCAATCCATACATGAGACGGCCCAATCCAGTTAGTCCT TATCCAAACTCTTCACACACTTCAGATAT CTATGGAAGCACCAGCCCTATGAACTTCTATTCCACCTCATC TCAAGCTGCAGGTTCATATTTGAATTCT TCTAATCCCATGAACCCTTACCCTGGGCTTTTGAATCAGAAT ACCCAATATCCATCATATCAATGCAATG GAAACCTATCAGTGGACAACTGCTCCCCATATCTGGGTTCC TATTCTCCCCAGTCTCAGCCGATGGATCT GTATAGGTATCCAAGCCAAGACCCTCTGTCTAAGCTCAGTC TACCACCCATCCATACACTTTACCAGCCA AGGTTTGGAAATAGCCAGAGTTTTACATCTAAATACTTAGG TTATGGAAACCAAAATATGCAGGGAGATG GTTTCAGCAGTTGTACCATTAGACCAAATGTACATCATGTA GGGAAATTGCCTCCTTATCCCACTCATGA GATGGATGGCCACTTCATGGGAGCCACCTCTAGATTACCAC CCAATCTGAGCAATCCAAACATGGACTAT AAAAATGGTGAACATCATTCACCTTCTCACATAATCCATAA CTACAGTGCAGCTCCGGGCATGTTCAACA GCTCTCTTCATGCCCTGCATCTCCAAAACAAGGAGAATGAC ATGCTTTCCCACACAGCTAATGGGTTATC AAAGATGCTTCCAGCTCTTAACCATGATAGAACTGCTTGTG TCCAAGGAGGCTTACACAAATTAAGTGAT GCTAATGGTCAGGAAAAGCAGCCATTGGCACTAGTCCAGG GTGTGGCTTCTGGTGCAGAGGACAACGATG AGGTCTGGTCAGACAGCGAGCAGAGCTTTCTGGATCCTGAC ATTGGGGGAGTGGCCGTGGCTCCAACTCA TGGGTCAATTCTCATTGAGTGTGCAAAGCGTGAGCTGCATG CCACAACCCCTTTAAAGAATCCCAATAGG AATCACCCCACCAGGATCTCCCTCGTCTTTTACCAGCATAA GAGCATGAATGAGCCAAAACATGGCTTGG CTCTTTGGGAAGCCAAAATGGCTGAAAAAGCCCGTGAGAA AGAGGAAGAGTGTGAAAAGTATGGCCCAGA CTATGTGCCTCAGAAATCCCATGGCAAAAAAGTGAAACGG GAGCCTGCTGAGCCACATGAAACTTCAGAG CCCACTTACCTGCGTTTCATCAAGTCTCTTGCCGAAAGGACC ATGTCCGTGACCACAGACTCCACAGTAA CTACATCTCCATATGCCTTCACTCGGGTCACAGGGCCTTACA ACAGATATATATGATATCACCCCCTTTT GTTGGTTACCTCACTTGAAAAGACCACAACCAACCTGTCAG TAGTATAGTTCTCATGACGTGGGCAGTGG GGAAAGGTCACAGTATTCATGACAAATGTGGTGGGAAAAA CCTCAGCTCACCAGCAACAAAAGAGGTTAT CTTACCATAGCACTTAATTTTCACTGGCTCCCAAGTGGTCAC

		AGATGGCATCTAGGAAAAGACCAAAGCA TTCTATGCAAAAAGAAGGTGGGGAAGAAAGTGTTCCGCAA TTTACATTTTTAAACACTGGTTCTATTATT GGACGAGATGATATGTAAATGTGATCCCCCCCCCCCCGCTTA CAACTCTACACATCTGTGACCACTTTTAA TAATATCAAGTTTGCATAGTCATGGAACACAAATCAAACAA GTACTGTAGTATTACAGTGACAGGAATCT TAAAATACCATCTGGTGCTGAATATATGATGTACTGAAATA CTGGAATTATGGCTTTTTGAAATGCAGTT TTTACTGTAATCTTAACTTTTATTTATCAAAATAGCTACAGG AAACATGAATAGCAGGAAAACACTGAAT TTGTTTGGATGTTCTAAGAAATGGTGCTAAGAAAATGGTGT CTTTAATAGCTAAAAATTTAATGCCTTTA TATCATCAAGATGCTATCAGTGTACTCCAGTGCCCTTGAAT AATAGGGGTACCTTTTCATTCAAGTTTTT ATCATAATTACCTATTCTTACACAAGCTTAGTTTTTAAAATG TGGACATTTTAAAGGCCTCTGGATTTTG CTCATCCAGTGAAGTCCTTGTAGGACAATAAACGTATATAT GTACATATATACACAAACATGTATATGTG CACACACATGTATATGTATAAATATTTTAAATGGTGTTTTAG AAGCACTTTGTCTACCTAAGCTTTGACA ACTTGAACAATGCTAAGGTACTGAGATGTTTAAAAAACAAG TTTACTTTCATTTTAGAATGCAAAGTTGA TTTTTTTAAGGAAACAAAGAAAGCTTTTAAAATATTTTTGCT TTTAGCCATGCATCTGCTGATGAGCAAT TGTGTCCATTTTTAACACAGCCAGTTAAATCCACCATGGGG CTTACTGGATTCAAGGGAATACGTTAGTC CACAAAACATGTTTTCTGGTGCTCATCTCACATGCTATACTG TAAAACAGTTTTATACAAAATTGTATGA CAAGTTCATTGCTCAAAAATGTACAGTTTTAAGAATTTTCTA TTAACTGCAGGTAATAATTAGCTGCATG CTGCAGACTCAACAAAGCTAGTTCACTGAAGCCTATGCTAT TTTATGGATCATAGGCTCTTCAGAGAACT GAATGGCAGTCTGCCTTTGTGTTGATAATTATGTACATTGTG ACGTTGTCATTTCTTAGCTTAAGTGTCC TCTTTAACAAGAGGATTGAGCAGACTGATGCCTGCATAAGA TGAATAAACAGGGTTAGTTCCATGTGAAT CTGTCAGTTAAAAAGAAACAAAAACAGGCAGCTGGTTTGCT GTGGTGGTTTTAAATCATTAATTTGTATA AAGAAGTGAAAGAGTTGTATAGTAAATTAAATTGTAAACA AAACTTTTTTAATGCAATGCTTTAGTATTT TAGTACTGTAAAAAAATTAAATATATACATATATATATATA TATATATATATATATATATGAGTTTGAAG CAGAATTCACATCATGATGGTGCTACTCAGCCTGCTACAAA TATATCATAATGTGAGCTAAGAATTCATT AAATGTTTGAGTGATGTTCCTACTTGTCATATACCTCAACAC TAGTTTGGCAATAGGATATTGAACTGAG AGTGAAAGCATTGTGTACCATCATTTTTTTCCAAGTCCTTTT TTTTATTGTTAAAAAAAAAAGCATACCT TTTTTCAATACTTGATTTCTTAGCAAGTATAACTTGAACTTC

		AACCTTTTTGTTCTAAAAATTCAGGGAT ATTTCAGCTCATGCTCTCCCTATGCCAACATGTCACCTGTGT TTATGTAAAATTGTTGTAGGTTAATAAA TATATTCTTTGTCAGGGATTTAACCCTTTTATTTTGAATCCCT TCTATTTTACTTGTACATGTGCTGATG TAACTAAAACTAATTTTGTAAATCTGTTGGCTCTTTTTATTG TAAAGAAAAGCATTTTAAAAGTTTGAGG AATCTTTTGACTGTTTCAAGCAGGAAAAAAAAATTACATGA AAATAGAATGCACTGAGTTGATAAAGGGA AAAATTGTAAGGCAGGAGTTTGGCAAGTGGCTGTTGGCCAG AGACTTACTTGTAACTCTCTAAATGAAGT TTTTTTGATCCTGTAATCACTGAAGGTACATACTCCATGTGG ACTTCCCTTAAACAGGCAAACACCTACA GGTATGGTGTGCAACAGATTGTACAATTACATTTTGGCCTA AATACATTTTTGCTTACTAGTATTTAAAA TAAATTCTTAATCAGAGGAGGCCTTTGGGTTTTATTGGTCAA ATCTTTGTAAGCTGGCTTTTGTCTTTTT AAAAAATTTCTTGAATTTGTGGTTGTGTCCAATTTGCAAACA TTTCCAAAAATGTTTGCTTTGCTTACAA ACCACATGATTTTAATGTTTTTTGTATACCATAATATCTAGC CCCAAACATTTGATTACTACATGTGCAT TGGTGATTTTGATCATCCATTCTTAATATTTGATTTCTGTGTC ACCTACTGTCATTTGTTAAACTGCTGG CCAACAAGAACAGGAAGTATAGTTTGGGGGGTTGGGGAGA GTTTACATAAGGAAGAGAAGAAATTGAGTG GCATATTGTAAATATCAGATCTATAATTGTAAATATAAAAC CTGCCTCAGTTAGAATGAATGGAAAGCAG ATCTACAATTTGCTAATATAGGAATATCAGGTTGACTATAT AGCCATACTTGAAAATGCTTCTGAGTGGT GTCAACTTTACTTGAATGAATTTTTCATCTTGATTGACGCAC AGTGATGTACAGTTCACTTCTGAAGCTA GTGGTTAACTTGTGTAGGAAACTTTTGCAGTTTGACACTAA GATAACTTCTGTGTGCATTTTTCTATGCT TTTTTAAAAACTAGTTTCATTTCATTTTCATGAGATGTTTGG TTTATAAGATCTGAGGATGGTTATAAAT ACTGTAAGTATTGTAATGTTATGAATGCAGGTTATTTGAAA GCTGTTTATTATTATATCATTCCTGATAA TGCTATGTGAGTGTTTTTAATAAAATTTATATTTATTTAATG CACTCTAAAAAAAAAAAAAAAAAA

PPREDICTED: Homo sapiens tet methylcytosine dioxygenase 2 (TET2), transcript variant X1, mRNA [SEQ ID NO: 1359]	XXM_005263082.1	AAGCAGAAGGAAGCAAGATGGCTGCCCTTTAGGATTTGTTA GAAAGGAGACCCGACTGCAACTGCTGGAT TGCTGCAAGGCTGAGGGACGAGAACGAGAATTCAACTAGA GGGCAGCCTTGTGGATGGCCCCGAAGCAAG CCTGATGGAACAGGATAGAACCAACCATGTTGAGGGCAAC AGACTAAGTCCATTCCTGATACCATCACCT CCCATTTGCCAGACAGAACCTCTGGCTACAAAGCTCCAGAA TGGAAGCCCACTGCCTGAGAGAGCTCATC CAGAAGTAAATGGAGACACCAAGTGGCACTCTTTCAAAAGT TATTATGGAATACCCTGTATGAAGGGAAG CCAGAATAGTCGTGTGAGTCCTGACTTTACACAAGAAAGTA GAGGGTATTCCAAGTGTTTGCAAAATGGA GGAATAAAACGCACAGTTAGTGAACCTTCTCTCTCTGGGCT CCTTCAGATCAAGAAATTGAAACAAGACC AAAAGGCTAATGGAGAAAGACGTAACTTCGGGGTAAGCCA AGAAAGAAATCCAGGTGAAAGCAGTCAACC AAATGTCTCCGATTTGAGTGATAAGAAAGAATCTGTGAGTT CTGTAGCCCAAGAAAATGCAGTTAAAGAT TTCACCAGTTTTTCAACACATAACTGCAGTGGGCCTGAAAA TCCAGAGCTTCAGATTCTGAATGAGCAGG AGGGGAAAAGTGCTAATTACCATGACAAGAACATTGTATTA CTTAAAAACAAGGCAGTGCTAATGCCTAA TGGTGCTACAGTTTCTGCCTCTTCCGTGGAACACACACATG GTGAACTCCTGGAAAAAACACTGTCTCAA TATTATCCAGATTGTGTTTCCATTGCGGTGCAGAAAACCAC ATCTCACATAAATGCCATTAACAGTCAGG CTACTAATGAGTTGTCCTGTGAGATCACTCACCCATCGCAT ACCTCAGGGCAGATCAATTCCGCACAGAC CTCTAACTCTGAGCTGCCTCCAAAGCCAGCTGCAGTGGTGA GTGAGGCCTGTGATGCTGATGATGCTGAT AATGCCAGTAAACTAGCTGCAATGCTAAATACCTGTTCCTT TCAGAAACCAGAACAACTACAACAACAAA AATCAGTTTTTGAGATATGCCCATCTCCTGCAGAAAATAAC ATCCAGGGAACCACAAAGCTAGCGTCTGG TGAAGAATTCTGTTCAGGTTCCAGCAGCAATTTGCAAGCTC CTGGTGGCAGCTCTGAACGGTATTTAAAA CAAAATGAAATGAATGGTGCTTACTTCAAGCAAAGCTCAGT GTTCACTAAGGATTCCTTTTCTGCCACTA CCACACCACCACCACCATCACAATTGCTTCTTTCTCCCCCTC CTCCTCTTCCACAGGTTCCTCAGCTTCC TTCAGAAGGAAAAAGCACTCTGAATGGTGGAGTTTTAGAAG AACACCACCACTACCCCAACCAAAGTAAC ACAACACTTTTAAGGGAAGTGAAAATAGAGGGTAAACCTG AGGCACCACCTTCCCAGAGTCCTAATCCAT CTACACATGTATGCAGCCCTTCTCCGATGCTTTCTGAAAGGC CTCAGAATAATTGTGTGAACAGGAATGA CATACAGACTGCAGGGACAATGACTGTTCCATTGTGTTCTG AGAAAACAAGACCAATGTCAGAACACCTC AAGCATAACCCACCAATTTTTGGTAGCAGTGGAGAGCTACA GGACAACTGCCAGCAGTTGATGAGAAACA

		AAGAGCAAGAGATTCTGAAGGGTCGAGACAAGGAGCAAAC ACGAGATCTTGTGCCCCCAACACAGCACTA TCTGAAACCAGGATGGATTGAATTGAAGGCCCCTCGTTTTC ACCAAGCGGAATCCCATCTAAAACGTAAT GAGGCATCACTGCCATCAATTCTTCAGTATCAACCCAATCT CTCCAATCAAATGACCTCCAAACAATACA CTGGAAATTCCAACATGCCTGGGGGGCTCCCAAGGCAAGCT TACACCCAGAAAACAACACAGCTGGAGCA CAAGTCACAAATGTACCAAGTTGAAATGAATCAAGGGCAG TCCCAAGGTACAGTGGACCAACATCTCCAG TTCCAAAAACCCTCACACCAGGTGCACTTCTCCAAAACAGA CCATTTACCAAAAGCTCATGTGCAGTCAC TGTGTGGCACTAGATTTCATTTTCAACAAAGAGCAGATTCC CAAACTGAAAAACTTATGTCCCCAGTGTT GAAACAGCACTTGAATCAACAGGCTTCAGAGACTGAGCCAT TTTCAAACTCACACCTTTTGCAACATAAG CCTCATAAACAGGCAGCACAAACACAACCATCCCAGAGTTC ACATCTCCCTCAAAACCAGCAACAGCAGC AAAAATTACAAATAAAGAATAAAGAGGAAATACTCCAGAC TTTTCCTCACCCCCAAAGCAACAATGATCA GCAAAGAGAAGGATCATTCTTTGGCCAGACTAAAGTGGAA GAATGTTTTCATGGTGAAAATCAGTATTCA AAATCAAGCGAGTTCGAGACTCATAATGTCCAAATGGGACT GGAGGAAGTACAGAATATAAATCGTAGAA ATTCCCCTTATAGTCAGACCATGAAATCAAGTGCATGCAAA ATACAGGTTTCTTGTTCAAACAATACACA CCTAGTTTCAGAGAATAAAGAACAGACTACACATCCTGAAC TTTTTGCAGGAAACAAGACCCAAAACTTG CATCACATGCAATATTTTCCAAATAATGTGATCCCAAAGCA AGATCTTCTTCACAGGTGCTTTCAAGAAC AGGAGCAGAAGTCACAACAAGCTTCAGTTCTACAGGGATAT AAAAATAGAAACCAAGATATGTCTGGTCA ACAAGCTGCGCAACTTGCTCAGCAAAGGTACTTGATACATA ACCATGCAAATGTTTTTCCTGTGCCTGAC CAGGGAGGAAGTCACACTCAGACCCCTCCCCAGAAGGACA CTCAAAAGCATGCTGCTCTAAGGTGGCATC TCTTACAGAAGCAAGAACAGCAGCAAACACAGCAACCCCA AACTGAGTCTTGCCATAGTCAGATGCACAG GCCAATTAAGGTGGAACCTGGATGCAAGCCACATGCCTGTA TGCACACAGCACCACCAGAAAACAAAACA TGGAAAAAGGTAACTAAGCAAGAGAATCCACCTGCAAGCT GTGATAATGTGCAGCAAAAGAGCATCATTG AGACCATGGAGCAGCATCTGAAGCAGTTTCACGCCAAGTCG TTATTTGACCATAAGGCTCTTACTCTCAA ATCACAGAAGCAAGTAAAAGTTGAAATGTCAGGGCCAGTC ACAGTTTTGACTAGACAAACCACTGCTGCA GAACTTGATAGCCACACCCCAGCTTTAGAGCAGCAAACAAC TTCTTCAGAAAAGACACCAACCAAAAGAA CAGCTGCTTCTGTTCTCAATAATTTTATAGAGTCACCTTCCA AATTACTAGATACTCCTATAAAAAATTT

		ATTGGATACACCTGTCAAGACTCAATATGATTTCCCATCTTG CAGATGTGTAGAGCAAATTATTGAAAAA GATGAAGGTCCTTTTTATACCCATCTAGGAGCAGGTCCTAA TGTGGCAGCTATTAGAGAAATCATGGAAG AAAGGTTTGGACAGAAGGGTAAAGCTATTAGGATTGAAAG AGTCATCTATACTGGTAAAGAAGGCAAAAG TTCTCAGGGATGTCCTATTGCTAAGTGGGTGGTTCGCAGAA GCAGCAGTGAAGAGAAGCTACTGTGTTTG GTGCGGGAGCGAGCTGGCCACACCTGTGAGGCTGCAGTGAT TGTGATTCTCATCCTGGTGTGGGAAGGAA TCCCGCTGTCTCTGGCTGACAAACTCTACTCGGAGCTTACCG AGACGCTGAGGAAATACGGCACGCTCAC CAATCGCCGGTGTGCCTTGAATGAAGAGAGAACTTGCGCCT GTCAGGGGCTGGATCCAGAAACCTGTGGT GCCTCCTTCTCTTTTGGTTGTTCATGGAGCATGTACTACAAT GGATGTAAGTTTGCCAGAAGCAAGATCC CAAGGAAGTTTAAGCTGCTTGGGGATGACCCAAAAGAGGA AGAGAAACTGGAGTCTCATTTGCAAAACCT GTCCACTCTTATGGCACCAACATATAAGAAACTTGCACCTG ATGCATATAATAATCAGATTGAATATGAA CACAGAGCACCAGAGTGCCGTCTGGGTCTGAAGGAAGGCC GTCCATTCTCAGGGGTCACTGCATGTTTGG ACTTCTGTGCTCATGCCCACAGAGACTTGCACAACATGCAG AATGGCAGCACATTGGTATGCACTCTCAC TAGAGAAGACAATCGAGAATTTGGAGGAAAACCTGAGGAT GAGCAGCTTCACGTTCTGCCTTTATACAAA GTCTCTGACGTGGATGAGTTTGGGAGTGTGGAAGCTCAGGA GGAGAAAAAACGGAGTGGTGCCATTCAGG TACTGAGTTCTTTTCGGCGAAAAGTCAGGATGTTAGCAGAG CCAGTCAAGACTTGCCGACAAAGGAAACT AGAAGCCAAGAAAGCTGCAGCTGAAAAGCTTTCCTCCCTGG AGAACAGCTCAAATAAAAATGAAAAGGAA AAGTCAGCCCCATCACGTACAAAACAAACTGAAAACGCAA GCCAGGCTAAACAGTTGGCAGAACTTTTGC GACTTTCAGGACCAGTCATGCAGCAGTCCCAGCAGCCCCAG CCTCTACAGAAGCAGCCACCACAGCCCCA GCAGCAGCAGAGACCCCAGCAGCAGCAGCCACATCACCCT CAGACAGAGTCTGTCAACTCTTATTCTGCT TCTGGATCCACCAATCCATACATGAGACGGCCCAATCCAGT TAGTCCTTATCCAAACTCTTCACACACTT CAGATATCTATGGAAGCACCAGCCCTATGAACTTCTATTCC ACCTCATCTCAAGCTGCAGGTTCATATTT GAATTCTTCTAATCCCATGAACCCTTACCCTGGGCTTTTGAA TCAGAATACCCAATATCCATCATATCAA TGCAATGGAAACCTATCAGTGGACAACTGCTCCCCATATCT GGGTTCCTATTCTCCCCAGTCTCAGCCGA TGGATCTGTATAGGTATCCAAGCCAAGACCCTCTGTCTAAG CTCAGTCTACCACCCATCCATACACTTTA CCAGCCAAGGTTTGGAAATAGCCAGAGTTTTACATCTAAAT ACTTAGGTTATGGAAACCAAAATATGCAG

		GGAGATGGTTTCAGCAGTTGTACCATTAGACCAAATGTACA TCATGTAGGGAAATTGCCTCCTTATCCCA CTCATGAGATGGATGGCCACTTCATGGGAGCCACCTCTAGA TTACCACCCAATCTGAGCAATCCAAACAT GGACTATAAAAATGGTGAACATCATTCACCTTCTCACATAA TCCATAACTACAGTGCAGCTCCGGGCATG TTCAACAGCTCTCTTCATGCCCTGCATCTCCAAAACAAGGA GAATGACATGCTTTCCCACACAGCTAATG GGTTATCAAAGATGCTTCCAGCTCTTAACCATGATAGAACT GCTTGTGTCCAAGGAGGCTTACACAAATT AAGTGATGCTAATGGTCAGGAAAAGCAGCCATTGGCACTA GTCCAGGGTGTGGCTTCTGGTGCAGAGGAC AACGATGAGGTCTGGTCAGACAGCGAGCAGAGCTTTCTGGA TCCTGACATTGGGGGAGTGGCCGTGGCTC CAACTCATGGGTCAATTCTCATTGAGTGTGCAAAGCGTGAG CTGCATGCCACAACCCCTTTAAAGAATCC CAATAGGAATCACCCCACCAGGATCTCCCTCGTCTTTTACC AGCATAAGAGCATGAATGAGCCAAAACAT GGCTTGGCTCTTTGGGAAGCCAAAATGGCTGAAAAAGCCCG TGAGAAAGAGGAAGAGTGTGAAAAGTATG GCCCAGACTATGTGCCTCAGAAATCCCATGGCAAAAAAGTG AAACGGGAGCCTGCTGAGCCACATGAAAC TTCAGAGCCCACTTACCTGCGTTTCATCAAGTCTCTTGCCGA AAGGACCATGTCCGTGACCACAGACTCC ACAGTAACTACATCTCCATATGCCTTCACTCGGGTCACAGG GCCTTACAACAGATATATATGATATCACC CCCTTTTGTTGGTTACCTCACTTGAAAAGACCACAACCAAC CTGTCAGTAGTATAGTTCTCATGACGTGG GCAGTGGGGAAAGGTCACAGTATTCATGACAAATGTGGTG GGAAAAACCTCAGCTCACCAGCAACAAAAG AGGTTATCTTACCATAGCACTTAATTTTCACTGGCTCCCAAG TGGTCACAGATGGCATCTAGGAAAAGAC CAAAGCATTCTATGCAAAAAGAAGGTGGGGAAGAAAGTGT TCCGCAATTTACATTTTTAAACACTGGTTC TATTATTGGACGAGATGATATGTAAATGTGATCCCCCCCCC CCGCTTACAACTCTACACATCTGTGACCA CTTTTAATAATATCAAGTTTGCATAGTCATGGAACACAAAT CAAACAAGTACTGTAGTATTACAGTGACA GGAATCTTAAAATACCATCTGGTGCTGAATATATGATGTAC TGAAATACTGGAATTATGGCTTTTTGAAA TGCAGTTTTTACTGTAATCTTAACTTTTATTTATCAAAATAG CTACAGGAAACATGAATAGCAGGAAAAC ACTGAATTTGTTTGGATGTTCTAAGAAATGGTGCTAAGAAA ATGGTGTCTTTAATAGCTAAAAATTTAAT GCCTTTATATCATCAAGATGCTATCAGTGTACTCCAGTGCCC TTGAATAATAGGGGTACCTTTTCATTCA AGTTTTTATCATAATTACCTATTCTTACACAAGCTTAGTTTT TAAAATGTGGACATTTTAAAGGCCTCTG GATTTTGCTCATCCAGTGAAGTCCTTGTAGGACAATAAACG TATATATGTACATATATACACAAACATGT

		ATATGTGCACACACATGTATATGTATAAATATTTTAAATGG TGTTTTAGAAGCACTTTGTCTACCTAAGC TTTGACAACTTGAACAATGCTAAGGTACTGAGATGTTTAAA AAACAAGTTTACTTTCATTTTAGAATGCA AAGTTGATTTTTTTAAGGAAACAAAGAAAGCTTTTAAAATA TTTTTGCTTTTAGCCATGCATCTGCTGAT GAGCAATTGTGTCCATTTTTAACACAGCCAGTTAAATCCAC CATGGGGCTTACTGGATTCAAGGGAATAC GTTAGTCCACAAAACATGTTTTCTGGTGCTCATCTCACATGC TATACTGTAAAACAGTTTTATACAAAAT TGTATGACAAGTTCATTGCTCAAAAATGTACAGTTTTAAGA ATTTTCTATTAACTGCAGGTAATAATTAG CTGCATGCTGCAGACTCAACAAAGCTAGTTCACTGAAGCCT ATGCTATTTTATGGATCATAGGCTCTTCA GAGAACTGAATGGCAGTCTGCCTTTGTGTTGATAATTATGT ACATTGTGACGTTGTCATTTCTTAGCTTA AGTGTCCTCTTTAACAAGAGGATTGAGCAGACTGATGCCTG CATAAGATGAATAAACAGGGTTAGTTCCA TGTGAATCTGTCAGTTAAAAAGAAACAAAAACAGGCAGCT GGTTTGCTGTGGTGGTTTTAAATCATTAAT TTGTATAAAGAAGTGAAAGAGTTGTATAGTAAATTAAATTG TAAACAAAACTTTTTTAATGCAATGCTTT AGTATTTTAGTACTGTAAAAAAATTAAATATATACATATAT ATATATATATATATATATATATATATGAG TTTGAAGCAGAATTCACATCATGATGGTGCTACTCAGCCTG CTACAAATATATCATAATGTGAGCTAAGA ATTCATTAAATGTTTGAGTGATGTTCCTACTTGTCATATACC TCAACACTAGTTTGGCAATAGGATATTG AACTGAGAGTGAAAGCATTGTGTACCATCATTTTTTTCCAA GTCCTTTTTTTTATTGTTAAAAAAAAAAG CATACCTTTTTTCAATACTTGATTTCTTAGCAAGTATAACTT GAACTTCAACCTTTTTGTTCTAAAAATT CAGGGATATTTCAGCTCATGCTCTCCCTATGCCAACATGTCA CCTGTGTTTATGTAAAATTGTTGTAGGT TAATAAATATATTCTTTGTCAGGGATTTAACCCTTTTATTTT GAATCCCTTCTATTTTACTTGTACATGT GCTGATGTAACTAAAACTAATTTTGTAAATCTGTTGGCTCTT TTTATTGTAAAGAAAAGCATTTTAAAAG TTTGAGGAATCTTTTGACTGTTTCAAGCAGGAAAAAAAAAT TACATGAAAATAGAATGCACTGAGTTGAT AAAGGGAAAAATTGTAAGGCAGGAGTTTGGCAAGTGGCTG TTGGCCAGAGACTTACTTGTAACTCTCTAA ATGAAGTTTTTTTGATCCTGTAATCACTGAAGGTACATACTC CATGTGGACTTCCCTTAAACAGGCAAAC ACCTACAGGTATGGTGTGCAACAGATTGTACAATTACATTT TGGCCTAAATACATTTTTGCTTACTAGTA TTTAAAATAAATTCTTAATCAGAGGAGGCCTTTGGGTTTTAT TGGTCAAATCTTTGTAAGCTGGCTTTTG TCTTTTTAAAAAATTTCTTGAATTTGTGGTTGTGTCCAATTT GCAAACATTTCCAAAAATGTTTGCTTTG

		CTTACAAACCACATGATTTTAATGTTTTTTGTATACCATAAT ATCTAGCCCCAAACATTTGATTACTACA TGTGCATTGGTGATTTTGATCATCCATTCTTAATATTTGATT TCTGTGTCACCTACTGTCATTTGTTAAA CTGCTGGCCAACAAGAACAGGAAGTATAGTTTGGGGGGTTG GGGAGAGTTTACATAAGGAAGAGAAGAAA TTGAGTGGCATATTGTAAATATCAGATCTATAATTGTAAAT ATAAAACCTGCCTCAGTTAGAATGAATGG AAAGCAGATCTACAATTTGCTAATATAGGAATATCAGGTTG ACTATATAGCCATACTTGAAAATGCTTCT GAGTGGTGTCAACTTTACTTGAATGAATTTTTCATCTTGATT GACGCACAGTGATGTACAGTTCACTTCT GAAGCTAGTGGTTAACTTGTGTAGGAAACTTTTGCAGTTTG ACACTAAGATAACTTCTGTGTGCATTTTT CTATGCTTTTTTAAAAACTAGTTTCATTTCATTTTCATGAGA TGTTTGGTTTATAAGATCTGAGGATGGT TATAAATACTGTAAGTATTGTAATGTTATGAATGCAGGTTA TTTGAAAGCTGTTTATTATTATATCATTC CTGATAATGCTATGTGAGTGTTTTTAATAAAATTTATATTTA TTTAATGCACTCTAA
PPREDICTED: Homo sapiens tet methylcytosine dioxygenase 2 (TET2), transcript variant X2, mRNA [SEQ ID NO: 1360]	XXM_006714242.2	GTAGAGAAGCAGAAGGAAGCAAGATGGCTGCCCTTTAGGA TTTGTTAGAAAGGAGACCCGACTGCAACTG CTGGATTGCTGCAAGGCTGAGGGACGAGAACGAGGCTGGC AAACATTCAGCAGCACACCCTCTCAAGATT GTTTACTTGCCTTTGCTCCTGTTGAGTTACAACGCTTGGAAG CAGGAGATGGGCTCAGCAGCAGCCAATA GGACATGATCCAGGAAGAGCAGTAAGGGACTGAGCTGCTG AATTCAACTAGAGGGCAGCCTTGTGGATGG CCCCGAAGCAAGCCTGATGGAACAGGATAGAACCAACCAT GTTGAGGGCAACAGACTAAGTCCATTCCTG ATACCATCACCTCCCATTTGCCAGACAGAACCTCTGGCTAC AAAGCTCCAGAATGGAAGCCCACTGCCTG AGAGAGCTCATCCAGAAGTAAATGGAGACACCAAGTGGCA CTCTTTCAAAAGTTATTATGGAATACCCTG TATGAAGGGAAGCCAGAATAGTCGTGTGAGTCCTGACTTTA CACAAGAAAGTAGAGGGTATTCCAAGTGT TTGCAAAATGGAGGAATAAAACGCACAGTTAGTGAACCTTC TCTCTCTGGGCTCCTTCAGATCAAGAAAT TGAAACAAGACCAAAAGGCTAATGGAGAAAGACGTAACTT CGGGGTAAGCCAAGAAAGAAATCCAGGTGA AAGCAGTCAACCAAATGTCTCCGATTTGAGTGATAAGAAAG AATCTGTGAGTTCTGTAGCCCAAGAAAAT GCAGTTAAAGATTTCACCAGTTTTTCAACACATAACTGCAG TGGGCCTGAAAATCCAGAGCTTCAGATTC TGAATGAGCAGGAGGGGAAAAGTGCTAATTACCATGACAA GAACATTGTATTACTTAAAAACAAGGCAGT GCTAATGCCTAATGGTGCTACAGTTTCTGCCTCTTCCGTGGA ACACACACATGGTGAACTCCTGGAAAAA ACACTGTCTCAATATTATCCAGATTGTGTTTCCATTGCGGTG CAGAAAACCACATCTCACATAAATGCCA

		TTAACAGTCAGGCTACTAATGAGTTGTCCTGTGAGATCACT CACCCATCGCATACCTCAGGGCAGATCAA TTCCGCACAGACCTCTAACTCTGAGCTGCCTCCAAAGCCAG CTGCAGTGGTGAGTGAGGCCTGTGATGCT GATGATGCTGATAATGCCAGTAAACTAGCTGCAATGCTAAA TACCTGTTCCTTTCAGAAACCAGAACAAC TACAACAACAAAAATCAGTTTTTGAGATATGCCCATCTCCT GCAGAAAATAACATCCAGGGAACCACAAA GCTAGCGTCTGGTGAAGAATTCTGTTCAGGTTCCAGCAGCA ATTTGCAAGCTCCTGGTGGCAGCTCTGAA CGGTATTTAAAACAAAATGAAATGAATGGTGCTTACTTCAA GCAAAGCTCAGTGTTCACTAAGGATTCCT TTTCTGCCACTACCACACCACCACCACCATCACAATTGCTTC TTTCTCCCCCTCCTCCTCTTCCACAGGT TCCTCAGCTTCCTTCAGAAGGAAAAAGCACTCTGAATGGTG GAGTTTTAGAAGAACACCACCACTACCCC AACCAAAGTAACACAACACTTTTAAGGGAAGTGAAAATAG AGGGTAAACCTGAGGCACCACCTTCCCAGA GTCCTAATCCATCTACACATGTATGCAGCCCTTCTCCGATGC TTTCTGAAAGGCCTCAGAATAATTGTGT GAACAGGAATGACATACAGACTGCAGGGACAATGACTGTT CCATTGTGTTCTGAGAAAACAAGACCAATG TCAGAACACCTCAAGCATAACCCACCAATTTTTGGTAGCAG TGGAGAGCTACAGGACAACTGCCAGCAGT TGATGAGAAACAAAGAGCAAGAGATTCTGAAGGGTCGAGA CAAGGAGCAAACACGAGATCTTGTGCCCCC AACACAGCACTATCTGAAACCAGGATGGATTGAATTGAAG GCCCCTCGTTTTCACCAAGCGGAATCCCAT CTAAAACGTAATGAGGCATCACTGCCATCAATTCTTCAGTA TCAACCCAATCTCTCCAATCAAATGACCT CCAAACAATACACTGGAAATTCCAACATGCCTGGGGGGCTC CCAAGGCAAGCTTACACCCAGAAAACAAC ACAGCTGGAGCACAAGTCACAAATGTACCAAGTTGAAATG AATCAAGGGCAGTCCCAAGGTACAGTGGAC CAACATCTCCAGTTCCAAAAACCCTCACACCAGGTGCACTT CTCCAAAACAGACCATTTACCAAAAGCTC ATGTGCAGTCACTGTGTGGCACTAGATTTCATTTTCAACAA AGAGCAGATTCCCAAACTGAAAAACTTAT GTCCCCAGTGTTGAAACAGCACTTGAATCAACAGGCTTCAG AGACTGAGCCATTTTCAAACTCACACCTT TTGCAACATAAGCCTCATAAACAGGCAGCACAAACACAAC CATCCCAGAGTTCACATCTCCCTCAAAACC AGCAACAGCAGCAAAAATTACAAATAAAGAATAAAGAGGA AATACTCCAGACTTTTCCTCACCCCCAAAG CAACAATGATCAGCAAAGAGAAGGATCATTCTTTGGCCAGA CTAAAGTGGAAGAATGTTTTCATGGTGAA AATCAGTATTCAAAATCAAGCGAGTTCGAGACTCATAATGT CCAAATGGGACTGGAGGAAGTACAGAATA TAAATCGTAGAAATTCCCCTTATAGTCAGACCATGAAATCA AGTGCATGCAAAATACAGGTTTCTTGTTC

		AAACAATACACACCTAGTTTCAGAGAATAAAGAACAGACT ACACATCCTGAACTTTTTGCAGGAAACAAG ACCCAAAACTTGCATCACATGCAATATTTTCCAAATAATGT GATCCCAAAGCAAGATCTTCTTCACAGGT GCTTTCAAGAACAGGAGCAGAAGTCACAACAAGCTTCAGTT CTACAGGGATATAAAAATAGAAACCAAGA TATGTCTGGTCAACAAGCTGCGCAACTTGCTCAGCAAAGGT ACTTGATACATAACCATGCAAATGTTTTT CCTGTGCCTGACCAGGGAGGAAGTCACACTCAGACCCCTCC CCAGAAGGACACTCAAAAGCATGCTGCTC TAAGGTGGCATCTCTTACAGAAGCAAGAACAGCAGCAAAC ACAGCAACCCCAAACTGAGTCTTGCCATAG TCAGATGCACAGGCCAATTAAGGTGGAACCTGGATGCAAG CCACATGCCTGTATGCACACAGCACCACCA GAAAACAAAACATGGAAAAAGGTAACTAAGCAAGAGAATC CACCTGCAAGCTGTGATAATGTGCAGCAAA AGAGCATCATTGAGACCATGGAGCAGCATCTGAAGCAGTTT CACGCCAAGTCGTTATTTGACCATAAGGC TCTTACTCTCAAATCACAGAAGCAAGTAAAAGTTGAAATGT CAGGGCCAGTCACAGTTTTGACTAGACAA ACCACTGCTGCAGAACTTGATAGCCACACCCCAGCTTTAGA GCAGCAAACAACTTCTTCAGAAAAGACAC CAACCAAAAGAACAGCTGCTTCTGTTCTCAATAATTTTATA GAGTCACCTTCCAAATTACTAGATACTCC TATAAAAAATTTATTGGATACACCTGTCAAGACTCAATATG ATTTCCCATCTTGCAGATGTGTAGGTTTG GACAGAAGGGTAAAGCTATTAGGATTGAAAGAGTCATCTAT ACTGGTAAAGAAGGCAAAAGTTCTCAGGG ATGTCCTATTGCTAAGTGGGAGAACTTGCGCCTGTCAGGGG CTGGATCCAGAAACCTGTGGTGCCTCCTT CTCTTTTGGTTGTTCATGGAGCATGTACTACAATGGATGTAA GTTTGCCAGAAGCAAGATCCCAAGGAAG TTTAAGCTGCTTGGGGATGACCCAAAAGAGGAAGAGAAAC TGGAGTCTCATTTGCAAAACCTGTCCACTC TTATGGCACCAACATATAAGAAACTTGCACCTGATGCATAT AATAATCAGATTGAATATGAACACAGAGC ACCAGAGTGCCGTCTGGGTCTGAAGGAAGGCCGTCCATTCT CAGGGGTCACTGCATGTTTGGACTTCTGT GCTCATGCCCACAGAGACTTGCACAACATGCAGAATGGCAG CACATTGGTATGCACTCTCACTAGAGAAG ACAATCGAGAATTTGGAGGAAAACCTGAGGATGAGCAGCT TCACGTTCTGCCTTTATACAAAGTCTCTGA CGTGGATGAGTTTGGGAGTGTGGAAGCTCAGGAGGAGAAA AAACGGAGTGGTGCCATTCAGGTACTGAGT TCTTTTCGGCGAAAAGTCAGGATGTTAGCAGAGCCAGTCAA GACTTGCCGACAAAGGAAACTAGAAGCCA AGAAAGCTGCAGCTGAAAAGCTTTCCTCCCTGGAGAACAGC TCAAATAAAAATGAAAAGGAAAAGTCAGC CCCATCACGTACAAAACAAACTGAAAACGCAAGCCAGGCT AAACAGTTGGCAGAACTTTTGCGACTTTCA

		GGACCAGTCATGCAGCAGTCCCAGCAGCCCCAGCCTCTACA GAAGCAGCCACCACAGCCCCAGCAGCAGC AGAGACCCCAGCAGCAGCAGCCACATCACCCTCAGACAGA GTCTGTCAACTCTTATTCTGCTTCTGGATC CACCAATCCATACATGAGACGGCCCAATCCAGTTAGTCCTT ATCCAAACTCTTCACACACTTCAGATATC TATGGAAGCACCAGCCCTATGAACTTCTATTCCACCTCATCT CAAGCTGCAGGTTCATATTTGAATTCTT CTAATCCCATGAACCCTTACCCTGGGCTTTTGAATCAGAAT ACCCAATATCCATCATATCAATGCAATGG AAACCTATCAGTGGACAACTGCTCCCCATATCTGGGTTCCT ATTCTCCCCAGTCTCAGCCGATGGATCTG TATAGGTATCCAAGCCAAGACCCTCTGTCTAAGCTCAGTCT ACCACCCATCCATACACTTTACCAGCCAA GGTTTGGAAATAGCCAGAGTTTTACATCTAAATACTTAGGT TATGGAAACCAAAATATGCAGGGAGATGG TTTCAGCAGTTGTACCATTAGACCAAATGTACATCATGTAG GGAAATTGCCTCCTTATCCCACTCATGAG ATGGATGGCCACTTCATGGGAGCCACCTCTAGATTACCACC CAATCTGAGCAATCCAAACATGGACTATA AAAATGGTGAACATCATTCACCTTCTCACATAATCCATAAC TACAGTGCAGCTCCGGGCATGTTCAACAG CTCTCTTCATGCCCTGCATCTCCAAAACAAGGAGAATGACA TGCTTTCCCACACAGCTAATGGGTTATCA AAGATGCTTCCAGCTCTTAACCATGATAGAACTGCTTGTGT CCAAGGAGGCTTACACAAATTAAGTGATG CTAATGGTCAGGAAAAGCAGCCATTGGCACTAGTCCAGGGT GTGGCTTCTGGTGCAGAGGACAACGATGA GGTCTGGTCAGACAGCGAGCAGAGCTTTCTGGATCCTGACA TTGGGGGAGTGGCCGTGGCTCCAACTCAT GGGTCAATTCTCATTGAGTGTGCAAAGCGTGAGCTGCATGC CACAACCCCTTTAAAGAATCCCAATAGGA ATCACCCCACCAGGATCTCCCTCGTCTTTTACCAGCATAAG AGCATGAATGAGCCAAAACATGGCTTGGC TCTTTGGGAAGCCAAAATGGCTGAAAAAGCCCGTGAGAAA GAGGAAGAGTGTGAAAAGTATGGCCCAGAC TATGTGCCTCAGAAATCCCATGGCAAAAAAGTGAAACGGG AGCCTGCTGAGCCACATGAAACTTCAGAGC CCACTTACCTGCGTTTCATCAAGTCTCTTGCCGAAAGGACC ATGTCCGTGACCACAGACTCCACAGTAAC TACATCTCCATATGCCTTCACTCGGGTCACAGGGCCTTACA ACAGATATATATGATATCACCCCCTTTTG TTGGTTACCTCACTTGAAAAGACCACAACCAACCTGTCAGT AGTATAGTTCTCATGACGTGGGCAGTGGG GAAAGGTCACAGTATTCATGACAAATGTGGTGGGAAAAAC CTCAGCTCACCAGCAACAAAAGAGGTTATC TTACCATAGCACTTAATTTTCACTGGCTCCCAAGTGGTCACA GATGGCATCTAGGAAAAGACCAAAGCAT TCTATGCAAAAAGAAGGTGGGGAAGAAAGTGTTCCGCAAT TTACATTTTTAAACACTGGTTCTATTATTG

		GACGAGATGATATGTAAATGTGATCCCCCCCCCCCCGCTTAC AACTCTACACATCTGTGACCACTTTTAAT AATATCAAGTTTGCATAGTCATGGAACACAAATCAAACAAG TACTGTAGTATTACAGTGACAGGAATCTT AAAATACCATCTGGTGCTGAATATATGATGTACTGAAATAC TGGAATTATGGCTTTTTGAAATGCAGTTT TTACTGTAATCTTAACTTTTATTTATCAAAATAGCTACAGGA AACATGAATAGCAGGAAAACACTGAATT TGTTTGGATGTTCTAAGAAATGGTGCTAAGAAAATGGTGTC TTTAATAGCTAAAAATTTAATGCCTTTAT ATCATCAAGATGCTATCAGTGTACTCCAGTGCCCTTGAATA ATAGGGGTACCTTTTCATTCAAGTTTTTA TCATAATTACCTATTCTTACACAAGCTTAGTTTTTAAAATGT GGACATTTTAAAGGCCTCTGGATTTTGC TCATCCAGTGAAGTCCTTGTAGGACAATAAACGTATATATG TACATATATACACAAACATGTATATGTGC ACACACATGTATATGTATAAATATTTTAAATGGTGTTTTAGA AGCACTTTGTCTACCTAAGCTTTGACAA CTTGAACAATGCTAAGGTACTGAGATGTTTAAAAAACAAGT TTACTTTCATTTTAGAATGCAAAGTTGAT TTTTTTAAGGAAACAAAGAAAGCTTTTAAAATATTTTTGCTT TTAGCCATGCATCTGCTGATGAGCAATT GTGTCCATTTTTTAACACAGCCAGTTAAATCCACCATGGGGC TTACTGGATTCAAGGGAATACGTTAGTCC ACAAAACATGTTTTCTGGTGCTCATCTCACATGCTATACTGT AAAACAGTTTTATACAAAATTGTATGAC AAGTTCATTGCTCAAAAATGTACAGTTTTAAGAATTTTCTAT TAACTGCAGGTAATAATTAGCTGCATGC TGCAGACTCAACAAAGCTAGTTCACTGAAGCCTATGCTATT TTATGGATCATAGGCTCTTCAGAGAACTG AATGGCAGTCTGCCTTTGTGTTGATAATTATGTACATTGTGA CGTTGTCATTTCTTAGCTTAAGTGTCCT CTTTAACAAGAGGATTGAGCAGACTGATGCCTGCATAAGAT GAATAAACAGGGTTAGTTCCATGTGAATC TGTCAGTTAAAAAGAAACAAAAACAGGCAGCTGGTTTGCTG TGGTGGTTTTAAATCATTAATTTGTATAA AGAAGTGAAAGAGTTGTATAGTAAATTAAATTGTAAACAA AACTTTTTTAATGCAATGCTTTAGTATTTT AGTACTGTAAAAAAATTAAATATATACATATATATATATAT ATATATATATATATATATATGAGTTTGAAGC AGAATTCACATCATGATGGTGCTACTCAGCCTGCTACAAAT ATATCATAATGTGAGCTAAGAATTCATTA AATGTTTGAGTGATGTTCCTACTTGTCATATACCTCAACACT AGTTTGGCAATAGGATATTGAACTGAGA GTGAAAGCATTGTGTACCATCATTTTTTTCCAAGTCCTTTTT TTTATTGTTAAAAAAAAAAGCATACCTT TTTTCAATACTTGATTTCTTAGCAAGTATAACTTGAACTTCA ACCTTTTTGTTCTAAAAATTCAGGGATA TTTCAGCTCATGCTCTCCCTATGCCAACATGTCACCTGTGTT TATGTAAAATTGTTGTAGGTTAATAAAT

		ATATTCTTTGTCAGGGATTTAACCCTTTTATTTTGAATCCCTT CTATTTTACTTGTACATGTGCTGATGT AACTAAAACTAATTTTGTAAATCTGTTGGCTCTTTTTATTGT AAAGAAAAGCATTTTAAAAGTTTGAGGA ATCTTTTGACTGTTTCAAGCAGGAAAAAAAAATTACATGAA AATAGAATGCACTGAGTTGATAAAGGGAA AAATTGTAAGGCAGGAGTTTGGCAAGTGGCTGTTGGCCAGA GACTTACTTGTAACTCTCTAAATGAAGTT TTTTTGATCCTGTAATCACTGAAGGTACATACTCCATGTGGA CTTCCCTTAAACAGGCAAACACCTACAG GTATGGTGTGCAACAGATTGTACAATTACATTTTGGCCTAA ATACATTTTTGCTTACTAGTATTTAAAAT AAATTCTTAATCAGAGGAGGCCTTTGGGTTTTATTGGTCAA ATCTTTGTAAGCTGGCTTTTGTCTTTTTA AAAAATTTCTTGAATTTGTGGTTGTGTCCAATTTGCAAACAT TTCCAAAAATGTTTGCTTTGCTTACAAA CCACATGATTTTAATGTTTTTTGTATACCATAATATCTAGCC CCAAACATTTGATTACTACATGTGCATT GGTGATTTTGATCATCCATTCTTAATATTTGATTTCTGTGTC ACCTACTGTCATTTGTTAAACTGCTGGC CAACAAGAACAGGAAGTATAGTTTGGGGGGTTGGGGAGAG TTTACATAAGGAAGAGAAGAAATTGAGTGG CATATTGTAAATATCAGATCTATAATTGTAAATATAAAACC TGCCTCAGTTAGAATGAATGGAAAGCAGA TCTACAATTTGCTAATATAGGAATATCAGGTTGACTATATA GCCATACTTGAAAATGCTTCTGAGTGGTG TCAACTTTACTTGAATGAATTTTTCATCTTGATTGACGCACA GTGATGTACAGTTCACTTCTGAAGCTAG TGGTTAACTTGTGTAGGAAACTTTTGCAGTTTGACACTAAG ATAACTTCTGTGTGCATTTTTCTATGCTT TTTTAAAAACTAGTTTCATTTCATTTTCATGAGATGTTTGGT TTATAAGATCTGAGGATGGTTATAAATA CTGTAAGTATTGTAATGTTATGAATGCAGGTTATTTGAAAG CTGTTTATTATTATATCATTCCTGATAAT GCTATGTGAGTGTTTTTAATAAAATTTATATTTATTTAATGC ACTCTAA
HHomo sapiens tet methylcytosine dioxygenase 2 (TET2), transcript variant 2, mRNA [SEQ ID NO: 1361]	NM_017628.4	AAACAGAAGGTGGGCCGGGGCGGGGAGAAACAGAACTCGG TCAATTTCCCAGTTTGTCGGGTCTTTAAAA ATACAGGCCCCTAAAGCACTAAGGGCATGCCCTCGGTGAAA CAGGGGAGCGCTTCTGCTGAATGAGATTA AAGCGACAGAAAAGGGAAAGGAGAGCGCGGGCAACGGGA TCTAAAGGGAGATAGAGACGCGGGCCTCTGA GGGCTGGCAAACATTCAGCAGCACACCCTCTCAAGATTGTT TACTTGCCTTTGCTCCTGTTGAGTTACAA CGCTTGGAAGCAGGAGATGGGCTCAGCAGCAGCCAATAGG ACATGATCCAGGAAGAGCAGTAAGGGACTG AGCTGCTGAATTCAACTAGAGGGCAGCCTTGTGGATGGCCC CGAAGCAAGCCTGATGGAACAGGATAGAA CCAACCATGTTGAGGGCAACAGACTAAGTCCATTCCTGATA CCATCACCTCCCATTTGCCAGACAGAACC

		TCTGGCTACAAAGCTCCAGAATGGAAGCCCACTGCCTGAGA GAGCTCATCCAGAAGTAAATGGAGACACC AAGTGGCACTCTTTCAAAAGTTATTATGGAATACCCTGTAT GAAGGGAAGCCAGAATAGTCGTGTGAGTC CTGACTTTACACAAGAAAGTAGAGGGTATTCCAAGTGTTTG CAAAATGGAGGAATAAAACGCACAGTTAG TGAACCTTCTCTCTCTGGGCTCCTTCAGATCAAGAAATTGAA ACAAGACCAAAAGGCTAATGGAGAAAGA CGTAACTTCGGGGTAAGCCAAGAAAGAAATCCAGGTGAAA GCAGTCAACCAAATGTCTCCGATTTGAGTG ATAAGAAAGAATCTGTGAGTTCTGTAGCCCAAGAAAATGCA GTTAAAGATTTCACCAGTTTTTCAACACA TAACTGCAGTGGGCCTGAAAATCCAGAGCTTCAGATTCTGA ATGAGCAGGAGGGGAAAAGTGCTAATTAC CATGACAAGAACATTGTATTACTTAAAAACAAGGCAGTGCT AATGCCTAATGGTGCTACAGTTTCTGCCT CTTCCGTGGAACACACACATGGTGAACTCCTGGAAAAAACA CTGTCTCAATATTATCCAGATTGTGTTTC CATTGCGGTGCAGAAAACCACATCTCACATAAATGCCATTA ACAGTCAGGCTACTAATGAGTTGTCCTGT GAGATCACTCACCCATCGCATACCTCAGGGCAGATCAATTC CGCACAGACCTCTAACTCTGAGCTGCCTC CAAAGCCAGCTGCAGTGGTGAGTGAGGCCTGTGATGCTGAT GATGCTGATAATGCCAGTAAACTAGCTGC AATGCTAAATACCTGTTCCTTTCAGAAACCAGAACAACTAC AACAACAAAAATCAGTTTTTGAGATATGC CCATCTCCTGCAGAAAATAACATCCAGGGAACCACAAAGCT AGCGTCTGGTGAAGAATTCTGTTCAGGTT CCAGCAGCAATTTGCAAGCTCCTGGTGGCAGCTCTGAACGG TATTTAAAACAAAATGAAATGAATGGTGC TTACTTCAAGCAAAGCTCAGTGTTCACTAAGGATTCCTTTTC TGCCACTACCACACCACCACCACCATCA CAATTGCTTCTTTCTCCCCCTCCTCCTCTTCCACAGGTTCCTC AGCTTCCTTCAGAAGGAAAAAGCACTC TGAATGGTGGAGTTTTAGAAGAACACCACCACTACCCCAAC CAAAGTAACACAACACTTTTAAGGGAAGT GAAAATAGAGGGTAAACCTGAGGCACCACCTTCCCAGAGT CCTAATCCATCTACACATGTATGCAGCCCT TCTCCGATGCTTTCTGAAAGGCCTCAGAATAATTGTGTGAA CAGGAATGACATACAGACTGCAGGGACAA TGACTGTTCCATTGTGTTCTGAGAAAACAAGACCAATGTCA GAACACCTCAAGCATAACCCACCAATTTT TGGTAGCAGTGGAGAGCTACAGGACAACTGCCAGCAGTTG ATGAGAAACAAAGAGCAAGAGATTCTGAAG GGTCGAGACAAGGAGCAAACACGAGATCTTGTGCCCCCAA CACAGCACTATCTGAAACCAGGATGGATTG AATTGAAGGCCCCTCGTTTTCACCAAGCGGAATCCCATCTA AAACGTAATGAGGCATCACTGCCATCAAT TCTTCAGTATCAACCCAATCTCTCCAATCAAATGACCTCCAA ACAATACACTGGAAATTCCAACATGCCT

		GGGGGGCTCCCAAGGCAAGCTTACACCCAGAAAACAACAC AGCTGGAGCACAAGTCACAAATGTACCAAG TTGAAATGAATCAAGGGCAGTCCCAAGGTACAGTGGACCA ACATCTCCAGTTCCAAAAACCCTCACACCA GGTGCACTTCTCCAAAACAGACCATTTACCAAAAGCTCATG TGCAGTCACTGTGTGGCACTAGATTTCAT TTTCAACAAAGAGCAGATTCCCAAACTGAAAAACTTATGTC CCCAGTGTTGAAACAGCACTTGAATCAAC AGGCTTCAGAGACTGAGCCATTTTCAAACTCACACCTTTTG CAACATAAGCCTCATAAACAGGCAGCACA AACACAACCATCCCAGAGTTCACATCTCCCTCAAAACCAGC AACAGCAGCAAAAATTACAAATAAAGAAT AAAGAGGAAATACTCCAGACTTTTCCTCACCCCCAAAGCAA CAATGATCAGCAAAGAGAAGGATCATTCT TTGGCCAGACTAAAGTGGAAGAATGTTTTCATGGTGAAAAT CAGTATTCAAAATCAAGCGAGTTCGAGAC TCATAATGTCCAAATGGGACTGGAGGAAGTACAGAATATA AATCGTAGAAATTCCCCTTATAGTCAGACC ATGAAATCAAGTGCATGCAAAATACAGGTTTCTTGTTCAAA CAATACACACCTAGTTTCAGAGAATAAAG AACAGACTACACATCCTGAACTTTTTGCAGGAAACAAGACC CAAAACTTGCATCACATGCAATATTTTCC AAATAATGTGATCCCAAAGCAAGATCTTCTTCACAGGTGCT TTCAAGAACAGGAGCAGAAGTCACAACAA GCTTCAGTTCTACAGGGATATAAAAATAGAAACCAAGATAT GTCTGGTCAACAAGCTGCGCAACTTGCTC AGCAAAGGTACTTGATACATAACCATGCAAATGTTTTTCCT GTGCCTGACCAGGGAGGAAGTCACACTCA GACCCCTCCCCAGAAGGACACTCAAAAGCATGCTGCTCTAA GGTGGCATCTCTTACAGAAGCAAGAACAG CAGCAAACACAGCAACCCCAAACTGAGTCTTGCCATAGTCA GATGCACAGGCCAATTAAGGTGGAACCTG GATGCAAGCCACATGCCTGTATGCACACAGCACCACCAGAA AACAAAACATGGAAAAAGGTAACTAAGCA AGAGAATCCACCTGCAAGCTGTGATAATGTGCAGCAAAAG AGCATCATTGAGACCATGGAGCAGCATCTG AAGCAGTTTCACGCCAAGTCGTTATTTGACCATAAGGCTCT TACTCTCAAATCACAGAAGCAAGTAAAAG TTGAAATGTCAGGGCCAGTCACAGTTTTGACTAGACAAACC ACTGCTGCAGAACTTGATAGCCACACCCC AGCTTTAGAGCAGCAAACAACTTCTTCAGAAAAGACACCAA CCAAAAGAACAGCTGCTTCTGTTCTCAAT AATTTTATAGAGTCACCTTCCAAATTACTAGATACTCCTATA AAAAATTTATTGGATACACCTGTCAAGA CTCAATATGATTTCCCATCTTGCAGATGTGTAGGTAAGTGCC AGAAATGTACTGAGACACATGGCGTTTA TCCAGAATTAGCAAATTTATCTTCAGATATGGGATTTTCCTT CTTTTTTTAAATCTTGAGTCTGGCAGCA ATTTGTAAAGGCTCATAAAAATCTGAAGCTTACATTTTTTGT CAAGTTACCGATGCTTGTGTCTTGTGAA

		AGAGAACTTCACTTACATGCAGTTTTTCCAAAAGAATTAAA TAATCGTGCATGTTTATTTTTCCCTCTCT TCAGATCCTGTAAAATTTGAATGTATCTGTTTTAGATCAATT CGCCTATTTAGCTCTTTGTATATTATCT CCTGGAGAGACAGCTAGGCAGCAAAAAAACAATCTATTAA AATGAGAAAATAACGACCATAGGCAGTCTA ATGTACGAACTTTAAATATTTTTTAATTCAAGGTAAAATATA TTAGTTTCACAAGATTTCTGGCTAATAG GGAAATTATTATCTTCAGTCTTCATGAGTTGGGGGAAATGA TAATGCTGACACTCTTAGTGCTCCTAAAG TTTCCTTTTCTCCATTTATACATTTGGAATGTTGTGATTTATA TTCATTTTGATTCCCTTTTCTCTAAAA TTTCATCTTTTTGATTAAAAAATATGATACAGGCATACCTCA GAGATATTGTGGGTTTGGCTCCATACCA CAATAAAATGAATATTACAATAAAGCAAGTTGTAAGGACTT TTTGGTTTCTCACTGTATGTAAAAGTTAT TTATATACTATACTGTAACATACTAAGTGTGCAATAGCATT GTGTCTAAAAAATATATACTTTAAAAATA ATTTATTGTTAAAAAAATGCCAACAATTATCTGGGCCTTTA GTGAGTGCTAATCTTTTTGCTGGTGGAGG GTCGTGCTTCAGTATTGATCGCTGTGGACTGATCATGGTGGT AGTTGCTGAAGGTTGCTGGGATGGCTGT GTGTGTGGCAATTTCTTAAAATAAGACAACAGTGAAGTGCT GTATCAATTGATTTTTCCATTCACAAAAG ATTTCTCTGTAGCATGCAATGCTGTTTGATAGCATTTAACCC ACAGCAGAATTTCTTTGAAAATTGGACT CAGTCCTCTCAAACTGTGCTGCTGCTTTATCAACTAAGTTTT TGTAATTTTCTGAATCCTTTGTTGTCAT TTCAGCAGTTTACAGCATCTTCATTGGAAGTATATTCCATCT CAAACATTCTTTGTTCATCCATAAGAAG CAACTTCTTATCAAGTTTTTTCATGACATTGCAGTAACTCAG CCCCATCTTCAGGCTCTACTTCTAATTC TGGTTCTCTTGCTACATCTCCCTCATCTGCAGTGACCTCTCC ACGGAAGTCTTGAACTCCTCAAAGTAAT CCATGAGGGTTGGAATCAACTTCTAAACTCCTGTTAATGTT GATATATTGACCCCCTCCCATGAATTATG AATGTTCTTAATAACTTCTAAATGGTGATACCTTTCCAGAAG GCTTTCAATGTACTTTGCCCGGATCCAT CAGAAGACTATCTTGGCAGCTGTAGACTAACAATATATTTC TTAAATGATAAGACTTGAAAGTCAAAAGT ACTCCTTAATCCATAGGCTGCAGAATCAATGTTGTATTAAC AGGCACGAAAACAGCATTAATCTTGTGCA TCTCCATCGGAGCTCTTGGGTGACTAGGTGCCTTGAGCAGT AATATTTTGAAAGGAGGTTTTGGTTTTGT TTTTTGTTTTTTTTTTTTGTTTTTTAGCAGTAAGTCTCAACAC TGGGCTTAAAATATTCAGTAAACTATG TTGTAAAAAGATGTGTTATCATCCAGACTTTGTTGTTCCATT ACTCTACACAAGCAGGGTACACTTAGCA TAATTCTTAAGGGCCTTGGAATTTTCAGAATGGTAAATGAG TATGGGCTTCAACTTAAAATCATCAACTG

		CATTAGCCTGTAACAAGAGAGTCAGCCTGTCCTTTGAAGCA AGGCATTGACTTCTATCTATGAAAGTCTT AGATGGCACCTTGTTTCAATAGTAGGCTGTTTAGTACAGCC ACCTTCATCAGTGATCTTAGCTAGATCTT CTGCATAACTTGCTGCAGCTTCTACATCAGCACTTGCTGCCT CACCTTGTCCTTTTATGTTATAGAGACA GCTGCGCTTCTTAAACTTTATAAACCAACTTCTGCTAGCTTC CAACTTCTCTTCTGCAGCTTCCTCATTC TCTTCATAGAACTGAAGGGAGTCAAGGCCTTGCTCTGGATT AAGCTTTGGCTTAAGGAATGTTGTGGCTG ACGTGATCTTCTATCCAGACCACTAAAGCGCTCTCCATATC AGCAATAAGGCCGTTTTGCTTTCTTACCT TTCATGTGTTCACTGGAGTAATTTCCTTCAAGAATTTTTCCT TTACATTCACAACTTGGCTAACTGGCAT GCAAGGCCTAGCTTTCAGCCTGTCTTGGCTTTTGACATGCCT TCCTCACTTAGCTCGTCATATCTAGCTT TTGATTTAAAGTGGCAGGCATACAACTCTTCCTTTCACTTGA ACACTTAGAGGCCACTGTAGGGTTATTA ATTGGCCTAATTTCAATATTGTTGTGTTTTAGGGAATAGAGA GGCCCAGGGAGAGGGAGAGAGCCCAAAC GGCTGGTTGATAGAGCAGGCAGAATGCACACAACATTTATC AGATTATGTTTGCACCATTTACCAGATTA TGGGTACGGTTTGTGGCACCCCCCAAAAATTAGAATAGTAA CATCAAAGATCACTGATCACAGATCGCCA TAACATAAATAATAATAAACTTTAAAATACTGTGAGAATTA CCAAAATGTGATACAGAGACATGAAGTGA GCACATGCTGTTGAAAAAAATGACACTGATAGACATACTTA ACACGTGGGATTGCCACAAACCTTCAGTT TGTAAAAGTCACAGTAACTGTGACTCACAAAAGAACAAAG CACAATAAAACGAGGTATGCCTGTATTTTT AAAAAAAGCTTTTTGTTAAAATTCAGGATATGTAATAGGTC TGTAGGAATAGTGAAATATTTTTGCTGAT GGATGTAGATATATACGTGGATAGAGATGAAGATCTTAATT ATAGCTATGCAGCATAGATTTAGTCAAAG ACATTTGAAAAGACAAATGTTAAATTAGTGTGGCTAATGAC CTACCCGTGCCATGTTTTCCCTCTTGCAA TGAGATACCCCACACTGTGTAGAAGGATGGAGGGAGGACT CCTACTGTCCCTCTTTGCGTGTGGTTATTA AGTTGCCTCACTGGGCTAAAACACCACACATCTCATAGATA ATATTTGGTAAGTTGTAATCGTCTTCACT CTTCTCTTATCACCCACCCCTATCTTCCCACTTTTCCATCTTT GTTGGTTTGCAACAGCCCCTTCTTTTT GCCTGACTCTCCAGGATTTTCTCTCATCATAAATTGTTCTAA AGTACATACTAATATGGGTCTGGATTGA CTATTCTTATTTGCAAAACAGCAATTAAATGTTATAGGGAA GTAGGAAGAAAAAGGGGTATCCTTGACAA TAAACCAAGCAATATTCTGGGGGTGGGATAGAGCAGGAAA TTTTATTTTTAATCTTTTAAAATCCAAGTA ATAGGTAGGCTTCCAGTTAGCTTTAAATGTTTTTTTTTTCCA GCTCAAAAAATTGGATTGTAGTTGATAC

		TACATATAATACATTCTAATTCCCTCACTGTATTCTTTGTTT AGTTTCATTTATTTGGTTTAAAATAATT TTTTATCCCATATCTGAAATGTAATATATTTTTATCCAACAA CCAGCATGTACATATACTTAATTATGTG GCACATTTTCTAATAGATCAGTCCATCAATCTACTCATTTTA AAGAAAAAAAAATTTTAAAGTCACTTTT AGAGCCCTTAATGTGTAGTTGGGGGTTAAGCTTTGTGGATG TAGCCTTTATATTTAGTATAATTGAGGTC TAAAATAATAATCTTCTATTATCTCAACAGAGCAAATTATT GAAAAAGATGAAGGTCCTTTTTATACCCA TCTAGGAGCAGGTCCTAATGTGGCAGCTATTAGAGAAATCA TGGAAGAAAGGTAATTAACGCAAAGGCAC AGGGCAGATTAACGTTTATCCTTTTGTATATGTCAGAATTTT TCCAGCCTTCACACACAAAGCAGTAAAC AATTGTAAATTGAGTAATTATTAGTAGGCTTAGCTATTCTAG GGTTGCCAACACTACACACTGTGCTATT CACCAGAGAGTCACAATATTTGACAGGACTAATAGTCTGCT AGCTGGCACAGGCTGCCCACTTTGCGATG GATGCCAGAAAACCCAGGCATGAACAGGAATCGGCCAGCC AGGCTGCCAGCCACAAGGTACTGGCACAGG CTCCAACGAGAGGTCCCACTCTGGCTTTCCCACCTGATAAT AAAGTGTCAAAGCAGAAAGACTGGTAAAG TGTGGTATAAGAAAAGAACCACTGAATTAAATTCACCTAGT GTTGCAAATGAGTACTTATCTCTAAGTTT TCTTTTACCATAAAAAGAGAGCAAGTGTGATATGTTGAATA GAAAGAGAAACATACTATTTACAGCTGCC TTTTTTTTTTTTTTTCGCTATCAATCACAGGTATACAAGTACT TGCCTTTACTCCTGCATGTAGAAGACT CTTATGAGCGAGATAATGCAGAGAAGGCCTTTCATATAAAT TTATACAGCTCTGAGCTGTTCTTCTTCTA GGGTGCCTTTTCATTAAGAGGTAGGCAGTATTATTATTAAA GTACTTAGGATACATTGGGGCAGCTAGGA CATATTCAGTATCATTCTTGCTCCATTTCCAAATTATTCATTT CTAAATTAGCATGTAGAAGTTCACTAA ATAATCATCTAGTGGCCTGGCAGAAATAGTGAATTTCCCTA AGTGCCTTTTTTTTGTTGTTTTTTTGTTT TGTTTTTTAAACAAGCAGTAGGTGGTGCTTTGGTCATAAGG GAAGATATAGTCTATTTCTAGGACTATTC CATATTTTCCATGTGGCTGGATACTAACTATTTGCCAGCCTC CTTTTCTAAATTGTGAGACATTCTTGGA GGAACAGTTCTAACTAAAATCTATTATGACTCCCCAAGTTTT AAAATAGCTAAATTTAGTAAGGGAAAAA ATAGTTTATGTTTTAGAAGACTGAACTTAGCAAACTAACCT GAATTTTGTGCTTTGTGAAATTTTATATC GAAATGAGCTTTCCCATTTTCACCCACATGTAATTTACAAA ATAGTTCATTACAATTATCTGTACATTTT GATATTGAGGAAAAACAAGGCTTAAAAACCATTATCCAGTT TGCTTGGCGTAGACCTGTTTAAAAAATAA TAAACCGTTCATTTCTCAGGATGTGGTCATAGAATAAAGTT ATGCTCAAATGTTCAAATATTTAAA

PPREDICTED: Homo sapiens tet methylcytosine dioxygenase 2 (TET2), transcript variant X9, mRNA [SEQ ID NO: 1362]	XXM_011532044.1	TCAGGCTCTACTTCTAATTCTGGTTCTCTTGCTACATCTCCCT CATCTGCAGTGACCTCTCCACGGAAGT CTTGAACTCCTCAAAAGCAAATTATTGAAAAAGATGAAGGT CCTTTTTATACCCATCTAGGAGCAGGTCC TAATGTGGCAGCTATTAGAGAAATCATGGAAGAAAGGTTTG GACAGAAGGGTAAAGCTATTAGGATTGAA AGAGTCATCTATACTGGTAAAGAAGGCAAAAGTTCTCAGGG ATGTCCTATTGCTAAGTGGGTGGTTCGCA GAAGCAGCAGTGAAGAGAAGCTACTGTGTTTGGTGCGGGA GCGAGCTGGCCACACCTGTGAGGCTGCAGT GATTGTGATTCTCATCCTGGTGTGGGAAGGAATCCCGCTGT CTCTGGCTGACAAACTCTACTCGGAGCTT ACCGAGACGCTGAGGAAATACGGCACGCTCACCAATCGCC GGTGTGCCTTGAATGAAGAGAGAACTTGCG CCTGTCAGGGGCTGGATCCAGAAACCTGTGGTGCCTCCTTC TCTTTTGGTTGTTCATGGAGCATGTACTA CAATGGATGTAAGTTTGCCAGAAGCAAGATCCCAAGGAAG TTTAAGCTGCTTGGGGATGACCCAAAAGAG GAAGAGAAACTGGAGTCTCATTTGCAAAACCTGTCCACTCT TATGGCACCAACATATAAGAAACTTGCAC CTGATGCATATAATAATCAGATTGAATATGAACACAGAGCA CCAGAGTGCCGTCTGGGTCTGAAGGAAGG CCGTCCATTCTCAGGGGTCACTGCATGTTTGGACTTCTGTGC TCATGCCCACAGAGACTTGCACAACATG CAGAATGGCAGCACATTGGTATGCACTCTCACTAGAGAAGA CAATCGAGAATTTGGAGGAAAACCTGAGG ATGAGCAGCTTCACGTTCTGCCTTTATACAAAGTCTCTGACG TGGATGAGTTTGGGAGTGTGGAAGCTCA GGAGGAGAAAAAACGGAGTGGTGCCATTCAGGTACTGAGT TCTTTTCGGCGAAAAGTCAGGATGTTAGCA GAGCCAGTCAAGACTTGCCGACAAAGGAAACTAGAAGCCA AGAAAGCTGCAGCTGAAAAGCTTTCCTCCC TGGAGAACAGCTCAAATAAAAATGAAAAGGAAAAGTCAGC CCCATCACGTACAAAACAAACTGAAAACGC AAGCCAGGCTAAACAGTTGGCAGAACTTTTGCGACTTTCAG GACCAGTCATGCAGCAGTCCCAGCAGCCC CAGCCTCTACAGAAGCAGCCACCACAGCCCCAGCAGCAGC AGAGACCCCAGCAGCAGCAGCCACATCACC CTCAGACAGAGTCTGTCAACTCTTATTCTGCTTCTGGATCCA CCAATCCATACATGAGACGGCCCAATCC AGTTAGTCCTTATCCAAACTCTTCACACACTTCAGATATCTA TGGAAGCACCAGCCCTATGAACTTCTAT TCCACCTCATCTCAAGCTGCAGGTTCATATTTGAATTCTTCT AATCCCATGAACCCTTACCCTGGGCTTT TGAATCAGAATACCCAATATCCATCATATCAATGCAATGGA AACCTATCAGTGGACAACTGCTCCCCATA TCTGGGTTCCTATTCTCCCCAGTCTCAGCCGATGGATCTGTA TAGGTATCCAAGCCAAGACCCTCTGTCT AAGCTCAGTCTACCACCCATCCATACACTTTACCAGCCAAG GTTTGGAAATAGCCAGAGTTTTACATCTA

		AATACTTAGGTTATGGAAACCAAAATATGCAGGGAGATGGT TTCAGCAGTTGTACCATTAGACCAAATGT ACATCATGTAGGGAAATTGCCTCCTTATCCCACTCATGAGA TGGATGGCCACTTCATGGGAGCCACCTCT AGATTACCACCCAATCTGAGCAATCCAAACATGGACTATAA AAATGGTGAACATCATTCACCTTCTCACA TAATCCATAACTACAGTGCAGCTCCGGGCATGTTCAACAGC TCTCTTCATGCCCTGCATCTCCAAAACAA GGAGAATGACATGCTTTCCCACACAGCTAATGGGTTATCAA AGATGCTTCCAGCTCTTAACCATGATAGA ACTGCTTGTGTCCAAGGAGGCTTACACAAATTAAGTGATGC TAATGGTCAGGAAAAGCAGCCATTGGCAC TAGTCCAGGGTGTGGCTTCTGGTGCAGAGGACAACGATGAG GTCTGGTCAGACAGCGAGCAGAGCTTTCT GGATCCTGACATTGGGGGAGTGGCCGTGGCTCCAACTCATG GGTCAATTCTCATTGAGTGTGCAAAGCGT GAGCTGCATGCCACAACCCCTTTAAAGAATCCCAATAGGAA TCACCCCACCAGGATCTCCCTCGTCTTTT ACCAGCATAAGAGCATGAATGAGCCAAAACATGGCTTGGC TCTTTGGGAAGCCAAAATGGCTGAAAAAGC CCGTGAGAAAGAGGAAGAGTGTGAAAAGTATGGCCCAGAC TATGTGCCTCAGAAATCCCATGGCAAAAAA GTGAAACGGGAGCCTGCTGAGCCACATGAAACTTCAGAGC CCACTTACCTGCGTTTCATCAAGTCTCTTG CCGAAAGGACCATGTCCGTGACCACAGACTCCACAGTAACT ACATCTCCATATGCCTTCACTCGGGTCAC AGGGCCTTACAACAGATATATATGATATCACCCCCTTTTGTT GGTTACCTCACTTGAAAAGACCACAACC AACCTGTCAGTAGTATAGTTCTCATGACGTGGGCAGTGGGG AAAGGTCACAGTATTCATGACAAATGTGG TGGGAAAAACCTCAGCTCACCAGCAACAAAAGAGGTTATCT TACCATAGCACTTAATTTTCACTGGCTCC CAAGTGGTCACAGATGGCATCTAGGAAAAGACCAAAGCAT TCTATGCAAAAAGAAGGTGGGGAAGAAAGT GTTCCGCAATTTACATTTTTAAACACTGGTTCTATTATTGGA CGAGATGATATGTAAATGTGATCCCCCC CCCCCGCTTACAACTCTACACATCTGTGACCACTTTTAATAA TATCAAGTTTGCATAGTCATGGAACACA AATCAAACAAGTACTGTAGTATTACAGTGACAGGAATCTTA AAATACCATCTGGTGCTGAATATATGATG TACTGAAATACTGGAATTATGGCTTTTTGAAATGCAGTTTTT ACTGTAATCTTAACTTTTATTTATCAAA ATAGCTACAGGAAACATGAATAGCAGGAAAACACTGAATT TGTTTGGATGTTCTAAGAAATGGTGCTAAG AAAATGGTGTCTTTAATAGCTAAAAATTTAATGCCTTTATAT CATCAAGATGCTATCAGTGTACTCCAGT GCCCTTGAATAATAGGGGTACCTTTTCATTCAAGTTTTTATC ATAATTACCTATTCTTACACAAGCTTAG TTTTTAAAATGTGGACATTTTAAAGGCCTCTGGATTTTGCTC ATCCAGTGAAGTCCTTGTAGGACAATAA

		ACGTATATATGTACATATATACACAAACATGTATATGTGCA CACACATGTATATGTATAAATATTTTAAA TGGTGTTTTAGAAGCACTTTGTCTACCTAAGCTTTGACAACT TGAACAATGCTAAGGTACTGAGATGTTT AAAAAACAAGTTTACTTTCATTTTAGAATGCAAAGTTGATT TTTTTAAGGAAACAAAGAAAGCTTTTAAA ATATTTTTGCTTTTAGCCATGCATCTGCTGATGAGCAATTGT GTCCATTTTTAACACAGCCAGTTAAATC CACCATGGGGCTTACTGGATTCAAGGGAATACGTTAGTCCA CAAAACATGTTTTCTGGTGCTCATCTCAC ATGCTATACTGTAAAACAGTTTTATACAAAATTGTATGACA AGTTCATTGCTCAAAAATGTACAGTTTTA AGAATTTTCTATTAACTGCAGGTAATAATTAGCTGCATGCT GCAGACTCAACAAAGCTAGTTCACTGAAG CCTATGCTATTTTATGGATCATAGGCTCTTCAGAGAACTGA ATGGCAGTCTGCCTTTGTGTTGATAATTA TGTACATTGTGACGTTGTCATTTCTTAGCTTAAGTGTCCTCT TTAACAAGAGGATTGAGCAGACTGATGC CTGCATAAGATGAATAAACAGGGTTAGTTCCATGTGAATCT GTCAGTTAAAAAGAAACAAAAACAGGCAG CTGGTTTGCTGTGGTGGTTTTAAATCATTAATTTGTATAAAG AAGTGAAAGAGTTGTATAGTAAATTAAA TTGTAAACAAAACTTTTTTAATGCAATGCTTTAGTATTTTAG TACTGTAAAAAAATTAAATATATACATA TATATATATATATATATATATATATATATGAGTTTGAAGCAG AATTCACATCATGATGGTGCTACTCAGC CTGCTACAAATATATCATAATGTGAGCTAAGAATTCATTAA ATGTTTGAGTGATGTTCCTACTTGTCATA TACCTCAACACTAGTTTGGCAATAGGATATTGAACTGAGAG TGAAAGCATTGTGTACCATCATTTTTTTC CAAGTCCTTTTTTTTATTGTTAAAAAAAAAAGCATACCTTTT TTCAATACTTGATTTCTTAGCAAGTATA ACTTGAACTTCAACCTTTTTGTTCTAAAAATTCAGGGATATT TCAGCTCATGCTCTCCCTATGCCAACAT GTCACCTGTGTTTATGTAAAATTGTTGTAGGTTAATAAATAT ATTCTTTGTCAGGGATTTAACCCTTTTA TTTTGAATCCCTTCTATTTTACTTGTACATGTGCTGATGTAA CTAAAACTAATTTTGTAAATCTGTTGGC TCTTTTTATTGTAAAGAAAAGCATTTTAAAAGTTTGAGGAA TCTTTTGACTGTTTCAAGCAGGAAAAAAA AATTACATGAAAATAGAATGCACTGAGTTGATAAAGGGAA AAATTGTAAGGCAGGAGTTTGGCAAGTGGC TGTTGGCCAGAGACTTACTTGTAACTCTCTAAATGAAGTTTT TTTGATCCTGTAATCACTGAAGGTACAT ACTCCATGTGGACTTCCCTTAAACAGGCAAACACCTACAGG TATGGTGTGCAACAGATTGTACAATTACA TTTTGGCCTAAATACATTTTTGCTTACTAGTATTTAAAATAA ATTCTTAATCAGAGGAGGCCTTTGGGTT TTATTGGTCAAATCTTTGTAAGCTGGCTTTTGTCTTTTTAAA AAATTTCTTGAATTTGTGGTTGTGTCCA

		ATTTGCAAACATTTCCAAAAATGTTTGCTTTGCTTACAAACC ACATGATTTTAATGTTTTTTGTATACCA TAATATCTAGCCCCAAACATTTGATTACTACATGTGCATTGG TGATTTTGATCATCCATTCTTAATATTT GATTTCTGTGTCACCTACTGTCATTTGTTAAACTGCTGGCCA ACAAGAACAGGAAGTATAGTTTGGGGGG TTGGGGAGAGTTTACATAAGGAAGAGAAGAAATTGAGTGG CATATTGTAAATATCAGATCTATAATTGTA AATATAAAACCTGCCTCAGTTAGAATGAATGGAAAGCAGAT CTACAATTTGCTAATATAGGAATATCAGG TTGACTATATAGCCATACTTGAAAATGCTTCTGAGTGGTGTC AACTTTACTTGAATGAATTTTTCATCTT GATTGACGCACAGTGATGTACAGTTCACTTCTGAAGCTAGT GGTTAACTTGTGTAGGAAACTTTTGCAGT TTGACACTAAGATAACTTCTGTGTGCATTTTTCTATGCTTTT TTAAAAACTAGTTTCATTTCATTTTCAT GAGATGTTTGGTTTATAAGATCTGAGGATGGTTATAAATAC TGTAAGTATTGTAATGTTATGAATGCAGG TTATTTGAAAGCTGTTTATTATTATATCATTCCTGATAATGC TATGTGAGTGTTTTTAATAAAATTTATA TTTATTTAATGCACTCTAA
PPREDICTED: Homo sapiens tet methylcytosine dioxygenase 2 (TET2), transcript variant X7, mRNA [SEQ ID NO: 1363]	XXM_011532043.1	GTAGAGAAGCAGAAGGAAGCAAGATGGCTGCCCTTTAGGA TTTGTTAGAAAGGAGACCCGACTGCAACTG CTGGATTGCTGCAAGGCTGAGGGACGAGAACGAGGCTGGC AAACATTCAGCAGCACACCCTCTCAAGATT GTTTACTTGCCTTTGCTCCTGTTGAGTTACAACGCTTGGAAG CAGGAGATGGGCTCAGCAGCAGCCAATA GGACATGATCCAGGAAGAGCAGTAAGGGACTGAGCTGCTG AATTCAACTAGAGGGCAGCCTTGTGGATGG CCCCGAAGCAAGCCTGATGGAACAGGATAGAACCAACCAT GTTGAGGGCAACAGACTAAGTCCATTCCTG ATACCATCACCTCCCATTTGCCAGACAGAACCTCTGGCTAC AAAGCTCCAGAATGGAAGCCCACTGCCTG AGAGAGCTCATCCAGAAGTAAATGGAGACACCAAGTGGCA CTCTTTCAAAAGTTATTATGGAATACCCTG TATGAAGGGAAGCCAGAATAGTCGTGTGAGTCCTGACTTTA CACAAGAAAGTAGAGGGTATTCCAAGTGT TTGCAAAATGGAGGAATAAAACGCACAGTTAGTGAACCTTC TCTCTCTGGGCTCCTTCAGATCAAGAAAT TGAAACAAGACCAAAAGGCTAATGGAGAAAGACGTAACTT CGGGGTAAGCCAAGAAAGAAATCCAGGTGA AAGCAGTCAACCAAATGTCTCCGATTTGAGTGATAAGAAAG AATCTGTGAGTTCTGTAGCCCAAGAAAAT GCAGTTAAAGATTTCACCAGTTTTTCAACACATAACTGCAG TGGGCCTGAAAATCCAGAGCTTCAGATTC TGAATGAGCAGGAGGGGAAAAGTGCTAATTACCATGACAA GAACATTGTATTACTTAAAAACAAGGCAGT GCTAATGCCTAATGGTGCTACAGTTTCTGCCTCTTCCGTGGA ACACACACATGGTGAACTCCTGGAAAAA ACACTGTCTCAATATTATCCAGATTGTGTTTCCATTGCGGTG

		CAGAAAACCACATCTCACATAAATGCCA TTAACAGTCAGGCTACTAATGAGTTGTCCTGTGAGATCACT CACCCATCGCATACCTCAGGGCAGATCAA TTCCGCACAGACCTCTAACTCTGAGCTGCCTCCAAAGCCAG CTGCAGTGGTGAGTGAGGCCTGTGATGCT GATGATGCTGATAATGCCAGTAAACTAGCTGCAATGCTAAA TACCTGTTCCTTTCAGAAACCAGAACAAC TACAACAACAAAAATCAGTTTTTGAGATATGCCCATCTCCT GCAGAAAATAACATCCAGGGAACCACAAA GCTAGCGTCTGGTGAAGAATTCTGTTCAGGTTCCAGCAGCA ATTTGCAAGCTCCTGGTGGCAGCTCTGAA CGGTATTTAAAACAAAATGAAATGAATGGTGCTTACTTCAA GCAAAGCTCAGTGTTCACTAAGGATTCCT TTTCTGCCACTACCACACCACCACCACCATCACAATTGCTTC TTTCTCCCCCTCCTCCTCTTCCACAGGT TCCTCAGCTTCCTTCAGAAGGAAAAAGCACTCTGAATGGTG GAGTTTTAGAAGAACACCACCACTACCCC AACCAAAGTAACACAACACTTTTAAGGGAAGTGAAAATAG AGGGTAAACCTGAGGCACCACCTTCCCAGA GTCCTAATCCATCTACACATGTATGCAGCCCTTCTCCGATGC TTTCTGAAAGGCCTCAGAATAATTGTGT GAACAGGAATGACATACAGACTGCAGGGACAATGACTGTT CCATTGTGTTCTGAGAAAACAAGACCAATG TCAGAACACCTCAAGCATAACCCACCAATTTTTGGTAGCAG TGGAGAGCTACAGGACAACTGCCAGCAGT TGATGAGAAACAAAGAGCAAGAGATTCTGAAGGGTCGAGA CAAGGAGCAAACACGAGATCTTGTGCCCCC AACACAGCACTATCTGAAACCAGGATGGATTGAATTGAAG GCCCCTCGTTTTCACCAAGCGGAATCCCAT CTAAAACGTAATGAGGCATCACTGCCATCAATTCTTCAGTA TCAACCCAATCTCTCCAATCAAATGACCT CCAAACAATACACTGGAAATTCCAACATGCCTGGGGGGCTC CCAAGGCAAGCTTACACCCAGAAAACAAC ACAGCTGGAGCACAAGTCACAAATGTACCAAGTTGAAATG AATCAAGGGCAGTCCCAAGGTACAGTGGAC CAACATCTCCAGTTCCAAAAACCCTCACACCAGGTGCACTT CTCCAAAACAGACCATTTACCAAAAGCTC ATGTGCAGTCACTGTGTGGCACTAGATTTCATTTTCAACAA AGAGCAGATTCCCAAACTGAAAAACTTAT GTCCCCAGTGTTGAAACAGCACTTGAATCAACAGGCTTCAG AGACTGAGCCATTTTCAAACTCACACCTT TTGCAACATAAGCCTCATAAACAGGCAGCACAAACACAAC CATCCCAGAGTTCACATCTCCCTCAAAACC AGCAACAGCAGCAAAAATTACAAATAAAGAATAAAGAGGA AATACTCCAGACTTTTCCTCACCCCCAAAG CAACAATGATCAGCAAAGAGAAGGATCATTCTTTGGCCAGA CTAAAGTGGAAGAATGTTTTCATGGTGAA AATCAGTATTCAAAATCAAGCGAGTTCGAGACTCATAATGT CCAAATGGGACTGGAGGAAGTACAGAATA TAAATCGTAGAAATTCCCCTTATAGTCAGACCATGAAATCA

		AGTGCATGCAAAATACAGGTTTCTTGTTC AAACAATACACACCTAGTTTCAGAGAATAAAGAACAGACT ACACATCCTGAACTTTTTGCAGGAAACAAG ACCCAAAACTTGCATCACATGCAATATTTTCCAAATAATGT GATCCCAAAGCAAGATCTTCTTCACAGGT GCTTTCAAGAACAGGAGCAGAAGTCACAACAAGCTTCAGTT CTACAGGGATATAAAAATAGAAACCAAGA TATGTCTGGTCAACAAGCTGCGCAACTTGCTCAGCAAAGGT ACTTGATACATAACCATGCAAATGTTTTT CCTGTGCCTGACCAGGGAGGAAGTCACACTCAGACCCCTCC CCAGAAGGACACTCAAAAGCATGCTGCTC TAAGGTGGCATCTCTTACAGAAGCAAGAACAGCAGCAAAC ACAGCAACCCCAAACTGAGTCTTGCCATAG TCAGATGCACAGGCCAATTAAGGTGGAACCTGGATGCAAG CCACATGCCTGTATGCACACAGCACCACCA GAAAACAAAACATGGAAAAAGGTAACTAAGCAAGAGAATC CACCTGCAAGCTGTGATAATGTGCAGCAAA AGAGCATCATTGAGACCATGGAGCAGCATCTGAAGCAGTTT CACGCCAAGTCGTTATTTGACCATAAGGC TCTTACTCTCAAATCACAGAAGCAAGTAAAAGTTGAAATGT CAGGGCCAGTCACAGTTTTGACTAGACAA ACCACTGCTGCAGAACTTGATAGCCACACCCCAGCTTTAGA GCAGCAAACAACTTCTTCAGAAAAGACAC CAACCAAAAGAACAGCTGCTTCTGTTCTCAATAATTTTATA GAGTCACCTTCCAAATTACTAGATACTCC TATAAAAAATTTATTGGATACACCTGTCAAGACTCAATATG ATTTCCCATCTTGCAGATGTGTAGAGCAA ATTATTGAAAAAGATGAAGGTCCTTTTTATACCCATCTAGG AGCAGGTCCTAATGTGGCAGCTATTAGAG AAATCATGGAAGAAAGGTATACAAGTACTTGCCTTTACTCC TGCATGTAGAAGACTCTTATGAGCGAGAT AATGCAGAGAAGGCCTTTCATATAAATTTATACAGCTCTGA GCTGTTCTTCTTCTAGGGTGCCTTTTCAT TAAGAGGTAGGCAGTATTATTATTAAAGTACTTAGGATACA TTGGGGCAGCTAGGACATATTCAGTATCA TTCTTGCTCCATTTCCAAATTATTCATTTCTAAATTAGCATG TAGAAGTTCACTAAATAATCATCTAGTG GCCTGGCAGAAATAGTGAATTTCCCTAAGTGCCTTTTTTTTG TTGTTTTTTTGTTTTGTTTTTTAAACAA GCAGTAGGTGGTGCTTTGGTCATAAGGGAAGATATAGTCTA TTTCTAGGACTATTCCATATTTTCCATGT GGCTGGATACTAACTATTTGCCAGCCTCCTTTTCTAAATTGT GAGACATTCTTGGAGGAACAGTTCTAAC TAAAATCTATTATGACTCCCCAAGTTTTAAAATAGCTAAATT TAGTAAGGGAAAAAATAGTTTATGTTTT AGAAGACTGAACTTAGCAAACTAACCTGAATTTTGTGCTTT GTGAAATTTTATATCGAAATGAGCTTTCC CATTTTCACCCACATGTAATTTACAAAATAGTTCATTACAAT TATCTGTACATTTTGATATTGAGGAAAA ACAAGGCTTAAAAACCATTATCCAGTTTGCTTGGCGTAGAC

		CTGTTTAAAAAATAATAAACCGTTCATTT CTCAGGATGTGGTCATAGAATAAAGTTATGCTCAAATGTTC AAA

"Tet inhibitor" or "Tet[x] inhibitor" (e.g., "Tet1 inhibitor," "Tet2 inhibitor", or "Tet3 inhibitor") as the terms are used herein, refers to a molecule, or group of molecules (e.g., a system) that reduces or eliminates the function and/or expression of the corresponding Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2. In embodiments, a Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 inhibitor is a molecule that inhibits the expression of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, e.g., reduces or eliminates expression of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2. In embodiments, the Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 inhibitor is a molecule that inhibits the function of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2. An example of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 inhibitor that inhibits the expression of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 is a gene editing system, e.g., as described herein, that is targeted to nucleic acid within the Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 gene, or its regulatory elements, such that modification of the nucleic acid at or near the gene editing system binding site(s) is modified to reduce or eliminate expression of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2. Another example of a Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 inhibitor that inhibits the expression of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 is a nucleic acid molecule, e.g., RNA molecule, e.g., a short hairpin RNA (shRNA) or short interfering RNA (siRNA), capable of hybridizing with Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 mRNA and causing a reduction or elimination of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 translation. Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 inhibitors also include nucleic acids encoding molecules which inhibit Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 expression (e.g., nucleic acid encoding an anti-Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 shRNA or siRNA, or nucleic acid encoding one or more, e.g., all, components of an anti-Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 gene editing system). An example of a molecule that inhibits the function of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 is a molecule, e.g., a protein or small molecule which inhibits one or more activities of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2. An example is a small molecule inhibitor of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2. Another example is a dominant negative Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 protein. Another example is a dominant negative version of a Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 binding partner, e.g., an associated histone deacetylase (HDAC). Another

example is a molecule, e.g., a small molecule, which inhibits a Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 binding partner, e.g., a Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2-associated HDAC inhibitor. Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 inhibitors also include nucleic acids encoding inhibitors of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 function.

A "system" as the term is used herein in connection with gene editing or Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 inhibition, refers to a group of molecules, e.g., one or more molecules, which together act to effect a desired function.

A "gene editing system" as the term is used herein, refers to a system, e.g., one or more molecules, that direct and effect an alteration, e.g., a deletion, of one or more nucleic acids at or near a site of genomic DNA targeted by said system. Gene editing systems are known in the art, and are described more fully below.

"binding partner" as the term is used herein in the context of a Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 binding partner, refers to a molecule, e.g., a protein, which interacts, e.g., binds to, Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 protein. Without being bound by theory, it is believed that Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 binds to one or more HDAC proteins. Such HDAC proteins are considered examples of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 binding partners.

A "dominant negative" gene product or protein is one that interferes with the function of another gene product or protein. The other gene product affected can be the same or different from the dominant negative protein. Dominant negative gene products can be of many forms, including truncations, full length proteins with point mutations or fragments thereof, or fusions of full length wild type or mutant proteins or fragments thereof with other proteins. The level of inhibition observed can be very low. For example, it may require a large excess of the dominant negative protein compared to the functional protein or proteins involved in a process in order to see an effect. It may be difficult to see effects under normal biological assay conditions. In one embodiment, a dominant negative Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 is a catalytically inactive Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2. In another embodiment, a dominant negative Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 binding partner is a catalytically inactive Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2-binding HDAC inhibitor.

Description

The present invention provides Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, inhibitors and methods of use therefore. In particular, the invention provides CAR-expressing T cells comprising Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, inhibitors, and use of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, in connection with CAR T cells. Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, inhibitor of the present invention, together with their methods of use, are described in more detail below. CARs, CAR T cells, and methods of use are further described below.

Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 Inhibitors

The present invention provides compositions, e.g., Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 inhibitors, and methods for enhancing immune effector cell functions, e.g., CAR-expressing cell functions, by using such compositions and/or other means as described herein. Any Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, inhibitors known in the art can be used as a Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, inhibitor according to the present invention. Examples of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, inhibitors are described below.

Gene Editing Systems

According to the present invention, gene editing systems can be used as Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, inhibitors. Also contemplated by the present invention are the uses of nucleic acid encoding one or more components of a Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, gene editing system.

CRISPR/Cas9 Gene Editing Systems

Naturally-occurring CRISPR/Cas systems are found in approximately 40% of sequenced eubacteria genomes and 90% of sequenced archaea. Grissa et al. (2007) BMC Bioinformatics 8: 172. This system is a type of prokaryotic immune system that confers resistance to foreign genetic elements such as plasmids and phages and provides a form of acquired immunity. Barrangou et al. (2007) Science 315: 1709-1712; Marragini et al. (2008) Science 322: 1843-1845.

The CRISPR/Cas system has been modified for use in gene editing (silencing, enhancing or changing specific genes) in eukaryotes such as mice or primates. Wiedenheft et al. (2012) Nature 482: 331-8. This is accomplished by, for example, introducing into the eukaryotic cell a plasmid containing a specifically designed CRISPR and one or more appropriate Cas.

The CRISPR sequence, sometimes called a CRISPR locus, comprises alternating repeats and spacers. In a naturally-occurring CRISPR, the spacers usually comprise sequences foreign to the bacterium such as a plasmid or phage sequence; in an exemplary Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, CRISPR/Cas system, the spacers are derived from the Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, gene sequence, or a sequence of its regulatory elements.

RNA from the CRISPR locus is constitutively expressed and processed into small RNAs. These comprise a spacer flanked by a repeat sequence. The RNAs guide other Cas proteins to silence exogenous genetic elements at the RNA or DNA level. Horvath et al. (2010) Science 327: 167-170; Makarova et al. (2006) Biology Direct 1: 7. The spacers thus serve as templates for RNA molecules, analogously to siRNAs. Pennisi (2013) Science 341: 833-836.

As these naturally occur in many different types of bacteria, the exact arrangements of the CRISPR and structure, function and number of Cas genes and their product differ somewhat from species to species. Haft et al. (2005) PLoS Comput. Biol. 1: e60; Kunin et al. (2007) Genome Biol. 8: R61; Mojica et al. (2005) J. Mol. Evol. 60: 174-182; Bolotin et al. (2005) Microbiol. 151: 2551-2561; Pourcel et al. (2005) Microbiol. 151: 653-663; and Stern et al. (2010) Trends. Genet. 28: 335-340. For example, the Cse (Cas subtype, *E. coli*) proteins (e.g., CasA) form a functional complex, Cascade, that processes CRISPR RNA transcripts into spacer-repeat units that Cascade retains. Brouns et al. (2008) *Science* 321: 960-964. In other prokaryotes, Cas6 processes the CRISPR transcript. The CRISPR-based phage inactivation in E. coli requires Cascade and Cas3, but not Cas1 or Cas2. The Cmr (Cas RAMP module) proteins in Pyrococcus furiosus and other prokaryotes form a functional complex with small CRISPR RNAs that recognizes and cleaves complementary target RNAs. A simpler CRISPR system relies on the protein Cas9, which is a nuclease with two active cutting sites, one for each strand of the double helix. Combining Cas9 and modified CRISPR locus RNA can be used in a system for gene editing. Pennisi (2013) Science 341: 833-836.

The CRISPR/Cas system can thus be used to modify, e.g., delete one or more nucleic acids, the Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, gene, or a Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, gene regulatory element, or introduce a premature stop which thus decreases expression of a functional Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2,. The CRISPR/Cas system can alternatively be used like RNA interference, turning off the Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, gene in a reversible fashion. In a mammalian cell, for example, the RNA can guide

the Cas protein to a Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, promoter, sterically blocking RNA polymerases.

CRISPR/Cas systems for gene editing in eukaryotic cells typically involve (1) a guide RNA molecule (gRNA) comprising a targeting sequence (which is capable of hybridizing to the genomic DNA target sequence), and sequence which is capable of binding to a Cas, e.g., Cas9 enzyme, and (2) a Cas, e.g., Cas9, protein. The targeting sequence and the sequence which is capable of binding to a Cas, e.g., Cas9 enzyme, may be disposed on the same or different molecules. If disposed on different molecules, each includes a hybridization domain which allows the molecules to associate, e.g., through hybridization.

An exemplary gRNA molecule of the present invention comprises, e.g., consists of a first nucleic acid having the sequence (where the "n"'s refer to the residues of the targeting sequence (e.g., as described herein, e.g., in Table 3), and may consist of 15-25 nucelotides, e.g., consist of 20 nucleotides):

nnnnnnnnnnnnnnnnnnnnGUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO: 40);

and a second nucleic acid sequence having the sequence:

AACUUACCAAGGAACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGC, optionally with 1, 2, 3, 4, 5, 6, or 7 (e.g., 4 or 7, e.g., 7) additional U nucleotides at the 3' end (SEQ ID NO: 41).

The second nucleic acid molecule may alternatively consist of a fragment of the sequence above, wherein such fragment is capable of hybridizing to the first nucleic acid. An example of such second nucleic acid molecule is:

AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGC, optionally with 1, 2, 3, 4, 5, 6, or 7 (e.g., 4 or 7, e.g., 7) additional U nucleotides at the 3' end (SEQ ID NO: 42).

Another exemplary gRNA molecule of the present invention comprises, e.g., consists of a first nucleic acid having the sequence (where the "n"'s refer to the residues of the targeting sequence (e.g., as described herein, e.g., in Table 3), and may consist of 15-25 nucelotides, e.g., consist of 20 nucleotides):

nnnnnnnnnnnnnnnnnnnnGUUUUAGAGCUAGAAAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGCACCGAGUCGGUGC (SEQ ID NO: 43), optionally with 1, 2, 3, 4, 5, 6, or 7 (e.g., 4 or 7, e.g., 4) additional U nucleotides at the 3'

end.Artificial CRISPR/Cas systems can be generated which inhibit Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, using technology known in the art, e.g., that are described in U.S. Publication No.20140068797, WO2015/048577, and Cong (2013) Science 339: 819-823. Other artificial CRISPR/Cas systems that are known in the art may also be generated which inhibit Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2,, e.g., that described in Tsai (2014) Nature Biotechnol., 32:6 569-576, U.S. Patent No.: 8,871,445; 8,865,406; 8,795,965; 8,771,945; and 8,697,359, the contents of which are hereby incorporated by reference in their entirety. Such systems can be generated which inhibit Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, by, for example, engineering a CRISPR/Cas system to include a gRNA molecule comprising a targeting sequence that hybridizes to a sequence of a tet gene, e.g., a Tet1, Tet2 and/or Tet3, e.g., Tet2 gene. In embodiments, the gRNA comprises a targeting sequence which is fully complementarity to 15-25 nucleotides, e.g., 20 nucleotides, of a tet gene, e.g., a Tet1, Tet2 and/or Tet3, e.g., Tet2 gene. In embodiments, the 15-25 nucleotides, e.g., 20 nucleotides, of a tet gene, e.g., a Tet1, Tet2 and/or Tet3, e.g., Tet2 gene, are disposed immediately 5' to a protospacer adjacent motif (PAM) sequence recognized by the Cas protein of the CRISPR/Cas system (e.g., where the system comprises a *S. pyogenes* Cas9 protein, the PAM sequence comprises NGG, where N can be any of A, T, G or C). In embodiments, the targeting sequence of the gRNA comprises, e.g., consists of, a RNA sequence complementary to a sequence listed in Table 2. In embodiments, the gRNA comprises a targeting sequence listed in Table 3.

In one embodiment, foreign DNA can be introduced into the cell along with the CRISPR/Cas system, e.g., DNA encoding a CAR, e.g., as described herein; depending on the sequences of the foreign DNA and chromosomal sequence, this process can be used to integrate the DNA encoding the CAR, e.g., as described herein, at or near the site targeted by the CRISPR/Cas system. As shown herein, in the examples, but without being bound by theory, such integration may lead to the expression of the CAR as well as disruption of the Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, gene. Such foreign DNA molecule is referred to herein as "template DNA." In embodiments, the template DNA further comprises homology arms 5' to, 3' to, or both 5' and 3' to the nucleic acid of the template DNA which encodes the molecule or molecules of interest (e.g., which encodes a CAR described herein), wherein said homology arms are complementary to genomic DNA sequence flanking the target sequence.

In an embodiment, the CRISPR/Cas system of the present invention comprises Cas9, e.g., S. pyogenes Cas9, and a gRNA comprising a targeting sequence which hybridizes to a sequence of the Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, gene. In an embodiment, the CRISPR/Cas system comprises nucleic acid encoding a Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, gRNA and nucleic acid encoding a Cas protein, e.g., Cas9, e.g., S. pyogenes Cas9. In an embodiment, the CRISPR/Cas system comprises a Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, gRNA and nucleic acid encoding a Cas protein, e.g., Cas9, e.g., S. pyogenes Cas9.

Examples of genomic target sequences for Tet2, for which gRNAs comprising complementary targeting sequences can be generated for use in the present invention are listed in the table 2 below. In embodiments, the gRNA comprises an RNA complement of a Target Sequence of the table below (e.g., for sgTET2_1, the gRNA would comprise CCUUGGACACCUUCUCCUCC (SEQ ID NO: 44)). In embodiments, the gRNA comprises the RNA analog of a Target sequence of the table 2 below (e.g., for sgTET2_1, the gRNA would comprise GGAACCUGUGGAAGAGGAGG (SEQ ID NO: 45). In embodiments, the Tet2 inhibitor is nucleic acid encoding a gRNA molecule specific for Tet2, wherein the nucleic acid comprises the sequence of a Target Sequence from the 2 table below, e.g., under the control of a U6- or H1- promoter:

Table 2

gRNA ID	Gene Symbol	Chromosome	Position	Strand	Target Sequence within the Tet2 gene sequence
sgTET2_1	TET2	chr4	106156327	-	GGAACCTGTGGAAGAGGAGG (SEQ ID NO: 46)
sgTET2_2	TET2	chr4	106156339	-	GAAGGAAGCTGAGGAACCTG (SEQ ID NO: 47)
sgTET2_3	TET2	chr4	106156897	+	ATGACCTCCAAACAATACAC (SEQ ID NO: 48)
sgTET2_4	TET2	chr4	106157189	-	CAAGTGCTGTTTCAACACTG (SEQ ID NO: 49)
sgTET2_5	TET2	chr4	106157296	-	GGGAGATGTGAACTCTGGGA (SEQ ID NO: 50)
sgTET2_6	TET2	chr4	106155148	-	GGAGGTGATGGTATCAGGAA (SEQ ID NO: 51)
sgTET2_7	TET2	chr4	106155166	-	GGTTCTGTCTGGCAAATGGG (SEQ ID NO: 52)
sgTET2_8	TET2	chr4	106155217	-	GGATGAGCTCTCTCAGGCAG

					(SEQ ID NO: 53)
sgTET2_9	TET2	chr4	106155403	-	TGAAGGAGCCCAGAGAGAGA (SEQ ID NO: 65)
sgTET2_10	TET2	chr4	106155478	+	GTAAGCCAAGAAAGAAATCC (SEQ ID NO: 66)

Examples of gRNA targeting sequences which are useful in the various embodiments of the present invention to inhibit a Tet, e.g., Tet2, are provided below in Table 3. In embodiments a CRISPR/Cas system of the present invention comprises a gRNA molecule comprising a targeting sequence comprising a sequence listed in Table 3. In embodiments, a CRISPR/Cas system of the present invention comprises a gRNA molecule comprising a targeting sequence that is a sequence listed in Table 3.

Table 3

ID	TARGET	TARGET REGION	STRAND	Location of Genomic Target Sequence (hg38)	gRNA Targeting sequence	SEQ ID NO:
54790_1_1	TET2	EXON	+	chr4:105145928 -105145948	UGUCGGGUCUUUAAAAAUAC	73
54790_1_3	TET2	EXON	+	chr4:105145945 -105145965	UACAGGCCCCUAAAGCACUA	74
54790_1_4	TET2	EXON	+	chr4:105145946 -105145966	ACAGGCCCCUAAAGCACUAA	75
54790_1_5	TET2	EXON	+	chr4:105145957 -105145977	AAGCACUAAGGGCAUGCCCU	76
54790_1_8	TET2	EXON	+	chr4:105145966 -105145986	GGGCAUGCCCUCGGUGAAAC	77
54790_1_10	TET2	EXON	+	chr4:105145967 -105145987	GGCAUGCCCUCGGUGAAACA	78
54790_1_12	TET2	EXON	+	chr4:105145968 -105145988	GCAUGCCCUCGGUGAAACAG	79
54790_1_20	TET2	EXON	+	chr4:105146006 -105146026	UGAGAUUAAAGCGACAGAAA	80
54790_1_23	TET2	EXON	+	chr4:105146007 -105146027	GAGAUUAAAGCGACAGAAAA	81
54790_1_25	TET2	EXON	+	chr4:105146012 -105146032	UAAAGCGACAGAAAAGGGAA	82
54790_1_30	TET2	EXON	+	chr4:105146021 -105146041	AGAAAAGGGAAAGGAGAGCG	83
54790_1_31	TET2	EXON	+	chr4:105146022 -105146042	GAAAAGGGAAAGGAGAGCGC	84

54790_1_33	TET2	EXON	+	chr4:105146028 -105146048	GGAAAGGAGAGCGCGGGCAA	85
54790_1_35	TET2	EXON	+	chr4:105146029 -105146049	GAAAGGAGAGCGCGGGCAAC	86
54790_1_38	TET2	EXON	+	chr4:105146038 -105146058	GCGCGGGCAACGGGAUCUAA	87
54790_1_39	TET2	EXON	+	chr4:105146039 -105146059	CGCGGGCAACGGGAUCUAAA	88
54790_1_43	TET2	EXON	+	chr4:105146053 -105146073	UCUAAAGGGAGAUAGAGACG	89
54790_1_44	TET2	EXON	+	chr4:105146054 -105146074	CUAAAGGGAGAUAGAGACGC	90
54790_1_47	TET2	EXON	+	chr4:105146063 -105146083	GAUAGAGACGCGGGCCUCUG	91
54790_1_48	TET2	EXON	+	chr4:105146064 -105146084	AUAGAGACGCGGGCCUCUGA	92
54790_1_49	TET2	EXON	+	chr4:105146069 -105146089	GACGCGGGCCUCUGAGGGUA	93
54790_1_51	TET2	EXON	+	chr4:105146072 -105146092	GCGGGCCUCUGAGGGUAAGG	94
54790_1_52	TET2	EXON	+	chr4:105146073 -105146093	CGGGCCUCUGAGGGUAAGGU	95
54790_1_54	TET2	EXON	+	chr4:105146082 -105146102	GAGGGUAAGGUGGGCGCAAG	96
54790_1_61	TET2	EXON	-	chr4:105145954 -105145974	GCAUGCCCUUAGUGCUUUAG	97
54790_1_62	TET2	EXON	-	chr4:105145955 -105145975	GGCAUGCCCUUAGUGCUUUA	98
54790_1_64	TET2	EXON	-	chr4:105145956 -105145976	GGGCAUGCCCUUAGUGCUUU	99
54790_1_68	TET2	EXON	-	chr4:105145976 -105145996	GCGCUCCCCUGUUUCACCGA	100
54790_1_69	TET2	EXON	-	chr4:105145977 -105145997	AGCGCUCCCCUGUUUCACCG	101
54790_1_87	TET2	EXON	-	chr4:105146080 -105146100	UGCGCCCACCUUACCCUCAG	102
54790_2_1	TET2	EXON	+	chr4:105146669 -105146689	AGAGCCGGCGGUAGCGGCAG	103
54790_2_2	TET2	EXON	+	chr4:105146675 -105146695	GGCGGUAGCGGCAGUGGCAG	104
54790_2_6	TET2	EXON	+	chr4:105146686 -105146706	CAGUGGCAGCGGCGAGAGCU	105
54790_2_7	TET2	EXON	+	chr4:105146687 -105146707	AGUGGCAGCGGCGAGAGCUU	106

54790_2_8	TET2	EXON	+	chr4:105146690 -105146710	GGCAGCGGCGAGAGCUUGGG	107
54790_2_12	TET2	EXON	+	chr4:105146725 -105146745	CCUCGCGAGCGCCGCGCGCC	108
54790_2_13	TET2	EXON	+	chr4:105146726 -105146746	CUCGCGAGCGCCGCGCGCCC	109
54790_2_14	TET2	EXON	+	chr4:105146761 -105146781	GCAAGUCACGUCCGCCCCCU	110
54790_2_15	TET2	EXON	+	chr4:105146766 -105146786	UCACGUCCGCCCCCUCGGCG	111
54790_2_17	TET2	EXON	+	chr4:105146783 -105146803	GCGCGGCCGCCCCGAGACGC	112
54790_2_24	TET2	EXON	+	chr4:105146836 -105146856	CUGCCUUAUGAAUAUUGAUG	113
54790_2_25	TET2	EXON	+	chr4:105146839 -105146859	CCUUAUGAAUAUUGAUGCGG	114
54790_2_27	TET2	EXON	+	chr4:105146844 -105146864	UGAAUAUUGAUGCGGAGGCU	115
54790_2_34	TET2	EXON	+	chr4:105146868 -105146888	UGCUUUCGUAGAGAAGCAGA	116
54790_2_37	TET2	EXON	+	chr4:105146879 -105146899	AGAAGCAGAAGGAAGCAAGA	117
54790_2_39	TET2	EXON	+	chr4:105146891 -105146911	AAGCAAGAUGGCUGCCCUUU	118
54790_2_44	TET2	EXON	+	chr4:105146905 -105146925	CCCUUUAGGAUUUGUUAGAA	119
54790_2_51	TET2	EXON	+	chr4:105146926 -105146946	GGAGACCCGACUGCAACUGC	120
54790_2_52	TET2	EXON	+	chr4:105146938 -105146958	GCAACUGCUGGAUUGCUGCA	121
54790_2_56	TET2	EXON	+	chr4:105146944 -105146964	GCUGGAUUGCUGCAAGGCUG	122
54790_2_57	TET2	EXON	+	chr4:105146945 -105146965	CUGGAUUGCUGCAAGGCUGA	123
54790_2_62	TET2	EXON	+	chr4:105146957 -105146977	AAGGCUGAGGGACGAGAACG	124
54790_2_64	TET2	EXON	-	chr4:105146676 -105146696	GCUGCCACUGCCGCUACCGC	125
54790_2_65	TET2	EXON	-	chr4:105146716 -105146736	CGCUCGCGAGGAGGCGGCGG	126
54790_2_66	TET2	EXON	-	chr4:105146719 -105146739	CGGCGCUCGCGAGGAGGCGG	127
54790_2_67	TET2	EXON	-	chr4:105146722 -105146742	GCGCGGCGCUCGCGAGGAGG	128

54790_2_68	TET2	EXON	-	chr4:105146725-105146745	GGCGCGCGGCGCUCGCGAGG	129
54790_2_69	TET2	EXON	-	chr4:105146728-105146748	CCGGGCGCGCGGCGCUCGCG	130
54790_2_74	TET2	EXON	-	chr4:105146739-105146759	GCGAGCGGGACCCGGGCGCG	131
54790_2_75	TET2	EXON	-	chr4:105146746-105146766	CUUGCAUGCGAGCGGGACCC	132
54790_2_76	TET2	EXON	-	chr4:105146747-105146767	ACUUGCAUGCGAGCGGGACC	133
54790_2_78	TET2	EXON	-	chr4:105146753-105146773	GACGUGACUUGCAUGCGAGC	134
54790_2_79	TET2	EXON	-	chr4:105146754-105146774	GGACGUGACUUGCAUGCGAG	135
54790_2_83	TET2	EXON	-	chr4:105146775-105146795	GGGCGGCCGCGCCGAGGGGG	136
54790_2_85	TET2	EXON	-	chr4:105146778-105146798	UCGGGGCGGCCGCGCCGAGG	137
54790_2_86	TET2	EXON	-	chr4:105146779-105146799	CUCGGGGCGGCCGCGCCGAG	138
54790_2_88	TET2	EXON	-	chr4:105146780-105146800	UCUCGGGGCGGCCGCGCCGA	139
54790_2_89	TET2	EXON	-	chr4:105146781-105146801	GUCUCGGGGCGGCCGCGCCG	140
54790_2_93	TET2	EXON	-	chr4:105146792-105146812	GCGGGGCCGGCGUCUCGGGG	141
54790_2_94	TET2	EXON	-	chr4:105146795-105146815	UCAGCGGGGCCGGCGUCUCG	142
54790_2_95	TET2	EXON	-	chr4:105146796-105146816	CUCAGCGGGGCCGGCGUCUC	143
54790_2_97	TET2	EXON	-	chr4:105146797-105146817	ACUCAGCGGGGCCGGCGUCU	144
54790_2_100	TET2	EXON	-	chr4:105146805-105146825	UUCUCAUCACUCAGCGGGGC	145
54790_2_101	TET2	EXON	-	chr4:105146809-105146829	UCUGUUCUCAUCACUCAGCG	146
54790_2_103	TET2	EXON	-	chr4:105146810-105146830	GUCUGUUCUCAUCACUCAGC	147
54790_2_106	TET2	EXON	-	chr4:105146811-105146831	CGUCUGUUCUCAUCACUCAG	148
54790_2_109	TET2	EXON	-	chr4:105146842-105146862	CCUCCGCAUCAAUAUUCAUA	149
54790_2_117	TET2	EXON	-	chr4:105146908-105146928	CCUUUCUAACAAAUCCUAAA	150

54790_2_118	TET2	EXON	-	chr4:105146909-105146929	UCCUUUCUAACAAAUCCUAA	151
54790_2_122	TET2	EXON	-	chr4:105146934-105146954	GCAAUCCAGCAGUUGCAGUC	152
54790_2_123	TET2	EXON	-	chr4:105146935-105146955	AGCAAUCCAGCAGUUGCAGU	153
54790_3_1	TET2	EXON	+	chr4:105190341-105190361	AAACUCUGUCUUCUCUAGGC	154
54790_3_13	TET2	EXON	+	chr4:105190411-105190431	UCCUGUUGAGUUACAACGCU	155
54790_3_16	TET2	EXON	+	chr4:105190418-105190438	GAGUUACAACGCUUGGAAGC	156
54790_3_19	TET2	EXON	+	chr4:105190424-105190444	CAACGCUUGGAAGCAGGAGA	157
54790_3_21	TET2	EXON	+	chr4:105190425-105190445	AACGCUUGGAAGCAGGAGAU	158
54790_3_24	TET2	EXON	+	chr4:105190444-105190464	UGGGCUCAGCAGCAGCCAAU	159
54790_3_26	TET2	EXON	+	chr4:105190456-105190476	CAGCCAAUAGGACAUGAUCC	160
54790_3_30	TET2	EXON	+	chr4:105190469-105190489	AUGAUCCAGGAAGAGCAGUA	161
54790_3_32	TET2	EXON	+	chr4:105190470-105190490	UGAUCCAGGAAGAGCAGUAA	162
54790_3_34	TET2	EXON	+	chr4:105190483-105190503	GCAGUAAGGGACUGAGCUGC	163
54790_3_37	TET2	EXON	+	chr4:105190494-105190514	CUGAGCUGCUGGUAAGACAG	164
54790_3_46	TET2	EXON	-	chr4:105190385-105190405	GCAAGUAAACAAUCUUGAGA	165
54790_3_47	TET2	EXON	-	chr4:105190386-105190406	GGCAAGUAAACAAUCUUGAG	166
54790_3_52	TET2	EXON	-	chr4:105190407-105190427	UUGUAACUCAACAGGAGCAA	167
54790_3_55	TET2	EXON	-	chr4:105190415-105190435	UCCAAGCGUUGUAACUCAAC	168
54790_3_60	TET2	EXON	-	chr4:105190462-105190482	CUUCCUGGAUCAUGUCCUAU	169
54790_3_62	TET2	EXON	-	chr4:105190477-105190497	CAGUCCCUUACUGCUCUUCC	170
54790_4_7	TET2	EXON	+	chr4:105233887-105233907	GCUCUUUAGAAUUCAACUAG	171
54790_4_8	TET2	EXON	+	chr4:105233888-105233908	CUCUUUAGAAUUCAACUAGA	172

54790_4_12	TET2	EXON	+	chr4:105233899 -105233919	UCAACUAGAGGGCAGCCUUG	173
54790_4_14	TET2	EXON	+	chr4:105233903 -105233923	CUAGAGGGCAGCCUUGUGGA	174
54790_4_19	TET2	EXON	+	chr4:105233923 -105233943	UGGCCCCGAAGCAAGCCUGA	175
54790_4_21	TET2	EXON	+	chr4:105233929 -105233949	CGAAGCAAGCCUGAUGGAAC	176
54790_4_25	TET2	EXON	+	chr4:105233950 -105233970	GGAUAGAACCAACCAUGUUG	177
54790_4_26	TET2	EXON	+	chr4:105233951 -105233971	GAUAGAACCAACCAUGUUGA	178
54790_4_30	TET2	EXON	+	chr4:105234010 -105234030	CAUUUGCCAGACAGAACCUC	179
54790_4_37	TET2	EXON	+	chr4:105234029 -105234049	CUGGCUACAAAGCUCCAGAA	180
54790_4_44	TET2	EXON	+	chr4:105234068 -105234088	AGAGCUCAUCCAGAAGUAAA	181
54790_4_45	TET2	EXON	+	chr4:105234081 -105234101	AAGUAAAUGGAGACACCAAG	182
54790_4_47	TET2	EXON	+	chr4:105234104 -105234124	CACUCUUUCAAAAGUUAUUA	183
54790_4_54	TET2	EXON	+	chr4:105234121 -105234141	UUAUGGAAUACCCUGUAUGA	184
54790_4_57	TET2	EXON	+	chr4:105234122 -105234142	UAUGGAAUACCCUGUAUGAA	185
54790_4_66	TET2	EXON	+	chr4:105234170 -105234190	GACUUUACACAAGAAAGUAG	186
54790_4_67	TET2	EXON	+	chr4:105234171 -105234191	ACUUUACACAAGAAAGUAGA	187
54790_4_72	TET2	EXON	+	chr4:105234194 -105234214	UAUUCCAAGUGUUUGCAAAA	188
54790_4_74	TET2	EXON	+	chr4:105234197 -105234217	UCCAAGUGUUUGCAAAAUGG	189
54790_4_81	TET2	EXON	+	chr4:105234233 -105234253	GUUAGUGAACCUUCUCUCUC	190
54790_4_82	TET2	EXON	+	chr4:105234234 -105234254	UUAGUGAACCUUCUCUCUCU	191
54790_4_89	TET2	EXON	+	chr4:105234271 -105234291	GAAAUUGAAACAAGACCAAA	192
54790_4_93	TET2	EXON	+	chr4:105234278 -105234298	AAACAAGACCAAAAGGCUAA	193
54790_4_97	TET2	EXON	+	chr4:105234296 -105234316	AAUGGAGAAAGACGUAACUU	194

54790_4_99	TET2	EXON	+	chr4:105234297 -105234317	AUGGAGAAAGACGUAACUUC	195
54790_4_100	TET2	EXON	+	chr4:105234298 -105234318	UGGAGAAAGACGUAACUUCG	196
54790_4_106	TET2	EXON	+	chr4:105234320 -105234340	GUAAGCCAAGAAAGAAAUCC	197
54790_4_123	TET2	EXON	+	chr4:105234437 -105234457	UUUUCAACACAUAACUGCAG	198
54790_4_124	TET2	EXON	+	chr4:105234438 -105234458	UUUCAACACAUAACUGCAGU	199
54790_4_134	TET2	EXON	+	chr4:105234475 -105234495	GCUUCAGAUUCUGAAUGAGC	200
54790_4_138	TET2	EXON	+	chr4:105234478 -105234498	UCAGAUUCUGAAUGAGCAGG	201
54790_4_140	TET2	EXON	+	chr4:105234479 -105234499	CAGAUUCUGAAUGAGCAGGA	202
54790_4_141	TET2	EXON	+	chr4:105234480 -105234500	AGAUUCUGAAUGAGCAGGAG	203
54790_4_147	TET2	EXON	+	chr4:105234529 -105234549	CAUUGUAUUACUUAAAAACA	204
54790_4_151	TET2	EXON	+	chr4:105234548 -105234568	AAGGCAGUGCUAAUGCCUAA	205
54790_4_153	TET2	EXON	+	chr4:105234574 -105234594	UACAGUUUCUGCCUCUUCCG	206
54790_4_157	TET2	EXON	+	chr4:105234587 -105234607	UCUUCCGUGGAACACACACA	207
54790_4_161	TET2	EXON	+	chr4:105234598 -105234618	ACACACACAUGGUGAACUCC	208
54790_4_163	TET2	EXON	+	chr4:105234643 -105234663	UCCAGAUUGUGUUUCCAUUG	209
54790_4_171	TET2	EXON	+	chr4:105234685 -105234705	CAUAAAUGCCAUUAACAGUC	210
54790_4_177	TET2	EXON	+	chr4:105234734 -105234754	ACUCACCCAUCGCAUACCUC	211
54790_4_178	TET2	EXON	+	chr4:105234735 -105234755	CUCACCCAUCGCAUACCUCA	212
54790_4_181	TET2	EXON	+	chr4:105234793 -105234813	GCCUCCAAAGCCAGCUGCAG	213
54790_4_184	TET2	EXON	+	chr4:105234802 -105234822	GCCAGCUGCAGUGGUGAGUG	214
54790_4_200	TET2	EXON	+	chr4:105234943 -105234963	UCCUGCAGAAAAUAACAUCC	215
54790_4_201	TET2	EXON	+	chr4:105234944 -105234964	CCUGCAGAAAAUAACAUCCA	216

54790_4_203	TET2	EXON	+	chr4:105234965 -105234985	GGAACCACAAAGCUAGCGUC	217
54790_4_207	TET2	EXON	+	chr4:105234983 -105235003	UCUGGUGAAGAAUUCUGUUC	218
54790_4_211	TET2	EXON	+	chr4:105235010 -105235030	AGCAGCAAUUUGCAAGCUCC	219
54790_4_212	TET2	EXON	+	chr4:105235013 -105235033	AGCAAUUUGCAAGCUCCUGG	220
54790_4_216	TET2	EXON	+	chr4:105235026 -105235046	CUCCUGGUGGCAGCUCUGAA	221
54790_4_219	TET2	EXON	+	chr4:105235052 -105235072	UUAAAACAAAAUGAAAUGAA	222
54790_4_225	TET2	EXON	+	chr4:105235087 -105235107	GCAAAGCUCAGUGUUCACUA	223
54790_4_235	TET2	EXON	+	chr4:105235162 -105235182	UCCCCCUCCUCCUCUUCCAC	224
54790_4_240	TET2	EXON	+	chr4:105235184 -105235204	GUUCCUCAGCUUCCUUCAGA	225
54790_4_245	TET2	EXON	+	chr4:105235202 -105235222	GAAGGAAAAAGCACUCUGAA	226
54790_4_247	TET2	EXON	+	chr4:105235205 -105235225	GGAAAAAGCACUCUGAAUGG	227
54790_4_256	TET2	EXON	+	chr4:105235260 -105235280	AAAGUAACACAACACUUUUA	228
54790_4_258	TET2	EXON	+	chr4:105235261 -105235281	AAGUAACACAACACUUUUAA	229
54790_4_262	TET2	EXON	+	chr4:105235276 -105235296	UUUAAGGGAAGUGAAAAUAG	230
54790_4_263	TET2	EXON	+	chr4:105235277 -105235297	UUAAGGGAAGUGAAAAUAGA	231
54790_4_268	TET2	EXON	+	chr4:105235288 -105235308	GAAAAUAGAGGGUAAACCUG	232
54790_4_272	TET2	EXON	+	chr4:105235356 -105235376	CUUCUCCGAUGCUUUCUGAA	233
54790_4_280	TET2	EXON	+	chr4:105235380 -105235400	CUCAGAAUAAUUGUGUGAAC	234
54790_4_284	TET2	EXON	+	chr4:105235400 -105235420	AGGAAUGACAUACAGACUGC	235
54790_4_286	TET2	EXON	+	chr4:105235401 -105235421	GGAAUGACAUACAGACUGCA	236
54790_4_294	TET2	EXON	+	chr4:105235478 -105235498	AAGCAUAACCCACCAAUUUU	237
54790_4_297	TET2	EXON	+	chr4:105235487 -105235507	CCACCAAUUUUUGGUAGCAG	238

54790_4_302	TET2	EXON	+	chr4:105235498 -105235518	UGGUAGCAGUGGAGAGCUAC	239
54790_4_313	TET2	EXON	+	chr4:105235546 -105235566	CAAAGAGCAAGAGAUUCUGA	240
54790_4_314	TET2	EXON	+	chr4:105235547 -105235567	AAAGAGCAAGAGAUUCUGAA	241
54790_4_317	TET2	EXON	+	chr4:105235558 -105235578	GAUUCUGAAGGGUCGAGACA	242
54790_4_324	TET2	EXON	+	chr4:105235607 -105235627	ACACAGCACUAUCUGAAACC	243
54790_4_326	TET2	EXON	+	chr4:105235611 -105235631	AGCACUAUCUGAAACCAGGA	244
54790_4_329	TET2	EXON	+	chr4:105235624 -105235644	ACCAGGAUGGAUUGAAUUGA	245
54790_4_333	TET2	EXON	+	chr4:105235645 -105235665	GGCCCCUCGUUUUCACCAAG	246
54790_4_339	TET2	EXON	+	chr4:105235669 -105235689	AUCCCAUCUAAAACGUAAUG	247
54790_4_343	TET2	EXON	+	chr4:105235739 -105235759	AUGACCUCCAAACAAUACAC	248
54790_4_347	TET2	EXON	+	chr4:105235757 -105235777	ACUGGAAAUUCCAACAUGCC	249
54790_4_349	TET2	EXON	+	chr4:105235758 -105235778	CUGGAAAUUCCAACAUGCCU	250
54790_4_351	TET2	EXON	+	chr4:105235759 -105235779	UGGAAAUUCCAACAUGCCUG	251
54790_4_352	TET2	EXON	+	chr4:105235760 -105235780	GGAAAUUCCAACAUGCCUGG	252
54790_4_353	TET2	EXON	+	chr4:105235761 -105235781	GAAAUUCCAACAUGCCUGGG	253
54790_4_355	TET2	EXON	+	chr4:105235770 -105235790	ACAUGCCUGGGGGGCUCCCA	254
54790_4_360	TET2	EXON	+	chr4:105235801 -105235821	CACCCAGAAAACAACACAGC	255
54790_4_365	TET2	EXON	+	chr4:105235841 -105235861	UACCAAGUUGAAAUGAAUCA	256
54790_4_366	TET2	EXON	+	chr4:105235842 -105235862	ACCAAGUUGAAAUGAAUCAA	257
54790_4_368	TET2	EXON	+	chr4:105235853 -105235873	AUGAAUCAAGGGCAGUCCCA	258
54790_4_370	TET2	EXON	+	chr4:105235861 -105235881	AGGGCAGUCCCAAGGUACAG	259
54790_4_371	TET2	EXON	+	chr4:105235897 -105235917	GUUCCAAAAACCCUCACACC	260

54790_4_376	TET2	EXON	+	chr4:105235952 -105235972	GCUCAUGUGCAGUCACUGUG	261
54790_4_388	TET2	EXON	+	chr4:105236038 -105236058	GAAACAGCACUUGAAUCAAC	262
54790_4_399	TET2	EXON	+	chr4:105236098 -105236118	GCAACAUAAGCCUCAUAAAC	263
54790_4_407	TET2	EXON	+	chr4:105236182 -105236202	AUUACAAAUAAAGAAUAAAG	264
54790_4_416	TET2	EXON	+	chr4:105236237 -105236257	AACAAUGAUCAGCAAAGAGA	265
54790_4_417	TET2	EXON	+	chr4:105236249 -105236269	CAAAGAGAAGGAUCAUUCUU	266
54790_4_419	TET2	EXON	+	chr4:105236263 -105236283	AUUCUUUGGCCAGACUAAAG	267
54790_4_426	TET2	EXON	+	chr4:105236279 -105236299	AAAGUGGAAGAAUGUUUUCA	268
54790_4_435	TET2	EXON	+	chr4:105236332 -105236352	CGAGACUCAUAAUGUCCAAA	269
54790_4_438	TET2	EXON	+	chr4:105236333 -105236353	GAGACUCAUAAUGUCCAAAU	270
54790_4_440	TET2	EXON	+	chr4:105236338 -105236358	UCAUAAUGUCCAAAUGGGAC	271
54790_4_444	TET2	EXON	+	chr4:105236341 -105236361	UAAUGUCCAAAUGGGACUGG	272
54790_4_452	TET2	EXON	+	chr4:105236413 -105236433	AUCAAGUGCAUGCAAAAUAC	273
54790_4_466	TET2	EXON	+	chr4:105236486 -105236506	ACACAUCCUGAACUUUUUGC	274
54790_4_475	TET2	EXON	+	chr4:105236562 -105236582	CAAAGCAAGAUCUUCUUCAC	275
54790_4_479	TET2	EXON	+	chr4:105236578 -105236598	UCACAGGUGCUUUCAAGAAC	276
54790_4_486	TET2	EXON	+	chr4:105236611 -105236631	ACAACAAGCUUCAGUUCUAC	277
54790_4_488	TET2	EXON	+	chr4:105236612 -105236632	CAACAAGCUUCAGUUCUACA	278
54790_4_493	TET2	EXON	+	chr4:105236642 -105236662	AAUAGAAACCAAGAUAUGUC	279
54790_4_494	TET2	EXON	+	chr4:105236673 -105236693	CUGCGCAACUUGCUCAGCAA	280
54790_4_498	TET2	EXON	+	chr4:105236719 -105236739	UGUUUUUCCUGUGCCUGACC	281
54790_4_501	TET2	EXON	+	chr4:105236720 -105236740	GUUUUUCCUGUGCCUGACCA	282

54790_4_503	TET2	EXON	+	chr4:105236723-105236743	UUUCCUGUGCCUGACCAGGG	283
54790_4_511	TET2	EXON	+	chr4:105236752-105236772	CACUCAGACCCCUCCCCAGA	284
54790_4_512	TET2	EXON	+	chr4:105236778-105236798	CUCAAAAGCAUGCUGCUCUA	285
54790_4_513	TET2	EXON	+	chr4:105236781-105236801	AAAAGCAUGCUGCUCUAAGG	286
54790_4_518	TET2	EXON	+	chr4:105236856-105236876	CUUGCCAUAGUCAGAUGCAC	287
54790_4_520	TET2	EXON	+	chr4:105236866-105236886	UCAGAUGCACAGGCCAAUUA	288
54790_4_522	TET2	EXON	+	chr4:105236869-105236889	GAUGCACAGGCCAAUUAAGG	289
54790_4_525	TET2	EXON	+	chr4:105236876-105236896	AGGCCAAUUAAGGUGGAACC	290
54790_4_531	TET2	EXON	+	chr4:105236928-105236948	CACCACCAGAAAACAAAACA	291
54790_4_532	TET2	EXON	+	chr4:105236935-105236955	AGAAAACAAAACAUGGAAAA	292
54790_4_540	TET2	EXON	+	chr4:105237004-105237024	AAAGAGCAUCAUUGAGACCA	293
54790_4_545	TET2	EXON	+	chr4:105237052-105237072	CAAGUCGUUAUUUGACCAUA	294
54790_4_553	TET2	EXON	+	chr4:105237098-105237118	CAAGUAAAAGUUGAAAUGUC	295
54790_4_554	TET2	EXON	+	chr4:105237099-105237119	AAGUAAAAGUUGAAAUGUCA	296
54790_4_578	TET2	EXON	+	chr4:105237280-105237300	UACUCCUAUAAAAAAUUUAU	297
54790_4_582	TET2	EXON	+	chr4:105237329-105237349	UUCCCAUCUUGCAGAUGUGU	298
54790_4_589	TET2	EXON	+	chr4:105237359-105237379	CAGAAAUGUACUGAGACACA	299
54790_4_596	TET2	EXON	+	chr4:105237397-105237417	AGCAAAUUUAUCUUCAGAUA	300
54790_4_597	TET2	EXON	+	chr4:105237398-105237418	GCAAAUUUAUCUUCAGAUAU	301
54790_4_606	TET2	EXON	+	chr4:105237430-105237450	CUUUUUUUAAAUCUUGAGUC	302
54790_4_614	TET2	EXON	+	chr4:105237446-105237466	AGUCUGGCAGCAAUUUGUAA	303
54790_4_657	TET2	EXON	+	chr4:105237650-105237670	GCUCUUUGUAUAUUAUCUCC	304

54790_4_662	TET2	EXON	+	chr4:105237663 -105237683	UAUCUCCUGGAGAGACAGCU	305
54790_4_668	TET2	EXON	+	chr4:105237708 -105237728	AAUGAGAAAAUAACGACCAU	306
54790_4_670	TET2	EXON	+	chr4:105237748 -105237768	UUUAAAUAUUUUUUAAUUCA	307
54790_4_679	TET2	EXON	+	chr4:105237778 -105237798	UAUUAGUUUCACAAGAUUUC	308
54790_4_682	TET2	EXON	+	chr4:105237786 -105237806	UCACAAGAUUUCUGGCUAAU	309
54790_4_686	TET2	EXON	+	chr4:105237787 -105237807	CACAAGAUUUCUGGCUAAUA	310
54790_4_693	TET2	EXON	+	chr4:105237817 -105237837	UAUCUUCAGUCUUCAUGAGU	311
54790_4_695	TET2	EXON	+	chr4:105237818 -105237838	AUCUUCAGUCUUCAUGAGUU	312
54790_4_697	TET2	EXON	+	chr4:105237819 -105237839	UCUUCAGUCUUCAUGAGUUG	313
54790_4_700	TET2	EXON	+	chr4:105237820 -105237840	CUUCAGUCUUCAUGAGUUGG	314
54790_4_709	TET2	EXON	+	chr4:105237882 -105237902	CUUUUCUCCAUUUAUACAUU	315
54790_4_741	TET2	EXON	+	chr4:105240332 -105240352	AAAGCUUUUUGUUAAAAUUC	316
54790_4_746	TET2	EXON	+	chr4:105240344 -105240364	UAAAAUUCAGGAUAUGUAAU	317
54790_4_750	TET2	EXON	+	chr4:105240352 -105240372	AGGAUAUGUAAUAGGUCUGU	318
54790_4_754	TET2	EXON	+	chr4:105240377 -105240397	UAGUGAAAUAUUUUUGCUGA	319
54790_4_760	TET2	EXON	+	chr4:105240395 -105240415	GAUGGAUGUAGAUAUAUACG	320
54790_4_770	TET2	EXON	+	chr4:105240478 -105240498	AGACAAAUGUUAAAUUAGUG	321
54790_4_780	TET2	EXON	+	chr4:105240541 -105240561	GAUACCCCACACUGUGUAGA	322
54790_4_783	TET2	EXON	+	chr4:105240545 -105240565	CCCCACACUGUGUAGAAGGA	323
54790_4_785	TET2	EXON	+	chr4:105240548 -105240568	CACACUGUGUAGAAGGAUGG	324
54790_4_787	TET2	EXON	+	chr4:105240549 -105240569	ACACUGUGUAGAAGGAUGGA	325
54790_4_790	TET2	EXON	+	chr4:105240552 -105240572	CUGUGUAGAAGGAUGGAGGG	326

54790_4_791	TET2	EXON	+	chr4:105240579 -105240599	CUACUGUCCCUCUUUGCGUG	327
54790_4_795	TET2	EXON	+	chr4:105240599 -105240619	UGGUUAUUAAGUUGCCUCAC	328
54790_4_796	TET2	EXON	+	chr4:105240600 -105240620	GGUUAUUAAGUUGCCUCACU	329
54790_4_800	TET2	EXON	+	chr4:105240634 -105240654	CACAUCUCAUAGAUAAUAUU	330
54790_4_807	TET2	EXON	+	chr4:105240703 -105240723	UCCCACUUUUCCAUCUUUGU	331
54790_4_818	TET2	EXON	+	chr4:105240740 -105240760	UUCUUUUUGCCUGACUCUCC	332
54790_4_829	TET2	EXON	+	chr4:105240784 -105240804	UUCUAAAGUACAUACUAAUA	333
54790_4_830	TET2	EXON	+	chr4:105240785 -105240805	UCUAAAGUACAUACUAAUAU	334
54790_4_833	TET2	EXON	+	chr4:105240790 -105240810	AGUACAUACUAAUAUGGGUC	335
54790_4_841	TET2	EXON	+	chr4:105240833 -105240853	AAACAGCAAUUAAAUGUUAU	336
54790_4_842	TET2	EXON	+	chr4:105240834 -105240854	AACAGCAAUUAAAUGUUAUA	337
54790_4_845	TET2	EXON	+	chr4:105240841 -105240861	AUUAAAUGUUAUAGGGAAGU	338
54790_4_851	TET2	EXON	+	chr4:105240851 -105240871	AUAGGGAAGUAGGAAGAAAA	339
54790_4_853	TET2	EXON	+	chr4:105240852 -105240872	UAGGGAAGUAGGAAGAAAAA	340
54790_4_855	TET2	EXON	+	chr4:105240853 -105240873	AGGGAAGUAGGAAGAAAAAG	341
54790_4_858	TET2	EXON	+	chr4:105240885 -105240905	CAAUAAACCAAGCAAUAUUC	342
54790_4_861	TET2	EXON	+	chr4:105240886 -105240906	AAUAAACCAAGCAAUAUUCU	343
54790_4_862	TET2	EXON	+	chr4:105240887 -105240907	AUAAACCAAGCAAUAUUCUG	344
54790_4_863	TET2	EXON	+	chr4:105240888 -105240908	UAAACCAAGCAAUAUUCUGG	345
54790_4_865	TET2	EXON	+	chr4:105240891 -105240911	ACCAAGCAAUAUUCUGGGGG	346
54790_4_867	TET2	EXON	+	chr4:105240892 -105240912	CCAAGCAAUAUUCUGGGGGU	347
54790_4_870	TET2	EXON	+	chr4:105240902 -105240922	UUCUGGGGGUGGGAUAGAGC	348

54790_4_880	TET2	EXON	+	chr4:105240940 -105240960	UCUUUUAAAAUCCAAGUAAU	349
54790_4_881	TET2	EXON	+	chr4:105240944 -105240964	UUAAAAUCCAAGUAAUAGGU	350
54790_4_891	TET2	EXON	+	chr4:105240991 -105241011	UUUUUUCCAGCUCAAAAAAU	351
54790_4_905	TET2	EXON	+	chr4:105241063 -105241083	UUUGUUUAGUUUCAUUUAUU	352
54790_4_929	TET2	EXON	+	chr4:105241146 -105241166	UGUACAUAUACUUAAUUAUG	353
54790_4_945	TET2	EXON	+	chr4:105241237 -105241257	UAGAGCCCUUAAUGUGUAGU	354
54790_4_949	TET2	EXON	+	chr4:105241238 -105241258	AGAGCCCUUAAUGUGUAGUU	355
54790_4_951	TET2	EXON	+	chr4:105241239 -105241259	GAGCCCUUAAUGUGUAGUUG	356
54790_4_953	TET2	EXON	+	chr4:105241240 -105241260	AGCCCUUAAUGUGUAGUUGG	357
54790_4_956	TET2	EXON	+	chr4:105241253 -105241273	UAGUUGGGGGUUAAGCUUUG	358
54790_4_962	TET2	EXON	+	chr4:105241283 -105241303	CUUUAUAUUUAGUAUAAUUG	359
54790_4_973	TET2	EXON	+	chr4:105241340 -105241360	CAAAUUAUUGAAAAAGAUGA	360
54790_4_977	TET2	EXON	+	chr4:105241361 -105241381	GGUCCUUUUUAUACCCAUCU	361
54790_4_979	TET2	EXON	+	chr4:105241367 -105241387	UUUUAUACCCAUCUAGGAGC	362
54790_4_984	TET2	EXON	+	chr4:105241378 -105241398	UCUAGGAGCAGGUCCUAAUG	363
54790_4_990	TET2	EXON	+	chr4:105241399 -105241419	GGCAGCUAUUAGAGAAAUCA	364
54790_4_993	TET2	EXON	+	chr4:105241407 -105241427	UUAGAGAAAUCAUGGAAGAA	365
54790_4_995	TET2	EXON	+	chr4:105241422 -105241442	AAGAAAGGUAAUUAACGCAA	366
54790_4_997	TET2	EXON	+	chr4:105241428 -105241448	GGUAAUUAACGCAAAGGCAC	367
54790_4_998	TET2	EXON	+	chr4:105241429 -105241449	GUAAUUAACGCAAAGGCACA	368
54790_4_1014	TET2	EXON	+	chr4:105241523 -105241543	UAAAUUGAGUAAUUAUUAGU	369
54790_4_1019	TET2	EXON	+	chr4:105241538 -105241558	UUAGUAGGCUUAGCUAUUCU	370

54790_4_1020	TET2	EXON	+	chr4:105241539 -105241559	UAGUAGGCUUAGCUAUUCUA	371
54790_4_1029	TET2	EXON	+	chr4:105241592 -105241612	AGAGAGUCACAAUAUUUGAC	372
54790_4_1032	TET2	EXON	+	chr4:105241612 -105241632	AGGACUAAUAGUCUGCUAGC	373
54790_4_1033	TET2	EXON	+	chr4:105241618 -105241638	AAUAGUCUGCUAGCUGGCAC	374
54790_4_1035	TET2	EXON	+	chr4:105241636 -105241656	ACAGGCUGCCCACUUUGCGA	375
54790_4_1040	TET2	EXON	+	chr4:105241653 -105241673	CGAUGGAUGCCAGAAAACCC	376
54790_4_1043	TET2	EXON	+	chr4:105241663 -105241683	CAGAAAACCCAGGCAUGAAC	377
54790_4_1045	TET2	EXON	+	chr4:105241669 -105241689	ACCCAGGCAUGAACAGGAAU	378
54790_4_1046	TET2	EXON	+	chr4:105241678 -105241698	UGAACAGGAAUCGGCCAGCC	379
54790_4_1047	TET2	EXON	+	chr4:105241693 -105241713	CAGCCAGGCUGCCAGCCACA	380
54790_4_1048	TET2	EXON	+	chr4:105241699 -105241719	GGCUGCCAGCCACAAGGUAC	381
54790_4_1049	TET2	EXON	+	chr4:105241705 -105241725	CAGCCACAAGGUACUGGCAC	382
54790_4_1052	TET2	EXON	+	chr4:105241718 -105241738	CUGGCACAGGCUCCAACGAG	383
54790_4_1053	TET2	EXON	+	chr4:105241729 -105241749	UCCAACGAGAGGUCCCACUC	384
54790_4_1058	TET2	EXON	+	chr4:105241770 -105241790	AAGUGUCAAAGCAGAAAGAC	385
54790_4_1059	TET2	EXON	+	chr4:105241780 -105241800	GCAGAAAGACUGGUAAAGUG	386
54790_4_1092	TET2	EXON	+	chr4:105241946 -105241966	UUUUUUUCGCUAUCAAUCAC	387
54790_4_1109	TET2	EXON	+	chr4:105242012 -105242032	UGAGCGAGAUAAUGCAGAGA	388
54790_4_1117	TET2	EXON	+	chr4:105242057 -105242077	CUCUGAGCUGUUCUUCUUCU	389
54790_4_1118	TET2	EXON	+	chr4:105242058 -105242078	UCUGAGCUGUUCUUCUUCUA	390
54790_4_1123	TET2	EXON	+	chr4:105242076 -105242096	UAGGGUGCCUUUUCAUUAAG	391
54790_4_1124	TET2	EXON	+	chr4:105242080 -105242100	GUGCCUUUUCAUUAAGAGGU	392

54790_4_1130	TET2	EXON	+	chr4:105242105 -105242125	GUAUUAUUAUUAAAGUACUU	393
54790_4_1135	TET2	EXON	+	chr4:105242114 -105242134	UUAAAGUACUUAGGAUACAU	394
54790_4_1136	TET2	EXON	+	chr4:105242115 -105242135	UAAAGUACUUAGGAUACAUU	395
54790_4_1137	TET2	EXON	+	chr4:105242116 -105242136	AAAGUACUUAGGAUACAUUG	396
54790_4_1140	TET2	EXON	+	chr4:105242124 -105242144	UAGGAUACAUUGGGGCAGCU	397
54790_4_1154	TET2	EXON	+	chr4:105242210 -105242230	UUCACUAAAUAAUCAUCUAG	398
54790_4_1156	TET2	EXON	+	chr4:105242215 -105242235	UAAAUAAUCAUCUAGUGGCC	399
54790_4_1162	TET2	EXON	+	chr4:105242287 -105242307	UUGUUUUUUAAACAAGCAGU	400
54790_4_1163	TET2	EXON	+	chr4:105242290 -105242310	UUUUUUAAACAAGCAGUAGG	401
54790_4_1164	TET2	EXON	+	chr4:105242298 -105242318	ACAAGCAGUAGGUGGUGCUU	402
54790_4_1167	TET2	EXON	+	chr4:105242306 -105242326	UAGGUGGUGCUUUGGUCAUA	403
54790_4_1169	TET2	EXON	+	chr4:105242307 -105242327	AGGUGGUGCUUUGGUCAUAA	404
54790_4_1173	TET2	EXON	+	chr4:105242328 -105242348	GGAAGAUAUAGUCUAUUUCU	405
54790_4_1176	TET2	EXON	+	chr4:105242351 -105242371	ACUAUUCCAUAUUUUCCAUG	406
54790_4_1178	TET2	EXON	+	chr4:105242355 -105242375	UUCCAUAUUUUCCAUGUGGC	407
54790_4_1187	TET2	EXON	+	chr4:105242404 -105242424	UCUAAAUUGUGAGACAUUCU	408
54790_4_1193	TET2	EXON	+	chr4:105242407 -105242427	AAAUUGUGAGACAUUCUUGG	409
54790_4_1201	TET2	EXON	+	chr4:105242469 -105242489	UAAAAUAGCUAAAUUUAGUA	410
54790_4_1205	TET2	EXON	+	chr4:105242470 -105242490	AAAAUAGCUAAAUUUAGUAA	411
54790_4_1241	TET2	EXON	+	chr4:105242625 -105242645	AUCUGUACAUUUUGAUAUUG	412
54790_4_1244	TET2	EXON	+	chr4:105242635 -105242655	UUUGAUAUUGAGGAAAAACA	413
54790_4_1250	TET2	EXON	+	chr4:105242663 -105242683	AAACCAUUAUCCAGUUUGCU	414

54790_4_1258	TET2	EXON	+	chr4:105242705-105242725	UAAUAAACCGUUCAUUUCUC	415
54790_4_1259	TET2	EXON	+	chr4:105242711-105242731	ACCGUUCAUUUCUCAGGAUG	416
54790_4_1269	TET2	EXON	-	chr4:105233886-105233906	UAGUUGAAUUCUAAAGAGCA	417
54790_4_1276	TET2	EXON	-	chr4:105233917-105233937	UUGCUUCGGGGCCAUCCACA	418
54790_4_1278	TET2	EXON	-	chr4:105233929-105233949	GUUCCAUCAGGCUUGCUUCG	419
54790_4_1279	TET2	EXON	-	chr4:105233930-105233950	UGUUCCAUCAGGCUUGCUUC	420
54790_4_1281	TET2	EXON	-	chr4:105233931-105233951	CUGUUCCAUCAGGCUUGCUU	421
54790_4_1285	TET2	EXON	-	chr4:105233941-105233961	UGGUUCUAUCCUGUUCCAUC	422
54790_4_1288	TET2	EXON	-	chr4:105233961-105233981	UCUGUUGCCCUCAACAUGGU	423
54790_4_1289	TET2	EXON	-	chr4:105233965-105233985	UUAGUCUGUUGCCCUCAACA	424
54790_4_1290	TET2	EXON	-	chr4:105233990-105234010	GGAGGUGAUGGUAUCAGGAA	425
54790_4_1293	TET2	EXON	-	chr4:105233995-105234015	AAAUGGGAGGUGAUGGUAUC	426
54790_4_1296	TET2	EXON	-	chr4:105234002-105234022	GUCUGGCAAAUGGGAGGUGA	427
54790_4_1297	TET2	EXON	-	chr4:105234008-105234028	GGUUCUGUCUGGCAAAUGGG	428
54790_4_1298	TET2	EXON	-	chr4:105234011-105234031	AGAGGUUCUGUCUGGCAAAU	429
54790_4_1300	TET2	EXON	-	chr4:105234012-105234032	CAGAGGUUCUGUCUGGCAAA	430
54790_4_1305	TET2	EXON	-	chr4:105234019-105234039	UUGUAGCCAGAGGUUCUGUC	431
54790_4_1308	TET2	EXON	-	chr4:105234029-105234049	UUCUGGAGCUUUGUAGCCAG	432
54790_4_1310	TET2	EXON	-	chr4:105234046-105234066	CAGGCAGUGGGCUUCCAUUC	433
54790_4_1314	TET2	EXON	-	chr4:105234058-105234078	GAUGAGCUCUCUCAGGCAGU	434
54790_4_1315	TET2	EXON	-	chr4:105234059-105234079	GGAUGAGCUCUCUCAGGCAG	435
54790_4_1319	TET2	EXON	-	chr4:105234065-105234085	ACUUCUGGAUGAGCUCUCUC	436

54790_4_1322	TET2	EXON	-	chr4:105234080 -105234100	UUGGUGUCUCCAUUUACUUC	437
54790_4_1327	TET2	EXON	-	chr4:105234099 -105234119	ACUUUUGAAAGAGUGCCACU	438
54790_4_1334	TET2	EXON	-	chr4:105234134 -105234154	UUCUGGCUUCCCUUCAUACA	439
54790_4_1335	TET2	EXON	-	chr4:105234135 -105234155	AUUCUGGCUUCCCUUCAUAC	440
54790_4_1337	TET2	EXON	-	chr4:105234151 -105234171	CAGGACUCACACGACUAUUC	441
54790_4_1341	TET2	EXON	-	chr4:105234170 -105234190	CUACUUUCUUGUGUAAAGUC	442
54790_4_1351	TET2	EXON	-	chr4:105234201 -105234221	UCCUCCAUUUUGCAAACACU	443
54790_4_1355	TET2	EXON	-	chr4:105234245 -105234265	UGAAGGAGCCCAGAGAGAGA	444
54790_4_1367	TET2	EXON	-	chr4:105234262 -105234282	GUUUCAAUUUCUUGAUCUGA	445
54790_4_1378	TET2	EXON	-	chr4:105234289 -105234309	GUCUUUCUCCAUUAGCCUUU	446
54790_4_1388	TET2	EXON	-	chr4:105234328 -105234348	UUUCACCUGGAUUUCUUUCU	447
54790_4_1392	TET2	EXON	-	chr4:105234341 -105234361	UUUGGUUGACUGCUUUCACC	448
54790_4_1396	TET2	EXON	-	chr4:105234359 -105234379	UCACUCAAAUCGGAGACAUU	449
54790_4_1399	TET2	EXON	-	chr4:105234369 -105234389	UUCUUUCUUAUCACUCAAAU	450
54790_4_1410	TET2	EXON	-	chr4:105234408 -105234428	AUCUUUAACUGCAUUUUCUU	451
54790_4_1411	TET2	EXON	-	chr4:105234409 -105234429	AAUCUUUAACUGCAUUUUCU	452
54790_4_1416	TET2	EXON	-	chr4:105234435 -105234455	GCAGUUAUGUGUUGAAAAAC	453
54790_4_1422	TET2	EXON	-	chr4:105234464 -105234484	AUCUGAAGCUCUGGAUUUUC	454
54790_4_1423	TET2	EXON	-	chr4:105234473 -105234493	UCAUUCAGAAUCUGAAGCUC	455
54790_4_1435	TET2	EXON	-	chr4:105234520 -105234540	GUAAUACAAUGUUCUUGUCA	456
54790_4_1441	TET2	EXON	-	chr4:105234566 -105234586	GCAGAAACUGUAGCACCAUU	457
54790_4_1444	TET2	EXON	-	chr4:105234588 -105234608	AUGUGUGUGUUCCACGGAAG	458

54790_4_1448	TET2	EXON	-	chr4:105234594-105234614	UUCACCAUGUGUGUGUUCCA	459
54790_4_1457	TET2	EXON	-	chr4:105234619-105234639	AUUGAGACAGUGUUUUUUCC	460
54790_4_1461	TET2	EXON	-	chr4:105234647-105234667	ACCGCAAUGGAAACACAAUC	461
54790_4_1466	TET2	EXON	-	chr4:105234660-105234680	UGUGGUUUUCUGCACCGCAA	462
54790_4_1471	TET2	EXON	-	chr4:105234678-105234698	AAUGGCAUUUAUGUGAGAUG	463
54790_4_1474	TET2	EXON	-	chr4:105234696-105234716	AUUAGUAGCCUGACUGUUAA	464
54790_4_1475	TET2	EXON	-	chr4:105234726-105234746	CGAUGGGUGAGUGAUCUCAC	465
54790_4_1479	TET2	EXON	-	chr4:105234742-105234762	UCUGCCCUGAGGUAUGCGAU	466
54790_4_1480	TET2	EXON	-	chr4:105234743-105234763	AUCUGCCCUGAGGUAUGCGA	467
54790_4_1482	TET2	EXON	-	chr4:105234753-105234773	UGCGGAAUUGAUCUGCCCUG	468
54790_4_1485	TET2	EXON	-	chr4:105234771-105234791	CUCAGAGUUAGAGGUCUGUG	469
54790_4_1490	TET2	EXON	-	chr4:105234780-105234800	UGGAGGCAGCUCAGAGUUAG	470
54790_4_1493	TET2	EXON	-	chr4:105234797-105234817	ACCACUGCAGCUGGCUUUGG	471
54790_4_1495	TET2	EXON	-	chr4:105234800-105234820	CUCACCACUGCAGCUGGCUU	472
54790_4_1497	TET2	EXON	-	chr4:105234806-105234826	GCCUCACUCACCACUGCAGC	473
54790_4_1499	TET2	EXON	-	chr4:105234828-105234848	AUCAGCAUCAUCAGCAUCAC	474
54790_4_1505	TET2	EXON	-	chr4:105234855-105234875	UAGCAUUGCAGCUAGUUUAC	475
54790_4_1510	TET2	EXON	-	chr4:105234882-105234902	UUCUGGUUUCUGAAAGGAAC	476
54790_4_1514	TET2	EXON	-	chr4:105234888-105234908	UAGUUGUUCUGGUUUCUGAA	477
54790_4_1521	TET2	EXON	-	chr4:105234899-105234919	UUUUGUUGUUGUAGUUGUUC	478
54790_4_1526	TET2	EXON	-	chr4:105234940-105234960	UGUUAUUUUCUGCAGGAGAU	479
54790_4_1527	TET2	EXON	-	chr4:105234941-105234961	AUGUUAUUUUCUGCAGGAGA	480

54790_4_1531	TET2	EXON	-	chr4:105234947-105234967	CCCUGGAUGUUAUUUUCUGC	481
54790_4_1535	TET2	EXON	-	chr4:105234964-105234984	ACGCUAGCUUUGUGGUUCCC	482
54790_4_1539	TET2	EXON	-	chr4:105234972-105234992	UUCACCAGACGCUAGCUUUG	483
54790_4_1545	TET2	EXON	-	chr4:105235011-105235031	AGGAGCUUGCAAAUUGCUGC	484
54790_4_1551	TET2	EXON	-	chr4:105235031-105235051	UACCGUUCAGAGCUGCCACC	485
54790_4_1569	TET2	EXON	-	chr4:105235116-105235136	ACCACACCAUCACCCAGAAA	486
54790_4_1577	TET2	EXON	-	chr4:105235166-105235186	ACCUGUGGAAGAGGAGGAGG	487
54790_4_1579	TET2	EXON	-	chr4:105235167-105235187	AACCUGUGGAAGAGGAGGAG	488
54790_4_1581	TET2	EXON	-	chr4:105235168-105235188	GAACCUGUGGAAGAGGAGGA	489
54790_4_1582	TET2	EXON	-	chr4:105235169-105235189	GGAACCUGUGGAAGAGGAGG	490
54790_4_1586	TET2	EXON	-	chr4:105235172-105235192	UGAGGAACCUGUGGAAGAGG	491
54790_4_1588	TET2	EXON	-	chr4:105235175-105235195	AGCUGAGGAACCUGUGGAAG	492
54790_4_1593	TET2	EXON	-	chr4:105235181-105235201	GAAGGAAGCUGAGGAACCUG	493
54790_4_1600	TET2	EXON	-	chr4:105235190-105235210	UUUCCUUCUGAAGGAAGCUG	494
54790_4_1606	TET2	EXON	-	chr4:105235199-105235219	AGAGUGCUUUUUCCUUCUGA	495
54790_4_1617	TET2	EXON	-	chr4:105235246-105235266	UACUUUGGUUGGGGUAGUGG	496
54790_4_1618	TET2	EXON	-	chr4:105235249-105235269	UGUUACUUUGGUUGGGGUAG	497
54790_4_1620	TET2	EXON	-	chr4:105235255-105235275	GUGUUGUGUUACUUUGGUUG	498
54790_4_1621	TET2	EXON	-	chr4:105235256-105235276	AGUGUUGUGUUACUUUGGUU	499
54790_4_1623	TET2	EXON	-	chr4:105235257-105235277	AAGUGUUGUGUUACUUUGGU	500
54790_4_1626	TET2	EXON	-	chr4:105235261-105235281	UUAAAAGUGUUGUGUUACUU	501
54790_4_1633	TET2	EXON	-	chr4:105235307-105235327	CUCUGGGAAGGUGGUGCCUC	502

54790_4_1634	TET2	EXON	-	chr4:105235316-105235336	GGAUUAGGACUCUGGGAAGG	503
54790_4_1635	TET2	EXON	-	chr4:105235319-105235339	GAUGGAUUAGGACUCUGGGA	504
54790_4_1636	TET2	EXON	-	chr4:105235323-105235343	UGUAGAUGGAUUAGGACUCU	505
54790_4_1638	TET2	EXON	-	chr4:105235324-105235344	GUGUAGAUGGAUUAGGACUC	506
54790_4_1641	TET2	EXON	-	chr4:105235331-105235351	CAUACAUGUGUAGAUGGAUU	507
54790_4_1643	TET2	EXON	-	chr4:105235337-105235357	GGGCUGCAUACAUGUGUAGA	508
54790_4_1647	TET2	EXON	-	chr4:105235357-105235377	UUUCAGAAAGCAUCGGAGAA	509
54790_4_1648	TET2	EXON	-	chr4:105235358-105235378	CUUUCAGAAAGCAUCGGAGA	510
54790_4_1653	TET2	EXON	-	chr4:105235364-105235384	UGAGGCCUUUCAGAAAGCAU	511
54790_4_1660	TET2	EXON	-	chr4:105235382-105235402	CUGUUCACACAAUUAUUCUG	512
54790_4_1668	TET2	EXON	-	chr4:105235439-105235459	CUUGUUUUCUCAGAACACAA	513
54790_4_1676	TET2	EXON	-	chr4:105235463-105235483	UGCUUGAGGUGUUCUGACAU	514
54790_4_1678	TET2	EXON	-	chr4:105235477-105235497	AAAUUGGUGGGUUAUGCUUG	515
54790_4_1680	TET2	EXON	-	chr4:105235489-105235509	CACUGCUACCAAAAAUUGGU	516
54790_4_1681	TET2	EXON	-	chr4:105235490-105235510	CCACUGCUACCAAAAAUUGG	517
54790_4_1683	TET2	EXON	-	chr4:105235493-105235513	UCUCCACUGCUACCAAAAAU	518
54790_4_1690	TET2	EXON	-	chr4:105235531-105235551	CUUUGUUUCUCAUCAACUGC	519
54790_4_1699	TET2	EXON	-	chr4:105235604-105235624	UUCAGAUAGUGCUGUGUUGG	520
54790_4_1700	TET2	EXON	-	chr4:105235605-105235625	UUUCAGAUAGUGCUGUGUUG	521
54790_4_1702	TET2	EXON	-	chr4:105235606-105235626	GUUUCAGAUAGUGCUGUGUU	522
54790_4_1703	TET2	EXON	-	chr4:105235607-105235627	GGUUUCAGAUAGUGCUGUGU	523
54790_4_1708	TET2	EXON	-	chr4:105235628-105235648	GCCUUCAAUUCAAUCCAUCC	524

54790_4_1711	TET2	EXON	-	chr4:105235650 -105235670	UUCCGCUUGGUGAAAACGAG	525
54790_4_1712	TET2	EXON	-	chr4:105235651 -105235671	AUUCCGCUUGGUGAAAACGA	526
54790_4_1713	TET2	EXON	-	chr4:105235652 -105235672	GAUUCCGCUUGGUGAAAACG	527
54790_4_1722	TET2	EXON	-	chr4:105235663 -105235683	GUUUUAGAUGGGAUUCCGCU	528
54790_4_1723	TET2	EXON	-	chr4:105235674 -105235694	UGCCUCAUUACGUUUUAGAU	529
54790_4_1724	TET2	EXON	-	chr4:105235675 -105235695	AUGCCUCAUUACGUUUUAGA	530
54790_4_1730	TET2	EXON	-	chr4:105235703 -105235723	GGUUGAUACUGAAGAAUUGA	531
54790_4_1737	TET2	EXON	-	chr4:105235724 -105235744	GUCAUUUGAUUGGAGAGAUU	532
54790_4_1738	TET2	EXON	-	chr4:105235725 -105235745	GGUCAUUUGAUUGGAGAGAU	533
54790_4_1743	TET2	EXON	-	chr4:105235734 -105235754	UUGUUUGGAGGUCAUUUGAU	534
54790_4_1749	TET2	EXON	-	chr4:105235746 -105235766	AUUUCCAGUGUAUUGUUUGG	535
54790_4_1751	TET2	EXON	-	chr4:105235749 -105235769	GGAAUUUCCAGUGUAUUGUU	536
54790_4_1756	TET2	EXON	-	chr4:105235770 -105235790	UGGGAGCCCCCCAGGCAUGU	537
54790_4_1758	TET2	EXON	-	chr4:105235778 -105235798	GCUUGCCUUGGGAGCCCCCC	538
54790_4_1763	TET2	EXON	-	chr4:105235789 -105235809	UCUGGGUGUAAGCUUGCCUU	539
54790_4_1766	TET2	EXON	-	chr4:105235790 -105235810	UUCUGGGUGUAAGCUUGCCU	540
54790_4_1769	TET2	EXON	-	chr4:105235806 -105235826	CUCCAGCUGUGUUGUUUUCU	541
54790_4_1770	TET2	EXON	-	chr4:105235807 -105235827	GCUCCAGCUGUGUUGUUUUC	542
54790_4_1779	TET2	EXON	-	chr4:105235846 -105235866	GCCCUUGAUUCAUUUCAACU	543
54790_4_1782	TET2	EXON	-	chr4:105235872 -105235892	AUGUUGGUCCACUGUACCUU	544
54790_4_1783	TET2	EXON	-	chr4:105235873 -105235893	GAUGUUGGUCCACUGUACCU	545
54790_4_1790	TET2	EXON	-	chr4:105235888 -105235908	GUUUUUGGAACUGGAGAUGU	546

54790_4_1791	TET2	EXON	-	chr4:105235897-105235917	GGUGUGAGGGUUUUUGGAAC	547
54790_4_1795	TET2	EXON	-	chr4:105235903-105235923	GCACCUGGUGUGAGGGUUUU	548
54790_4_1800	TET2	EXON	-	chr4:105235910-105235930	GAGAAGUGCACCUGGUGUGA	549
54790_4_1801	TET2	EXON	-	chr4:105235911-105235931	GGAGAAGUGCACCUGGUGUG	550
54790_4_1804	TET2	EXON	-	chr4:105235918-105235938	CUGUUUUGGAGAAGUGCACC	551
54790_4_1811	TET2	EXON	-	chr4:105235932-105235952	UUUUGGUAAAUGGUCUGUUU	552
54790_4_1813	TET2	EXON	-	chr4:105235942-105235962	GCACAUGAGCUUUUGGUAAA	553
54790_4_1814	TET2	EXON	-	chr4:105235949-105235969	AGUGACUGCACAUGAGCUUU	554
54790_4_1828	TET2	EXON	-	chr4:105236010-105236030	GGACAUAAGUUUUUCAGUUU	555
54790_4_1829	TET2	EXON	-	chr4:105236011-105236031	GGGACAUAAGUUUUUCAGUU	556
54790_4_1836	TET2	EXON	-	chr4:105236031-105236051	CAAGUGCUGUUUCAACACUG	557
54790_4_1838	TET2	EXON	-	chr4:105236032-105236052	UCAAGUGCUGUUUCAACACU	558
54790_4_1839	TET2	EXON	-	chr4:105236033-105236053	UUCAAGUGCUGUUUCAACAC	559
54790_4_1846	TET2	EXON	-	chr4:105236078-105236098	AAAAGGUGUGAGUUUGAAAA	560
54790_4_1852	TET2	EXON	-	chr4:105236095-105236115	UAUGAGGCUUAUGUUGCAAA	561
54790_4_1856	TET2	EXON	-	chr4:105236111-105236131	GUUUGUGCUGCCUGUUUAUG	562
54790_4_1861	TET2	EXON	-	chr4:105236138-105236158	GGGAGAUGUGAACUCUGGGA	563
54790_4_1862	TET2	EXON	-	chr4:105236142-105236162	UUGAGGGAGAUGUGAACUCU	564
54790_4_1864	TET2	EXON	-	chr4:105236143-105236163	UUUGAGGGAGAUGUGAACUC	565
54790_4_1873	TET2	EXON	-	chr4:105236158-105236178	GCUGCUGUUGCUGGUUUUGA	566
54790_4_1875	TET2	EXON	-	chr4:105236159-105236179	UGCUGCUGUUGCUGGUUUUG	567
54790_4_1880	TET2	EXON	-	chr4:105236167-105236187	GUAAUUUUUGCUGCUGUUGC	568

54790_4_1892	TET2	EXON	-	chr4:105236215-105236235	UUUGGGGGUGAGGAAAAGUC	569
54790_4_1896	TET2	EXON	-	chr4:105236225-105236245	UCAUUGUUGCUUUGGGGGUG	570
54790_4_1901	TET2	EXON	-	chr4:105236230-105236250	GCUGAUCAUUGUUGCUUUGG	571
54790_4_1902	TET2	EXON	-	chr4:105236231-105236251	UGCUGAUCAUUGUUGCUUUG	572
54790_4_1904	TET2	EXON	-	chr4:105236232-105236252	UUGCUGAUCAUUGUUGCUUU	573
54790_4_1906	TET2	EXON	-	chr4:105236233-105236253	UUUGCUGAUCAUUGUUGCUU	574
54790_4_1914	TET2	EXON	-	chr4:105236275-105236295	AACAUUCUUCCACUUUAGUC	575
54790_4_1931	TET2	EXON	-	chr4:105236350-105236370	GUACUUCCUCCAGUCCCAUU	576
54790_4_1941	TET2	EXON	-	chr4:105236394-105236414	UUUCAUGGUCUGACUAUAAG	577
54790_4_1943	TET2	EXON	-	chr4:105236395-105236415	AUUUCAUGGUCUGACUAUAA	578
54790_4_1944	TET2	EXON	-	chr4:105236396-105236416	GAUUUCAUGGUCUGACUAUA	579
54790_4_1950	TET2	EXON	-	chr4:105236409-105236429	UUUGCAUGCACUUGAUUUCA	580
54790_4_1960	TET2	EXON	-	chr4:105236461-105236481	GUUCUUUAUUCUCUGAAACU	581
54790_4_1966	TET2	EXON	-	chr4:105236495-105236515	UUGUUUCCUGCAAAAAGUUC	582
54790_4_1972	TET2	EXON	-	chr4:105236520-105236540	UUGCAUGUGAUGCAAGUUUU	583
54790_4_1973	TET2	EXON	-	chr4:105236521-105236541	AUUGCAUGUGAUGCAAGUUU	584
54790_4_1982	TET2	EXON	-	chr4:105236549-105236569	UGCUUUGGGAUCACAUUAUU	585
54790_4_1984	TET2	EXON	-	chr4:105236563-105236583	UGUGAAGAAGAUCUUGCUUU	586
54790_4_1985	TET2	EXON	-	chr4:105236564-105236584	CUGUGAAGAAGAUCUUGCUU	587
54790_4_2009	TET2	EXON	-	chr4:105236653-105236673	CUUGUUGACCAGACAUAUCU	588
54790_4_2017	TET2	EXON	-	chr4:105236713-105236733	GCACAGGAAAAACAUUUGCA	589
54790_4_2019	TET2	EXON	-	chr4:105236729-105236749	CUUCCUCCCUGGUCAGGCAC	590

54790_4_2022	TET2	EXON	-	chr4:105236735-105236755	GUGUGACUUCCUCCCUGGUC	591
54790_4_2023	TET2	EXON	-	chr4:105236740-105236760	UCUGAGUGUGACUUCCUCCC	592
54790_4_2029	TET2	EXON	-	chr4:105236763-105236783	UUGAGUGUCCUUCUGGGGAG	593
54790_4_2030	TET2	EXON	-	chr4:105236764-105236784	UUUGAGUGUCCUUCUGGGGA	594
54790_4_2031	TET2	EXON	-	chr4:105236765-105236785	UUUUGAGUGUCCUUCUGGGG	595
54790_4_2034	TET2	EXON	-	chr4:105236768-105236788	UGCUUUUGAGUGUCCUUCUG	596
54790_4_2037	TET2	EXON	-	chr4:105236769-105236789	AUGCUUUUGAGUGUCCUUCU	597
54790_4_2039	TET2	EXON	-	chr4:105236770-105236790	CAUGCUUUUGAGUGUCCUUC	598
54790_4_2053	TET2	EXON	-	chr4:105236846-105236866	CUAUGGCAAGACUCAGUUUG	599
54790_4_2054	TET2	EXON	-	chr4:105236847-105236867	ACUAUGGCAAGACUCAGUUU	600
54790_4_2055	TET2	EXON	-	chr4:105236848-105236868	GACUAUGGCAAGACUCAGUU	601
54790_4_2060	TET2	EXON	-	chr4:105236863-105236883	UUGGCCUGUGCAUCUGACUA	602
54790_4_2063	TET2	EXON	-	chr4:105236882-105236902	CAUCCAGGUUCCACCUUAAU	603
54790_4_2064	TET2	EXON	-	chr4:105236897-105236917	CAGGCAUGUGGCUUGCAUCC	604
54790_4_2065	TET2	EXON	-	chr4:105236909-105236929	GCUGUGUGCAUACAGGCAUG	605
54790_4_2069	TET2	EXON	-	chr4:105236916-105236936	UGGUGGUGCUGUGUGCAUAC	606
54790_4_2077	TET2	EXON	-	chr4:105236933-105236953	UUCCAUGUUUUGUUUUCUGG	607
54790_4_2079	TET2	EXON	-	chr4:105236936-105236956	UUUUUCCAUGUUUUGUUUUC	608
54790_4_2085	TET2	EXON	-	chr4:105236978-105236998	ACAUUAUCACAGCUUGCAGG	609
54790_4_2089	TET2	EXON	-	chr4:105236981-105237001	UGCACAUUAUCACAGCUUGC	610
54790_4_2092	TET2	EXON	-	chr4:105237024-105237044	CUGCUUCAGAUGCUGCUCCA	611
54790_4_2096	TET2	EXON	-	chr4:105237054-105237074	CUUAUGGUCAAAUAACGACU	612

54790_4_2099	TET2	EXON	-	chr4:105237070 -105237090	AUUUGAGAGUAAGAGCCUUA	613
54790_4_2112	TET2	EXON	-	chr4:105237125 -105237145	UGUCUAGUCAAAACUGUGAC	614
54790_4_2114	TET2	EXON	-	chr4:105237150 -105237170	GCUAUCAAGUUCUGCAGCAG	615
54790_4_2118	TET2	EXON	-	chr4:105237172 -105237192	GCUGCUCUAAAGCUGGGGUG	616
54790_4_2119	TET2	EXON	-	chr4:105237177 -105237197	UGUUUGCUGCUCUAAAGCUG	617
54790_4_2120	TET2	EXON	-	chr4:105237178 -105237198	UUGUUUGCUGCUCUAAAGCU	618
54790_4_2122	TET2	EXON	-	chr4:105237179 -105237199	GUUGUUUGCUGCUCUAAAGC	619
54790_4_2135	TET2	EXON	-	chr4:105237218 -105237238	GAAGCAGCUGUUCUUUUGGU	620
54790_4_2137	TET2	EXON	-	chr4:105237222 -105237242	AACAGAAGCAGCUGUUCUUU	621
54790_4_2148	TET2	EXON	-	chr4:105237266 -105237286	GGAGUAUCUAGUAAUUUGGA	622
54790_4_2153	TET2	EXON	-	chr4:105237270 -105237290	UAUAGGAGUAUCUAGUAAUU	623
54790_4_2156	TET2	EXON	-	chr4:105237287 -105237307	GUAUCCAAUAAAUUUUUUAU	624
54790_4_2160	TET2	EXON	-	chr4:105237311 -105237331	AAAUCAUAUUGAGUCUUGAC	625
54790_4_2163	TET2	EXON	-	chr4:105237334 -105237354	UACCUACACAUCUGCAAGAU	626
54790_4_2165	TET2	EXON	-	chr4:105237335 -105237355	UUACCUACACAUCUGCAAGA	627
54790_4_2170	TET2	EXON	-	chr4:105237361 -105237381	CAUGUGUCUCAGUACAUUUC	628
54790_4_2174	TET2	EXON	-	chr4:105237392 -105237412	GAAGAUAAAUUUGCUAAUUC	629
54790_4_2180	TET2	EXON	-	chr4:105237429 -105237449	ACUCAAGAUUUAAAAAAAGA	630
54790_4_2197	TET2	EXON	-	chr4:105237510 -105237530	CUUUCACAAGACACAAGCAU	631
54790_4_2206	TET2	EXON	-	chr4:105237558 -105237578	GCACGAUUAUUUAAUUCUUU	632
54790_4_2213	TET2	EXON	-	chr4:105237593 -105237613	UUUUACAGGAUCUGAAGAGA	633
54790_4_2215	TET2	EXON	-	chr4:105237594 -105237614	AUUUUACAGGAUCUGAAGAG	634

54790_4_2221	TET2	EXON	-	chr4:105237607-105237627	CAGAUACAUUCAAAUUUUAC	635
54790_4_2225	TET2	EXON	-	chr4:105237645-105237665	UAAUAUACAAAGAGCUAAAU	636
54790_4_2233	TET2	EXON	-	chr4:105237671-105237691	UGCUGCCUAGCUGUCUCUCC	637
54790_4_2247	TET2	EXON	-	chr4:105237727-105237747	UUCGUACAUUAGACUGCCUA	638
54790_4_2270	TET2	EXON	-	chr4:105237874-105237894	AAUGGAGAAAAGGAAACUUU	639
54790_4_2274	TET2	EXON	-	chr4:105237884-105237904	CAAAUGUAUAAAUGGAGAAA	640
54790_4_2277	TET2	EXON	-	chr4:105237892-105237912	CAACAUUCCAAAUGUAUAAA	641
54790_4_2284	TET2	EXON	-	chr4:105237936-105237956	AGAUGAAAUUUUAGAGAAAA	642
54790_4_2287	TET2	EXON	-	chr4:105237937-105237957	AAGAUGAAAUUUUAGAGAAA	643
54790_4_2323	TET2	EXON	-	chr4:105240511-105240531	AGGGAAAACAUGGCACGGGU	644
54790_4_2325	TET2	EXON	-	chr4:105240515-105240535	CAAGAGGGAAAACAUGGCAC	645
54790_4_2326	TET2	EXON	-	chr4:105240516-105240536	GCAAGAGGGAAAACAUGGCA	646
54790_4_2328	TET2	EXON	-	chr4:105240521-105240541	UCAUUGCAAGAGGGAAAACA	647
54790_4_2330	TET2	EXON	-	chr4:105240530-105240550	UGGGGUAUCUCAUUGCAAGA	648
54790_4_2331	TET2	EXON	-	chr4:105240531-105240551	GUGGGGUAUCUCAUUGCAAG	649
54790_4_2336	TET2	EXON	-	chr4:105240548-105240568	CCAUCCUUCUACACAGUGUG	650
54790_4_2337	TET2	EXON	-	chr4:105240549-105240569	UCCAUCCUUCUACACAGUGU	651
54790_4_2338	TET2	EXON	-	chr4:105240550-105240570	CUCCAUCCUUCUACACAGUG	652
54790_4_2342	TET2	EXON	-	chr4:105240581-105240601	CACACGCAAAGAGGGACAGU	653
54790_4_2345	TET2	EXON	-	chr4:105240589-105240609	UUAAUAACCACACGCAAAGA	654
54790_4_2347	TET2	EXON	-	chr4:105240590-105240610	CUUAAUAACCACACGCAAAG	655
54790_4_2353	TET2	EXON	-	chr4:105240616-105240636	UGUGGUGUUUUAGCCCAGUG	656

54790_4_2357	TET2	EXON	-	chr4:105240634-105240654	AAUAUUAUCUAUGAGAUGUG	657
54790_4_2365	TET2	EXON	-	chr4:105240693-105240713	AAAAGUGGGAAGAUAGGGGU	658
54790_4_2366	TET2	EXON	-	chr4:105240694-105240714	GAAAAGUGGGAAGAUAGGGG	659
54790_4_2368	TET2	EXON	-	chr4:105240697-105240717	AUGGAAAAGUGGGAAGAUAG	660
54790_4_2369	TET2	EXON	-	chr4:105240698-105240718	GAUGGAAAAGUGGGAAGAUA	661
54790_4_2370	TET2	EXON	-	chr4:105240699-105240719	AGAUGGAAAAGUGGGAAGAU	662
54790_4_2373	TET2	EXON	-	chr4:105240707-105240727	ACCAACAAAGAUGGAAAAGU	663
54790_4_2377	TET2	EXON	-	chr4:105240708-105240728	AACCAACAAAGAUGGAAAAG	664
54790_4_2380	TET2	EXON	-	chr4:105240716-105240736	CUGUUGCAAACCAACAAAGA	665
54790_4_2382	TET2	EXON	-	chr4:105240739-105240759	GAGAGUCAGGCAAAAAGAAG	666
54790_4_2383	TET2	EXON	-	chr4:105240740-105240760	GGAGAGUCAGGCAAAAAGAA	667
54790_4_2384	TET2	EXON	-	chr4:105240741-105240761	UGGAGAGUCAGGCAAAAAGA	668
54790_4_2389	TET2	EXON	-	chr4:105240752-105240772	AGAGAAAAUCCUGGAGAGUC	669
54790_4_2393	TET2	EXON	-	chr4:105240761-105240781	UUUAUGAUGAGAGAAAAUCC	670
54790_4_2422	TET2	EXON	-	chr4:105240882-105240902	UAUUGCUUGGUUUAUUGUCA	671
54790_4_2424	TET2	EXON	-	chr4:105240895-105240915	CCCACCCCCAGAAUAUUGCU	672
54790_4_2434	TET2	EXON	-	chr4:105240954-105240974	CUGGAAGCCUACCUAUUACU	673
54790_4_2439	TET2	EXON	-	chr4:105240973-105240993	AAAAAACAUUUAAAGCUAAC	674
54790_4_2446	TET2	EXON	-	chr4:105241000-105241020	UACAAUCCAAUUUUUUGAGC	675
54790_4_2454	TET2	EXON	-	chr4:105241052-105241072	CUAAACAAAGAAUACAGUGA	676
54790_4_2456	TET2	EXON	-	chr4:105241053-105241073	ACUAAACAAAGAAUACAGUG	677
54790_4_2468	TET2	EXON	-	chr4:105241107-105241127	AUAUAUUACAUUUCAGAUAU	678

54790_4_2469	TET2	EXON	-	chr4:105241108 -105241128	AAUAUAUUACAUUUCAGAUA	679
54790_4_2475	TET2	EXON	-	chr4:105241136 -105241156	UAUAUGUACAUGCUGGUUGU	680
54790_4_2477	TET2	EXON	-	chr4:105241143 -105241163	AAUUAAGUAUAUGUACAUGC	681
54790_4_2488	TET2	EXON	-	chr4:105241193 -105241213	CUUUAAAAUGAGUAGAUUGA	682
54790_4_2498	TET2	EXON	-	chr4:105241245 -105241265	AACCCCCAACUACACAUUAA	683
54790_4_2499	TET2	EXON	-	chr4:105241246 -105241266	UAACCCCCAACUACACAUUA	684
54790_4_2503	TET2	EXON	-	chr4:105241285 -105241305	CUCAAUUAUACUAAAUAUAA	685
54790_4_2519	TET2	EXON	-	chr4:105241367 -105241387	GCUCCUAGAUGGGUAUAAAA	686
54790_4_2522	TET2	EXON	-	chr4:105241377 -105241397	AUUAGGACCUGCUCCUAGAU	687
54790_4_2523	TET2	EXON	-	chr4:105241378 -105241398	CAUUAGGACCUGCUCCUAGA	688
54790_4_2527	TET2	EXON	-	chr4:105241394 -105241414	UCUCUAAUAGCUGCCACAUU	689
54790_4_2538	TET2	EXON	-	chr4:105241470 -105241490	AAAAUUCUGACAUAUACAAA	690
54790_4_2546	TET2	EXON	-	chr4:105241494 -105241514	ACUGCUUUGUGUGUGAAGGC	691
54790_4_2548	TET2	EXON	-	chr4:105241498 -105241518	GUUUACUGCUUUGUGUGUGA	692
54790_4_2555	TET2	EXON	-	chr4:105241568 -105241588	AAUAGCACAGUGUGUAGUGU	693
54790_4_2558	TET2	EXON	-	chr4:105241593 -105241613	UGUCAAAUAUUGUGACUCUC	694
54790_4_2563	TET2	EXON	-	chr4:105241647 -105241667	UCUGGCAUCCAUCGCAAAGU	695
54790_4_2564	TET2	EXON	-	chr4:105241648 -105241668	UUCUGGCAUCCAUCGCAAAG	696
54790_4_2568	TET2	EXON	-	chr4:105241665 -105241685	CUGUUCAUGCCUGGGUUUUC	697
54790_4_2569	TET2	EXON	-	chr4:105241673 -105241693	GCCGAUUCCUGUUCAUGCCU	698
54790_4_2570	TET2	EXON	-	chr4:105241674 -105241694	GGCCGAUUCCUGUUCAUGCC	699
54790_4_2573	TET2	EXON	-	chr4:105241695 -105241715	CUUGUGGCUGGCAGCCUGGC	700

54790_4_2574	TET2	EXON	-	chr4:105241699-105241719	GUACCUUGUGGCUGGCAGCC	701
54790_4_2575	TET2	EXON	-	chr4:105241707-105241727	CUGUGCCAGUACCUUGUGGC	702
54790_4_2577	TET2	EXON	-	chr4:105241711-105241731	GAGCCUGUGCCAGUACCUUG	703
54790_4_2578	TET2	EXON	-	chr4:105241733-105241753	GCCAGAGUGGGACCUCUCGU	704
54790_4_2582	TET2	EXON	-	chr4:105241745-105241765	UCAGGUGGGAAAGCCAGAGU	705
54790_4_2585	TET2	EXON	-	chr4:105241746-105241766	AUCAGGUGGGAAAGCCAGAG	706
54790_4_2591	TET2	EXON	-	chr4:105241759-105241779	UUGACACUUUAUUAUCAGGU	707
54790_4_2595	TET2	EXON	-	chr4:105241760-105241780	UUUGACACUUUAUUAUCAGG	708
54790_4_2598	TET2	EXON	-	chr4:105241763-105241783	UGCUUUGACACUUUAUUAUC	709
54790_4_2609	TET2	EXON	-	chr4:105241819-105241839	ACUAGGUGAAUUUAAUUCAG	710
54790_4_2613	TET2	EXON	-	chr4:105241836-105241856	AAGUACUCAUUUGCAACACU	711
54790_4_2622	TET2	EXON	-	chr4:105241878-105241898	UCACACUUGCUCUCUUUUUA	712
54790_4_2629	TET2	EXON	-	chr4:105241939-105241959	AUAGCGAAAAAAAAAAAAAA	713
54790_4_2633	TET2	EXON	-	chr4:105241986-105242006	UCUUCUACAUGCAGGAGUAA	714
54790_4_2635	TET2	EXON	-	chr4:105241994-105242014	CAUAAGAGUCUUCUACAUGC	715
54790_4_2642	TET2	EXON	-	chr4:105242038-105242058	GCUGUAUAAAUUUAUAUGAA	716
54790_4_2652	TET2	EXON	-	chr4:105242086-105242106	CUGCCUACCUCUUAAUGAAA	717
54790_4_2663	TET2	EXON	-	chr4:105242173-105242193	AGAAAUGAAUAAUUUGGAAA	718
54790_4_2665	TET2	EXON	-	chr4:105242179-105242199	UAAUUUAGAAAUGAAUAAUU	719
54790_4_2679	TET2	EXON	-	chr4:105242236-105242256	GGAAAUUCACUAUUUCUGCC	720
54790_4_2681	TET2	EXON	-	chr4:105242257-105242277	GUUGUUUUUUUUGGCACUUA	721
54790_4_2683	TET2	EXON	-	chr4:105242258-105242278	UGUUGUUUUUUUUGGCACUU	722

54790_4_2685	TET2	EXON	-	chr4:105242266-105242286	UGUUUUUUUGUUGUUUUUUU	723
54790_4_2694	TET2	EXON	-	chr4:105242360-105242380	AUCCAGCCACAUGGAAAAUA	724
54790_4_2697	TET2	EXON	-	chr4:105242369-105242389	AUAGUUAGUAUCCAGCCACA	725
54790_4_2701	TET2	EXON	-	chr4:105242395-105242415	CACAAUUUAGAAAAGGAGGC	726
54790_4_2702	TET2	EXON	-	chr4:105242399-105242419	GUCUCACAAUUUAGAAAAGG	727
54790_4_2703	TET2	EXON	-	chr4:105242402-105242422	AAUGUCUCACAAUUUAGAAA	728
54790_4_2721	TET2	EXON	-	chr4:105242462-105242482	UUUAGCUAUUUUAAAACUUG	729
54790_4_2723	TET2	EXON	-	chr4:105242463-105242483	AUUUAGCUAUUUUAAAACUU	730
54790_4_2726	TET2	EXON	-	chr4:105242464-105242484	AAUUUAGCUAUUUUAAAACU	731
54790_4_2742	TET2	EXON	-	chr4:105242539-105242559	UUUCACAAAGCACAAAAUUC	732
54790_4_2749	TET2	EXON	-	chr4:105242583-105242603	AAUUACAUGUGGGUGAAAAU	733
54790_4_2752	TET2	EXON	-	chr4:105242584-105242604	AAAUUACAUGUGGGUGAAAA	734
54790_4_2755	TET2	EXON	-	chr4:105242593-105242613	CUAUUUUGUAAAUUACAUGU	735
54790_4_2756	TET2	EXON	-	chr4:105242594-105242614	ACUAUUUUGUAAAUUACAUG	736
54790_4_2769	TET2	EXON	-	chr4:105242669-105242689	ACGCCAAGCAAACUGGAUAA	737
54790_4_2772	TET2	EXON	-	chr4:105242676-105242696	CAGGUCUACGCCAAGCAAAC	738
54790_4_2780	TET2	EXON	-	chr4:105242695-105242715	CGGUUUAUUAUUUUUUAAAC	739
54790_4_2781	TET2	EXON	-	chr4:105242715-105242735	ACCACAUCCUGAGAAAUGAA	740
54790_5_3	TET2	EXON	+	chr4:105242816-105242836	CUGUGGGUUUCUUUAAGGUU	741
54790_5_7	TET2	EXON	+	chr4:105242824-105242844	UUCUUUAAGGUUUGGACAGA	742
54790_5_8	TET2	EXON	+	chr4:105242825-105242845	UCUUUAAGGUUUGGACAGAA	743
54790_5_15	TET2	EXON	+	chr4:105242838-105242858	GACAGAAGGGUAAAGCUAUU	744

54790_5_20	TET2	EXON	+	chr4:105242861 -105242881	AUUGAAAGAGUCAUCUAUAC	745
54790_5_23	TET2	EXON	+	chr4:105242870 -105242890	GUCAUCUAUACUGGUAAAGA	746
54790_5_26	TET2	EXON	+	chr4:105242884 -105242904	UAAAGAAGGCAAAAGUUCUC	747
54790_5_27	TET2	EXON	+	chr4:105242885 -105242905	AAAGAAGGCAAAAGUUCUCA	748
54790_5_30	TET2	EXON	+	chr4:105242904 -105242924	AGGGAUGUCCUAUUGCUAAG	749
54790_5_31	TET2	EXON	+	chr4:105242905 -105242925	GGGAUGUCCUAUUGCUAAGU	750
54790_5_51	TET2	EXON	-	chr4:105242915 -105242935	ACACUUACCCACUUAGCAAU	751
54790_6_1	TET2	EXON	+	chr4:105243550 -105243570	GGAAUGGUGAUCCACGCAGG	752
54790_6_7	TET2	EXON	+	chr4:105243589 -105243609	UGAAGAGAAGCUACUGUGUU	753
54790_6_9	TET2	EXON	+	chr4:105243594 -105243614	AGAAGCUACUGUGUUUGGUG	754
54790_6_12	TET2	EXON	+	chr4:105243595 -105243615	GAAGCUACUGUGUUUGGUGC	755
54790_6_14	TET2	EXON	+	chr4:105243605 -105243625	UGUUUGGUGCGGGAGCGAGC	756
54790_6_18	TET2	EXON	+	chr4:105243619 -105243639	GCGAGCUGGCCACACCUGUG	757
54790_6_19	TET2	EXON	+	chr4:105243646 -105243666	AGUGAUUGUGAUUCUCAUCC	758
54790_6_21	TET2	EXON	+	chr4:105243651 -105243671	UUGUGAUUCUCAUCCUGGUG	759
54790_6_24	TET2	EXON	+	chr4:105243652 -105243672	UGUGAUUCUCAUCCUGGUGU	760
54790_6_27	TET2	EXON	+	chr4:105243656 -105243676	AUUCUCAUCCUGGUGUGGGA	761
54790_6_30	TET2	EXON	+	chr4:105243673 -105243693	GGAAGGAAUCCCGCUGUCUC	762
54790_6_32	TET2	EXON	+	chr4:105243691 -105243711	UCUGGCUGACAAACUCUACU	763
54790_6_37	TET2	EXON	+	chr4:105243711 -105243731	CGGAGCUUACCGAGACGCUG	764
54790_6_39	TET2	EXON	+	chr4:105243719 -105243739	ACCGAGACGCUGAGGAAAUA	765
54790_6_41	TET2	EXON	+	chr4:105243738 -105243758	ACGGCACGCUCACCAAUCGC	766

54790_6_48	TET2	EXON	+	chr4:105243771-105243791	AUGAAGAGUAAGUGAAGCCC	767
54790_6_49	TET2	EXON	+	chr4:105243772-105243792	UGAAGAGUAAGUGAAGCCCA	768
54790_6_51	TET2	EXON	-	chr4:105243564-105243584	GCUUCUGCGAACCACCUGCG	769
54790_6_56	TET2	EXON	-	chr4:105243631-105243651	UCACUGCAGCCUCACAGGUG	770
54790_6_57	TET2	EXON	-	chr4:105243636-105243656	CACAAUCACUGCAGCCUCAC	771
54790_6_62	TET2	EXON	-	chr4:105243667-105243687	GCGGGAUUCCUUCCCACACC	772
54790_6_66	TET2	EXON	-	chr4:105243685-105243705	GUUUGUCAGCCAGAGACAGC	773
54790_6_67	TET2	EXON	-	chr4:105243686-105243706	AGUUUGUCAGCCAGAGACAG	774
54790_6_75	TET2	EXON	-	chr4:105243723-105243743	GCCGUAUUUCCUCAGCGUCU	775
54790_6_80	TET2	EXON	-	chr4:105243753-105243773	AUUCAAGGCACACCGGCGAU	776
54790_6_82	TET2	EXON	-	chr4:105243760-105243780	ACUCUUCAUUCAAGGCACAC	777
54790_6_84	TET2	EXON	-	chr4:105243768-105243788	CUUCACUUACUCUUCAUUCA	778
54790_7_10	TET2	EXON	+	chr4:105259615-105259635	CAGGAGAACUUGCGCCUGUC	779
54790_7_12	TET2	EXON	+	chr4:105259616-105259636	AGGAGAACUUGCGCCUGUCA	780
54790_7_14	TET2	EXON	+	chr4:105259617-105259637	GGAGAACUUGCGCCUGUCAG	781
54790_7_16	TET2	EXON	+	chr4:105259621-105259641	AACUUGCGCCUGUCAGGGGC	782
54790_7_20	TET2	EXON	+	chr4:105259637-105259657	GGGCUGGAUCCAGAAACCUG	783
54790_7_21	TET2	EXON	+	chr4:105259655-105259675	UGUGGUGCCUCCUUCUCUUU	784
54790_7_23	TET2	EXON	+	chr4:105259665-105259685	CCUUCUCUUUUGGUUGUUCA	785
54790_7_31	TET2	EXON	+	chr4:105259682-105259702	UCAUGGAGCAUGUACUACAA	786
54790_7_35	TET2	EXON	+	chr4:105259713-105259733	UUGCCAGAAGCAAGAUCCCA	787
54790_7_41	TET2	EXON	+	chr4:105259730-105259750	CCAAGGAAGUUUAAGCUGCU	788

54790_7_42	TET2	EXON	+	chr4:105259731-105259751	CAAGGAAGUUUAAGCUGCUU	789
54790_7_44	TET2	EXON	+	chr4:105259732-105259752	AAGGAAGUUUAAGCUGCUUG	790
54790_7_48	TET2	EXON	+	chr4:105259747-105259767	GCUUGGGGAUGACCCAAAAG	791
54790_7_53	TET2	EXON	-	chr4:105259632-105259652	UUCUGGAUCCAGCCCCUGAC	792
54790_7_54	TET2	EXON	-	chr4:105259649-105259669	AAGGAGGCACCACAGGUUUC	793
54790_7_56	TET2	EXON	-	chr4:105259656-105259676	AAAAGAGAAGGAGGCACCAC	794
54790_7_57	TET2	EXON	-	chr4:105259665-105259685	UGAACAACCAAAAGAGAAGG	795
54790_7_58	TET2	EXON	-	chr4:105259668-105259688	CCAUGAACAACCAAAAGAGA	796
54790_7_72	TET2	EXON	-	chr4:105259719-105259739	CUUCCUUGGGAUCUUGCUUC	797
54790_7_73	TET2	EXON	-	chr4:105259732-105259752	CAAGCAGCUUAAACUUCCUU	798
54790_7_74	TET2	EXON	-	chr4:105259733-105259753	CCAAGCAGCUUAAACUUCCU	799
54790_7_80	TET2	EXON	-	chr4:105259762-105259782	GAAGUAAACAAACCUCUUUU	800
54790_7_81	TET2	EXON	-	chr4:105259763-105259783	GGAAGUAAACAAACCUCUUU	801
54790_8_8	TET2	EXON	+	chr4:105261748-105261768	CUUUAUACAGGAAGAGAAAC	802
54790_8_12	TET2	EXON	+	chr4:105261781-105261801	GCAAAACCUGUCCACUCUUA	803
54790_8_18	TET2	EXON	+	chr4:105261826-105261846	ACCUGAUGCAUAUAAUAAUC	804
54790_8_27	TET2	EXON	-	chr4:105261790-105261810	UUGGUGCCAUAAGAGUGGAC	805
54790_8_30	TET2	EXON	-	chr4:105261795-105261815	AUAUGUUGGUGCCAUAAGAG	806
54790_8_34	TET2	EXON	-	chr4:105261809-105261829	GGUGCAAGUUUCUUAUAUGU	807
54790_8_38	TET2	EXON	-	chr4:105261830-105261850	ACCUGAUUAUUAUAUGCAUC	808
54790_9_14	TET2	EXON	+	chr4:105269623-105269643	CAGAGCACCAGAGUGCCGUC	809
54790_9_15	TET2	EXON	+	chr4:105269624-105269644	AGAGCACCAGAGUGCCGUCU	810

54790_9_19	TET2	EXON	+	chr4:105269632-105269652	AGAGUGCCGUCUGGGUCUGA	811
54790_9_20	TET2	EXON	+	chr4:105269636-105269656	UGCCGUCUGGGUCUGAAGGA	812
54790_9_22	TET2	EXON	+	chr4:105269651-105269671	AAGGAAGGCCGUCCAUUCUC	813
54790_9_24	TET2	EXON	+	chr4:105269652-105269672	AGGAAGGCCGUCCAUUCUCA	814
54790_9_25	TET2	EXON	+	chr4:105269653-105269673	GGAAGGCCGUCCAUUCUCAG	815
54790_9_27	TET2	EXON	+	chr4:105269668-105269688	CUCAGGGGUCACUGCAUGUU	816
54790_9_35	TET2	EXON	+	chr4:105269714-105269734	GACUUGCACAACAUGCAGAA	817
54790_9_37	TET2	EXON	+	chr4:105269725-105269745	CAUGCAGAAUGGCAGCACAU	818
54790_9_39	TET2	EXON	+	chr4:105269733-105269753	AUGGCAGCACAUUGGUAAGU	819
54790_9_40	TET2	EXON	+	chr4:105269734-105269754	UGGCAGCACAUUGGUAAGUU	820
54790_9_43	TET2	EXON	+	chr4:105269740-105269760	CACAUUGGUAAGUUGGGCUG	821
54790_9_49	TET2	EXON	-	chr4:105269633-105269653	UUCAGACCCAGACGGCACUC	822
54790_9_50	TET2	EXON	-	chr4:105269641-105269661	GGCCUUCCUUCAGACCCAGA	823
54790_9_51	TET2	EXON	-	chr4:105269662-105269682	CAGUGACCCCUGAGAAUGGA	824
54790_9_52	TET2	EXON	-	chr4:105269666-105269686	CAUGCAGUGACCCCUGAGAA	825
54790_9_61	TET2	EXON	-	chr4:105269709-105269729	CAUGUUGUGCAAGUCUCUGU	826
54790_9_62	TET2	EXON	-	chr4:105269710-105269730	GCAUGUUGUGCAAGUCUCUG	827
54790_10_10	TET2	EXON	+	chr4:105272578-105272598	AGAGAAGACAAUCGAGAAUU	828
54790_10_13	TET2	EXON	+	chr4:105272581-105272601	GAAGACAAUCGAGAAUUUGG	829
54790_10_16	TET2	EXON	+	chr4:105272592-105272612	AGAAUUUGGAGGAAAACCUG	830
54790_10_23	TET2	EXON	+	chr4:105272637-105272657	UUUAUACAAAGUCUCUGACG	831
54790_10_29	TET2	EXON	+	chr4:105272647-105272667	GUCUCUGACGUGGAUGAGUU	832

54790_10_30	TET2	EXON	+	chr4:105272648-105272668	UCUCUGACGUGGAUGAGUUU	833
54790_10_33	TET2	EXON	+	chr4:105272655-105272675	CGUGGAUGAGUUUGGGAGUG	834
54790_10_36	TET2	EXON	+	chr4:105272664-105272684	GUUUGGGAGUGUGGAAGCUC	835
54790_10_40	TET2	EXON	+	chr4:105272667-105272687	UGGGAGUGUGGAAGCUCAGG	836
54790_10_46	TET2	EXON	+	chr4:105272678-105272698	AAGCUCAGGAGGAGAAAAAA	837
54790_10_48	TET2	EXON	+	chr4:105272683-105272703	CAGGAGGAGAAAAAACGGAG	838
54790_10_49	TET2	EXON	+	chr4:105272694-105272714	AAAACGGAGUGGUGCCAUUC	839
54790_10_51	TET2	EXON	+	chr4:105272711-105272731	UUCAGGUACUGAGUUCUUUU	840
54790_10_55	TET2	EXON	+	chr4:105272723-105272743	GUUCUUUUCGGCGAAAAGUC	841
54790_10_64	TET2	EXON	+	chr4:105272759-105272779	CAGUCAAGACUUGCCGACAA	842
54790_10_71	TET2	EXON	+	chr4:105272805-105272825	AGCUGAAAAGCUUUCCUCCC	843
54790_10_78	TET2	EXON	+	chr4:105272832-105272852	CAGCUCAAAUAAAAAUGAAA	844
54790_10_81	TET2	EXON	+	chr4:105272880-105272900	ACAAACUGAAAACGCAAGCC	845
54790_10_82	TET2	EXON	+	chr4:105272892-105272912	CGCAAGCCAGGCUAAACAGU	846
54790_10_83	TET2	EXON	+	chr4:105272896-105272916	AGCCAGGCUAAACAGUUGGC	847
54790_10_85	TET2	EXON	-	chr4:105272557-105272577	GUGAGAGUGCAUACCUGGUA	848
54790_10_87	TET2	EXON	-	chr4:105272558-105272578	AGUGAGAGUGCAUACCUGGU	849
54790_10_91	TET2	EXON	-	chr4:105272562-105272582	CUCUAGUGAGAGUGCAUACC	850
54790_10_99	TET2	EXON	-	chr4:105272611-105272631	ACGUGAAGCUGCUCAUCCUC	851
54790_10_105	TET2	EXON	-	chr4:105272638-105272658	ACGUCAGAGACUUUGUAUAA	852
54790_10_114	TET2	EXON	-	chr4:105272711-105272731	AAAAGAACUCAGUACCUGAA	853
54790_10_127	TET2	EXON	-	chr4:105272761-105272781	CUUUGUCGGCAAGUCUUGAC	854

54790_10_132	TET2	EXON	-	chr4:105272775-105272795	UGGCUUCUAGUUUCCUUUGU	855
54790_10_136	TET2	EXON	-	chr4:105272795-105272815	CUUUUCAGCUGCAGCUUUCU	856
54790_10_145	TET2	EXON	-	chr4:105272822-105272842	AUUUGAGCUGUUCUCCAGGG	857
54790_10_147	TET2	EXON	-	chr4:105272825-105272845	UUUAUUUGAGCUGUUCUCCA	858
54790_10_150	TET2	EXON	-	chr4:105272826-105272846	UUUUAUUUGAGCUGUUCUCC	859
54790_10_167	TET2	EXON	-	chr4:105272867-105272887	AGUUUGUUUUGUACGUGAUG	860
54790_10_168	TET2	EXON	-	chr4:105272868-105272888	CAGUUUGUUUUGUACGUGAU	861
54790_10_169	TET2	EXON	-	chr4:105272869-105272889	UCAGUUUGUUUUGUACGUGA	862
54790_10_177	TET2	EXON	-	chr4:105272901-105272921	UACCUGCCAACUGUUUAGCC	863
54790_11_9	TET2	EXON	+	chr4:105275178-105275198	GUCAACUCUUAUUCUGCUUC	864
54790_11_14	TET2	EXON	+	chr4:105275203-105275223	CCACCAAUCCAUACAUGAGA	865
54790_11_19	TET2	EXON	+	chr4:105275256-105275276	UCACACACUUCAGAUAUCUA	866
54790_11_24	TET2	EXON	+	chr4:105275304-105275324	UCCACCUCAUCUCAAGCUGC	867
54790_11_34	TET2	EXON	+	chr4:105275346-105275366	AAUCCCAUGAACCCUUACCC	868
54790_11_35	TET2	EXON	+	chr4:105275347-105275367	AUCCCAUGAACCCUUACCCU	869
54790_11_44	TET2	EXON	+	chr4:105275391-105275411	UAUCCAUCAUAUCAAUGCAA	870
54790_11_47	TET2	EXON	+	chr4:105275405-105275425	AUGCAAUGGAAACCUAUCAG	871
54790_11_49	TET2	EXON	+	chr4:105275426-105275446	GGACAACUGCUCCCCAUAUC	872
54790_11_50	TET2	EXON	+	chr4:105275427-105275447	GACAACUGCUCCCCAUAUCU	873
54790_11_53	TET2	EXON	+	chr4:105275456-105275476	UUCUCCCCAGUCUCAGCCGA	874
54790_11_55	TET2	EXON	+	chr4:105275467-105275487	CUCAGCCGAUGGAUCUGUAU	875
54790_11_56	TET2	EXON	+	chr4:105275533-105275553	UCCAUACACUUUACCAGCCA	876

54790_11_59	TET2	EXON	+	chr4:105275538-105275558	ACACUUUACCAGCCAAGGUU	877
54790_11_65	TET2	EXON	+	chr4:105275571-105275591	AGUUUUACAUCUAAAUACUU	878
54790_11_68	TET2	EXON	+	chr4:105275577-105275597	ACAUCUAAAUACUUAGGUUA	879
54790_11_74	TET2	EXON	+	chr4:105275594-105275614	UUAUGGAAACCAAAAUAUGC	880
54790_11_77	TET2	EXON	+	chr4:105275595-105275615	UAUGGAAACCAAAAUAUGCA	881
54790_11_79	TET2	EXON	+	chr4:105275601-105275621	AACCAAAAUAUGCAGGGAGA	882
54790_11_85	TET2	EXON	+	chr4:105275643-105275663	AGACCAAAUGUACAUCAUGU	883
54790_11_86	TET2	EXON	+	chr4:105275644-105275664	GACCAAAUGUACAUCAUGUA	884
54790_11_92	TET2	EXON	+	chr4:105275675-105275695	UCCUUAUCCCACUCAUGAGA	885
54790_11_93	TET2	EXON	+	chr4:105275679-105275699	UAUCCCACUCAUGAGAUGGA	886
54790_11_96	TET2	EXON	+	chr4:105275690-105275710	UGAGAUGGAUGGCCACUUCA	887
54790_11_99	TET2	EXON	+	chr4:105275691-105275711	GAGAUGGAUGGCCACUUCAU	888
54790_11_104	TET2	EXON	+	chr4:105275735-105275755	CAAUCUGAGCAAUCCAAACA	889
54790_11_105	TET2	EXON	+	chr4:105275748-105275768	CCAAACAUGGACUAUAAAAA	890
54790_11_110	TET2	EXON	+	chr4:105275798-105275818	CCAUAACUACAGUGCAGCUC	891
54790_11_111	TET2	EXON	+	chr4:105275799-105275819	CAUAACUACAGUGCAGCUCC	892
54790_11_116	TET2	EXON	+	chr4:105275843-105275863	UGCCCUGCAUCUCCAAAACA	893
54790_11_120	TET2	EXON	+	chr4:105275874-105275894	AUGCUUUCCCACACAGCUAA	894
54790_11_121	TET2	EXON	+	chr4:105275875-105275895	UGCUUUCCCACACAGCUAAU	895
54790_11_129	TET2	EXON	+	chr4:105275928-105275948	GAUAGAACUGCUUGUGUCCA	896
54790_11_131	TET2	EXON	+	chr4:105275931-105275951	AGAACUGCUUGUGUCCAAGG	897
54790_11_133	TET2	EXON	+	chr4:105275958-105275978	CACAAAUUAAGUGAUGCUAA	898

54790_11_137	TET2	EXON	+	chr4:105275963-105275983	AUUAAGUGAUGCUAAUGGUC	899
54790_11_139	TET2	EXON	+	chr4:105275978-105275998	UGGUCAGGAAAAGCAGCCAU	900
54790_11_141	TET2	EXON	+	chr4:105275990-105276010	GCAGCCAUUGGCACUAGUCC	901
54790_11_142	TET2	EXON	+	chr4:105275991-105276011	CAGCCAUUGGCACUAGUCCA	902
54790_11_143	TET2	EXON	+	chr4:105275996-105276016	AUUGGCACUAGUCCAGGGUG	903
54790_11_145	TET2	EXON	+	chr4:105276003-105276023	CUAGUCCAGGGUGUGGCUUC	904
54790_11_148	TET2	EXON	+	chr4:105276011-105276031	GGGUGUGGCUUCUGGUGCAG	905
54790_11_150	TET2	EXON	+	chr4:105276023-105276043	UGGUGCAGAGGACAACGAUG	906
54790_11_152	TET2	EXON	+	chr4:105276028-105276048	CAGAGGACAACGAUGAGGUC	907
54790_11_156	TET2	EXON	+	chr4:105276053-105276073	AGACAGCGAGCAGAGCUUUC	908
54790_11_158	TET2	EXON	+	chr4:105276066-105276086	AGCUUUCUGGAUCCUGACAU	909
54790_11_160	TET2	EXON	+	chr4:105276067-105276087	GCUUUCUGGAUCCUGACAUU	910
54790_11_162	TET2	EXON	+	chr4:105276068-105276088	CUUUCUGGAUCCUGACAUUG	911
54790_11_165	TET2	EXON	+	chr4:105276069-105276089	UUUCUGGAUCCUGACAUUGG	912
54790_11_168	TET2	EXON	+	chr4:105276074-105276094	GGAUCCUGACAUUGGGGGAG	913
54790_11_169	TET2	EXON	+	chr4:105276080-105276100	UGACAUUGGGGGAGUGGCCG	914
54790_11_172	TET2	EXON	+	chr4:105276093-105276113	GUGGCCGUGGCUCCAACUCA	915
54790_11_173	TET2	EXON	+	chr4:105276094-105276114	UGGCCGUGGCUCCAACUCAU	916
54790_11_182	TET2	EXON	+	chr4:105276160-105276180	CCCCUUUAAAGAAUCCCAAU	917
54790_11_186	TET2	EXON	+	chr4:105276175-105276195	CCAAUAGGAAUCACCCCACC	918
54790_11_193	TET2	EXON	+	chr4:105276225-105276245	AGCAUGAAUGAGCCAAAACA	919
54790_11_194	TET2	EXON	+	chr4:105276230-105276250	GAAUGAGCCAAAACAUGGCU	920

54790_11_196	TET2	EXON	+	chr4:105276238-105276258	CAAAACAUGGCUUGGCUCUU	921
54790_11_199	TET2	EXON	+	chr4:105276239-105276259	AAAACAUGGCUUGGCUCUUU	922
54790_11_200	TET2	EXON	+	chr4:105276251-105276271	GGCUCUUUGGGAAGCCAAAA	923
54790_11_210	TET2	EXON	+	chr4:105276275-105276295	UGAAAAAGCCCGUGAGAAAG	924
54790_11_214	TET2	EXON	+	chr4:105276294-105276314	GAGGAAGAGUGUGAAAAGUA	925
54790_11_217	TET2	EXON	+	chr4:105276324-105276344	UAUGUGCCUCAGAAAUCCCA	926
54790_11_221	TET2	EXON	+	chr4:105276340-105276360	CCCAUGGCAAAAAAGUGAAA	927
54790_11_223	TET2	EXON	+	chr4:105276341-105276361	CCAUGGCAAAAAAGUGAAAC	928
54790_11_231	TET2	EXON	+	chr4:105276409-105276429	UCAUCAAGUCUCUUGCCGAA	929
54790_11_236	TET2	EXON	+	chr4:105276466-105276486	CAUCUCCAUAUGCCUUCACU	930
54790_11_237	TET2	EXON	+	chr4:105276467-105276487	AUCUCCAUAUGCCUUCACUC	931
54790_11_239	TET2	EXON	+	chr4:105276474-105276494	UAUGCCUUCACUCGGGUCAC	932
54790_11_240	TET2	EXON	+	chr4:105276475-105276495	AUGCCUUCACUCGGGUCACA	933
54790_11_243	TET2	EXON	+	chr4:105276515-105276535	AUGAUAUCACCCCCUUUUGU	934
54790_11_252	TET2	EXON	+	chr4:105276573-105276593	GUAGUAUAGUUCUCAUGACG	935
54790_11_253	TET2	EXON	+	chr4:105276574-105276594	UAGUAUAGUUCUCAUGACGU	936
54790_11_256	TET2	EXON	+	chr4:105276580-105276600	AGUUCUCAUGACGUGGGCAG	937
54790_11_258	TET2	EXON	+	chr4:105276581-105276601	GUUCUCAUGACGUGGGCAGU	938
54790_11_259	TET2	EXON	+	chr4:105276582-105276602	UUCUCAUGACGUGGGCAGUG	939
54790_11_262	TET2	EXON	+	chr4:105276587-105276607	AUGACGUGGGCAGUGGGGAA	940
54790_11_263	TET2	EXON	+	chr4:105276611-105276631	CACAGUAUUCAUGACAAAUG	941
54790_11_265	TET2	EXON	+	chr4:105276614-105276634	AGUAUUCAUGACAAAUGUGG	942

54790_11_267	TET2	EXON	+	chr4:105276615-105276635	GUAUUCAUGACAAAUGUGGU	943
54790_11_271	TET2	EXON	+	chr4:105276646-105276666	CAGCUCACCAGCAACAAAAG	944
54790_11_273	TET2	EXON	+	chr4:105276677-105276697	CCAUAGCACUUAAUUUUCAC	945
54790_11_275	TET2	EXON	+	chr4:105276688-105276708	AAUUUUCACUGGCUCCCAAG	946
54790_11_280	TET2	EXON	+	chr4:105276698-105276718	GGCUCCCAAGUGGUCACAGA	947
54790_11_283	TET2	EXON	+	chr4:105276706-105276726	AGUGGUCACAGAUGGCAUCU	948
54790_11_285	TET2	EXON	+	chr4:105276738-105276758	AAGCAUUCUAUGCAAAAAGA	949
54790_11_288	TET2	EXON	+	chr4:105276741-105276761	CAUUCUAUGCAAAAAGAAGG	950
54790_11_289	TET2	EXON	+	chr4:105276742-105276762	AUUCUAUGCAAAAAGAAGGU	951
54790_11_291	TET2	EXON	+	chr4:105276743-105276763	UUCUAUGCAAAAAGAAGGUG	952
54790_11_297	TET2	EXON	+	chr4:105276780-105276800	CAAUUUACAUUUUUAAACAC	953
54790_11_302	TET2	EXON	+	chr4:105276792-105276812	UUAAACACUGGUUCUAUUAU	954
54790_11_316	TET2	EXON	+	chr4:105276885-105276905	AUAUCAAGUUUGCAUAGUCA	955
54790_11_321	TET2	EXON	+	chr4:105276925-105276945	UACUGUAGUAUUACAGUGAC	956
54790_11_323	TET2	EXON	+	chr4:105276945-105276965	AGGAAUCUUAAAAUACCAUC	957
54790_11_329	TET2	EXON	+	chr4:105276975-105276995	UAUAUGAUGUACUGAAAUAC	958
54790_11_330	TET2	EXON	+	chr4:105276983-105277003	GUACUGAAAUACUGGAAUUA	959
54790_11_344	TET2	EXON	+	chr4:105277042-105277062	UUAUUUAUCAAAAUAGCUAC	960
54790_11_352	TET2	EXON	+	chr4:105277058-105277078	CUACAGGAAACAUGAAUAGC	961
54790_11_356	TET2	EXON	+	chr4:105277078-105277098	AGGAAAACACUGAAUUUGUU	962
54790_11_359	TET2	EXON	+	chr4:105277094-105277114	UGUUUGGAUGUUCUAAGAAA	963
54790_11_367	TET2	EXON	+	chr4:105277108-105277128	AAGAAAUGGUGCUAAGAAAA	964

54790_11_377	TET2	EXON	+	chr4:105277187-105277207	CUCCAGUGCCCUUGAAUAAU	965
54790_11_378	TET2	EXON	+	chr4:105277188-105277208	UCCAGUGCCCUUGAAUAAUA	966
54790_11_379	TET2	EXON	+	chr4:105277189-105277209	CCAGUGCCCUUGAAUAAUAG	967
54790_11_393	TET2	EXON	+	chr4:105277255-105277275	CAAGCUUAGUUUUUAAAAUG	968
54790_11_395	TET2	EXON	+	chr4:105277267-105277287	UUAAAAUGUGGACAUUUUAA	969
54790_11_401	TET2	EXON	+	chr4:105277274-105277294	GUGGACAUUUUAAAGGCCUC	970
54790_11_410	TET2	EXON	+	chr4:105277304-105277324	UCAUCCAGUGAAGUCCUUGU	971
54790_11_419	TET2	EXON	+	chr4:105277438-105277458	UGACAACUUGAACAAUGCUA	972
54790_11_437	TET2	EXON	+	chr4:105277501-105277521	AUGCAAAGUUGAUUUUUUUA	973
54790_11_465	TET2	EXON	+	chr4:105277599-105277619	ACAGCCAGUUAAAUCCACCA	974
54790_11_466	TET2	EXON	+	chr4:105277600-105277620	CAGCCAGUUAAAUCCACCAU	975
54790_11_467	TET2	EXON	+	chr4:105277601-105277621	AGCCAGUUAAAUCCACCAUG	976
54790_11_469	TET2	EXON	+	chr4:105277609-105277629	AAAUCCACCAUGGGGCUUAC	977
54790_11_472	TET2	EXON	+	chr4:105277617-105277637	CAUGGGGCUUACUGGAUUCA	978
54790_11_474	TET2	EXON	+	chr4:105277618-105277638	AUGGGGCUUACUGGAUUCAA	979
54790_11_478	TET2	EXON	+	chr4:105277649-105277669	AGUCCACAAAACAUGUUUUC	980
54790_11_492	TET2	EXON	+	chr4:105277753-105277773	AAGAAUUUUCUAUUAACUGC	981
54790_11_503	TET2	EXON	+	chr4:105277818-105277838	CUGAAGCCUAUGCUAUUUUA	982
54790_11_504	TET2	EXON	+	chr4:105277826-105277846	UAUGCUAUUUUAUGGAUCAU	983
54790_11_511	TET2	EXON	+	chr4:105277846-105277866	AGGCUCUUCAGAGAACUGAA	984
54790_11_524	TET2	EXON	+	chr4:105277924-105277944	UAAGUGUCCUCUUUAACAAG	985
54790_11_532	TET2	EXON	+	chr4:105277963-105277983	CCUGCAUAAGAUGAAUAAAC	986

54790_11_533	TET2	EXON	+	chr4:105277964 -105277984	CUGCAUAAGAUGAAUAAACA	987
54790_11_539	TET2	EXON	+	chr4:105278008 -105278028	AGUUAAAAAGAAACAAAAAC	988
54790_11_541	TET2	EXON	+	chr4:105278015 -105278035	AAGAAACAAAAACAGGCAGC	989
54790_11_542	TET2	EXON	+	chr4:105278025 -105278045	AACAGGCAGCUGGUUUGCUG	990
54790_11_543	TET2	EXON	+	chr4:105278028 -105278048	AGGCAGCUGGUUUGCUGUGG	991
54790_11_574	TET2	EXON	+	chr4:105278210 -105278230	AAGCAGAAUUCACAUCAUGA	992
54790_11_587	TET2	EXON	+	chr4:105278310 -105278330	CAUAUACCUCAACACUAGUU	993
54790_11_589	TET2	EXON	+	chr4:105278317 -105278337	CUCAACACUAGUUUGGCAAU	994
54790_11_627	TET2	EXON	+	chr4:105278467 -105278487	CCUUUUUGUUCUAAAAAUUC	995
54790_11_628	TET2	EXON	+	chr4:105278468 -105278488	CUUUUUGUUCUAAAAAUUCA	996
54790_11_637	TET2	EXON	+	chr4:105278532 -105278552	UGUUUAUGUAAAAUUGUUGU	997
54790_11_643	TET2	EXON	+	chr4:105278556 -105278576	UAAUAAAUAUAUUCUUUGUC	998
54790_11_645	TET2	EXON	+	chr4:105278557 -105278577	AAUAAAUAUAUUCUUUGUCA	999
54790_11_664	TET2	EXON	+	chr4:105278640 -105278660	AACUAAUUUUGUAAAUCUGU	1000
54790_11_679	TET2	EXON	+	chr4:105278680 -105278700	AAAAGCAUUUUAAAAGUUUG	1001
54790_11_686	TET2	EXON	+	chr4:105278704 -105278724	AUCUUUUGACUGUUUCAAGC	1002
54790_11_700	TET2	EXON	+	chr4:105278748 -105278768	AGAAUGCACUGAGUUGAUAA	1003
54790_11_701	TET2	EXON	+	chr4:105278749 -105278769	GAAUGCACUGAGUUGAUAAA	1004
54790_11_703	TET2	EXON	+	chr4:105278762 -105278782	UGAUAAAGGGAAAAAUUGUA	1005
54790_11_707	TET2	EXON	+	chr4:105278766 -105278786	AAAGGGAAAAAUUGUAAGGC	1006
54790_11_708	TET2	EXON	+	chr4:105278773 -105278793	AAAAUUGUAAGGCAGGAGUU	1007
54790_11_710	TET2	EXON	+	chr4:105278780 -105278800	UAAGGCAGGAGUUUGGCAAG	1008

54790_11_711	TET2	EXON	+	chr4:105278787-105278807	GGAGUUUGGCAAGUGGCUGU	1009
54790_11_721	TET2	EXON	+	chr4:105278846-105278866	UUUGAUCCUGUAAUCACUGA	1010
54790_11_728	TET2	EXON	+	chr4:105278862-105278882	CUGAAGGUACAUACUCCAUG	1011
54790_11_729	TET2	EXON	+	chr4:105278878-105278898	CAUGUGGACUUCCCUUAAAC	1012
54790_11_731	TET2	EXON	+	chr4:105278892-105278912	UUAAACAGGCAAACACCUAC	1013
54790_11_733	TET2	EXON	+	chr4:105278897-105278917	CAGGCAAACACCUACAGGUA	1014
54790_11_734	TET2	EXON	+	chr4:105278927-105278947	CAGAUUGUACAAUUACAUUU	1015
54790_11_748	TET2	EXON	+	chr4:105278978-105278998	UAAAAUAAAUUCUUAAUCAG	1016
54790_11_751	TET2	EXON	+	chr4:105278981-105279001	AAUAAAUUCUUAAUCAGAGG	1017
54790_11_753	TET2	EXON	+	chr4:105278988-105279008	UCUUAAUCAGAGGAGGCCUU	1018
54790_11_754	TET2	EXON	+	chr4:105278989-105279009	CUUAAUCAGAGGAGGCCUUU	1019
54790_11_757	TET2	EXON	+	chr4:105278998-105279018	AGGAGGCCUUUGGGUUUUAU	1020
54790_11_762	TET2	EXON	+	chr4:105279017-105279037	UUGGUCAAAUCUUUGUAAGC	1021
54790_11_772	TET2	EXON	+	chr4:105279052-105279072	UAAAAAAUUUCUUGAAUUUG	1022
54790_11_799	TET2	EXON	+	chr4:105279173-105279193	UUUGAUUACUACAUGUGCAU	1023
54790_11_813	TET2	EXON	+	chr4:105279240-105279260	ACUGUCAUUUGUUAAACUGC	1024
54790_11_818	TET2	EXON	+	chr4:105279254-105279274	AACUGCUGGCCAACAAGAAC	1025
54790_11_822	TET2	EXON	+	chr4:105279267-105279287	CAAGAACAGGAAGUAUAGUU	1026
54790_11_825	TET2	EXON	+	chr4:105279268-105279288	AAGAACAGGAAGUAUAGUUU	1027
54790_11_827	TET2	EXON	+	chr4:105279269-105279289	AGAACAGGAAGUAUAGUUUG	1028
54790_11_828	TET2	EXON	+	chr4:105279270-105279290	GAACAGGAAGUAUAGUUUGG	1029
54790_11_829	TET2	EXON	+	chr4:105279271-105279291	AACAGGAAGUAUAGUUUGGG	1030

54790_11_832	TET2	EXON	+	chr4:105279275-105279295	GGAAGUAUAGUUUGGGGGGU	1031
54790_11_833	TET2	EXON	+	chr4:105279276-105279296	GAAGUAUAGUUUGGGGGGUU	1032
54790_11_836	TET2	EXON	+	chr4:105279277-105279297	AAGUAUAGUUUGGGGGGUUG	1033
54790_11_841	TET2	EXON	+	chr4:105279292-105279312	GGUUGGGGAGAGUUUACAUA	1034
54790_11_851	TET2	EXON	+	chr4:105279311-105279331	AAGGAAGAGAAGAAAUUGAG	1035
54790_11_859	TET2	EXON	+	chr4:105279373-105279393	CCUGCCUCAGUUAGAAUGAA	1036
54790_11_864	TET2	EXON	+	chr4:105279402-105279422	GAUCUACAAUUUGCUAAUAU	1037
54790_11_865	TET2	EXON	+	chr4:105279411-105279431	UUUGCUAAUAUAGGAAUAUC	1038
54790_11_871	TET2	EXON	+	chr4:105279449-105279469	UACUUGAAAAUGCUUCUGAG	1039
54790_11_886	TET2	EXON	+	chr4:105279524-105279544	CAGUUCACUUCUGAAGCUAG	1040
54790_11_890	TET2	EXON	+	chr4:105279538-105279558	AGCUAGUGGUUAACUUGUGU	1041
54790_11_912	TET2	EXON	+	chr4:105279632-105279652	UUUCAUUUUCAUGAGAUGUU	1042
54790_11_920	TET2	EXON	+	chr4:105279648-105279668	UGUUUGGUUUAUAAGAUCUG	1043
54790_11_921	TET2	EXON	+	chr4:105279652-105279672	UGGUUUAUAAGAUCUGAGGA	1044
54790_11_928	TET2	EXON	+	chr4:105279691-105279711	UAUUGUAAUGUUAUGAAUGC	1045
54790_11_954	TET2	EXON	-	chr4:105275038-105275058	UCGCAAAAGUUCUGUGGACA	1046
54790_11_955	TET2	EXON	-	chr4:105275039-105275059	GUCGCAAAAGUUCUGUGGAC	1047
54790_11_957	TET2	EXON	-	chr4:105275044-105275064	ACAAAGUCGCAAAAGUUCUG	1048
54790_11_960	TET2	EXON	-	chr4:105275165-105275185	AGUUGACAGACUCUGUCUGA	1049
54790_11_961	TET2	EXON	-	chr4:105275166-105275186	GAGUUGACAGACUCUGUCUG	1050
54790_11_970	TET2	EXON	-	chr4:105275206-105275226	CCGUCUCAUGUAUGGAUUGG	1051
54790_11_972	TET2	EXON	-	chr4:105275209-105275229	GGGCCGUCUCAUGUAUGGAU	1052

54790_11_973	TET2	EXON	-	chr4:105275214-105275234	GGAUUGGGCCGUCUCAUGUA	1053
54790_11_977	TET2	EXON	-	chr4:105275229-105275249	GGAUAAGGACUAACUGGAUU	1054
54790_11_978	TET2	EXON	-	chr4:105275230-105275250	UGGAUAAGGACUAACUGGAU	1055
54790_11_980	TET2	EXON	-	chr4:105275235-105275255	GAGUUUGGAUAAGGACUAAC	1056
54790_11_982	TET2	EXON	-	chr4:105275244-105275264	GUGUGUGAAGAGUUUGGAUA	1057
54790_11_984	TET2	EXON	-	chr4:105275250-105275270	UCUGAAGUGUGUGAAGAGUU	1058
54790_11_991	TET2	EXON	-	chr4:105275287-105275307	GGAAUAGAAGUUCAUAGGGC	1059
54790_11_992	TET2	EXON	-	chr4:105275291-105275311	AGGUGGAAUAGAAGUUCAUA	1060
54790_11_993	TET2	EXON	-	chr4:105275292-105275312	GAGGUGGAAUAGAAGUUCAU	1061
54790_11_999	TET2	EXON	-	chr4:105275308-105275328	ACCUGCAGCUUGAGAUGAGG	1062
54790_11_1001	TET2	EXON	-	chr4:105275311-105275331	UGAACCUGCAGCUUGAGAUG	1063
54790_11_1012	TET2	EXON	-	chr4:105275352-105275372	AGCCCAGGGUAAGGGUUCAU	1064
54790_11_1013	TET2	EXON	-	chr4:105275353-105275373	AAGCCCAGGGUAAGGGUUCA	1065
54790_11_1017	TET2	EXON	-	chr4:105275360-105275380	GAUUCAAAAGCCCAGGGUAA	1066
54790_11_1018	TET2	EXON	-	chr4:105275361-105275381	UGAUUCAAAAGCCCAGGGUA	1067
54790_11_1021	TET2	EXON	-	chr4:105275366-105275386	UAUUCUGAUUCAAAAGCCCA	1068
54790_11_1022	TET2	EXON	-	chr4:105275367-105275387	GUAUUCUGAUUCAAAAGCCC	1069
54790_11_1026	TET2	EXON	-	chr4:105275389-105275409	GCAUUGAUAUGAUGGAUAUU	1070
54790_11_1027	TET2	EXON	-	chr4:105275390-105275410	UGCAUUGAUAUGAUGGAUAU	1071
54790_11_1031	TET2	EXON	-	chr4:105275397-105275417	UUUCCAUUGCAUUGAUAUGA	1072
54790_11_1034	TET2	EXON	-	chr4:105275420-105275440	GGGAGCAGUUGUCCACUGAU	1073
54790_11_1035	TET2	EXON	-	chr4:105275440-105275460	AGAAUAGGAACCCAGAUAUG	1074

54790_11_1037	TET2	EXON	-	chr4:105275441-105275461	GAGAAUAGGAACCCAGAUAU	1075
54790_11_1040	TET2	EXON	-	chr4:105275442-105275462	GGAGAAUAGGAACCCAGAUA	1076
54790_11_1042	TET2	EXON	-	chr4:105275455-105275475	CGGCUGAGACUGGGGAGAAU	1077
54790_11_1046	TET2	EXON	-	chr4:105275463-105275483	AGAUCCAUCGGCUGAGACUG	1078
54790_11_1049	TET2	EXON	-	chr4:105275464-105275484	CAGAUCCAUCGGCUGAGACU	1079
54790_11_1050	TET2	EXON	-	chr4:105275465-105275485	ACAGAUCCAUCGGCUGAGAC	1080
54790_11_1055	TET2	EXON	-	chr4:105275475-105275495	GGAUACCUAUACAGAUCCAU	1081
54790_11_1058	TET2	EXON	-	chr4:105275496-105275516	UUAGACAGAGGGUCUUGGCU	1082
54790_11_1060	TET2	EXON	-	chr4:105275501-105275521	UGAGCUUAGACAGAGGGUCU	1083
54790_11_1061	TET2	EXON	-	chr4:105275507-105275527	GUAGACUGAGCUUAGACAGA	1084
54790_11_1062	TET2	EXON	-	chr4:105275508-105275528	GGUAGACUGAGCUUAGACAG	1085
54790_11_1067	TET2	EXON	-	chr4:105275529-105275549	UGGUAAAGUGUAUGGAUGGG	1086
54790_11_1068	TET2	EXON	-	chr4:105275532-105275552	GGCUGGUAAAGUGUAUGGAU	1087
54790_11_1069	TET2	EXON	-	chr4:105275533-105275553	UGGCUGGUAAAGUGUAUGGA	1088
54790_11_1072	TET2	EXON	-	chr4:105275537-105275557	ACCUUGGCUGGUAAAGUGUA	1089
54790_11_1075	TET2	EXON	-	chr4:105275549-105275569	GGCUAUUUCCAAACCUUGGC	1090
54790_11_1076	TET2	EXON	-	chr4:105275553-105275573	CUCUGGCUAUUUCCAAACCU	1091
54790_11_1079	TET2	EXON	-	chr4:105275570-105275590	AGUAUUUAGAUGUAAAACUC	1092
54790_11_1085	TET2	EXON	-	chr4:105275606-105275626	AACCAUCUCCCUGCAUAUUU	1093
54790_11_1089	TET2	EXON	-	chr4:105275641-105275661	AUGAUGUACAUUUGGUCUAA	1094
54790_11_1092	TET2	EXON	-	chr4:105275649-105275669	UUCCCUACAUGAUGUACAUU	1095
54790_11_1093	TET2	EXON	-	chr4:105275676-105275696	AUCUCAUGAGUGGGAUAAGG	1096

54790_11_1095	TET2	EXON	-	chr4:105275679-105275699	UCCAUCUCAUGAGUGGGAUA	1097
54790_11_1097	TET2	EXON	-	chr4:105275685-105275705	UGGCCAUCCAUCUCAUGAGU	1098
54790_11_1098	TET2	EXON	-	chr4:105275686-105275706	GUGGCCAUCCAUCUCAUGAG	1099
54790_11_1102	TET2	EXON	-	chr4:105275705-105275725	UAGAGGUGGCUCCCAUGAAG	1100
54790_11_1105	TET2	EXON	-	chr4:105275719-105275739	AUUGGGUGGUAAUCUAGAGG	1101
54790_11_1107	TET2	EXON	-	chr4:105275722-105275742	CAGAUUGGGUGGUAAUCUAG	1102
54790_11_1111	TET2	EXON	-	chr4:105275733-105275753	UUUGGAUUGCUCAGAUUGGG	1103
54790_11_1112	TET2	EXON	-	chr4:105275736-105275756	AUGUUUGGAUUGCUCAGAUU	1104
54790_11_1113	TET2	EXON	-	chr4:105275737-105275757	CAUGUUUGGAUUGCUCAGAU	1105
54790_11_1120	TET2	EXON	-	chr4:105275751-105275771	CCAUUUUUAUAGUCCAUGUU	1106
54790_11_1125	TET2	EXON	-	chr4:105275787-105275807	UAGUUAUGGAUUAUGUGAGA	1107
54790_11_1129	TET2	EXON	-	chr4:105275801-105275821	CCGGAGCUGCACUGUAGUUA	1108
54790_11_1133	TET2	EXON	-	chr4:105275820-105275840	AGAGAGCUGUUGAACAUGCC	1109
54790_11_1144	TET2	EXON	-	chr4:105275848-105275868	CUCCUUGUUUUGGAGAUGCA	1110
54790_11_1145	TET2	EXON	-	chr4:105275849-105275869	UCUCCUUGUUUUGGAGAUGC	1111
54790_11_1148	TET2	EXON	-	chr4:105275858-105275878	GCAUGUCAUUCUCCUUGUUU	1112
54790_11_1154	TET2	EXON	-	chr4:105275884-105275904	UGAUAACCCAUUAGCUGUGU	1113
54790_11_1155	TET2	EXON	-	chr4:105275885-105275905	UUGAUAACCCAUUAGCUGUG	1114
54790_11_1161	TET2	EXON	-	chr4:105275916-105275936	GUUCUAUCAUGGUUAAGAGC	1115
54790_11_1165	TET2	EXON	-	chr4:105275927-105275947	GGACACAAGCAGUUCUAUCA	1116
54790_11_1169	TET2	EXON	-	chr4:105275948-105275968	UUAAUUUGUGUAAGCCUCCU	1117
54790_11_1175	TET2	EXON	-	chr4:105275997-105276017	ACACCCUGGACUAGUGCCAA	1118

54790_11_1176	TET2	EXON	-	chr4:105276011-105276031	CUGCACCAGAAGCCACACCC	1119
54790_11_1182	TET2	EXON	-	chr4:105276081-105276101	ACGGCCACUCCCCCAAUGUC	1120
54790_11_1186	TET2	EXON	-	chr4:105276100-105276120	UGACCCAUGAGUUGGAGCCA	1121
54790_11_1188	TET2	EXON	-	chr4:105276108-105276128	AUGAGAAUUGACCCAUGAGU	1122
54790_11_1200	TET2	EXON	-	chr4:105276157-105276177	GGGAUUCUUUAAAGGGGUUG	1123
54790_11_1202	TET2	EXON	-	chr4:105276163-105276183	CCUAUUGGGAUUCUUUAAAG	1124
54790_11_1203	TET2	EXON	-	chr4:105276164-105276184	UCCUAUUGGGAUUCUUUAAA	1125
54790_11_1205	TET2	EXON	-	chr4:105276165-105276185	UUCCUAUUGGGAUUCUUUAA	1126
54790_11_1207	TET2	EXON	-	chr4:105276177-105276197	CUGGUGGGGUGAUUCCUAUU	1127
54790_11_1209	TET2	EXON	-	chr4:105276178-105276198	CCUGGUGGGGUGAUUCCUAU	1128
54790_11_1211	TET2	EXON	-	chr4:105276191-105276211	AGACGAGGGAGAUCCUGGUG	1129
54790_11_1212	TET2	EXON	-	chr4:105276192-105276212	AAGACGAGGGAGAUCCUGGU	1130
54790_11_1214	TET2	EXON	-	chr4:105276193-105276213	AAAGACGAGGGAGAUCCUGG	1131
54790_11_1216	TET2	EXON	-	chr4:105276196-105276216	GUAAAAGACGAGGGAGAUCC	1132
54790_11_1219	TET2	EXON	-	chr4:105276205-105276225	CUUAUGCUGGUAAAAGACGA	1133
54790_11_1221	TET2	EXON	-	chr4:105276206-105276226	UCUUAUGCUGGUAAAAGACG	1134
54790_11_1228	TET2	EXON	-	chr4:105276218-105276238	GCUCAUUCAUGCUCUUAUGC	1135
54790_11_1230	TET2	EXON	-	chr4:105276240-105276260	CAAAGAGCCAAGCCAUGUUU	1136
54790_11_1241	TET2	EXON	-	chr4:105276268-105276288	ACGGGCUUUUUCAGCCAUUU	1137
54790_11_1246	TET2	EXON	-	chr4:105276286-105276306	ACACUCUUCCUCUUUCUCAC	1138
54790_11_1247	TET2	EXON	-	chr4:105276287-105276307	CACACUCUUCCUCUUUCUCA	1139
54790_11_1251	TET2	EXON	-	chr4:105276320-105276340	AUUUCUGAGGCACAUAGUCU	1140

54790_11_1252	TET2	EXON	-	chr4:105276321-105276341	GAUUUCUGAGGCACAUAGUC	1141
54790_11_1260	TET2	EXON	-	chr4:105276333-105276353	UUUUUGCCAUGGGAUUUCUG	1142
54790_11_1263	TET2	EXON	-	chr4:105276343-105276363	CCGUUUCACUUUUUUGCCAU	1143
54790_11_1265	TET2	EXON	-	chr4:105276344-105276364	CCCGUUUCACUUUUUUGCCA	1144
54790_11_1269	TET2	EXON	-	chr4:105276369-105276389	GAAGUUUCAUGUGGCUCAGC	1145
54790_11_1270	TET2	EXON	-	chr4:105276378-105276398	GUGGGCUCUGAAGUUUCAUG	1146
54790_11_1273	TET2	EXON	-	chr4:105276396-105276416	UUGAUGAAACGCAGGUAAGU	1147
54790_11_1274	TET2	EXON	-	chr4:105276397-105276417	CUUGAUGAAACGCAGGUAAG	1148
54790_11_1277	TET2	EXON	-	chr4:105276404-105276424	CAAGAGACUUGAUGAAACGC	1149
54790_11_1281	TET2	EXON	-	chr4:105276427-105276447	GGUCACGGACAUGGUCCUUU	1150
54790_11_1282	TET2	EXON	-	chr4:105276436-105276456	GGAGUCUGUGGUCACGGACA	1151
54790_11_1284	TET2	EXON	-	chr4:105276442-105276462	UACUGUGGAGUCUGUGGUCA	1152
54790_11_1286	TET2	EXON	-	chr4:105276448-105276468	UGUAGUUACUGUGGAGUCUG	1153
54790_11_1288	TET2	EXON	-	chr4:105276457-105276477	AUAUGGAGAUGUAGUUACUG	1154
54790_11_1290	TET2	EXON	-	chr4:105276474-105276494	GUGACCCGAGUGAAGGCAUA	1155
54790_11_1294	TET2	EXON	-	chr4:105276481-105276501	AGGCCCUGUGACCCGAGUGA	1156
54790_11_1297	TET2	EXON	-	chr4:105276501-105276521	UAUCAUAUAUAUCUGUUGUA	1157
54790_11_1300	TET2	EXON	-	chr4:105276527-105276547	GUGAGGUAACCAACAAAAGG	1158
54790_11_1301	TET2	EXON	-	chr4:105276528-105276548	AGUGAGGUAACCAACAAAAG	1159
54790_11_1303	TET2	EXON	-	chr4:105276529-105276549	AAGUGAGGUAACCAACAAAA	1160
54790_11_1305	TET2	EXON	-	chr4:105276530-105276550	CAAGUGAGGUAACCAACAAA	1161
54790_11_1310	TET2	EXON	-	chr4:105276544-105276564	GGUUGUGGUCUUUUCAAGUG	1162

54790_11_1312	TET2	EXON	-	chr4:105276559-105276579	UACUACUGACAGGUUGGUUG	1163
54790_11_1313	TET2	EXON	-	chr4:105276565-105276585	GAACUAUACUACUGACAGGU	1164
54790_11_1314	TET2	EXON	-	chr4:105276569-105276589	AUGAGAACUAUACUACUGAC	1165
54790_11_1331	TET2	EXON	-	chr4:105276646-105276666	CUUUUGUUGCUGGUGAGCUG	1166
54790_11_1334	TET2	EXON	-	chr4:105276656-105276676	AAGAUAACCUCUUUUGUUGC	1167
54790_11_1336	TET2	EXON	-	chr4:105276680-105276700	CCAGUGAAAAUUAAGUGCUA	1168
54790_11_1339	TET2	EXON	-	chr4:105276705-105276725	GAUGCCAUCUGUGACCACUU	1169
54790_11_1344	TET2	EXON	-	chr4:105276706-105276726	AGAUGCCAUCUGUGACCACU	1170
54790_11_1354	TET2	EXON	-	chr4:105276738-105276758	UCUUUUUGCAUAGAAUGCUU	1171
54790_11_1363	TET2	EXON	-	chr4:105276780-105276800	GUGUUUAAAAAUGUAAAUUG	1172
54790_11_1370	TET2	EXON	-	chr4:105276841-105276861	AGAGUUGUAAGCGGGGGGGG	1173
54790_11_1371	TET2	EXON	-	chr4:105276842-105276862	UAGAGUUGUAAGCGGGGGGG	1174
54790_11_1374	TET2	EXON	-	chr4:105276843-105276863	GUAGAGUUGUAAGCGGGGGG	1175
54790_11_1376	TET2	EXON	-	chr4:105276844-105276864	UGUAGAGUUGUAAGCGGGGG	1176
54790_11_1378	TET2	EXON	-	chr4:105276845-105276865	GUGUAGAGUUGUAAGCGGGG	1177
54790_11_1379	TET2	EXON	-	chr4:105276846-105276866	UGUGUAGAGUUGUAAGCGGG	1178
54790_11_1382	TET2	EXON	-	chr4:105276847-105276867	AUGUGUAGAGUUGUAAGCGG	1179
54790_11_1383	TET2	EXON	-	chr4:105276848-105276868	GAUGUGUAGAGUUGUAAGCG	1180
54790_11_1386	TET2	EXON	-	chr4:105276849-105276869	AGAUGUGUAGAGUUGUAAGC	1181
54790_11_1388	TET2	EXON	-	chr4:105276850-105276870	CAGAUGUGUAGAGUUGUAAG	1182
54790_11_1394	TET2	EXON	-	chr4:105276876-105276896	AAACUUGAUAUUAUUAAAAG	1183
54790_11_1406	TET2	EXON	-	chr4:105276963-105276983	AUCAUAUAUUCAGCACCAGA	1184

54790_11_1440	TET2	EXON	-	chr4:105277160 -105277180	AUAGCAUCUUGAUGAUAUAA	1185
54790_11_1444	TET2	EXON	-	chr4:105277192 -105277212	CCCCUAUUAUUCAAGGGCAC	1186
54790_11_1446	TET2	EXON	-	chr4:105277198 -105277218	AAGGUACCCCUAUUAUUCAA	1187
54790_11_1447	TET2	EXON	-	chr4:105277199 -105277219	AAAGGUACCCCUAUUAUUCA	1188
54790_11_1451	TET2	EXON	-	chr4:105277217 -105277237	UGAUAAAAACUUGAAUGAAA	1189
54790_11_1457	TET2	EXON	-	chr4:105277246 -105277266	AACUAAGCUUGUGUAAGAAU	1190
54790_11_1463	TET2	EXON	-	chr4:105277293 -105277313	ACUGGAUGAGCAAAAUCCAG	1191
54790_11_1469	TET2	EXON	-	chr4:105277311 -105277331	UUGUCCUACAAGGACUUCAC	1192
54790_11_1471	TET2	EXON	-	chr4:105277321 -105277341	AUAUCGUUUAUUGUCCUACA	1193
54790_11_1478	TET2	EXON	-	chr4:105277432 -105277452	UGUUCAAGUUGUCAAAGCUU	1194
54790_11_1501	TET2	EXON	-	chr4:105277563 -105277583	AUUGCUCAUCAGCAGAUGCA	1195
54790_11_1505	TET2	EXON	-	chr4:105277591 -105277611	UUAACUGGCUGUGUUAAAAA	1196
54790_11_1507	TET2	EXON	-	chr4:105277606 -105277626	AGCCCCAUGGUGGAUUUAAC	1197
54790_11_1509	TET2	EXON	-	chr4:105277616 -105277636	GAAUCCAGUAAGCCCCAUGG	1198
54790_11_1512	TET2	EXON	-	chr4:105277619 -105277639	CUUGAAUCCAGUAAGCCCCA	1199
54790_11_1517	TET2	EXON	-	chr4:105277655 -105277675	GCACCAGAAAACAUGUUUUG	1200
54790_11_1547	TET2	EXON	-	chr4:105277827 -105277847	UAUGAUCCAUAAAAUAGCAU	1201
54790_11_1553	TET2	EXON	-	chr4:105277879 -105277899	GUACAUAAUUAUCAACACAA	1202
54790_11_1558	TET2	EXON	-	chr4:105277934 -105277954	GCUCAAUCCUCUUGUUAAAG	1203
54790_11_1565	TET2	EXON	-	chr4:105277966 -105277986	CCUGUUUAUUCAUCUUAUGC	1204
54790_11_1574	TET2	EXON	-	chr4:105277996 -105278016	UUUUAACUGACAGAUUCACA	1205
54790_11_1613	TET2	EXON	-	chr4:105278246 -105278266	CAUUAUGAUAUAUUUGUAGC	1206

54790_11_1621	TET2	EXON	-	chr4:105278304-105278324	UGUUGAGGUAUAUGACAAGU	1207
54790_11_1624	TET2	EXON	-	chr4:105278319-105278339	CUAUUGCCAAACUAGUGUUG	1208
54790_11_1630	TET2	EXON	-	chr4:105278373-105278393	AAGGACUUGGAAAAAAAUGA	1209
54790_11_1636	TET2	EXON	-	chr4:105278386-105278406	UAACAAUAAAAAAAAGGACU	1210
54790_11_1643	TET2	EXON	-	chr4:105278392-105278412	UUUUUUUAACAAUAAAAAAA	1211
54790_11_1647	TET2	EXON	-	chr4:105278423-105278443	AGAAAUCAAGUAUUGAAAAA	1212
54790_11_1658	TET2	EXON	-	chr4:105278470-105278490	CCUGAAUUUUUAGAACAAAA	1213
54790_11_1667	TET2	EXON	-	chr4:105278513-105278533	ACAGGUGACAUGUUGGCAUA	1214
54790_11_1669	TET2	EXON	-	chr4:105278514-105278534	CACAGGUGACAUGUUGGCAU	1215
54790_11_1674	TET2	EXON	-	chr4:105278520-105278540	CAUAAACACAGGUGACAUGU	1216
54790_11_1675	TET2	EXON	-	chr4:105278531-105278551	CAACAAUUUUACAUAAACAC	1217
54790_11_1682	TET2	EXON	-	chr4:105278589-105278609	AGAAGGGAUUCAAAAUAAAA	1218
54790_11_1683	TET2	EXON	-	chr4:105278590-105278610	UAGAAGGGAUUCAAAAUAAA	1219
54790_11_1685	TET2	EXON	-	chr4:105278605-105278625	CAUGUACAAGUAAAAUAGAA	1220
54790_11_1687	TET2	EXON	-	chr4:105278606-105278626	ACAUGUACAAGUAAAAUAGA	1221
54790_11_1733	TET2	EXON	-	chr4:105278813-105278833	GAGAGUUACAAGUAAGUCUC	1222
54790_11_1739	TET2	EXON	-	chr4:105278855-105278875	UAUGUACCUUCAGUGAUUAC	1223
54790_11_1746	TET2	EXON	-	chr4:105278880-105278900	CUGUUUAAGGGAAGUCCACA	1224
54790_11_1749	TET2	EXON	-	chr4:105278892-105278912	GUAGGUGUUUGCCUGUUUAA	1225
54790_11_1751	TET2	EXON	-	chr4:105278893-105278913	UGUAGGUGUUUGCCUGUUUA	1226
54790_11_1754	TET2	EXON	-	chr4:105278910-105278930	CUGUUGCACACCAUACCUGU	1227
54790_11_1758	TET2	EXON	-	chr4:105278953-105278973	UAGUAAGCAAAAAUGUAUUU	1228

54790_11_1768	TET2	EXON	-	chr4:105279007 -105279027	AUUUGACCAAUAAAACCCAA	1229
54790_11_1784	TET2	EXON	-	chr4:105279084 -105279104	UUUUGGAAAUGUUUGCAAAU	1230
54790_11_1789	TET2	EXON	-	chr4:105279101 -105279121	GUAAGCAAAGCAAACAUUUU	1231
54790_11_1792	TET2	EXON	-	chr4:105279127 -105279147	CAAAAAACAUUAAAAUCAUG	1232
54790_11_1796	TET2	EXON	-	chr4:105279154 -105279174	AUGUUUGGGGCUAGAUAUUA	1233
54790_11_1797	TET2	EXON	-	chr4:105279167 -105279187	AUGUAGUAAUCAAAUGUUUG	1234
54790_11_1798	TET2	EXON	-	chr4:105279168 -105279188	CAUGUAGUAAUCAAAUGUUU	1235
54790_11_1800	TET2	EXON	-	chr4:105279169 -105279189	ACAUGUAGUAAUCAAAUGUU	1236
54790_11_1803	TET2	EXON	-	chr4:105279212 -105279232	CAGAAAUCAAAUAUUAAGAA	1237
54790_11_1809	TET2	EXON	-	chr4:105279240 -105279260	GCAGUUUAACAAAUGACAGU	1238
54790_11_1814	TET2	EXON	-	chr4:105279266 -105279286	ACUAUACUUCCUGUUCUUGU	1239
54790_11_1832	TET2	EXON	-	chr4:105279376 -105279396	CCAUUCAUUCUAACUGAGGC	1240
54790_11_1833	TET2	EXON	-	chr4:105279380 -105279400	CUUUCCAUUCAUUCUAACUG	1241
54790_11_1841	TET2	EXON	-	chr4:105279449 -105279469	CUCAGAAGCAUUUUCAAGUA	1242
54790_11_1877	TET2	EXON	-	chr4:105279748 -105279768	AACACUCACAUAGCAUUAUC	1243

TALEN gene editing systems

TALENs are produced artificially by fusing a TAL effector DNA binding domain to a DNA cleavage domain. Transcription activator-like effects (TALEs) can be engineered to bind any desired DNA sequence, including a portion of the HLA or TCR gene. By combining an engineered TALE with a DNA cleavage domain, a restriction enzyme can be produced which is specific to any desired DNA sequence, including a HLA or TCR sequence. These can then be introduced into a cell, wherein they can be used for genome editing. Boch (2011) Nature Biotech. 29: 135-6; and Boch et al. (2009) Science 326: 1509-12; Moscou et al. (2009) Science 326: 3501.

TALEs are proteins secreted by Xanthomonas bacteria. The DNA binding domain contains a repeated, highly conserved 33-34 amino acid sequence, with the exception of the 12th and 13th amino acids. These two positions are highly variable, showing a strong correlation with specific nucleotide recognition. They can thus be engineered to bind to a desired DNA sequence.

To produce a TALEN, a TALE protein is fused to a nuclease (N), which is, for example, a wild-type or mutated FokI endonuclease. Several mutations to FokI have been made for its use in TALENs; these, for example, improve cleavage specificity or activity. Cermak et al. (2011) Nucl. Acids Res. 39: e82; Miller et al. (2011) Nature Biotech. 29: 143-8; Hockemeyer et al. (2011) Nature Biotech. 29: 731-734; Wood et al. (2011) Science 333: 307; Doyon et al. (2010) Nature Methods 8: 74-79; Szczepek et al. (2007) Nature Biotech. 25: 786-793; and Guo et al. (2010) J. Mol. Biol. 200: 96.

The FokI domain functions as a dimer, requiring two constructs with unique DNA binding domains for sites in the target genome with proper orientation and spacing. Both the number of amino acid residues between the TALE DNA binding domain and the FokI cleavage domain and the number of bases between the two individual TALEN binding sites appear to be important parameters for achieving high levels of activity. Miller et al. (2011) Nature Biotech. 29: 143-8.

A Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, TALEN can be used inside a cell to produce a double-stranded break (DSB). A mutation can be introduced at the break site if the repair mechanisms improperly repair the break via non-homologous end joining. For example, improper repair may introduce a frame shift mutation. Alternatively, foreign DNA can be introduced into the cell along with the TALEN, e.g., DNA encoding a CAR, e.g., as described herein; depending on the sequences of the foreign DNA and chromosomal sequence, this process can be used to integrate the DNA encoding the CAR, e.g., as described herein, at or near the site targeted by the TALEN. As shown herein, in the examples, but without being bound by theory, such integration may lead to the expression of the CAR as well as disruption of the Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, gene. Such foreign DNA molecule is referred to herein as "template DNA." In embodiments, the template DNA further comprises homology arms 5' to, 3' to, or both 5' and 3' to the nucleic acid of the template DNA which encodes the molecule or

molecules of interest (e.g., which encodes a CAR described herein), wherein said homology arms are complementary to genomic DNA sequence flanking the target sequence.

TALENs specific to sequences in Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, can be constructed using any method known in the art, including various schemes using modular components. Zhang et al. (2011) Nature Biotech. 29: 149-53; Geibler et al. (2011) PLoS ONE 6: e19509; US 8,420,782 ; US 8,470,973, the contents of which are hereby incorproated by reference in their entirety.

Zinc finger nuclease to inhibit Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2

"ZFN" or "Zinc Finger Nuclease" refer to a zinc finger nuclease, an artificial nuclease which can be used to modify, e.g., delete one or more nucleic acids of, a desired nucleic acid sequence, e.g., Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2,.

Like a TALEN, a ZFN comprises a FokI nuclease domain (or derivative thereof) fused to a DNA-binding domain. In the case of a ZFN, the DNA-binding domain comprises one or more zinc fingers. Carroll et al. (2011) Genetics Society of America 188: 773-782; and Kim et al. (1996) Proc. Natl. Acad. Sci. USA 93: 1156-1160.

A zinc finger is a small protein structural motif stabilized by one or more zinc ions. A zinc finger can comprise, for example, Cys2His2, and can recognize an approximately 3-bp sequence. Various zinc fingers of known specificity can be combined to produce multi-finger polypeptides which recognize about 6, 9, 12, 15 or 18-bp sequences. Various selection and modular assembly techniques are available to generate zinc fingers (and combinations thereof) recognizing specific sequences, including phage display, yeast one-hybrid systems, bacterial one-hybrid and two-hybrid systems, and mammalian cells.

Like a TALEN, a ZFN must dimerize to cleave DNA. Thus, a pair of ZFNs are required to target non-palindromic DNA sites. The two individual ZFNs must bind opposite strands of the DNA with their nucleases properly spaced apart. Bitinaite et al. (1998) Proc. Natl. Acad. Sci. USA 95: 10570-5.

Also like a TALEN, a ZFN can create a double-stranded break in the DNA, which can create a frame-shift mutation if improperly repaired, leading to a decrease in the expression and amount of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, in a cell. ZFNs can also be used with homologous recombination to mutate the Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, gene, or to introduce nucleic acid encoding a CAR at a site at or near the targeted sequence. As discussed

above, the nucleci acid encoding a CAR may be introduced as part of a template DNA. In embodiments, the template DNA further comprises homology arms 5' to, 3' to, or both 5' and 3' to the nucleic acid of the template DNA which encodes the molecule or molecules of interest (e.g., which encodes a CAR described herein), wherein said homology arms are complementary to genomic DNA sequence flanking the target sequence.

ZFNs specific to sequences in the Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, gene can be constructed using any method known in the art. See, e.g., Provasi (2011) Nature Med. 18: 807-815; Torikai (2013) Blood 122: 1341-1349; Cathomen et al. (2008) Mol. Ther. 16: 1200-7; and Guo et al. (2010) J. Mol. Biol. 400: 96; U.S. Patent Publication 2011/0158957; and U.S. Patent Publication 2012/0060230, the contents of which are hereby incorporated by reference in their entirety. In embodiments, The ZFN gene editing system may also comprise nucleic acid encoding one or more components of the ZFN gene editing system, e.g., a ZFN gene editing system targeted to Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2.

Without being bound by theory, it is believed that use of gene editing systems (e.g., CRISPR/Cas gene editing systems) which target Tet, e.g., Tet1, Tet2, and/or Tet3, e.g., Tet2, may allow one to inhibit one or more functions of Tet, e.g., Tet1, Tet2, and/or Tet3, e.g., Tet2, by, for example, causing an editing event which results in expression of a truncated Tet, e.g., Tet1, Tet2, and/or Tet3, e.g., Tet2. Again, without being bound by theory, such truncated Tet, e.g., Tet1, Tet2, and/or Tet3, e.g., Tet2 proteins may preserve one or more functions of the Tet, e.g., Tet1, Tet2, and/or Tet3, e.g., Tet2 (e.g., a scaffolding function), while inhibiting onr or more other functions of the Tet, e.g., Tet1, Tet2, and/or Tet3, e.g., Tet2 (e.g., a catalytic function), and as such, may be preferable. Gene editing systems which target a late exon or intron of a Tet gene, e.g., Tet1, Tet2, and/or Tet3 gene, e.g., Tet2 gene, may be particularly preferred in this regard. In an aspect, the gene editing system Tet inhibitor, e.g., Tet1, Tet2, and/or Tet3 inhibitor, e.g., Tet2 inhibitor of the invention targets a late exon or intron of the tet gene. In an aspect, the gene editing system Tet inhibitor, e.g., Tet1, Tet2, and/or Tet3 inhibitor, e.g., Tet2 inhibitor of the invention targets an exon or intron downstream of exon 8. In an aspect, the gene editing system Tet inhibitor, e.g., Tet1, Tet2, and/or Tet3 inhibitor, e.g., Tet2 inhibitor, targets exon 8 or exon 9, e.g., exon 9, of the tet2 gene.

Without being bound by theory, it may also be preferable in other embodiments to target an early exon or intron of Tet gene, e.g., Tet1, Tet2, and/or Tet3 gene, e.g., Tet2 gene, for

example, to introduce a premature stop codon in the targeted gene which results in no expression of the gene product, or expression of a completely non-functional gene product. Gene editing systems which target an early exon or intron of a Tet gene, e.g., Tet1, Tet2, and/or Tet3 gene, e.g., Tet2 gene, may be particularly preferred in this regard. In an aspect, the gene editing system Tet inhibitor, e.g., Tet1, Tet2, and/or Tet3 inhibitor, e.g., Tet2 inhibitor of the invention targets an early exon or intron of the tet gene. In an aspect, the gene editing system Tet inhibitor, e.g., Tet1, Tet2, and/or Tet3 inhibitor, e.g., Tet2 inhibitor of the invention targets an exon or intron upstream of exon 4. In embodiments, the gene editing system Tet inhibitor, e.g., Tet1, Tet2, and/or Tet3 inhibitor, e.g., Tet2 inhibitor, targets exon 1, exon 2, or exon 3, e.g., exon 3, of the tet2 gene.

Without being bound by theory, it may also be preferable in other embodiments to target a sequence of a Tet gene, e.g., Tet1, Tet2, and/or Tet3 gene, e.g., Tet2 gene, that is specific to one or more isoforms of the tet (e.g., tet2 gene) but does not affect one or more other isoforms of the tet (e.g., tet2). In embodiments, it may be preferable to specifically target isoforms of the tet (e.g., tet2) which contain a catalytic domain.

dsRNA, e.g., siRNA or shRNA, inhibitors of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2

According to the present invention, double stranded RNA ("dsRNA"), e.g., siRNA or shRNA can be used as Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, inhibitors. Also contemplated by the present invention are the uses of nucleic acid encoding said dsRNA Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, inhibitors.

In an embodiment, the Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, inhibitor is a nucleic acid, e.g., a dsRNA, e.g., a siRNA or shRNA specific for nucleic acid encoding Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2,, e.g., genomic DNA or mRNA encoding Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2.

An aspect of the invention provides a composition comprising a dsRNA, e.g., a siRNA or shRNA, comprising at least 15 continguous nucleotides, e.g., 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 contiguous nucleotides, e.g., 21 contiguous nucleotides, which are complementary (e.g., 100% complementary) to a sequence of a Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, nucleic acid sequence (e.g., genomic DNA or mRNA encoding Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2). In embodiments, the at least 15 continguous nucleotides, e.g., 15, 16, 17, 18, 19, 20, 21,

22, 23, 24 or 25 contiguous nucleotides, e.g., 21 contiguous nucleotides, include contiguous nucleotides of a Target sequence of shRNA or Nucleic Acid encoding Tet2 shRNA listed in table 4. It is understood that some of the target sequences and/or shRNA molecules are presented as DNA, but the dsRNA agents targeting these sequences or comprising these sequences can be RNA, or any nucleotide, modified nucleotide or substitute disclosed herein and/or known in the art, provided that the molecule can still mediate RNA interference.

In an embodiment, a nucleic acid molecule that encodes a dsRNA molecule that inhibits expression of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, is operably linked to a promoter, e.g., a H1- or a U6-derived promoter such that the dsRNA molecule that inhibits expression of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, is expressed within a CAR-expressing cell. See e.g., Tiscornia *G.,* "Development of Lentiviral Vectors Expressing siRNA," Chapter 3, in *Gene Transfer: Delivery and Expression of DNA and RNA* (eds. Friedmann and Rossi). Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, USA, 2007; Brummelkamp TR, et al. (2002) Science 296: 550–553; Miyagishi M, et al. (2002) Nat. Biotechnol. 19: 497–500. In an embodiment the nucleic acid molecule that encodes a dsRNA molecule that inhibits Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, is present on the same vector, e.g., a lentiviral vector, that comprises a nucleic acid molecule that encodes a component, e.g., all of the components, of the CAR. In such an embodiment, the nucleic acid molecule that encodes a dsRNA molecule that inhibits Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, is located on the vector, e.g., the lentiviral vector, 5'- or 3'- to the nucleic acid that encodes a component, e.g., all of the components, of the CAR. The nucleic acid molecule that encodes a dsRNA molecule that inhibits expression of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, can be transcribed in the same or different direction as the nucleic acid that encodes a component, e.g., all of the components, of the CAR. In an embodiment the nucleic acid molecule that encodes a dsRNA molecule that inhibits expression of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, is present on a vector other than the vector that comprises a nucleic acid molecule that encodes a component, e.g., all of the components, of the CAR. In an embodiment, the nucleic acid molecule that encodes a dsRNA molecule that inhibits expression of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, is transiently expressed within a CAR-expressing cell. In an embodiment, the nucleic acid molecule that encodes a dsRNA molecule that inhibits expression of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, is stably integrated into the genome of a CAR-expressing cell.

Examples of nucleic acid sequences that encode shRNA sequences are provided below. The Target Sequence refers to the sequence within the Tet2 genomic DNA (or surrounding DNA). The nucleic acid encoding Tet2 shRNA encodes shRNA molecules useful in the present invention. In embodiments, the Tet2 inhibitor is an siRNA or shRNA specific for a Target sequence listed below, or specific for its mRNA complement. In embodiments, the Tet2 inhibitor is a shRNA encoded by the Nucleic Acid encoding Tet2 shRNA of the table 4 below. In embodiments, the Tet2 inhibitor is nucleic acid comprising by the Nucleic Acid encoding Tet2 shRNA of the table 4 below, e.g., which is under the control of a U6 or H1 promoter such that a Tet2 shRNA is produced. In embodiments, the invention provides a siRNA or shRNA comprising sequence which is the RNA analog (i.e., all T nucleic acid residues replaced with U nucleic acid residues) of the Target sequence of shRNA, e.g., the Target sequenc of shRNA of any of the shRNAs of Table 4.

Table 4

	SHRNA_NAME	Target sequence of shRNA	Nucleic Acid encoding Tet2 shRNA
TET2	TET2-3838_76472_insert (TET2 shRNA #1)	CACATGGCGTTTATCCAGAAT (SEQ ID NO: 1244)	CACATGGCGTTTATCCAGAAT CTCGAGATTCTGGATAAACGCCATGT GTTTTTTGAATTCGCACCAGCACGCT ACGCACACACAGTACACACACTGACG TTTCGCCGTCTTC (SEQ ID NO: 1253)
TET2	TET2_NM_017628.4_25616_concept (TET2 shRNA #2)	CAGATGCACAGGC CAATTAAG (SEQ ID NO: 1245)	GAAGACGCACCGGCAGATGTACAGG CTAATTAAGGTTAATATTCATAGCCTT AATTGGCCTGTGCATCTGTTTTTTGAA TTCGCACCAGCACGCTACGCAACACG TCAACCAGTGTCAGTGTTTCGCCGT (SEQ ID NO: 1254)
TET2	TET2_NM_017628.4_25625_concept (TET2 shRNA #3)	GAGCTGCTGAATT CAACTAGA (SEQ ID NO: 1246)	GAAGACGCACCGGGAGCTGCTGAAT TCAATTAGAGTTAATATTCATAGCTCT AGTTGAATTCAGCAGCTCTTTTTTGA ATTCGCACCAGCACGCTACGCATGCA GTCAACCAGTGTCAACCATTCGCCGT (SEQ ID NO: 1255)
TET2	TET2-6571_76471_target (TET2 shRNA #4)	CAGATCGCCATAA CATAAATA (SEQ ID NO: 1247)	CAGATCGCCATAACATAAATACTCGA GTATTTATGTTATGGCGATCTGTTTTT TGAATTCGCACCAGCACGCTACGCAT GACCAGTACACACACTGCATGTTCGC CGTCTTC (SEQ ID NO: 1256)

TET2	TET2_NM_017628.4_25619_target (TET2 shRNA #5)	GACCATGGAGCAGCATCTGAA (SEQ ID NO: 1248)	GAAGACGCACCGGGACCATGGAGTAGCATTTGAAGTTAATATTCATAGCTTCAGATGCTGCTCCATGGTCTTTTTTGAATTCGCACCAGCACGCTACGCATGGTGTCAACCAGTGTCAGTTGTTCGCCGT (SEQ ID NO: 1257)
TET2	TET2 shRNA #6	GCCAAGTCATTATTTGACCAT (SEQ ID NO: 1249)	GCCAAGTCATTATTTGACCATCTCGAGATGGTCAAATAATGACTTGGCTTTTTTGA (SEQ ID NO: 1258)
TET2	TET2 shRNA #7	CCTCAGAGATATTGTGGGTTT (SEQ ID NO: 1250)	CCTCAGAGATATTGTGGGTTTCTCGAGAAACCCACAATATCTCTGAGGTTTTTTGA (SEQ ID NO: 1259)
TET2	TET2 shRNA #8	GGGTAAGCCAAGAAAGAAA (SEQ ID NO: 1251)	GGGTAAGCCAAGAAAGAAACTCGAGTTTCTTTCTTGGCTTACCCTTTTTTGA (SEQ ID NO: 1260)
TET2	TET2 8 long (TET2 shRNA #9)	GGGTAAGCCAAGAAAGAAA (SEQ ID NO: 1252)	GAAGACGCACCGGGGGTAAGCCAAGAAAGAAAGTTAATATTCATAGCTTTCTTTCTTGGCTTACCCTTTTTTGAATTCGCACCAGCACGCTACGCAACACGTCAACCAGTGTCAGTGTTTCGCCGT (SEQ ID NO: 1261)

Additional dsRNA inhibitor of Tet2, e.g., shRNA and siRNA molecules can be designed and tested using methods known in the art and as described herein. In embodiments, the dsRNA Tet2 inhibitor, e.g., shRNA or siRNA, targets a sequence of SEQ ID NO: 1358. In embodiments, the dsRNA Tet2 inhibitor, e.g., shRNA or siRNA, targets a sequence of SEQ ID NO: 1359. In embodiments, the dsRNA Tet2 inhibitor, e.g., shRNA or siRNA, targets a sequence of SEQ ID NO: 1360. In embodiments, the dsRNA Tet2 inhibitor, e.g., shRNA or siRNA, targets a sequence of SEQ ID NO: 1361. In embodiments, the dsRNA Tet2 inhibitor, e.g., shRNA or siRNA, targets a sequence of SEQ ID NO: 1362. In embodiments, the dsRNA Tet2 inhibitor, e.g., shRNA or siRNA, targets a sequence of SEQ ID NO: 1363. In embodiments, the dsRNA Tet2 inhibitor, e.g., shRNA or siRNA, targets a sequence of an mRNA encoding Tet2.

In embodiments, the inhibitor is a nucleic acid, e.g., DNA, encoding a dsRNA Tet2 inhibitor, e.g., shRNA or siRNA, of any of the above embodiments. In embodiments, the nucleic acid, e.g., DNA, is disposed on a vector, e.g., any conventional expression system, e.g., as described herein, e.g., a lentiviral vector.

Without being bound by theory, a dsRNA TET inhibitor (e.g., siRNA or shRNA) which targets a sequence of a Tet mRNA, e.g., Tet1, Tet2, and/or Tet3 gene, e.g., Tet2 mRNA, that is specific to one or more isoforms of tet (e.g., tet2) but does not affect one or more other isoforms of tet (e.g., tet2) (for example, due to targeting a unique splice junction, or targeting a domain which is present in one or more isoforms of tet, e.g., tet2, but is not present in one or more other isoforms of tet, e.g., tet2). In embodiments, it may be preferable to specifically target isoforms of the tet (e.g., tet2) which contain a catalytic domain.

Small molecules

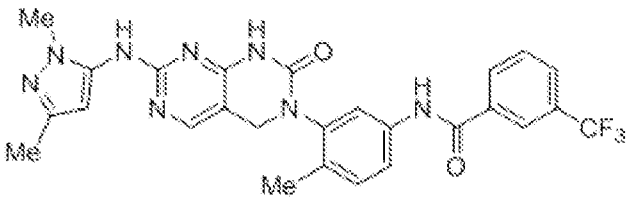
Tet inhibitors

In embodiments, a Tet inhibitor is a small molecule that inhibits expression and/or a function of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2.

Tet2 inhibitors

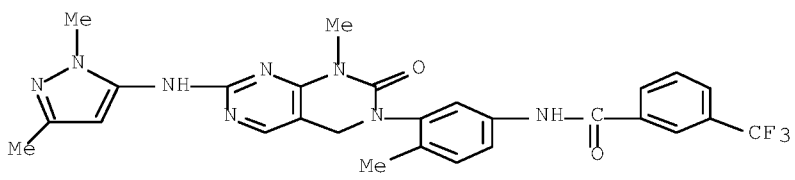
In embodiments, a Tet2 inhibitor is a small molecule that inhibits Tet2 expression and/or function. For example, a Tet2 inhibitor according to the present invention is 2-hydroxyglutarate (CAS #2889-31-8).

In another example, a Tet2 inhibitor according to the present invention has the following structure:

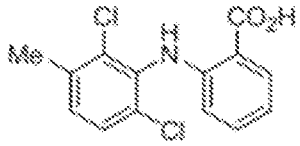


Pluripotin SC1

In another example, a Tet2 inhibitor according to the present invention is N-[3-[7-(2,5-Dimethyl-2H-pyrazol-3-ylamino)-1-methyl-2-oxo-1,4-dihydro-2H-pyrimido[4,5-d]pyrimidin-3-yl]-4-methylphenyl]-3-trifluoromethyl-benzamide (CAS #839707-37-8), and has the following structure:



In another example, a Tet2 inhibitor according to the present invention is 2-[(2,6-dichloro-3-methylphenyl)amino]benzoic acid (CAS # 644-62-2), and has the following structure:



meclofenamic acid

In embodiments, the Tet2 inhibitor of the present invention is a pharmaceutically acceptable salt of any of the foregoing.

HDAC inhibitors

Any known HDAC inhibitors can be used according to the present invention. Non-limiting examples of HDAC inhibitors include Voninostat (Zolinza®); Romidepsin (Istodax®); Treichostatin A (TSA); Oxamflatin; Vorinostat (Zolinza®, Suberoylanilide hydroxamic acid); Pyroxamide (syberoyl-3-aminopyridineamide hydroxamic acid); Trapoxin A (RF-1023A); Trapoxin B (RF-10238); Cyclo[(αS,2S)-α-amino-η-oxo-2-oxiraneoctanoyl-O-methyl-D-tyrosyl-L-isoleucyl-L-prolyl] (Cyl-1); Cyclo[(αS,2S)-α-amino-η-oxo-2-oxiraneoctanoyl-O-methyl-D-tyrosyl-L-isoleucyl-(2S)-2-piperidinecarbonyl] (Cyl-2); Cyclic[L-alanyl-D-alanyl-(2S)-η-oxo-L-α-aminooxiraneoctanoyl-D-prolyl] (HC-toxin); Cyclo[(αS,2S)-α-amino-η-oxo-2-oxiraneoctanoyl-D-phenylalanyl-L-leucyl-(2S)-2-piperidinecarbonyl] (WF-3161); Chlamydocin ((S)-Cyclic(2-methylalanyl-L-phenylalanyl-D-prolyl-η-oxo-L-α-aminooxiraneoctanoyl); Apicidin (Cyclo(8-oxo-L-2-aminodecanoyl-1-methoxy-L-tryptophyl-L-isoleucyl-D-2-piperidinecarbonyl); Romidepsin (Istodax®, FR-901228); 4-Phenylbutyrate; Spiruchostatin A; Mylproin (Valproic acid); Entinostat (MS-275, N-(2-Aminophenyl)-4-[N-(pyridine-3-yl-methoxycarbonyl)-amino-methyl]-benzamide); Depudecin (4,5:8,9-dianhydro-1,2,6,7,11-pentadeoxy- D-threo-D-ido-Undeca-1,6-dienitol); 4-(Acetylamino)-N-(2-aminophenyl)-benzamide (also known as CI-994); N1-(2-Aminophenyl)-N8-phenyl-octanediamide (also known as BML-210); 4-(Dimethylamino)-N-(7-(hydroxyamino)-7-oxoheptyl)benzamide (also known as M344); (E)-3-(4-(((2-(1H-indol-3-yl)ethyl)(2-hydroxyethyl)amino)-methyl)phenyl)-N-hydroxyacrylamide (NVP-LAQ824); Panobinostat (Farydak®); Mocetinostat, and Belinostat.

Proteins

Dominant Negative Tet2

According to the present invention, dominant negative Tet2 isoforms, and nucleic acid encoding said dominant negative Tet2, can be used as Tet2 inhibitors. In embodiments, the dominant negative Tet2 lacks catalytic function of Tet2. An example of a dominant negative Tet2 is a protein comprising or consisting of SEQ ID NO: 1357 with the mutation R1261G, according to the numbering of SEQ ID NO: 1357. An example of a dominant negative Tet2 is a protein comprising or consisting of SEQ ID NO: 1357 with the mutation R1262A, according to the numbering of SEQ ID NO: 1357. An example of a dominant negative Tet2 is a protein comprising or consisting of SEQ ID NO: 1357 with the mutation S1290A, according to the numbering of SEQ ID NO: 1357. An example of a dominant negative Tet2 is a protein comprising or consisting of SEQ ID NO: 1357 with the mutation WSMYYN (amino acids 1291-1296 of SEQ ID NO: 1357) to GGSGGS (SEQ ID NNO: 67), according to the numbering of SEQ ID NO: 1357. An example of a dominant negative Tet2 is a protein comprising or consisting of SEQ ID NO: 1357 with the mutation M1293A and Y1294A, according to the numbering of SEQ ID NO: 1357. An example of a dominant negative Tet2 is a protein comprising or consisting of SEQ ID NO: 1357 with the mutation Y1295A, according to the numbering of SEQ ID NO: 1357. An example of a dominant negative Tet2 is a protein comprising or consisting of SEQ ID NO: 1357 with the mutation S1303N, according to the numbering of SEQ ID NO: 1357. An example of a dominant negative Tet2 is a protein comprising or consisting of SEQ ID NO: 1357 with the mutation H1382Y, according to the numbering of SEQ ID NO: 1357. An example of a dominant negative Tet2 is a protein comprising or consisting of SEQ ID NO: 1357 with the mutation D1384A, according to the numbering of SEQ ID NO: 1357. An example of a dominant negative Tet2 is a protein comprising or consisting of SEQ ID NO: 1357 with the mutation D1384V, according to the numbering of SEQ ID NO: 1357. In embodiments, the dominant negative Tet2 may include combinations of any of the aforementioned mutations. Such mutations are additionally described in, for example, Chen et al., Nature, 493:561-564 (2013); Hu et al, Cell, 155:1545-1555 (2013), the contents of which are hereby incorporated by reference in their entirety.

Dominant Negative Tet2 binding partners

Without being bound by theory, it is believed that Tet2 interacts, e.g., binds, with one or more HDAC, e.g., one or more HDAC expressed in immune effector cells, e.g., in T cells, and that such Tet2:HDAC complexes may contribute to Tet2 activity in the cell. In embodiments, a Tet2 inhibitor of the invention is a dominant negative Tet2 binding partner, e.g., a dominant negative Tet2-binding HDAC. In other embodiments, a Tet2 inhibitor of the invention comprises nucleic acid encoding a dominant negative Tet2 binding partner, e.g., a dominant negative Tet2-binding HDAC.

Vectors encoding Tet2 inhibitors

As described herein, the invention provides vectors, e.g., as described herein, which encode Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, inhibitors, such as the gene editing systems, shRNA or siRNA inhibitors or dominant negative inhibitors of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 (e.g., as described herein).

In embodiments further comprising, for example, a CAR, the nucleic acid may further comprise sequence encoding a CAR, e.g., as described herein. In some embodiments, the invention provides a vector comprising a nucleic acid sequence encoding a Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2 inhibitor described herein and comprising a nucleic acid sequence encoding a CAR molecule described herein. In embodiments, nucleic acid sequences are disposed on separate vectors. In other embodiments, the two or more nucleic acid sequences are encoded by a single nucleic molecule in the same frame and as a single polypeptide chain. In this aspect, the two or more CARs can, e.g., be separated by one or more peptide cleavage sites. (e.g., an auto-cleavage site or a substrate for an intracellular protease). Examples of peptide cleavage sites include the following, wherein the GSG residues are optional:

T2A: (GSG) E G R G S L L T C G D V E E N P G P (SEQ ID NO: 68)

P2A: (GSG) A T N F S L L K Q A G D V E E N P G P (SEQ ID NO: 69)

E2A: (GSG) Q C T N Y A L L K L A G D V E S N P G P (SEQ ID NO: 70)

F2A: (GSG) V K Q T L N F D L L K L A G D V E S N P G P (SEQ ID NO: 71).

These peptide cleavage sites are referred to collectively herein as "2A sites." In embodiments, the vector comprises nucleic acid sequence encoding a CAR described herein and nucleic acid sequence encoding a shRNA or siRNA Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, Inhibitor described herein. In embodiments, the vector comprises nucleic acid sequence

encoding a CAR described herein and nucleic acid sequence encoding a genome editing system (e.g., a CRISPR/Cas system) Tet e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, Inhibitor described herein.

Methods of Use of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, Inhibitors

The invention provides methods of increasing the therapeutic efficacy of a CAR-expressing cell, e.g., a cell expressing a CAR as described herein, e.g., a CAR19-expressing cell (e.g., CTL019), comprising a step of decreasing the level of 5-hydroxymethylcytosine in said cell. In embodiments, the method comprises reducing or eliminating the function or expression of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2,. In embodiments, the method comprises contacting said cells with a Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, inhibitor as described herein.

The invention further provides methods of manufacturing a CAR-expressing cell, e.g., a CAR-expressing cell having improved function (e.g., having improved efficacy, e.g., tumor targeting, or proliferation) comprising the step of reducing or eliminating the expression or function of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, in said cell. In embodiments, the method comprises contacting said cells with a Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, inhibitor as described herein. In embodiments, the contacting is done *ex vivo*. In embodiments, the contacting is done *in vivo*. In embodiments, the contacting is done prior to, simultaneously with, or after said cells are modified to express a CAR, e.g., a CAR as described herein.

In embodiments, the invention provides a method for inhibiting a function or expression of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2,, in a CAR-expressing cell, e.g., a cell expressing a CAR as described herein, e.g., a CAR19-expressing cell (e.g., CTL019-expressing cell), the method comprising a step of decreasing the level of 5-hydroxymethylcytosine in said cell. In embodiments, the method comprises reducing or eliminating the function or expression of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2,. In embodiments, the method comprises contacting said cells with a Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, inhibitor as described herein.

In one embodiment, the invention provides a method, e.g., a method described above, comprises introducing nucleic acid encoding a CAR into a cell, e.g., an immune effector cell, e.g., a T cell, at a site within the Tet gene, or its regulatory elements, such that expression of Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, is disrupted. Integration at a site within the Tet, e.g.,

Tet1, Tet2 and/or Tet3, e.g., Tet2, gene may be accomplished, for example, using a Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2,-targeting gene editing system as described above.

In one embodiment, the invention provides a method, e.g., a method described above, comprising a step of introducing into the cell a gene editing system, e.g., a CRISPR/Cas gene editing system which targets Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2,, e.g., a CRISPR/Cas system comprising a gRNA which has a targeting sequence complementary to a target sequence of the Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2, gene. In embodiments, the CRISPR/Cas system is introduced into said cell as a ribonuclear protein complex of gRNA and Cas enzyme, e.g., is introduced via electroporation. In one embodiment, the method comprises introducing nucleic acid encoding one or more of the components of the CRISPR/Cas system into said cell. In one embodiment, said nucleic acid is disposed on the vector encoding a CAR, e.g., a CAR as described herein.

In one embodiment, the invention provides a method, e.g., a method described above, comprising a step of introducing into the cell an inhibitory dsRNA, e.g., a shRNA or siRNA, which targets Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2. In one embodiment, the method comprises introducing into said cell nucleic acid encoding an inhibitory dsRNA, e.g., a shRNA or siRNA, which targets Tet, e.g., Tet1, Tet2 and/or Tet3, e.g., Tet2,. In one embodiment, said nucleic acid is disposed on the vector encoding a CAR, e.g., a CAR as described herein.

Additional componentents of CARs and CAR T cells, and methods pertaining to the invention are described below.

Provided herein are compositions of matter and methods of use for the treatment of a disease such as cancer using immune effector cells (e.g., T cells, NK cells) engineered with CARs of the invention.

In one aspect, the invention provides a number of chimeric antigen receptors (CAR) comprising an antigen binding domain (e.g., antibody or antibody fragment, TCR or TCR fragment) engineered for specific binding to a tumor antigen, e.g., a tumor antigen described herein. In one aspect, the invention provides an immune effector cell (e.g., T cell, NK cell) engineered to express a CAR, wherein the engineered immune effector cell exhibits an anticancer property. In one aspect, a cell is transformed with the CAR and the CAR is expressed on the cell surface. In some embodiments, the cell (e.g., T cell, NK cell) is transduced with a

viral vector encoding a CAR. In some embodiments, the viral vector is a retroviral vector. In some embodiments, the viral vector is a lentiviral vector. In some such embodiments, the cell may stably express the CAR. In another embodiment, the cell (e.g., T cell, NK cell) is transfected with a nucleic acid, e.g., mRNA, cDNA, DNA, encoding a CAR. In some such embodiments, the cell may transiently express the CAR.

In one aspect, the antigen binding domain of a CAR described herein is a scFv antibody fragment. In one aspect, such antibody fragments are functional in that they retain the equivalent binding affinity, e.g., they bind the same antigen with comparable affinity, as the IgG antibody from which it is derived. In other embodiments, the antibody fragment has a lower binding affinity, e.g., it binds the same antigen with a lower binding affinity than the antibody from which it is derived, but is functional in that it provides a biological response described herein. In one embodiment, the CAR molecule comprises an antibody fragment that has a binding affinity KD of 10^{-4} M to 10^{-8} M, e.g., 10^{-5} M to 10^{-7} M, e.g., 10^{-6} M or 10^{-7} M, for the target antigen. In one embodiment, the antibody fragment has a binding affinity that is at least five-fold, 10-fold, 20-fold, 30-fold, 50-fold, 100-fold or 1,000-fold less than a reference antibody, e.g., an antibody described herein.

In one aspect such antibody fragments are functional in that they provide a biological response that can include, but is not limited to, activation of an immune response, inhibition of signal-transduction origination from its target antigen, inhibition of kinase activity, and the like, as will be understood by a skilled artisan.

In one aspect, the antigen binding domain of the CAR is a scFv antibody fragment that is humanized compared to the murine sequence of the scFv from which it is derived.

In one aspect, the antigen binding domain of a CAR of the invention (e.g., a scFv) is encoded by a nucleic acid molecule whose sequence has been codon optimized for expression in a mammalian cell. In one aspect, entire CAR construct of the invention is encoded by a nucleic acid molecule whose entire sequence has been codon optimized for expression in a mammalian cell. Codon optimization refers to the discovery that the frequency of occurrence of synonymous codons (i.e., codons that code for the same amino acid) in coding DNA is biased in different species. Such codon degeneracy allows an identical polypeptide to be encoded by a variety of nucleotide sequences. A variety of codon optimization methods is known in the art, and include, e.g., methods disclosed in at least US Patent Numbers 5,786,464 and 6,114,148.

In one aspect, the CARs of the invention combine an antigen binding domain of a specific antibody with an intracellular signaling molecule. For example, in some aspects, the intracellular signaling molecule includes, but is not limited to, CD3-zeta chain, 4-1BB and CD28 signaling modules and combinations thereof. In one aspect, the antigen binding domain binds to a tumor antigen as described herein.

Furthermore, the present invention provides CARs and CAR-expressing cells and their use in medicaments or methods for treating, among other diseases, cancer or any malignancy or autoimmune diseases involving cells or tissues which express a tumor antigen as described herein.

In one aspect, the CAR of the invention can be used to eradicate a normal cell that express a tumor antigen as described herein, thereby applicable for use as a cellular conditioning therapy prior to cell transplantation. In one aspect, the normal cell that expresses a tumor antigen as described herein is a normal stem cell and the cell transplantation is a stem cell transplantation.

In one aspect, the invention provides an immune effector cell (e.g., T cell, NK cell) engineered to express a chimeric antigen receptor (CAR), wherein the engineered immune effector cell exhibits an antitumor property. A preferred antigen is a cancer associated antigen (i.e., tumor antigen) described herein. In one aspect, the antigen binding domain of the CAR comprises a partially humanized antibody fragment. In one aspect, the antigen binding domain of the CAR comprises a partially humanized scFv. Accordingly, the invention provides CARs that comprises a humanized antigen binding domain and is engineered into a cell, e.g., a T cell or a NK cell, and methods of their use for adoptive therapy.

In one aspect, the CARs of the invention comprise at least one intracellular domain selected from the group of a CD137 (4-1BB) signaling domain, a CD28 signaling domain, a CD27 signal domain, a CD3zeta signal domain, and any combination thereof. In one aspect, the CARs of the invention comprise at least one intracellular signaling domain is from one or more costimulatory molecule(s) other than a CD137 (4-1BB) or CD28.

Sequences of some examples of various components of CARs of the instant invention is listed in Table 1, where aa stands for amino acids, and na stands for nucleic acids that encode the corresponding peptide.

Table 1. Sequences of various components of CAR (aa – amino acids, na – nucleic acids that encodes the corresponding protein)

SEQ ID NO	description	Sequence	Corresp. To huCD19
1	EF-1 promoter	CGTGAGGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCCAC AGTCCCCGAGAAGTTGGGGGGAGGGGTCGGCAATTGAACCGGTGC CTAGAGAAGGTGGCGCGGGGTAAACTGGGAAAGTGATGTCGTGTA CTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGTATATAAGT GCAGTAGTCGCCGTGAACGTTCTTTTTCGCAACGGGTTTGCCGCCAG AACACAGGTAAGTGCCGTGTGTGGTTCCCGCGGGCCTGGCCTCTTTA CGGGTTATGGCCCTTGCGTGCCTTGAATTACTTCCACCTGGCTGCAG TACGTGATTCTTGATCCCGAGCTTCGGGTTGGAAGTGGGTGGGAGA GTTCGAGGCCTTGCGCTTAAGGAGCCCCTTCGCCTCGTGCTTGAGTT GAGGCCTGGCCTGGGCGCTGGGGCCGCCGCGTGCGAATCTGGTGG CACCTTCGCGCCTGTCTCGCTGCTTTCGATAAGTCTCTAGCCATTTAA AATTTTTGATGACCTGCTGCGACGCTTTTTTTCTGGCAAGATAGTCTT GTAAATGCGGGCCAAGATCTGCACACTGGTATTTCGGTTTTTGGGGC CGCGGGCGGCGACGGGGCCCGTGCGTCCCAGCGCACATGTTCGGC GAGGCGGGGCCTGCGAGCGCGGCCACCGAGAATCGGACGGGGGTA GTCTCAAGCTGGCCGGCCTGCTCTGGTGCCTGGCCTCGCGCCGCCGT GTATCGCCCCGCCCTGGGCGGCAAGGCTGGCCCGGTCGGCACCAGT TGCGTGAGCGGAAAGATGGCCGCTTCCCGGCCCTGCTGCAGGGAGC TCAAAATGGAGGACGCGGCGCTCGGGAGAGCGGGCGGGTGAGTCA CCCACACAAAGGAAAAGGGCCTTTCCGTCCTCAGCCGTCGCTTCATG TGACTCCACGGAGTACCGGGCGCCGTCCAGGCACCTCGATTAGTTCT CGAGCTTTTGGAGTACGTCGTCTTTAGGTTGGGGGGAGGGGTTTTAT GCGATGGAGTTTCCCCACACTGAGTGGGTGGAGACTGAAGTTAGGC CAGCTTGGCACTTGATGTAATTCTCCTTGGAATTTGCCCTTTTTGAGT TTGGATCTTGGTTCATTCTCAAGCCTCAGACAGTGGTTCAAAGTTTTT TTCTTCCATTTCAGGTGTCGTGA	100
2	Leader (aa)	MALPVTALLLPLALLLHAARP	13
3	Leader (na)	ATGGCCCTGCCTGTGACAGCCCTGCTGCTGCCTCTGGCTCTGCTGCT GCATGCCGCTAGACCC	54
4	CD 8 hinge (aa)	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD	14
5	CD8 hinge (na)	ACCACGACGCCAGCGCCGCGACCACCAACACCGGCGCCCACCATCG CGTCGCAGCCCCTGTCCCTGCGCCCAGAGGCGTGCCGGCCAGCGGC GGGGGGCGCAGTGCACACGAGGGGGCTGGACTTCGCCTGTGAT	55
6	Ig4 hinge (aa)	ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSL TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKM	102
7	Ig4 hinge (na)	GAGAGCAAGTACGGCCCTCCCTGCCCCCCTTGCCCTGCCCCCGAGTT CCTGGGCGGACCCAGCGTGTTCCTGTTCCCCCCCAAGCCCAAGGACA	103

		CCCTGATGATCAGCCGGACCCCCGAGGTGACCTGTGTGGTGGTGGA CGTGTCCCAGGAGGACCCCGAGGTCCAGTTCAACTGGTACGTGGAC GGCGTGGAGGTGCACAACGCCAAGACCAAGCCCCGGGAGGAGCAG TTCAATAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCA GGACTGGCTGAACGGCAAGGAATACAAGTGTAAGGTGTCCAACAAG GGCCTGCCCAGCAGCATCGAGAAAACCATCAGCAAGGCCAAGGGCC AGCCTCGGGAGCCCCAGGTGTACACCCTGCCCCCTAGCCAAGAGGA GATGACCAAGAACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCT ACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCG AGAACAACTACAAGACCACCCCCCCTGTGCTGGACAGCGACGGCAG CTTCTTCCTGTACAGCCGGCTGACCGTGGACAAGAGCCGGTGGCAG GAGGGCAACGTCTTTAGCTGCTCCGTGATGCACGAGGCCCTGCACA ACCACTACACCCAGAAGAGCCTGAGCCTGTCCCTGGGCAAGATG	
8	IgD hinge (aa)	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGRGGEEKKKEK EKEEQEERETKTPECPSHTQPLGVYLLTPAVQDLWLRDKATFTCFVVGS DLKDAHLTWEVAGKVPTGGVEEGLLERHSNGSQSQHSRLTLPRSLWN AGTSVTCTLNHPSLPPQRLMALREPAAQAPVKLSLNLLASSDPPEAASW LLCEVSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFWAWSV LRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVSYVTDH	47
9	IgD hinge (na)	AGGTGGCCCGAAAGTCCCAAGGCCCAGGCATCTAGTGTTCCTACTGC ACAGCCCCAGGCAGAAGGCAGCCTAGCCAAAGCTACTACTGCACCT GCCACTACGCGCAATACTGGCCGTGGCGGGGAGGAGAAGAAAAAG GAGAAAGAGAAAGAAGAACAGGAAGAGAGGGAGACCAAGACCCCT GAATGTCCATCCCATACCCAGCCGCTGGGCGTCTATCTCTTGACTCCC GCAGTACAGGACTTGTGGCTTAGAGATAAGGCCACCTTTACATGTTT CGTCGTGGGCTCTGACCTGAAGGATGCCCATTTGACTTGGGAGGTT GCCGGAAAGGTACCCACAGGGGGGGTTGAGGAAGGGTTGCTGGAG CGCCATTCCAATGGCTCTCAGAGCCAGCACTCAAGACTCACCCTTCC GAGATCCCTGTGGAACGCCGGGACCTCTGTCACATGTACTCTAAATC ATCCTAGCCTGCCCCCACAGCGTCTGATGGCCCTTAGAGAGCCAGCC GCCCAGGCACCAGTTAAGCTTAGCCTGAATCTGCTCGCCAGTAGTGA TCCCCCAGAGGCCGCCAGCTGGCTCTTATGCGAAGTGTCCGGCTTTA GCCCGCCCAACATCTTGCTCATGTGGCTGGAGGACCAGCGAGAAGT GAACACCAGCGGCTTCGCTCCAGCCCGGCCCCCACCCCAGCCGGGTT CTACCACATTCTGGGCCTGGAGTGTCTTAAGGGTCCCAGCACCACCT AGCCCCCAGCCAGCCACATACACCTGTGTTGTGTCCCATGAAGATAG CAGGACCCTGCTAAATGCTTCTAGGAGTCTGGAGGTTTCCTACGTGA CTGACCATT	48
10	GS hinge/linker (aa)	GGGGSGGGGS	49
11	GS hinge/linker (na)	GGTGGCGGAGGTTCTGGAGGTGGAGGTTCC	50
12	CD8TM (aa)	IYIWAPLAGTCGVLLLSLVITLYC	15
13	CD8 TM (na)	ATCTACATCTGGGCGCCCTTGGCCGGGACTTGTGGGGTCCTTCTCCT GTCACTGGTTATCACCCTTTACTGC	56

14	4-1BB intracellular domain (aa)	KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL	16
15	4-1BB intracellular domain (na)	AAACGGGGCAGAAAGAAACTCCTGTATATATTCAAACAACCATTTAT GAGACCAGTACAAACTACTCAAGAGGAAGATGGCTGTAGCTGCCGA TTTCCAGAAGAAGAAGAAGGAGGATGTGAACTG	60
16	CD27 (aa)	QRRKYRSNKGESPVEPAEPCRYSCPREEEGSTIPIQEDYRKPEPACSP	51
17	CD27 (na)	AGGAGTAAGAGGAGCAGGCTCCTGCACAGTGACTACATGAACATGA CTCCCCGCCGCCCCGGGCCCACCCGCAAGCATTACCAGCCCTATGCC CCACCACGCGACTTCGCAGCCTATCGCTCC	52
18	CD3-zeta (aa)	RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGG KPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLS TATKDTYDALHMQALPPR	17
19	CD3-zeta (na)	AGAGTGAAGTTCAGCAGGAGCGCAGACGCCCCCGCGTACAAGCAG GGCCAGAACCAGCTCTATAACGAGCTCAATCTAGGACGAAGAGAGG AGTACGATGTTTTGGACAAGAGACGTGGCCGGGACCCTGAGATGGG GGGAAAGCCGAGAAGGAAGAACCCTCAGGAAGGCCTGTACAATGA ACTGCAGAAAGATAAGATGGCGGAGGCCTACAGTGAGATTGGGAT GAAAGGCGAGCGCCGGAGGGGCAAGGGGCACGATGGCCTTTACCA GGGTCTCAGTACAGCCACCAAGGACACCTACGACGCCCTTCACATGC AGGCCCTGCCCCCTCGC	101
20	CD3-zeta (aa)	RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGG KPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLS TATKDTYDALHMQALPPR	43
21	CD3-zeta (na)	AGAGTGAAGTTCAGCAGGAGCGCAGACGCCCCCGCGTACCAGCAG GGCCAG AACCAGCTCTATAACGAGCTCAATCTAGGACGAAGAGAGGAGTACG ATGTTT TGGACAAGAGACGTGGCCGGGACCCTGAGATGGGGGGAAAGCCGA GAAGGA AGAACCCTCAGGAAGGCCTGTACAATGAACTGCAGAAAGATAAGAT GGCGG AGGCCTACAGTGAGATTGGGATGAAAGGCGAGCGCCGGAGGGGCA AGGGGC ACGATGGCCTTTACCAGGGTCTCAGTACAGCCACCAAGGACACCTAC GACGC CCTTCACATGCAGGCCCTGCCCCCTCGC	44
22	linker	GGGGS	18
23	linker	GGTGGCGGAGGTTCTGGAGGTGGAGGTTCC	50
24	PD-1 extracellular domain (aa)	Pgwfldspdrpwnpptfspallvvtegdnatftcsfsntsesfvlnwyrmspsnqtdkl aafpedrsqpgqdcrfrvtqlpngrdfhmsvvrarrndsgtylcgaislapkaqikeslra elrvterraevptahpspsprpagqfqtlv	
25	PD-1 extracellular domain (na)	Cccggatggtttctggactctccggatcgcccgtggaatcccccaaccttctcaccggcact cttggttgtgactgagggcgataatgcgaccttcacgtgctcgttctccaacacctccgaat cattcgtgctgaactggtaccgcatgagcccgtcaaaccagaccgacaagctcgccgcgtt tccggaagatcggtcgcaaccgggacaggattgtcggttccgcgtgactcaactgccgaat ggcagagacttccacatgagcgtggtccgcgctaggcgaaacgactccgggacctacctg	

		tgcggagccatctcgctggcgcctaaggcccaaatcaaagagagcttgagggccgaactg agagtgaccgagcgcagagctgaggtgccaactgcacatccatccccatcgcctcggcct gcggggcagtttcagaccctggtc	
26	PD-1 CAR (aa) with signal	Malpvtalllplalllhaarppgwfldspdrpwnpptfspallvvtegdnatftcsfsntse sfvlnwyrmspsnqtdklaafpedrsqpgqdcrfrvtqlpngrdfhmsvvrarrndsgt ylcgaislapkaqikeslraelrvterraevptahpspsprpagqfqtlvtttpaprpptpa ptiasqplslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlllslvitlyckrgrkklly ifkqpfmrpvqttqeedgcscrfpeeeeggcelrvkfsrsadapaykqgqnqlynelnl grreeydvldkrrgrdpemggkprrknpqeglynelqkdkmaeayseigmkgerrrg kghdglyqglstatkdtydalhmqalppr	
27	PD-1 CAR (na)	Atggccctccctgtcactgccctgcttctccccctcgcactcctgctccacgccgctagacca cccggatggtttctggactctccggatcgcccgtggaatcccccaaccttctcaccggcact cttggttgtgactgagggcgataatgcgaccttcacgtgctcgttctccaacacctccgaat cattcgtgctgaactggtaccgcatgagcccgtcaaaccagaccgacaagctcgccgcgtt tccggaagatcggtcgcaaccgggacaggattgtcggttccgcgtgactcaactgccgaat ggcagagacttccacatgagcgtggtccgcgctaggcgaaacgactccgggacctacctg tgcggagccatctcgctggcgcctaaggcccaaatcaaagagagcttgagggccgaactg agagtgaccgagcgcagagctgaggtgccaactgcacatccatccccatcgcctcggcct gcggggcagtttcagaccctggtcacgaccactccggcgccgcgcccaccgactccggcc ccaactatcgcgagccagcccctgtcgctgaggccggaagcatgccgccctgccgccgga ggtgctgtgcatacccggggattggacttcgcatgcgacatctacatttgggctcctctcgc cggaacttgtggcgtgctccttctgtccctggtcatcaccctgtactgcaagcggggtcgga aaaagcttctgtacattttcaagcagcccttcatgaggcccgtgcaaaccacccaggagga ggacggttgctcctgccggttccccgaagaggaagaaggaggttgcgagctgcgcgtgaa gttctcccggagcgccgacgcccccgcctataagcagggccagaaccagctgtacaacga actgaacctgggacggcgggaagagtacgatgtgctggacaagcggcgcggccgggacc ccgaaatgggcgggaagcctagaagaaagaaccctcaggaaggcctgtataacgagctg cagaaggacaagatggccgaggcctactccgaaattgggatgaagggagagcggcgga ggggaaaggggcacgacggcctgtaccaaggactgtccaccgccaccaaggacacatac gatgccctgcacatgcaggcccttcccccctcgc	
28	linker	$(Gly-Gly-Gly-Ser)_n$, where n = 1-10	105
29	linker	(Gly4 Ser)4	106
30	linker	(Gly4 Ser)3	107
31	linker	(Gly3Ser)	108
32	polyA	aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa

		aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa

		aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa

		aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa

		tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt

		tttttt

		aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa

		aaaaaaaaaa aaaaaaaaaa	
38	polyA	aaaaaaaaaa aaaaaaaaaa	113
39	PD1 CAR (aa)	Pgwfldspdrpwnpptfspallvvtegdnatftcsfsntsesfvlnwyrmspsnqtdkl aafpedrsqpgqdcrfrvtqlpngrdfhmsvvrarrndsgtylcgaislapkaqikeslra elrvterraevptahpspsprpagqfqtlvtttpaprpptpaptiasqplslrpeacrpaa ggavhtrgldfacdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeed gcscrfpeeeeggcelrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpe mggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdglyqglstatkdty dalhmqalppr	

Cancer Associated Antigens

The present invention provides immune effector cells (e.g., T cells, NK cells) that are engineered to contain one or more CARs that direct the immune effector cells to cancer. This is achieved through an antigen binding domain on the CAR that is specific for a cancer associated antigen. There are two classes of cancer associated antigens (tumor antigens) that can be targeted by the CARs of the instant invention: (1) cancer associated antigens that are expressed on the surface of cancer cells; and (2) cancer associated antigens that itself is intracellar, however, a fragment of such antigen (peptide) is presented on the surface of the cancer cells by MHC (major histocompatibility complex).

Accordingly, the present invention provides CARs that target the following cancer associated antigens (tumor antigens): CD19, CD123, CD22, CD30, CD171, CS-1, CLL-1 (CLECL1), CD33, EGFRvIII , GD2, GD3, BCMA, Tn Ag, PSMA, ROR1, FLT3, FAP, TAG72, CD38, CD44v6, CEA, EPCAM, B7H3, KIT, IL-13Ra2, Mesothelin, IL-11Ra, PSCA, VEGFR2, LewisY, CD24, PDGFR-beta, PRSS21, SSEA-4, CD20, Folate receptor alpha, ERBB2 (Her2/neu), MUC1, EGFR, NCAM, Prostase, PAP, ELF2M, Ephrin B2, IGF-I receptor, CAIX, LMP2, gp100, bcr-abl, tyrosinase, EphA2, Fucosyl GM1, sLe, GM3, TGS5, HMWMAA, o-acetyl-GD2, Folate receptor beta, TEM1/CD248, TEM7R, CLDN6, TSHR, GPRC5D, CXORF61, CD97, CD179a, ALK, Polysialic acid, PLAC1, GloboH, NY-BR-1, UPK2, HAVCR1, ADRB3, PANX3, GPR20, LY6K, OR51E2, TARP, WT1, NY-ESO-1, LAGE-1a, legumain, HPV E6,E7, MAGE-A1, MAGE A1, ETV6-AML, sperm protein 17, XAGE1, Tie 2, MAD-CT-1, MAD-CT-2, Fos-related antigen 1, p53, p53 mutant, prostein, survivin and telomerase, PCTA-1/Galectin 8, MelanA/MART1, Ras mutant, hTERT, sarcoma translocation breakpoints, ML-IAP, ERG (TMPRSS2 ETS fusion gene), NA17, PAX3, Androgen receptor, Cyclin B1, MYCN, RhoC, TRP-2, CYP1B1, BORIS, SART3, PAX5, OY-TES1, LCK, AKAP-4, SSX2, RAGE-1, human telomerase reverse transcriptase, RU1, RU2, intestinal carboxyl esterase, mut hsp70-2, CD79a, CD79b, CD72, LAIR1, FCAR, LILRA2, CD300LF, CLEC12A, BST2, EMR2, LY75, GPC3, FCRL5, and IGLL1.

Tumor-supporting antigens

A CAR described herein can comprise an antigen binding domain (e.g., antibody or antibody fragment, TCR or TCR fragment) that binds to a tumor-supporting antigen (e.g., a tumor-supporting antigen as described herein). In some embodiments, the tumor-supporting antigen is an antigen present on a stromal cell or a myeloid-derived suppressor cell (MDSC). Stromal cells can secrete growth factors to promote cell division in the microenvironment. MDSC cells can inhibit T cell proliferation and activation. Without wishing to be bound by theory, in some embodiments, the CAR-expressing cells destroy the tumor-supporting cells, thereby indirectly inhibiting tumor growth or survival.

In embodiments, the stromal cell antigen is chosen from one or more of: bone marrow stromal cell antigen 2 (BST2), fibroblast activation protein (FAP) and tenascin. In an embodiment, the FAP-specific antibody is, competes for binding with, or has the same CDRs as,

sibrotuzumab. In embodiments, the MDSC antigen is chosen from one or more of: CD33, CD11b, C14, CD15, and CD66b. Accordingly, in some embodiments, the tumor-supporting antigen is chosen from one or more of: bone marrow stromal cell antigen 2 (BST2), fibroblast activation protein (FAP) or tenascin, CD33, CD11b, C14, CD15, and CD66b.

Chimeric Antigen Receptor (CAR)

The present invention encompasses a recombinant DNA construct comprising sequences encoding a CAR, wherein the CAR comprises an antigen binding domain (e.g., antibody or antibody fragment, TCR or TCR fragment) that binds specifically to a cancer associated antigen described herein, wherein the sequence of the antigen binding domain is contiguous with and in the same reading frame as a nucleic acid sequence encoding an intracellular signaling domain. The intracellular signaling domain can comprise a costimulatory signaling domain and/or a primary signaling domain, e.g., a zeta chain. The costimulatory signaling domain refers to a portion of the CAR comprising at least a portion of the intracellular domain of a costimulatory molecule.

In specific aspects, a CAR construct of the invention comprises a scFv domain, wherein the scFv may be preceded by an optional leader sequence such as provided in SEQ ID NO: 2, and followed by an optional hinge sequence such as provided in SEQ ID NO:4 or SEQ ID NO:6 or SEQ ID NO:8 or SEQ ID NO:10, a transmembrane region such as provided in SEQ ID NO:12, an intracellular signalling domain that includes SEQ ID NO:14 or SEQ ID NO:16 and a CD3 zeta sequence that includes SEQ ID NO:18 or SEQ ID NO:20, e.g., wherein the domains are contiguous with and in the same reading frame to form a single fusion protein.

In one aspect, an exemplary CAR constructs comprise an optional leader sequence (e.g., a leader sequence described herein), an extracellular antigen binding domain (e.g., an antigen binding domain described herein), a hinge (e.g., a hinge region described herein), a transmembrane domain (e.g., a transmembrane domain described herein), and an intracellular stimulatory domain (e.g., an intracellular stimulatory domain decribed herein). In one aspect, an exemplary CAR construct comprises an optional leader sequence (e.g., a leader sequence described herein), an extracellular antigen binding domain (e.g., an antigen binding domain described herein), a hinge (e.g., a hinge region described herein), a transmembrane domain (e.g., a transmembrane domain described herein), an intracellular costimulatory signaling domain (e.g.,

a costimulatory signaling domain described herein) and/or an intracellular primary signaling domain (e.g., a primary signaling domain described herein).

An exemplary leader sequence is provided as SEQ ID NO: 2. An exemplary hinge/spacer sequence is provided as SEQ ID NO: 4 or SEQ ID NO:6 or SEQ ID NO:8 or SEQ ID NO:10. An exemplary transmembrane domain sequence is provided as SEQ ID NO:12. An exemplary sequence of the intracellular signaling domain of the 4-1BB protein is provided as SEQ ID NO: 14. An exemplary sequence of the intracellular signaling domain of CD27 is provided as SEQ ID NO:16. An exemplary CD3zeta domain sequence is provided as SEQ ID NO: 18 or SEQ ID NO:20.

In one aspect, the present invention encompasses a recombinant nucleic acid construct comprising a nucleic acid molecule encoding a CAR, wherein the nucleic acid molecule comprises the nucleic acid sequence encoding an antigen binding domain, e.g., described herein, that is contiguous with and in the same reading frame as a nucleic acid sequence encoding an intracellular signaling domain.

In one aspect, the present invention encompasses a recombinant nucleic acid construct comprising a nucleic acid molecule encoding a CAR, wherein the nucleic acid molecule comprises a nucleic acid sequence encoding an antigen binding domain, wherein the sequence is contiguous with and in the same reading frame as the nucleic acid sequence encoding an intracellular signaling domain. An exemplary intracellular signaling domain that can be used in the CAR includes, but is not limited to, one or more intracellular signaling domains of, e.g., CD3-zeta, CD28, CD27, 4-1BB, and the like. In some instances, the CAR can comprise any combination of CD3-zeta, CD28, 4-1BB, and the like.

The nucleic acid sequences coding for the desired molecules can be obtained using recombinant methods known in the art, such as, for example by screening libraries from cells expressing the nucleic acid molecule, by deriving the nucleic acid molecule from a vector known to include the same, or by isolating directly from cells and tissues containing the same, using standard techniques. Alternatively, the nucleic acid of interest can be produced synthetically, rather than cloned.

The present invention includes retroviral and lentiviral vector constructs expressing a CAR that can be directly transduced into a cell.

The present invention also includes an RNA construct that can be directly transfected into a cell. A method for generating mRNA for use in transfection involves *in vitro* transcription (IVT) of a template with specially designed primers, followed by polyA addition, to produce a construct containing 3' and 5' untranslated sequence ("UTR") (e.g., a 3' and/or 5' UTR described herein), a 5' cap (e.g., a 5' cap described herein) and/or Internal Ribosome Entry Site (IRES) (e.g., an IRES described herein), the nucleic acid to be expressed, and a polyA tail, typically 50-2000 bases in length (SEQ ID NO:32). RNA so produced can efficiently transfect different kinds of cells. In one embodiment, the template includes sequences for the CAR. In an embodiment, an RNA CAR vector is transduced into a cell, e.g., a T cell or a NK cell, by electroporation.

Antigen binding domain

In one aspect, the CAR of the invention comprises a target-specific binding element otherwise referred to as an antigen binding domain. The choice of moiety depends upon the type and number of ligands that define the surface of a target cell. For example, the antigen binding domain may be chosen to recognize a ligand that acts as a cell surface marker on target cells associated with a particular disease state. Thus, examples of cell surface markers that may act as ligands for the antigen binding domain in a CAR of the invention include those associated with viral, bacterial and parasitic infections, autoimmune disease and cancer cells.

In one aspect, the CAR-mediated T-cell response can be directed to an antigen of interest by way of engineering an antigen binding domain that specifically binds a desired antigen into the CAR.

In one aspect, the portion of the CAR comprising the antigen binding domain comprises an antigen binding domain that targets a tumor antigen, e.g., a tumor antigen described herein.

The antigen binding domain can be any domain that binds to the antigen including but not limited to a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a human antibody, a humanized antibody, and a functional fragment thereof, including but not limited to a single-domain antibody such as a heavy chain variable domain (VH), a light chain variable domain (VL) and a variable domain (VHH) of camelid derived nanobody, and to an alternative scaffold known in the art to function as antigen binding domain, such as a recombinant fibronectin domain, a T cell receptor (TCR), or a fragment there of, e.g., single chain TCR, and

the like. In some instances, it is beneficial for the antigen binding domain to be derived from the same species in which the CAR will ultimately be used in. For example, for use in humans, it may be beneficial for the antigen binding domain of the CAR to comprise human or humanized residues for the antigen binding domain of an antibody or antibody fragment.

In one embodiment, the CD19 CAR is a CD19 CAR described in US Pat. No. 8,399,645; US Pat. No. 7,446,190; Xu et al., Leuk Lymphoma. 2013 54(2):255-260(2012); Cruz et al., Blood 122(17):2965-2973 (2013); Brentjens et al., Blood, 118(18):4817-4828 (2011); Kochenderfer et al., Blood 116(20):4099-102 (2010); Kochenderfer et al., Blood 122 (25):4129-39(2013); or 16th Annu Meet Am Soc Gen Cell Ther (ASGCT) (May 15-18, Salt Lake City) 2013, Abst 10 (each of which is herein incorporated by reference in their entirety). In one embodiment, an antigen binding domain against CD19 is an antigen binding portion, e.g., CDRs, of a CAR, antibody or antigen-binding fragment thereof described in, e.g., PCT publication WO2012/079000 (incorporated herein by reference in its entirety). In one embodiment, an antigen binding domain against CD19 is an antigen binding portion, e.g., CDRs, of a CAR, antibody or antigen-binding fragment thereof described in, e.g., PCT publication WO2014/153270; Kochenderfer, J.N. et al., J. Immunother. 32 (7), 689-702 (2009); Kochenderfer, J.N., et al., Blood, 116 (20), 4099-4102 (2010); PCT publication WO2014/031687; Bejcek, Cancer Research, 55, 2346-2351, 1995; or U.S. Patent No. 7,446,190 (each of which is herein incorporated by reference in their entirety).

In one embodiment, the antigen binding domain against mesothelin is or may be derived from an antigen binding domain, e.g., CDRs, scFv, or VH and VL, of an antibody, antigen-binding fragment or CAR described in, e.g., PCT publication WO2015/090230 (In one embodiment the CAR is a CAR described in WO2015/090230, the contents of which are incorporated herein in their entirety). In embodiments, the antigen binding domain against mesothelin is or is derived from an antigen binding portion, e.g., CDRs, scFv, or VH and VL, of an antibody, antigen-binding fragment, or CAR described in, e.g., PCT publication WO1997/025068, WO1999/028471, WO2005/014652, WO2006/099141, WO2009/045957, WO2009/068204, WO2013/142034, WO2013/040557, or WO2013/063419 (each of which is herein incorporated by reference in their entirety).

In one embodiment, an antigen binding domain against CD123 is or is derived from an antigen binding portion, e.g., CDRs, scFv or VH and VL, of an antibody, antigen-binding

fragment or CAR described in, e.g., PCT publication WO2014/130635 (incorporated herein by referenc in its entirety). In one embodiment, an antigen binding domain against CD123 is or is derived from an antigen binding portion, e.g., CDRs, scFv or VH and VL, of an antibody, antigen-binding fragment or CAR described in, e.g., PCT publication WO2016/028896 (incorporated herein by referenc in its entirety); in embodiments, the CAR is a CAR described in WO2016/028896. In one embodiment, an antigen binding domain against CD123 is or is derived from an antigen binding portion, e.g., CDRs, scFv, or VL and VH, of an antibody, antigen-binding fragment, or CAR described in, e.g., PCT publication WO1997/024373, WO2008/127735 (e.g., a CD123 binding domain of 26292, 32701, 37716 or 32703), WO2014/138805 (e.g., a CD123 binding domain of CSL362), WO2014/138819, WO2013/173820, WO2014/144622, WO2001/66139, WO2010/126066 (e.g., the CD123 binding domain of any of Old4, Old5, Old17, Old19, New102, or Old6), WO2014/144622, or US2009/0252742 (each of which is incorporated herein by referenc in its entirety).

In one embodiment, an antigen binding domain against CD22 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Haso et al., Blood, 121(7): 1165-1174 (2013); Wayne et al., Clin Cancer Res 16(6): 1894-1903 (2010); Kato et al., Leuk Res 37(1):83-88 (2013); Creative BioMart (creativebiomart.net): MOM-18047-S(P).

In one embodiment, an antigen binding domain against CS-1 is an antigen binding portion, e.g., CDRs, of Elotuzumab (BMS), see e.g., Tai et al., 2008, Blood 112(4):1329-37; Tai et al., 2007, Blood. 110(5):1656-63.

In one embodiment, an antigen binding domain against CLL-1 is an antigen binding portion, e.g., CDRs or VH and VL, of an antibody, antigen-binding fragment or CAR described in, e.g., PCT publication WO2016/014535, the contents of which are incorporated herein in their entirety. In one embodiment, an antigen binding domain against CLL-1 is an antigen binding portion, e.g., CDRs, of an antibody available from R&D, ebiosciences, Abcam, for example, PE-CLL1-hu Cat# 353604 (BioLegend); and PE-CLL1 (CLEC12A) Cat# 562566 (BD).

In one embodiment, an antigen binding domain against CD33 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Bross et al., Clin Cancer Res 7(6):1490-1496 (2001) (Gemtuzumab Ozogamicin, hP67.6),Caron et al., Cancer Res 52(24):6761-6767 (1992) (Lintuzumab, HuM195), Lapusan et al., Invest New Drugs 30(3):1121-1131 (2012) (AVE9633), Aigner et al., Leukemia 27(5): 1107-1115 (2013) (AMG330, CD33 BiTE), Dutour

et al., Adv hematol 2012:683065 (2012), and Pizzitola et al., Leukemia doi:10.1038/Lue.2014.62 (2014). Exemplary CAR molecules that target CD33 are described herein, and are provided in WO2016/014576, e.g., in Table 2 of WO2016/014576 (incorporated by reference in its entirety).

In one embodiment, an antigen binding domain against GD2 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Mujoo et al., Cancer Res. 47(4):1098-1104 (1987); Cheung et al., Cancer Res 45(6):2642-2649 (1985), Cheung et al., J Clin Oncol 5(9):1430-1440 (1987), Cheung et al., J Clin Oncol 16(9):3053-3060 (1998), Handgretinger et al., Cancer Immunol Immunother 35(3):199-204 (1992). In some embodiments, an antigen binding domain against GD2 is an antigen binding portion of an antibody selected from mAb 14.18, 14G2a, ch14.18, hu14.18, 3F8, hu3F8, 3G6, 8B6, 60C3, 10B8, ME36.1, and 8H9, see e.g., WO2012033885, WO2013040371, WO2013192294, WO2013061273, WO2013123061, WO2013074916, and WO201385552. In some embodiments, an antigen binding domain against GD2 is an antigen binding portion of an antibody described in US Publication No.: 20100150910 or PCT Publication No.: WO 2011160119.

In one embodiment, an antigen binding domain against BCMA is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., WO2012163805, WO200112812, and WO2003062401. In embodiments, additional exemplary BCMA CAR constructs are generated using an antigen binding domain, e.g., CDRs, scFv, or VH and VL sequences from PCT Publication WO2012/0163805 (the contents of which are hereby incorporated by reference in its entirety). In embodiments, additional exemplary BCMA CAR constructs are generated using an antigen binding domain, e.g., CDRs, scFv, or VH and VL sequences from PCT Publication WO2016/014565 (the contents of which are hereby incorporated by reference in its entirety). In embodiments, additional exemplary BCMA CAR constructs are generated using an antigen binding domain, e.g., CDRs, scFv, or VH and VL sequences from PCT Publication WO2014/122144 (the contents of which are hereby incorporated by reference in its entirety). In embodiments, additional exemplary BCMA CAR constructs are generated using the CAR molecules, and/or the BCMA binding domains (e.g., CDRs, scFv, or VH and VL sequences) from PCT Publication WO2016/014789 (the contents of which are hereby incorporated by reference in its entirety). In embodiments, additional exemplary BCMA CAR constructs are generated using the CAR molecules, and/or the BCMA binding domains (e.g., CDRs, scFv, or VH and VL sequences) from PCT Publication WO2014/089335 (the contents of which are

hereby incorporated by reference in its entirety). In embodiments, additional exemplary BCMA CAR constructs are generated using the CAR molecules, and/or the BCMA binding domains (e.g., CDRs, scFv, or VH and VL sequences) from PCT Publication WO2014/140248 (the contents of which are hereby incorporated by reference in its entirety).

In one embodiment, an antigen binding domain against Tn antigen is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., US 2014/0178365, US8,440,798, Brooks et al., PNAS 107(22):10056-10061 (2010), and Stone et al., OncoImmunology 1(6):863-873(2012).

In one embodiment, an antigen binding domain against PSMA is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Parker et al., Protein Expr Purif 89(2):136-145 (2013), US 20110268656 (J591 ScFv); Frigerio et al, European J Cancer 49(9):2223-2232 (2013) (scFvD2B); WO 2006125481 (mAbs 3/A12, 3/E7 and 3/F11) and single chain antibody fragments (scFv A5 and D7).

In one embodiment, an antigen binding domain against ROR1 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Hudecek et al., Clin Cancer Res 19(12):3153-3164 (2013); WO 2011159847; and US20130101607.

In one embodiment, an antigen binding domain against FLT3 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., WO2011076922, US5777084, EP0754230, US20090297529, and several commercial catalog antibodies (R&D, ebiosciences, Abcam).

In one embodiment, an antigen binding domain against TAG72 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Hombach et al., Gastroenterology 113(4):1163-1170 (1997); and Abcam ab691.

In one embodiment, an antigen binding domain against FAP is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Ostermann et al., Clinical Cancer Research 14:4584-4592 (2008) (FAP5), US Pat. Publication No. 2009/0304718; sibrotuzumab (see e.g., Hofheinz et al., Oncology Research and Treatment 26(1), 2003); and Tran et al., J Exp Med 210(6):1125-1135 (2013).

In one embodiment, an antigen binding domain against CD38 is an antigen binding portion, e.g., CDRs, of daratumumab (see, e.g., Groen et al., Blood 116(21):1261-1262 (2010); MOR202 (see, e.g., US8,263,746); or antibodies described in US8,362,211.

In one embodiment, an antigen binding domain against CD44v6 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Casucci et al., Blood 122(20):3461-3472 (2013).

In one embodiment, an antigen binding domain against CEA is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Chmielewski et al., Gastoenterology 143(4):1095-1107 (2012).

In one embodiment, an antigen binding domain against EPCAM is an antigen binding portion, e.g., CDRS, of an antibody selected from MT110, EpCAM-CD3 bispecific Ab (see, e.g., clinicaltrials.gov/ct2/show/NCT00635596); Edrecolomab; 3622W94; ING-1; and adecatumumab (MT201).

In one embodiment, an antigen binding domain against PRSS21 is an antigen binding portion, e.g., CDRs, of an antibody described in US Patent No.: 8,080,650.

In one embodiment, an antigen binding domain against B7H3 is an antigen binding portion, e.g., CDRs, of an antibody MGA271 (Macrogenics).

In one embodiment, an antigen binding domain against KIT is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., US7915391, US20120288506 , and several commercial catalog antibodies.

In one embodiment, an antigen binding domain against IL-13Ra2 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., WO2008/146911, WO2004087758, several commercial catalog antibodies, and WO2004087758.

In one embodiment, an antigen binding domain against CD30 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., US7090843 B1, and EP0805871.

In one embodiment, an antigen binding domain against GD3 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., US7253263; US 8,207,308; US 20120276046; EP1013761; WO2005035577; and US6437098.

In one embodiment, an antigen binding domain against CD171 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Hong et al., J Immunother 37(2):93-104 (2014).

In one embodiment, an antigen binding domain against IL-11Ra is an antigen binding portion, e.g., CDRs, of an antibody available from Abcam (cat# ab55262) or Novus Biologicals

(cat# EPR5446). In another embodiment, an antigen binding domain again IL-11Ra is a peptide, see, e.g., Huang et al., Cancer Res 72(1):271-281 (2012).

In one embodiment, an antigen binding domain against PSCA is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Morgenroth et al., Prostate 67(10):1121-1131 (2007) (scFv 7F5); Nejatollahi et al., J of Oncology 2013(2013), article ID 839831 (scFv C5-II); and US Pat Publication No. 20090311181.

In one embodiment, an antigen binding domain against VEGFR2 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Chinnasamy et al., J Clin Invest 120(11):3953-3968 (2010).

In one embodiment, an antigen binding domain against LewisY is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Kelly et al., Cancer Biother Radiopharm 23(4):411-423 (2008) (hu3S193 Ab (scFvs)); Dolezal et al., Protein Engineering 16(1):47-56 (2003) (NC10 scFv).

In one embodiment, an antigen binding domain against CD24 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Maliar et al., Gastroenterology 143(5):1375-1384 (2012).

In one embodiment, an antigen binding domain against PDGFR-beta is an antigen binding portion, e.g., CDRs, of an antibody Abcam ab32570.

In one embodiment, an antigen binding domain against SSEA-4 is an antigen binding portion, e.g., CDRs, of antibody MC813 (Cell Signaling), or other commercially available antibodies.

In one embodiment, an antigen binding domain against CD20 is an antigen binding portion, e.g., CDRs, of the antibody Rituximab, Ofatumumab, Ocrelizumab, Veltuzumab, or GA101.

In one embodiment, an antigen binding domain against Folate receptor alpha is an antigen binding portion, e.g., CDRs, of the antibody IMGN853, or an antibody described in US20120009181; US4851332, LK26: US5952484.

In one embodiment, an antigen binding domain against ERBB2 (Her2/neu) is an antigen binding portion, e.g., CDRs, of the antibody trastuzumab, or pertuzumab.

In one embodiment, an antigen binding domain against MUC1 is an antigen binding portion, e.g., CDRs, of the antibody SAR566658.

In one embodiment, the antigen binding domain against EGFR is antigen binding portion, e.g., CDRs, of the antibody cetuximab, panitumumab, zalutumumab, nimotuzumab, or matuzumab. In one embodiment, the antigen binding domain against EGFRvIII is or may be derived from an antigen binding domain, e.g., CDRs, scFv, or VH and VL, of an antibody, antigen-binding fragment or CAR described in, e.g., PCT publication WO2014/130657 (In one embodiment the CAR is a CAR described in WO2014/130657, the contents of which are incorporated herein in their entirety).

In one embodiment, an antigen binding domain against NCAM is an antigen binding portion, e.g., CDRs, of the antibody clone 2-2B: MAB5324 (EMD Millipore)

In one embodiment, an antigen binding domain against Ephrin B2 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Abengozar et al., Blood 119(19):4565-4576 (2012).

In one embodiment, an antigen binding domain against IGF-I receptor is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., US8344112 B2; EP2322550 A1; WO 2006/138315, or PCT/US2006/022995.

In one embodiment, an antigen binding domain against CAIX is an antigen binding portion, e.g., CDRs, of the antibody clone 303123 (R&D Systems).

In one embodiment, an antigen binding domain against LMP2 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., US7,410,640, or US20050129701.

In one embodiment, an antigen binding domain against gp100 is an antigen binding portion, e.g., CDRs, of the antibody HMB45, NKIbetaB, or an antibody described in WO2013165940, or US20130295007

In one embodiment, an antigen binding domain against tyrosinase is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., US5843674; or US19950504048.

In one embodiment, an antigen binding domain against EphA2 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Yu et al., Mol Ther 22(1):102-111 (2014).

In one embodiment, an antigen binding domain against GD3 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., US7253263; US 8,207,308; US 20120276046; EP1013761 A3; 20120276046; WO2005035577; or US6437098.

In one embodiment, an antigen binding domain against fucosyl GM1 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., US20100297138; or WO2007/067992.

In one embodiment, an antigen binding domain against sLe is an antigen binding portion, e.g., CDRs, of the antibody G193 (for lewis Y), see Scott AM et al, Cancer Res 60: 3254-61 (2000), also as described in Neeson et al, J Immunol May 2013 190 (Meeting Abstract Supplement) 177.10.

In one embodiment, an antigen binding domain against GM3 is an antigen binding portion, e.g., CDRs, of the antibody CA 2523449 (mAb 14F7).

In one embodiment, an antigen binding domain against HMWMAA is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Kmiecik et al., Oncoimmunology 3(1):e27185 (2014) (PMID: 24575382) (mAb9.2.27); US6528481; WO2010033866; or US 20140004124.

In one embodiment, an antigen binding domain against o-acetyl-GD2 is an antigen binding portion, e.g., CDRs, of the antibody 8B6.

In one embodiment, an antigen binding domain against TEM1/CD248 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Marty et al., Cancer Lett 235(2):298-308 (2006); Zhao et al., J Immunol Methods 363(2):221-232 (2011).

In one embodiment, an antigen binding domain against CLDN6 is an antigen binding portion, e.g., CDRs, of the antibody IMAB027 (Ganymed Pharmaceuticals), see e.g., clinicaltrial.gov/show/NCT02054351.

In one embodiment, an antigen binding domain against TSHR is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., US8,603,466; US8,501,415; or US8,309,693.

In one embodiment, an antigen binding domain against GPRC5D is an antigen binding portion, e.g., CDRs, of the antibody FAB6300A (R&D Systems); or LS-A4180 (Lifespan Biosciences).

In one embodiment, an antigen binding domain against CD97 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., US6,846,911;de Groot et al., J Immunol 183(6):4127-4134 (2009); or an antibody from R&D:MAB3734.

In one embodiment, an antigen binding domain against ALK is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Mino-Kenudson et al., Clin Cancer Res 16(5):1561-1571 (2010).

In one embodiment, an antigen binding domain against polysialic acid is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Nagae et al., J Biol Chem 288(47):33784-33796 (2013).

In one embodiment, an antigen binding domain against PLAC1 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Ghods et al., Biotechnol Appl Biochem 2013 doi:10.1002/bab.1177.

In one embodiment, an antigen binding domain against GloboH is an antigen binding portion of the antibody VK9; or an antibody described in, e.g., Kudryashov V et al, Glycoconj J.15(3):243-9 (1998), Lou et al., Proc Natl Acad Sci USA 111(7):2482-2487 (2014) ; MBr1: Bremer E-G et al. J Biol Chem 259:14773–14777 (1984).

In one embodiment, an antigen binding domain against NY-BR-1 is an antigen binding portion, e.g., CDRs of an antibody described in, e.g., Jager et al., Appl Immunohistochem Mol Morphol 15(1):77-83 (2007).

In one embodiment, an antigen binding domain against WT-1 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Dao et al., Sci Transl Med 5(176):176ra33 (2013); or WO2012/135854.

In one embodiment, an antigen binding domain against MAGE-A1 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Willemsen et al., J Immunol 174(12):7853-7858 (2005) (TCR-like scFv).

In one embodiment, an antigen binding domain against sperm protein 17 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Song et al., Target Oncol 2013 Aug 14 (PMID: 23943313); Song et al., Med Oncol 29(4):2923-2931 (2012).

In one embodiment, an antigen binding domain against Tie 2 is an antigen binding portion, e.g., CDRs, of the antibody AB33 (Cell Signaling Technology).

In one embodiment, an antigen binding domain against MAD-CT-2 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., PMID: 2450952; US7635753.

In one embodiment, an antigen binding domain against Fos-related antigen 1 is an antigen binding portion, e.g., CDRs, of the antibody 12F9 (Novus Biologicals).

In one embodiment, an antigen binding domain against MelanA/MART1 is an antigen binding portion, e.g., CDRs, of an antibody described in, EP2514766 A2; or US 7,749,719.

In one embodiment, an antigen binding domain against sarcoma translocation breakpoints is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Luo et al, EMBO Mol. Med. 4(6):453-461 (2012).

In one embodiment, an antigen binding domain against TRP-2 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Wang et al, J Exp Med. 184(6):2207-16 (1996).

In one embodiment, an antigen binding domain against CYP1B1 is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., Maecker et al, Blood 102 (9): 3287-3294 (2003).

In one embodiment, an antigen binding domain against RAGE-1 is an antigen binding portion, e.g., CDRs, of the antibody MAB5328 (EMD Millipore).

In one embodiment, an antigen binding domain against human telomerase reverse transcriptase is an antigen binding portion, e.g., CDRs, of the antibody cat no: LS-B95-100 (Lifespan Biosciences)

In one embodiment, an antigen binding domain against intestinal carboxyl esterase is an antigen binding portion, e.g., CDRs, of the antibody 4F12: cat no: LS-B6190-50 (Lifespan Biosciences).

In one embodiment, an antigen binding domain against mut hsp70-2 is an antigen binding portion, e.g., CDRs, of the antibody Lifespan Biosciences: monoclonal: cat no: LS-C133261-100 (Lifespan Biosciences).

In one embodiment, an antigen binding domain against CD79a is an antigen binding portion, e.g., CDRs, of the antibody Anti-CD79a antibody [HM47/A9] (ab3121), available from Abcam; antibody CD79A Antibody #3351 available from Cell Signalling Technology; or antibody HPA017748 - Anti-CD79A antibody produced in rabbit, available from Sigma Aldrich.

In one embodiment, an antigen binding domain against CD79b is an antigen binding portion, e.g., CDRs, of the antibody polatuzumab vedotin, anti-CD79b described in Dornan et al., "Therapeutic potential of an anti-CD79b antibody-drug conjugate, anti-CD79b-vc-MMAE, for the treatment of non-Hodgkin lymphoma" Blood. 2009 Sep 24;114(13):2721-9. doi: 10.1182/blood-2009-02-205500. Epub 2009 Jul 24, or the bispecific antibody Anti-CD79b/CD3

described in "4507 Pre-Clinical Characterization of T Cell-Dependent Bispecific Antibody Anti-CD79b/CD3 As a Potential Therapy for B Cell Malignancies" Abstracts of 56th ASH Annual Meeting and Exposition, San Francisco, CA December 6-9 2014.

In one embodiment, an antigen binding domain against CD72 is an antigen binding portion, e.g., CDRs, of the antibody J3-109 described in Myers, and Uckun, "An anti-CD72 immunotoxin against therapy-refractory B-lineage acute lymphoblastic leukemia." Leuk Lymphoma. 1995 Jun;18(1-2):119-22, or anti-CD72 (10D6.8.1, mIgG1) described in Polson et al., "Antibody-Drug Conjugates for the Treatment of Non–Hodgkin's Lymphoma: Target and Linker-Drug Selection" Cancer Res March 15, 2009 69; 2358.

In one embodiment, an antigen binding domain against LAIR1 is an antigen binding portion, e.g., CDRs, of the antibody ANT-301 LAIR1 antibody, available from ProSpec; or anti-human CD305 (LAIR1) Antibody, available from BioLegend.

In one embodiment, an antigen binding domain against FCAR is an antigen binding portion, e.g., CDRs, of the antibody CD89/FCARAntibody (Catalog#10414-H08H), available from Sino Biological Inc.

In one embodiment, an antigen binding domain against LILRA2 is an antigen binding portion, e.g., CDRs, of the antibody LILRA2 monoclonal antibody (M17), clone 3C7, available from Abnova, or Mouse Anti-LILRA2 antibody, Monoclonal (2D7), available from Lifespan Biosciences..

In one embodiment, an antigen binding domain against CD300LF is an antigen binding portion, e.g., CDRs, of the antibody Mouse Anti-CMRF35-like molecule 1 antibody, Monoclonal[UP-D2], available from BioLegend, or Rat Anti-CMRF35-like molecule 1 antibody, Monoclonal[234903], available from R&D Systems..

In one embodiment, an antigen binding domain against CLEC12A is an antigen binding portion, e.g., CDRs, of the antibody Bispecific T cell Engager (BiTE) scFv-antibody and ADC described in Noordhuis et al., "Targeting of CLEC12A In Acute Myeloid Leukemia by Antibody-Drug-Conjugates and Bispecific CLL-1xCD3 BiTE Antibody" 53rd ASH Annual Meeting and Exposition, December 10-13, 2011, and MCLA-117 (Merus).

In one embodiment, an antigen binding domain against BST2 (also called CD317) is an antigen binding portion, e.g., CDRs, of the antibody Mouse Anti-CD317 antibody,

Monoclonal[3H4], available from Antibodies-Online or Mouse Anti-CD317 antibody, Monoclonal[696739], available from R&D Systems.

In one embodiment, an antigen binding domain against EMR2 (also called CD312) is an antigen binding portion, e.g., CDRs, of the antibody Mouse Anti-CD312 antibody, Monoclonal[LS-B8033] available from Lifespan Biosciences, or Mouse Anti-CD312 antibody, Monoclonal[494025] available from R&D Systems.

In one embodiment, an antigen binding domain against LY75 is an antigen binding portion, e.g., CDRs, of the antibody Mouse Anti-Lymphocyte antigen 75 antibody, Monoclonal[HD30] available from EMD Millipore or Mouse Anti-Lymphocyte antigen 75 antibody, Monoclonal[A15797] available from Life Technologies.

In one embodiment, an antigen binding domain against GPC3 is an antigen binding portion, e.g., CDRs, of the antibody hGC33 described in Nakano K, Ishiguro T, Konishi H, et al. Generation of a humanized anti-glypican 3 antibody by CDR grafting and stability optimization. Anticancer Drugs. 2010 Nov;21(10):907–916, or MDX-1414, HN3, or YP7, all three of which are described in Feng et al., "Glypican-3 antibodies: a new therapeutic target for liver cancer." FEBS Lett. 2014 Jan 21;588(2):377-82.

In one embodiment, an antigen binding domain against FCRL5 is an antigen binding portion, e.g., CDRs, of the anti-FcRL5 antibody described in Elkins et al., "FcRL5 as a target of antibody-drug conjugates for the treatment of multiple myeloma" Mol Cancer Ther. 2012 Oct;11(10):2222-32. .

In one embodiment, an antigen binding domain against IGLL1 is an antigen binding portion, e.g., CDRs, of the antibody Mouse Anti-Immunoglobulin lambda-like polypeptide 1 antibody, Monoclonal[AT1G4] available from Lifespan Biosciences, Mouse Anti-Immunoglobulin lambda-like polypeptide 1 antibody, Monoclonal[HSL11] available from BioLegend.

In one embodiment, the antigen binding domain comprises one, two three (e.g., all three) heavy chain CDRs, HC CDR1, HC CDR2 and HC CDR3, from an antibody listed above, and/or one, two, three (e.g., all three) light chain CDRs, LC CDR1, LC CDR2 and LC CDR3, from an antibody listed above. In one embodiment, the antigen binding domain comprises a heavy chain variable region and/or a variable light chain region of an antibody listed above.

In another aspect, the antigen binding domain comprises a humanized antibody or an antibody fragment. In some aspects, a non-human antibody is humanized, where specific sequences or regions of the antibody are modified to increase similarity to an antibody naturally produced in a human or fragment thereof. In one aspect, the antigen binding domain is humanized.

A humanized antibody can be produced using a variety of techniques known in the art, including but not limited to, CDR-grafting (see, e.g., European Patent No. EP 239,400; International Publication No. WO 91/09967; and U.S. Pat. Nos. 5,225,539, 5,530,101, and 5,585,089, each of which is incorporated herein in its entirety by reference), veneering or resurfacing (see, e.g., European Patent Nos. EP 592,106 and EP 519,596; Padlan, 1991, Molecular Immunology, 28(4/5):489-498; Studnicka et al., 1994, Protein Engineering, 7(6):805-814; and Roguska et al., 1994, PNAS, 91:969-973, each of which is incorporated herein by its entirety by reference), chain shuffling (see, e.g., U.S. Pat. No. 5,565,332, which is incorporated herein in its entirety by reference), and techniques disclosed in, e.g., U.S. Patent Application Publication No. US2005/0042664, U.S. Patent Application Publication No. US2005/0048617, U.S. Pat. No. 6,407,213, U.S. Pat. No. 5,766,886, International Publication No. WO 9317105, Tan et al., J. Immunol., 169:1119-25 (2002), Caldas et al., Protein Eng., 13(5):353-60 (2000), Morea et al., Methods, 20(3):267-79 (2000), Baca et al., J. Biol. Chem., 272(16):10678-84 (1997), Roguska et al., Protein Eng., 9(10):895-904 (1996), Couto et al., Cancer Res., 55 (23 Supp):5973s-5977s (1995), Couto et al., Cancer Res., 55(8):1717-22 (1995), Sandhu J S, Gene, 150(2):409-10 (1994), and Pedersen et al., J. Mol. Biol., 235(3):959-73 (1994), each of which is incorporated herein in its entirety by reference. Often, framework residues in the framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, for example improve, antigen binding. These framework substitutions are identified by methods well-known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Pat. No. 5,585,089; and Riechmann et al., 1988, Nature, 332:323, which are incorporated herein by reference in their entireties.)

A humanized antibody or antibody fragment has one or more amino acid residues remaining in it from a source which is nonhuman. These nonhuman amino acid residues are

often referred to as "import" residues, which are typically taken from an "import" variable domain. As provided herein, humanized antibodies or antibody fragments comprise one or more CDRs from nonhuman immunoglobulin molecules and framework regions wherein the amino acid residues comprising the framework are derived completely or mostly from human germline. Multiple techniques for humanization of antibodies or antibody fragments are well-known in the art and can essentially be performed following the method of Winter and co-workers (Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-327 (1988); Verhoeyen et al., Science, 239:1534-1536 (1988)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody, i.e., CDR-grafting (EP 239,400; PCT Publication No. WO 91/09967; and U.S. Pat. Nos. 4,816,567; 6,331,415; 5,225,539; 5,530,101; 5,585,089; 6,548,640, the contents of which are incorporated herein by reference herein in their entirety). In such humanized antibodies and antibody fragments, substantially less than an intact human variable domain has been substituted by the corresponding sequence from a nonhuman species. Humanized antibodies are often human antibodies in which some CDR residues and possibly some framework (FR) residues are substituted by residues from analogous sites in rodent antibodies. Humanization of antibodies and antibody fragments can also be achieved by veneering or resurfacing (EP 592,106; EP 519,596; Padlan, 1991, Molecular Immunology, 28(4/5):489-498; Studnicka et al., Protein Engineering, 7(6):805-814 (1994); and Roguska et al., PNAS, 91:969-973 (1994)) or chain shuffling (U.S. Pat. No. 5,565,332), the contents of which are incorporated herein by reference herein in their entirety.

The choice of human variable domains, both light and heavy, to be used in making the humanized antibodies is to reduce antigenicity. According to the so-called "best-fit" method, the sequence of the variable domain of a rodent antibody is screened against the entire library of known human variable-domain sequences. The human sequence which is closest to that of the rodent is then accepted as the human framework (FR) for the humanized antibody (Sims et al., J. Immunol., 151:2296 (1993); Chothia et al., J. Mol. Biol., 196:901 (1987), the contents of which are incorporated herein by reference herein in their entirety). Another method uses a particular framework derived from the consensus sequence of all human antibodies of a particular subgroup of light or heavy chains. The same framework may be used for several different humanized antibodies (see, e.g., Nicholson et al. Mol. Immun. 34 (16-17): 1157-1165 (1997); Carter et al., Proc. Natl. Acad. Sci. USA, 89:4285 (1992); Presta et al., J. Immunol., 151:2623

(1993), the contents of which are incorporated herein by reference herein in their entirety). In some embodiments, the framework region, e.g., all four framework regions, of the heavy chain variable region are derived from a VH4_4-59 germline sequence. In one embodiment, the framework region can comprise, one, two, three, four or five modifications, e.g., substitutions, e.g., from the amino acid at the corresponding murine sequence. In one embodiment, the framework region, e.g., all four framework regions of the light chain variable region are derived from a VK3_1.25 germline sequence. In one embodiment, the framework region can comprise, one, two, three, four or five modifications, e.g., substitutions, e.g., from the amino acid at the corresponding murine sequence.

In some aspects, the portion of a CAR composition of the invention that comprises an antibody fragment is humanized with retention of high affinity for the target antigen and other favorable biological properties. According to one aspect of the invention, humanized antibodies and antibody fragments are prepared by a process of analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, e.g., the analysis of residues that influence the ability of the candidate immunoglobulin to bind the target antigen. In this way, FR residues can be selected and combined from the recipient and import sequences so that the desired antibody or antibody fragment characteristic, such as increased affinity for the target antigen, is achieved. In general, the CDR residues are directly and most substantially involved in influencing antigen binding.

A humanized antibody or antibody fragment may retain a similar antigenic specificity as the original antibody, e.g., in the present invention, the ability to bind human a cancer associated antigen as described herein. In some embodiments, a humanized antibody or antibody fragment may have improved affinity and/or specificity of binding to human a cancer associated antigen as described herein.

In one aspect, the antigen binding domain of the invention is characterized by particular functional features or properties of an antibody or antibody fragment. For example, in one

aspect, the portion of a CAR composition of the invention that comprises an antigen binding domain specifically binds a tumor antigen as described herein.

In one aspect, the anti-cancer associated antigen as described herein binding domain is a fragment, e.g., a single chain variable fragment (scFv). In one aspect, the anti- cancer associated antigen as described herein binding domain is a Fv, a Fab, a (Fab')2, or a bi-functional (e.g. bi-specific) hybrid antibody (e.g., Lanzavecchia et al., Eur. J. Immunol. 17, 105 (1987)). In one aspect, the antibodies and fragments thereof of the invention binds a cancer associated antigen as described herein protein with wild-type or enhanced affinity.

In some instances, scFvs can be prepared according to method known in the art (see, for example, Bird et al., (1988) Science 242:423-426 and Huston et al., (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883). ScFv molecules can be produced by linking VH and VL regions together using flexible polypeptide linkers. The scFv molecules comprise a linker (e.g., a Ser-Gly linker) with an optimized length and/or amino acid composition. The linker length can greatly affect how the variable regions of a scFv fold and interact. In fact, if a short polypeptide linker is employed (e.g., between 5-10 amino acids) intrachain folding is prevented. Interchain folding is also required to bring the two variable regions together to form a functional epitope binding site. For examples of linker orientation and size see, e.g., Hollinger et al. 1993 Proc Natl Acad. Sci. U.S.A. 90:6444-6448, U.S. Patent Application Publication Nos. 2005/0100543, 2005/0175606, 2007/0014794, and PCT publication Nos. WO2006/020258 and WO2007/024715, is incorporated herein by reference.

An scFv can comprise a linker of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, or more amino acid residues between its VL and VH regions. The linker sequence may comprise any naturally occurring amino acid. In some embodiments, the linker sequence comprises amino acids glycine and serine. In another embodiment, the linker sequence comprises sets of glycine and serine repeats such as $(Gly_4Ser)n$, where n is a positive integer equal to or greater than 1 (SEQ ID NO:22). In one embodiment, the linker can be $(Gly_4Ser)_4$ (SEQ ID NO:29) or $(Gly_4Ser)_3$(SEQ ID NO:30). Variation in the linker length may retain or enhance activity, giving rise to superior efficacy in activity studies.

In another aspect, the antigen binding domain is a T cell receptor ("TCR"), or a fragment thereof, for example, a single chain TCR (scTCR). Methods to make such TCRs are known in the art. See, e.g., Willemsen RA et al, Gene Therapy 7: 1369–1377 (2000); Zhang T et al,

Cancer Gene Ther 11: 487–496 (2004); Aggen et al, Gene Ther. 19(4):365-74 (2012) (references are incorporated herein by its entirety). For example, scTCR can be engineered that contains the Vα and Vβ genes from a T cell clone linked by a linker (e.g., a flexible peptide). This approach is very useful to cancer associated target that itself is intracellar, however, a fragment of such antigen (peptide) is presented on the surface of the cancer cells by MHC.

Bispecific CARs

In an embodiment a multispecific antibody molecule is a bispecific antibody molecule. A bispecific antibody has specificity for no more than two antigens. A bispecific antibody molecule is characterized by a first immunoglobulin variable domain sequence which has binding specificity for a first epitope and a second immunoglobulin variable domain sequence that has binding specificity for a second epitope. In an embodiment the first and second epitopes are on the same antigen, e.g., the same protein (or subunit of a multimeric protein). In an embodiment the first and second epitopes overlap. In an embodiment the first and second epitopes do not overlap. In an embodiment the first and second epitopes are on different antigens, e.g., different proteins (or different subunits of a multimeric protein). In an embodiment a bispecific antibody molecule comprises a heavy chain variable domain sequence and a light chain variable domain sequence which have binding specificity for a first epitope and a heavy chain variable domain sequence and a light chain variable domain sequence which have binding specificity for a second epitope. In an embodiment a bispecific antibody molecule comprises a half antibody having binding specificity for a first epitope and a half antibody having binding specificity for a second epitope. In an embodiment a bispecific antibody molecule comprises a half antibody, or fragment thereof, having binding specificity for a first epitope and a half antibody, or fragment thereof, having binding specificity for a second epitope. In an embodiment a bispecific antibody molecule comprises a scFv, or fragment thereof, have binding specificity for a first epitope and a scFv, or fragment thereof, have binding specificity for a second epitope.

In certain embodiments, the antibody molecule is a multi-specific (*e.g.*, a bispecific or a trispecific) antibody molecule. Protocols for generating bispecific or heterodimeric antibody molecules are known in the art; including but not limited to, for example, the "knob in a hole" approach described in, *e.g.*, US 5731168; the electrostatic steering Fc pairing as described in,

e.g., WO 09/089004, WO 06/106905 and WO 2010/129304; Strand Exchange Engineered Domains (SEED) heterodimer formation as described in, *e.g.*, WO 07/110205; Fab arm exchange as described in, *e.g.*, WO 08/119353, WO 2011/131746, and WO 2013/060867; double antibody conjugate, *e.g.*, by antibody cross-linking to generate a bi-specific structure using a heterobifunctional reagent having an amine-reactive group and a sulfhydryl reactive group as described in, *e.g.*, US 4433059; bispecific antibody determinants generated by recombining half antibodies (heavy-light chain pairs or Fabs) from different antibodies through cycle of reduction and oxidation of disulfide bonds between the two heavy chains, as described in, *e.g.*, US 4444878; trifunctional antibodies, *e.g.*, three Fab' fragments cross-linked through sulfhdryl reactive groups, as described in, *e.g.*, US5273743; biosynthetic binding proteins, *e.g.*, pair of scFvs cross-linked through C-terminal tails preferably through disulfide or amine-reactive chemical cross-linking, as described in, *e.g.*, US5534254; bifunctional antibodies, *e.g.*, Fab fragments with different binding specificities dimerized through leucine zippers (*e.g.*, c-fos and c-jun) that have replaced the constant domain, as described in, *e.g.*, US5582996; bispecific and oligospecific mono-and oligovalent receptors, *e.g.*, VH-CH1 regions of two antibodies (two Fab fragments) linked through a polypeptide spacer between the CH1 region of one antibody and the VH region of the other antibody typically with associated light chains, as described in, *e.g.*, US5591828; bispecific DNA-antibody conjugates, *e.g.*, crosslinking of antibodies or Fab fragments through a double stranded piece of DNA, as described in, *e.g.*, US5635602; bispecific fusion proteins, *e.g.*, an expression construct containing two scFvs with a hydrophilic helical peptide linker between them and a full constant region, as described in, *e.g.*, US5637481; multivalent and multispecific binding proteins, *e.g.*, dimer of polypeptides having first domain with binding region of Ig heavy chain variable region, and second domain with binding region of Ig light chain variable region, generally termed diabodies (higher order structures are also encompassed creating for bispecifc, trispecific, or tetraspecific molecules, as described in, *e.g.*, US5837242; minibody constructs with linked VL and VH chains further connected with peptide spacers to an antibody hinge region and CH3 region, which can be dimerized to form bispecific/multivalent molecules, as described in, *e.g.*, US5837821; VH and VL domains linked with a short peptide linker (*e.g.*, 5 or 10 amino acids) or no linker at all in either orientation, which can form dimers to form bispecific diabodies; trimers and tetramers, as described in, *e.g.*, US5844094; String of VH domains (or VL domains in family members) connected by peptide

linkages with crosslinkable groups at the C-terminus futher associated with VL domains to form a series of FVs (or scFvs), as described in, *e.g.*, US5864019; and single chain binding polypeptides with both a VH and a VL domain linked through a peptide linker are combined into multivalent structures through non-covalent or chemical crosslinking to form, *e.g.*, homobivalent, heterobivalent, trivalent, and tetravalent structures using both scFV or diabody type format, as described in, *e.g.*, US5869620. Additional exemplary multispecific and bispecific molecules and methods of making the same are found, for example, in US5910573, US5932448, US5959083, US5989830, US6005079, US6239259, US6294353, US6333396, US6476198, US6511663, US6670453, US6743896, US6809185, US6833441, US7129330, US7183076, US7521056, US7527787, US7534866, US7612181, US2002004587A1, US2002076406A1, US2002103345A1, US2003207346A1, US2003211078A1, US2004219643A1, US2004220388A1, US2004242847A1, US2005003403A1, US2005004352A1, US2005069552A1, US2005079170A1, US2005100543A1, US2005136049A1, US2005136051A1, US2005163782A1, US2005266425A1, US2006083747A1, US2006120960A1, US2006204493A1, US2006263367A1, US2007004909A1, US2007087381A1, US2007128150A1, US2007141049A1, US2007154901A1, US2007274985A1, US2008050370A1, US2008069820A1, US2008152645A1, US2008171855A1, US2008241884A1, US2008254512A1, US2008260738A1, US2009130106A1, US2009148905A1, US2009155275A1, US2009162359A1, US2009162360A1, US2009175851A1, US2009175867A1, US2009232811A1, US2009234105A1, US2009263392A1, US2009274649A1, EP346087A2, WO0006605A2, WO02072635A2, WO04081051A1, WO06020258A2, WO2007044887A2, WO2007095338A2, WO2007137760A2, WO2008119353A1, WO2009021754A2, WO2009068630A1, WO9103493A1, WO9323537A1, WO9409131A1, WO9412625A2, WO9509917A1, WO9637621A2, WO9964460A1. The contents of the above-referenced applications are incorporated herein by reference in their entireties.

Within each antibody or antibody fragment (e.g., scFv) of a bispecific antibody molecule, the VH can be upstream or downstream of the VL. In some embodiments, the upstream antibody or antibody fragment (e.g., scFv) is arranged with its VH (VH_1) upstream of its VL (VL_1) and the downstream antibody or antibody fragment (e.g., scFv) is arranged with its VL (VL_2) upstream of its VH (VH_2), such that the overall bispecific antibody molecule has the arrangement VH_1-

VL_1-VL_2-VH_2. In other embodiments, the upstream antibody or antibody fragment (e.g., scFv) is arranged with its VL (VL_1) upstream of its VH (VH_1) and the downstream antibody or antibody fragment (e.g., scFv) is arranged with its VH (VH_2) upstream of its VL (VL_2), such that the overall bispecific antibody molecule has the arrangement VL_1-VH_1-VH_2-VL_2. Optionally, a linker is disposed between the two antibodies or antibody fragments (e.g., scFvs), e.g., between VL_1 and VL_2 if the construct is arranged as VH_1-VL_1-VL_2-VH_2, or between VH_1 and VH_2 if the construct is arranged as VL_1-VH_1-VH_2-VL_2. The linker may be a linker as described herein, e.g., a (Gly_4-Ser)n linker, wherein n is 1, 2, 3, 4, 5, or 6, preferably 4 (SEQ ID NO: 72). In general, the linker between the two scFvs should be long enough to avoid mispairing between the domains of the two scFvs. Optionally, a linker is disposed between the VL and VH of the first scFv. Optionally, a linker is disposed between the VL and VH of the second scFv. In constructs that have multiple linkers, any two or more of the linkers can be the same or different. Accordingly, in some embodiments, a bispecific CAR comprises VLs, VHs, and optionally one or more linkers in an arrangement as described herein.

Stability and Mutations

The stability of an antigen binding domain to a cancer associated antigen as described herein, e.g., scFv molecules (e.g., soluble scFv), can be evaluated in reference to the biophysical properties (e.g., thermal stability) of a conventional control scFv molecule or a full length antibody. In one embodiment, the humanized scFv has a thermal stability that is greater than about 0.1, about 0.25, about 0.5, about 0.75, about 1, about 1.25, about 1.5, about 1.75, about 2, about 2.5, about 3, about 3.5, about 4, about 4.5, about 5, about 5.5, about 6, about 6.5, about 7, about 7.5, about 8, about 8.5, about 9, about 9.5, about 10 degrees, about 11 degrees, about 12 degrees, about 13 degrees, about 14 degrees, or about 15 degrees Celsius than a control binding molecule (e.g. a conventional scFv molecule) in the described assays.

The improved thermal stability of the antigen binding domain to a cancer associated antigen described herein, e.g., scFv is subsequently conferred to the entire CAR construct, leading to improved therapeutic properties of the CAR construct. The thermal stability of the antigen binding domain of -a cancer associated antigen described herein, e.g., scFv, can be improved by at least about 2°C or 3°C as compared to a conventional antibody. In one embodiment, the antigen binding domain of-a cancer associated antigen described herein, e.g.,

scFv, has a 1°C improved thermal stability as compared to a conventional antibody. In another embodiment, the antigen binding domain of a cancer associated antigen described herein, e.g., scFv, has a 2°C improved thermal stability as compared to a conventional antibody. In another embodiment, the scFv has a 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15°C improved thermal stability as compared to a conventional antibody. Comparisons can be made, for example, between the scFv molecules disclosed herein and scFv molecules or Fab fragments of an antibody from which the scFv VH and VL were derived. Thermal stability can be measured using methods known in the art. For example, in one embodiment, Tm can be measured. Methods for measuring Tm and other methods of determining protein stability are described in more detail below.

Mutations in scFv (arising through humanization or direct mutagenesis of the soluble scFv) can alter the stability of the scFv and improve the overall stability of the scFv and the CAR construct. Stability of the humanized scFv is compared against the murine scFv using measurements such as Tm, temperature denaturation and temperature aggregation.

The binding capacity of the mutant scFvs can be determined using assays know in the art and described herein.

In one embodiment, the antigen binding domain of -a cancer associated antigen described herein, e.g., scFv, comprises at least one mutation arising from the humanization process such that the mutated scFv confers improved stability to the CAR construct. In another embodiment, the antigen binding domain of -a cancer associated antigen described herein, e.g., scFv, comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 mutations arising from the humanization process such that the mutated scFv confers improved stability to the CAR construct.

Methods of Evaluating Protein Stability

The stability of an antigen binding domain may be assessed using, e.g., the methods described below. Such methods allow for the determination of multiple thermal unfolding transitions where the least stable domain either unfolds first or limits the overall stability threshold of a multidomain unit that unfolds cooperatively (e.g., a multidomain protein which exhibits a single unfolding transition). The least stable domain can be identified in a number of additional ways. Mutagenesis can be performed to probe which domain limits the overall stability. Additionally, protease resistance of a multidomain protein can be performed under conditions where the least stable domain is known to be intrinsically unfolded via DSC or other spectroscopic methods (Fontana, et al., (1997) Fold. Des., 2: R17-26; Dimasi et al. (2009) J. Mol.

Biol. 393: 672-692). Once the least stable domain is identified, the sequence encoding this domain (or a portion thereof) may be employed as a test sequence in the methods.

a) Thermal Stability

The thermal stability of the compositions may be analyzed using a number of non-limiting biophysical or biochemical techniques known in the art. In certain embodiments, thermal stability is evaluated by analytical spectroscopy.

An exemplary analytical spectroscopy method is Differential Scanning Calorimetry (DSC). DSC employs a calorimeter which is sensitive to the heat absorbances that accompany the unfolding of most proteins or protein domains (see, e.g. Sanchez-Ruiz, et al., Biochemistry, 27: 1648-52, 1988). To determine the thermal stability of a protein, a sample of the protein is inserted into the calorimeter and the temperature is raised until the Fab or scFv unfolds. The temperature at which the protein unfolds is indicative of overall protein stability.

Another exemplary analytical spectroscopy method is Circular Dichroism (CD) spectroscopy. CD spectrometry measures the optical activity of a composition as a function of increasing temperature. Circular dichroism (CD) spectroscopy measures differences in the absorption of left-handed polarized light versus right-handed polarized light which arise due to structural asymmetry. A disordered or unfolded structure results in a CD spectrum very different from that of an ordered or folded structure. The CD spectrum reflects the sensitivity of the proteins to the denaturing effects of increasing temperature and is therefore indicative of a protein's thermal stability (see van Mierlo and Steemsma, J. Biotechnol., 79(3):281-98, 2000).

Another exemplary analytical spectroscopy method for measuring thermal stability is Fluorescence Emission Spectroscopy (see van Mierlo and Steemsma, supra). Yet another exemplary analytical spectroscopy method for measuring thermal stability is Nuclear Magnetic Resonance (NMR) spectroscopy (see, e.g. van Mierlo and Steemsma, supra).

The thermal stability of a composition can be measured biochemically. An exemplary biochemical method for assessing thermal stability is a thermal challenge assay. In a "thermal challenge assay", a composition is subjected to a range of elevated temperatures for a set period of time. For example, in one embodiment, test scFv molecules or molecules comprising scFv molecules are subject to a range of increasing temperatures, e.g., for 1-1.5 hours. The activity of the protein is then assayed by a relevant biochemical assay. For example, if the protein is a

binding protein (e.g. an scFv or scFv-containing polypeptide) the binding activity of the binding protein may be determined by a functional or quantitative ELISA.

Such an assay may be done in a high-throughput format and those disclosed in the Examples using *E. coli* and high throughput screening. A library of antigen binding domains, e.g., that includes an antigen binding domain to -a cancer associated antigen described herein, e.g., scFv variants, may be created using methods known in the art. Antigen binding domain, e.g., to -a cancer associated antigen described herein, e.g., scFv, expression may be induced and the antigen binding domain, e.g., to -a cancer associated antigen described herein, e.g., scFv, may be subjected to thermal challenge. The challenged test samples may be assayed for binding and those antigen binding domains to -a cancer associated antigen described herein, e.g., scFvs, which are stable may be scaled up and further characterized.

Thermal stability is evaluated by measuring the melting temperature (Tm) of a composition using any of the above techniques (e.g. analytical spectroscopy techniques). The melting temperature is the temperature at the midpoint of a thermal transition curve wherein 50% of molecules of a composition are in a folded state (See e.g., Dimasi et al. (2009) J. Mol Biol. 393: 672-692). In one embodiment, Tm values for an antigen binding domain to -a cancer associated antigen described herein, e.g., scFv, are about 40°C, 41°C, 42°C, 43°C, 44°C, 45°C, 46°C, 47°C, 48°C, 49°C, 50°C, 51°C, 52°C, 53°C, 54°C, 55°C, 56°C, 57°C, 58°C, 59°C, 60°C, 61°C, 62°C, 63°C, 64°C, 65°C, 66°C, 67°C, 68°C, 69°C, 70°C, 71°C, 72°C, 73°C, 74°C, 75°C, 76°C, 77°C, 78°C, 79°C, 80°C, 81°C, 82°C, 83°C, 84°C, 85°C, 86°C, 87°C, 88°C, 89°C, 90°C, 91°C, 92°C, 93°C, 94°C, 95°C, 96°C, 97°C, 98°C, 99°C, 100°C. In one embodiment, Tm values for an IgG is about 40°C, 41°C, 42°C, 43°C, 44°C, 45°C, 46°C, 47°C, 48°C, 49°C, 50°C, 51°C, 52°C, 53°C, 54°C, 55°C, 56°C, 57°C, 58°C, 59°C, 60°C, 61°C, 62°C, 63°C, 64°C, 65°C, 66°C, 67°C, 68°C, 69°C, 70°C, 71°C, 72°C, 73°C, 74°C, 75°C, 76°C, 77°C, 78°C, 79°C, 80°C, 81°C, 82°C, 83°C, 84°C, 85°C, 86°C, 87°C, 88°C, 89°C, 90°C, 91°C, 92°C, 93°C, 94°C, 95°C, 96°C, 97°C, 98°C, 99°C, 100°C. In one embodiment, Tm values for an multivalent antibody is about 40°C, 41°C, 42°C, 43°C, 44°C, 45°C, 46°C, 47°C, 48°C, 49°C, 50°C, 51°C, 52°C, 53°C, 54°C, 55°C, 56°C, 57°C, 58°C, 59°C, 60°C, 61°C, 62°C, 63°C, 64°C, 65°C, 66°C, 67°C, 68°C, 69°C, 70°C, 71°C, 72°C, 73°C, 74°C, 75°C, 76°C, 77°C, 78°C, 79°C, 80°C, 81°C, 82°C, 83°C, 84°C, 85°C, 86°C, 87°C, 88°C, 89°C, 90°C, 91°C, 92°C, 93°C, 94°C, 95°C, 96°C, 97°C, 98°C, 99°C, 100°C.

Thermal stability is also evaluated by measuring the specific heat or heat capacity (Cp) of a composition using an analytical calorimetric technique (e.g. DSC). The specific heat of a composition is the energy (e.g. in kcal/mol) is required to rise by 1°C, the temperature of 1 mol of water. As large Cp is a hallmark of a denatured or inactive protein composition. The change in heat capacity (ΔCp) of a composition is measured by determining the specific heat of a composition before and after its thermal transition. Thermal stability may also be evaluated by measuring or determining other parameters of thermodynamic stability including Gibbs free energy of unfolding (ΔG), enthalpy of unfolding (ΔH), or entropy of unfolding (ΔS). One or more of the above biochemical assays (e.g. a thermal challenge assay) are used to determine the temperature (i.e. the T_C value) at which 50% of the composition retains its activity (e.g. binding activity).

In addition, mutations to the antigen binding domain of a cancer associated antigen described herein, e.g., scFv, can be made to alter the thermal stability of the antigen binding domain of a cancer associated antigen described herein, e.g., scFv, as compared with the unmutated antigen binding domain of a cancer associated antigen described herein, e.g., scFv. When the humanized antigen binding domain of a cancer associated antigen described herein, e.g., scFv, is incorporated into a CAR construct, the antigen binding domain of the cancer associated antigen described herein, e.g., humanized scFv, confers thermal stability to the overall CARs of the present invention. In one embodiment, the antigen binding domain to a cancer associated antigen described herein, e.g., scFv, comprises a single mutation that confers thermal stability to the antigen binding domain of the cancer associated antigen described herein, e.g., scFv. In another embodiment, the antigen binding domain to a cancer associated antigen described herein, e.g., scFv, comprises multiple mutations that confer thermal stability to the antigen binding domain to the cancer associated antigen described herein, e.g., scFv. In one embodiment, the multiple mutations in the antigen binding domain to a cancer associated antigen described herein, e.g., scFv, have an additive effect on thermal stability of the antigen binding domain to the cancer associated antigen described herein binding domain, e.g., scFv.

b) % Aggregation

The stability of a composition can be determined by measuring its propensity to aggregate. Aggregation can be measured by a number of non-limiting biochemical or biophysical techniques. For example, the aggregation of a composition may be evaluated using

chromatography, e.g. Size-Exclusion Chromatography (SEC). SEC separates molecules on the basis of size. A column is filled with semi-solid beads of a polymeric gel that will admit ions and small molecules into their interior but not large ones. When a protein composition is applied to the top of the column, the compact folded proteins (i.e. non-aggregated proteins) are distributed through a larger volume of solvent than is available to the large protein aggregates. Consequently, the large aggregates move more rapidly through the column, and in this way the mixture can be separated or fractionated into its components. Each fraction can be separately quantified (e.g. by light scattering) as it elutes from the gel. Accordingly, the % aggregation of a composition can be determined by comparing the concentration of a fraction with the total concentration of protein applied to the gel. Stable compositions elute from the column as essentially a single fraction and appear as essentially a single peak in the elution profile or chromatogram.

c) Binding Affinity

The stability of a composition can be assessed by determining its target binding affinity. A wide variety of methods for determining binding affinity are known in the art. An exemplary method for determining binding affinity employs surface plasmon resonance. Surface plasmon resonance is an optical phenomenon that allows for the analysis of real-time biospecific interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIAcore system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, N.J.). For further descriptions, see Jonsson, U., et al. (1993) Ann. Biol. Clin. 51:19-26; Jonsson, U., i (1991) Biotechniques 11:620-627; Johnsson, B., et al. (1995) J. Mol. Recognit. 8:125-131; and Johnnson, B., et al. (1991) Anal. Biochem. 198:268-277.

In one aspect, the antigen binding domain of the CAR comprises an amino acid sequence that is homologous to an antigen binding domain amino acid sequence described herein, and the antigen binding domain retains the desired functional properties of the antigen binding domain described herein.

In one specific aspect, the CAR composition of the invention comprises an antibody fragment. In a further aspect, the antibody fragment comprises an scFv.

In various aspects, the antigen binding domain of the CAR is engineered by modifying one or more amino acids within one or both variable regions (e.g., VH and/or VL), for example within one or more CDR regions and/or within one or more framework regions. In one specific

aspect, the CAR composition of the invention comprises an antibody fragment. In a further aspect, the antibody fragment comprises an scFv.

It will be understood by one of ordinary skill in the art that the antibody or antibody fragment of the invention may further be modified such that they vary in amino acid sequence (e.g., from wild-type), but not in desired activity. For example, additional nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues may be made to the protein For example, a nonessential amino acid residue in a molecule may be replaced with another amino acid residue from the same side chain family. In another embodiment, a string of amino acids can be replaced with a structurally similar string that differs in order and/or composition of side chain family members, e.g., a conservative substitution, in which an amino acid residue is replaced with an amino acid residue having a similar side chain, may be made.

Families of amino acid residues having similar side chains have been defined in the art, including 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), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine).

Percent identity in the context of two or more nucleic acids or polypeptide sequences, refers to two or more sequences that are the same. Two sequences are "substantially identical" if two sequences have a specified percentage of amino acid residues or nucleotides that are the same (e.g., 60% identity, optionally 70%, 71%. 72%. 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%,81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity over a specified region, or, when not specified, over the entire sequence), when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using one of the following sequence comparison algorithms or by manual alignment and visual inspection. Optionally, the identity exists over a region that is at least about 50 nucleotides (or 10 amino acids) in length, or more preferably over a region that is 100 to 500 or 1000 or more nucleotides (or 20, 50, 200 or more amino acids) in length.

For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are entered into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. Default program parameters can be used, or alternative parameters can be designated. The sequence comparison algorithm then calculates the percent sequence identities for the test sequences relative to the reference sequence, based on the program parameters. Methods of alignment of sequences for comparison are well known in the art. Optimal alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith and Waterman, (1970) Adv. Appl. Math. 2:482c, by the homology alignment algorithm of Needleman and Wunsch, (1970) J. Mol. Biol. 48:443, by the search for similarity method of Pearson and Lipman, (1988) Proc. Nat'l. Acad. Sci. USA 85:2444, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by manual alignment and visual inspection (see, e.g., Brent et al., (2003) Current Protocols in Molecular Biology).

Two examples of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al., (1977) Nuc. Acids Res. 25:3389-3402; and Altschul et al., (1990) J. Mol. Biol. 215:403-410, respectively. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information.

The percent identity between two amino acid sequences can also be determined using the algorithm of E. Meyers and W. Miller, (1988) Comput. Appl. Biosci. 4:11-17) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch (1970) J. Mol. Biol. 48:444-453) algorithm which has been incorporated into the GAP program in the GCG software package (available at www.gcg.com), using either a Blossom 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

In one aspect, the present invention contemplates modifications of the starting antibody or fragment (e.g., scFv) amino acid sequence that generate functionally equivalent molecules. For example, the VH or VL of an antigen binding domain to -a cancer associated antigen

described herein, e.g., scFv, comprised in the CAR can be modified to retain at least about 70%, 71%. 72%. 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%,81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity of the starting VH or VL framework region of the antigen binding domain to the cancer associated antigen described herein, e.g., scFv. The present invention contemplates modifications of the entire CAR construct, e.g., modifications in one or more amino acid sequences of the various domains of the CAR construct in order to generate functionally equivalent molecules. The CAR construct can be modified to retain at least about 70%, 71%. 72%. 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% identity of the starting CAR construct.

Transmembrane domain

With respect to the transmembrane domain, in various embodiments, a CAR can be designed to comprise a transmembrane domain that is attached to the extracellular domain of the CAR. A transmembrane domain can include one or more additional amino acids adjacent to the transmembrane region, e.g., one or more amino acid associated with the extracellular region of the protein from which the transmembrane was derived (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 up to 15 amino acids of the extracellular region) and/or one or more additional amino acids associated with the intracellular region of the protein from which the transmembrane protein is derived (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 up to 15 amino acids of the intracellular region). In one aspect, the transmembrane domain is one that is associated with one of the other domains of the CAR e.g., in one embodiment, the transmembrane domain may be from the same protein that the signaling domain, costimulatory domain or the hinge domain is derived from. In another aspect, the transmembrane domain is not derived from the same protein that any other domain of the CAR is derived from. 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, e.g., to minimize interactions with other members of the receptor complex. In one aspect, the transmembrane domain is capable of homodimerization with another CAR on the cell surface of a CAR-expressing cell. In a different aspect, the amino acid sequence of the transmembrane domain may be modified or substituted so

as to minimize interactions with the binding domains of the native binding partner present in the same CAR-expressing cell.

The transmembrane domain may be derived either from a natural or from a recombinant source. Where the source is natural, the domain may be derived from any membrane-bound or transmembrane protein. In one aspect the transmembrane domain is capable of signaling to the intracellular domain(s) whenever the CAR has bound to a target. A transmembrane domain of particular use in this invention may include at least the transmembrane region(s) of e.g., the alpha, beta or zeta chain of the T-cell receptor, CD28, CD27, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154. In some embodiments, a transmembrane domain may include at least the transmembrane region(s) of, e.g., KIRDS2, OX40, CD2, CD27, LFA-1 (CD11a, CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD40, BAFFR, HVEM (LIGHTR), SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD160, CD19, IL2R beta, IL2R gamma, IL7R α, ITGA1, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, TNFR2, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, PAG/Cbp, NKG2D, NKG2C.

In some instances, the transmembrane domain can be attached to the extracellular region of the CAR, e.g., the antigen binding domain of the CAR, via a hinge, e.g., a hinge from a human protein. For example, in one embodiment, the hinge can be a human Ig (immunoglobulin) hinge (e.g., an IgG4 hinge, an IgD hinge), a GS linker (e.g., a GS linker described herein), a KIR2DS2 hinge or a CD8a hinge. In one embodiment, the hinge or spacer comprises (e.g., consists of) the amino acid sequence of SEQ ID NO:4. In one aspect, the transmembrane domain comprises (e.g., consists of) a transmembrane domain of SEQ ID NO: 12.

In one aspect, the hinge or spacer comprises an IgG4 hinge. For example, in one embodiment, the hinge or spacer comprises a hinge of the amino acid sequence ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP

VLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKM (SEQ ID NO:6). In some embodiments, the hinge or spacer comprises a hinge encoded by a nucleotide sequence of

GAGAGCAAGTACGGCCCTCCCTGCCCCCCTTGCCCTGCCCCCGAGTTCCTGGGCGGA
CCCAGCGTGTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCCGGACC
CCCGAGGTGACCTGTGTGGTGGTGGACGTGTCCCAGGAGGACCCCGAGGTCCAGTT
CAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCCCGGGAG
GAGCAGTTCAATAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGA
CTGGCTGAACGGCAAGGAATACAAGTGTAAGGTGTCCAACAAGGGCCTGCCCAGCA
GCATCGAGAAAACCATCAGCAAGGCCAAGGGCCAGCCTCGGGAGCCCCAGGTGTAC
ACCCTGCCCCCTAGCCAAGAGGAGATGACCAAGAACCAGGTGTCCCTGACCTGCCT
GGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGC
CCGAGAACAACTACAAGACCACCCCCCCTGTGCTGGACAGCGACGGCAGCTTCTTC
CTGTACAGCCGGCTGACCGTGGACAAGAGCCGGTGGCAGGAGGGCAACGTCTTTAG
CTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGAGCCTGAGCC
TGTCCCTGGGCAAGATG (SEQ ID NO:7).

In one aspect, the hinge or spacer comprises an IgD hinge. For example, in one embodiment, the hinge or spacer comprises a hinge of the amino acid sequence RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGRGGEEKKKEKEKEEQEERETK TPECPSHTQPLGVYLLTPAVQDLWLRDKATFTCFVVGSDLKDAHLTWEVAGKVPTGGV EEGLLERHSNGSQSQHSRLTLPRSLWNAGTSVTCTLNHPSLPPQRLMALREPAAQAPVK LSLNLLASSDPPEAASWLLCEVSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTF WAWSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVSYVTDH (SEQ ID NO:8). In some embodiments, the hinge or spacer comprises a hinge encoded by a nucleotide sequence of

AGGTGGCCCGAAAGTCCCAAGGCCCAGGCATCTAGTGTTCCTACTGCACAGCCCCA
GGCAGAAGGCAGCCTAGCCAAAGCTACTACTGCACCTGCCACTACGCGCAATACTG
GCCGTGGCGGGGAGGAGAAGAAAAAGGAGAAAGAGAAAGAAGAACAGGAAGAGA
GGGAGACCAAGACCCCTGAATGTCCATCCCATACCCAGCCGCTGGGCGTCTATCTCT
TGACTCCCGCAGTACAGGACTTGTGGCTTAGAGATAAGGCCACCTTTACATGTTTCG
TCGTGGGCTCTGACCTGAAGGATGCCCATTTGACTTGGGAGGTTGCCGGAAAGGTAC
CCACAGGGGGGGTTGAGGAAGGGTTGCTGGAGCGCCATTCCAATGGCTCTCAGAGC

CAGCACTCAAGACTCACCCTTCCGAGATCCCTGTGGAACGCCGGGACCTCTGTCACA
TGTACTCTAAATCATCCTAGCCTGCCCCCACAGCGTCTGATGGCCCTTAGAGAGCCA
GCCGCCCAGGCACCAGTTAAGCTTAGCCTGAATCTGCTCGCCAGTAGTGATCCCCCA
GAGGCCGCCAGCTGGCTCTTATGCGAAGTGTCCGGCTTTAGCCCGCCCAACATCTTG
CTCATGTGGCTGGAGGACCAGCGAGAAGTGAACACCAGCGGCTTCGCTCCAGCCCG
GCCCCCACCCCAGCCGGGTTCTACCACATTCTGGGCCTGGAGTGTCTTAAGGGTCCC
AGCACCACCTAGCCCCCAGCCAGCCACATACACCTGTGTTGTGTCCCATGAAGATAG
CAGGACCCTGCTAAATGCTTCTAGGAGTCTGGAGGTTTCCTACGTGACTGACCATT
(SEQ ID NO:9).

In one aspect, the transmembrane domain may be recombinant, in which case it will comprise predominantly hydrophobic residues such as leucine and valine. In one aspect a triplet of phenylalanine, tryptophan and valine can be found at each end of a recombinant transmembrane domain.

Optionally, a short oligo- or polypeptide linker, between 2 and 10 amino acids in length may form the linkage between the transmembrane domain and the cytoplasmic region of the CAR. A glycine-serine doublet provides a particularly suitable linker. For example, in one aspect, the linker comprises the amino acid sequence of GGGGSGGGGS (SEQ ID NO: 10). In some embodiments, the linker is encoded by a nucleotide sequence of GGTGGCGGAGGTTCTGGAGGTGGAGGTTCC (SEQ ID NO: 11).

In one aspect, the hinge or spacer comprises a KIR2DS2 hinge.

Cytoplasmic domain

The cytoplasmic domain or region of the CAR includes an intracellular signaling domain. An intracellular signaling domain is generally responsible for activation of at least one of the normal effector functions of the immune cell in which the CAR has been introduced. The term "effector function" refers to a specialized function of a cell. Effector function of a T cell, for example, may be cytolytic activity or helper activity including the secretion of cytokines. Thus the term "intracellular signaling domain" refers to the portion of a protein which transduces the effector function signal and directs the cell to perform a specialized function. While usually the entire intracellular signaling domain can be employed, in many cases it is not necessary to use the entire chain. To the extent that a truncated portion of the intracellular signaling domain is

used, such truncated portion may be used in place of the intact chain as long as it transduces the effector function signal. The term intracellular signaling domain is thus meant to include any truncated portion of the intracellular signaling domain sufficient to transduce the effector function signal.

Examples of intracellular signaling domains for use in the CAR of the invention include the 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 recombinant sequence that has the same functional capability.

It is known that signals generated through the TCR alone are insufficient for full activation of the T cell and that a secondary and/or costimulatory signal is also required. Thus, T cell activation can be said to be mediated by two distinct classes of cytoplasmic signaling sequences: those that initiate antigen-dependent primary activation through the TCR (primary intracellular signaling domains) and those that act in an antigen-independent manner to provide a secondary or costimulatory signal (secondary cytoplasmic domain, e.g., a costimulatory domain).

A primary signaling domain regulates primary activation of the TCR complex either in a stimulatory way, or in an inhibitory way. Primary intracellular signaling domains that act in a stimulatory manner may contain signaling motifs which are known as immunoreceptor tyrosine-based activation motifs or ITAMs.

Examples of ITAM containing primary intracellular signaling domains that are of particular use in the invention include those of CD3 zeta, common FcR gamma (FCER1G), Fc gamma RIIa, FcR beta (Fc Epsilon R1b), CD3 gamma, CD3 delta, CD3 epsilon, CD79a, CD79b, DAP10, and DAP12. In one embodiment, a CAR of the invention comprises an intracellular signaling domain, e.g., a primary signaling domain of CD3-zeta.

In one embodiment, a primary signaling domain comprises a modified ITAM domain, e.g., a mutated ITAM domain which has altered (e.g., increased or decreased) activity as compared to the native ITAM domain. In one embodiment, a primary signaling domain comprises a modified ITAM-containing primary intracellular signaling domain, e.g., an optimized and/or truncated ITAM-containing primary intracellular signaling domain. In an embodiment, a primary signaling domain comprises one, two, three, four or more ITAM motifs.

The intracellular signalling domain of the CAR can comprise the CD3-zeta signaling domain by itself or it can be combined with any other desired intracellular signaling domain(s)

useful in the context of a CAR of the invention. For example, the intracellular signaling domain of the CAR can comprise a CD3 zeta chain portion and a costimulatory signaling domain. The costimulatory signaling domain refers to a portion of the CAR comprising the intracellular domain of a costimulatory molecule. A costimulatory molecule is a cell surface molecule other than an antigen receptor or its ligands that is required for an efficient response of lymphocytes to an antigen. Examples of such molecules include CD27, CD28, 4-1BB (CD137), OX40, CD30, CD40, PD-1, ICOS, lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, B7-H3, and a ligand that specifically binds with CD83, and the like. For example, CD27 costimulation has been demonstrated to enhance expansion, effector function, and survival of human CART cells in vitro and augments human T cell persistence and antitumor activity in vivo (Song et al. Blood. 2012; 119(3):696-706). Further examples of such costimulatory molecules include CDS, ICAM-1, GITR, BAFFR, HVEM (LIGHTR), SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD160, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), NKG2D, CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, and CD19a.

The intracellular signaling sequences within the cytoplasmic portion of the CAR of the invention may be linked to each other in a random or specified order. Optionally, a short oligo- or polypeptide linker, for example, between 2 and 10 amino acids (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids) in length may form the linkage between intracellular signaling sequence. In one embodiment, a glycine-serine doublet can be used as a suitable linker. In one embodiment, a single amino acid, e.g., an alanine, a glycine, can be used as a suitable linker.

In one aspect, the intracellular signaling domain is designed to comprise two or more, e.g., 2, 3, 4, 5, or more, costimulatory signaling domains. In an embodiment, the two or more, e.g., 2, 3, 4, 5, or more, costimulatory signaling domains, are separated by a linker molecule, e.g., a linker molecule described herein. In one embodiment, the intracellular signaling domain

comprises two costimulatory signaling domains. In some embodiments, the linker molecule is a glycine residue. In some embodiments, the linker is an alanine residue.

In one aspect, the intracellular signaling domain is designed to comprise the signaling domain of CD3-zeta and the signaling domain of CD28. In one aspect, the intracellular signaling domain is designed to comprise the signaling domain of CD3-zeta and the signaling domain of 4-1BB. In one aspect, the signaling domain of 4-1BB is a signaling domain of SEQ ID NO: 14. In one aspect, the signaling domain of CD3-zeta is a signaling domain of SEQ ID NO: 18.

In one aspect, the intracellular signaling domain is designed to comprise the signaling domain of CD3-zeta and the signaling domain of CD27. In one aspect, the signaling domain of CD27 comprises an amino acid sequence of QRRKYRSNKGESPVEPAEPCRYSCPREEEGSTIPIQEDYRKPEPACSP (SEQ ID NO: 16). In one aspect, the signalling domain of CD27 is encoded by a nucleic acid sequence of AGGAGTAAGAGGAGCAGGCTCCTGCACAGTGACTACATGAACATGACTCCCCGCCG CCCCGGGCCCACCCGCAAGCATTACCAGCCCTATGCCCCACCACGCGACTTCGCAGC CTATCGCTCC (SEQ ID NO: 17).

In one aspect, the CAR-expressing cell described herein can further comprise a second CAR, e.g., a second CAR that includes a different antigen binding domain, e.g., to the same target or a different target (e.g., a target other than a cancer associated antigen described herein or a different cancer associated antigen described herein). In one embodiment, the second CAR includes an antigen binding domain to a target expressed the same cancer cell type as the cancer associated antigen. In one embodiment, the CAR-expressing cell comprises a first CAR that targets a first antigen and includes an intracellular signaling domain having a costimulatory signaling domain but not a primary signaling domain, and a second CAR that targets a second, different, antigen and includes an intracellular signaling domain having a primary signaling domain but not a costimulatory signaling domain. While not wishing to be bound by theory, placement of a costimulatory signaling domain, e.g., 4-1BB, CD28, CD27 or OX-40, onto the first CAR, and the primary signaling domain, e.g., CD3 zeta, on the second CAR can limit the CAR activity to cells where both targets are expressed. In one embodiment, the CAR expressing cell comprises a first cancer associated antigen CAR that includes an antigen binding domain that binds a target antigen described herein, a transmembrane domain and a costimulatory domain and a second CAR that targets a different target antigen (e.g., an antigen

expressed on that same cancer cell type as the first target antigen) and includes an antigen binding domain, a transmembrane domain and a primary signaling domain. In another embodiment, the CAR expressing cell comprises a first CAR that includes an antigen binding domain that binds a target antigen described herein, a transmembrane domain and a primary signaling domain and a second CAR that targets an antigen other than the first target antigen (e.g., an antigen expressed on the same cancer cell type as the first target antigen) and includes an antigen binding domain to the antigen, a transmembrane domain and a costimulatory signaling domain.

In one embodiment, the CAR-expressing cell comprises an XCAR described herein and an inhibitory CAR. In one embodiment, the inhibitory CAR comprises an antigen binding domain that binds an antigen found on normal cells but not cancer cells, e.g., normal cells that also express CLL. In one embodiment, the inhibitory CAR comprises the antigen binding domain, a transmembrane domain and an intracellular domain of an inhibitory molecule. For example, the intracellular domain of the inhibitory CAR can be an intracellular domain of PD1, PD-L1, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 or TGF beta.

In one embodiment, when the CAR-expressing cell comprises two or more different CARs, the antigen binding domains of the different CARs can be such that the antigen binding domains do not interact with one another. For example, a cell expressing a first and second CAR can have an antigen binding domain of the first CAR, e.g., as a fragment, e.g., an scFv, that does not form an association with the antigen binding domain of the second CAR, e.g., the antigen binding domain of the second CAR is a VHH.

In some embodiments, the antigen binding domain comprises a single domain antigen binding (SDAB) molecules include molecules whose complementary determining regions are part of a single domain polypeptide. Examples include, but are not limited to, heavy chain variable domains, binding molecules naturally devoid of light chains, single domains derived from conventional 4-chain antibodies, engineered domains and single domain scaffolds other than those derived from antibodies. SDAB molecules may be any of the art, or any future single domain molecules. SDAB molecules may be derived from any species including, but not limited to mouse, human, camel, llama, lamprey, fish, shark, goat, rabbit, and bovine. This term also

includes naturally occurring single domain antibody molecules from species other than Camelidae and sharks.

In one aspect, an SDAB molecule can be derived from a variable region of the immunoglobulin found in fish, such as, for example, that which is derived from the immunoglobulin isotype known as Novel Antigen Receptor (NAR) found in the serum of shark. Methods of producing single domain molecules derived from a variable region of NAR ("IgNARs") are described in WO 03/014161 and Streltsov (2005) Protein Sci. 14:2901-2909.

According to another aspect, an SDAB molecule is a naturally occurring single domain antigen binding molecule known as heavy chain devoid of light chains. Such single domain molecules are disclosed in WO 9404678 and Hamers-Casterman, C. et al. (1993) Nature 363:446-448, for example. For clarity reasons, this variable domain derived from a heavy chain molecule naturally devoid of light chain is known herein as a VHH or nanobody to distinguish it from the conventional VH of four chain immunoglobulins. Such a VHH molecule can be derived from Camelidae species, for example in camel, llama, dromedary, alpaca and guanaco. Other species besides Camelidae may produce heavy chain molecules naturally devoid of light chain; such VHHs are within the scope of the invention.

The SDAB molecules can be recombinant, CDR-grafted, humanized, camelized, de-immunized and/or in vitro generated (e.g., selected by phage display).

It has also been discovered, that cells having a plurality of chimeric membrane embedded receptors comprising an antigen binding domain that interactions between the antigen binding domain of the receptors can be undesirable, e.g., because it inhibits the ability of one or more of the antigen binding domains to bind its cognate antigen. Accordingly, disclosed herein are cells having a first and a second non-naturally occurring chimeric membrane embedded receptor comprising antigen binding domains that minimize such interactions. Also disclosed herein are nucleic acids encoding a first and a second non-naturally occurring chimeric membrane embedded receptor comprising a antigen binding domains that minimize such interactions, as well as methods of making and using such cells and nucleic acids. In an embodiment the antigen binding domain of one of said first said second non-naturally occurring chimeric membrane embedded receptor, comprises an scFv, and the other comprises a single VH domain, e.g., a camelid, shark, or lamprey single VH domain, or a single VH domain derived from a human or mouse sequence.

In some embodiments, the claimed invention comprises a first and second CAR, wherein the antigen binding domain of one of said first CAR said second CAR does not comprise a variable light domain and a variable heavy domain. In some embodiments, the antigen binding domain of one of said first CAR said second CAR is an scFv, and the other is not an scFv. In some embodiments, the antigen binding domain of one of said first CAR said second CAR comprises a single VH domain, e.g., a camelid, shark, or lamprey single VH domain, or a single VH domain derived from a human or mouse sequence. In some embodiments, the antigen binding domain of one of said first CAR said second CAR comprises a nanobody. In some embodiments, the antigen binding domain of one of said first CAR said second CAR comprises a camelid VHH domain.

In some embodiments, the antigen binding domain of one of said first CAR said second CAR comprises an scFv, and the other comprises a single VH domain, e.g., a camelid, shark, or lamprey single VH domain, or a single VH domain derived from a human or mouse sequence. In some embodiments, the antigen binding domain of one of said first CAR said second CAR comprises an scFv, and the other comprises a nanobody. In some embodiments, the antigen binding domain of one of said first CAR said second CAR comprises comprises an scFv, and the other comprises a camelid VHH domain.

In some embodiments, when present on the surface of a cell, binding of the antigen binding domain of said first CAR to its cognate antigen is not substantially reduced by the presence of said second CAR. In some embodiments, binding of the antigen binding domain of said first CAR to its cognate antigen in the presence of said second CAR is 85%, 90%, 95%, 96%, 97%, 98% or 99% of binding of the antigen binding domain of said first CAR to its cognate antigen in the absence of said second CAR.

In some embodiments, when present on the surface of a cell, the antigen binding domains of said first CAR said second CAR, associate with one another less than if both were scFv antigen binding domains. In some embodiments, the antigen binding domains of said first CAR said second CAR, associate with one another 85%, 90%, 95%, 96%, 97%, 98% or 99% less than if both were scFv antigen binding domains.

In another aspect, the CAR-expressing cell described herein can further express another agent, e.g., an agent which enhances the activity of a CAR-expressing cell. For example, in one embodiment, the agent can be an agent which inhibits an inhibitory molecule. Inhibitory

molecules, e.g., PD1, can, in some embodiments, decrease the ability of a CAR-expressing cell to mount an immune effector response. Examples of inhibitory molecules include PD1, PD-L1, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and TGF beta. In one embodiment, the agent which inhibits an inhibitory molecule, e.g., is a molecule described herein, e.g., an agent that comprises a first polypeptide, e.g., an inhibitory molecule, associated with a second polypeptide that provides a positive signal to the cell, e.g., an intracellular signaling domain described herein. In one embodiment, the agent comprises a first polypeptide, e.g., of an inhibitory molecule such as PD1, PD-L1, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 or TGF beta, or a fragment of any of these (e.g., at least a portion of an extracellular domain of any of these), and a second polypeptide which is an intracellular signaling domain described herein (e.g., comprising a costimulatory domain (e.g., 41BB, CD27 or CD28, e.g., as described herein) and/or a primary signaling domain (e.g., a CD3 zeta signaling domain described herein). In one embodiment, the agent comprises a first polypeptide of PD1 or a fragment thereof (e.g., at least a portion of an extracellular domain of PD1), and a second polypeptide of an intracellular signaling domain described herein (e.g., a CD28 signaling domain described herein and/or a CD3 zeta signaling domain described herein). PD1 is an inhibitory member of the CD28 family of receptors that also includes CD28, CTLA-4, ICOS, and BTLA. PD-1 is expressed on activated B cells, T cells and myeloid cells (Agata et al. 1996 Int. Immunol 8:765-75). Two ligands for PD1, PD-L1 and PD-L2 have been shown to downregulate T cell activation upon binding to PD1 (Freeman et a. 2000 J Exp Med 192:1027-34; Latchman et al. 2001 Nat Immunol 2:261-8; Carter et al. 2002 Eur J Immunol 32:634-43). PD-L1 is abundant in human cancers (Dong et al. 2003 J Mol Med 81:281-7; Blank et al. 2005 Cancer Immunol. Immunother 54:307-314; Konishi et al. 2004 Clin Cancer Res 10:5094). Immune suppression can be reversed by inhibiting the local interaction of PD1 with PD-L1.

In one embodiment, the agent comprises the extracellular domain (ECD) of an inhibitory molecule, e.g., Programmed Death 1 (PD1), fused to a transmembrane domain and intracellular signaling domains such as 41BB and CD3 zeta (also referred to herein as a PD1 CAR). In one embodiment, the PD1 CAR, when used incombinations with a XCAR described herein, improves the persistence of the T cell. In one embodiment, the CAR is a PD1 CAR comprising

the extracellular domain of PD1 indicated as underlined in SEQ ID NO: 26. In one embodiment, the PD1 CAR comprises the amino acid sequence of SEQ ID NO: 26.

Malpvtalllplalllhaarppgwfldspdrpwnpptfspallvvtegdnatftcsfsntsesfvlnwyrmspsnqtdklaafpedrsqpg qdcrfrvtqlpngrdfhmsvvrarrndsgtylcgaislapkaqikeslraelrvterraevptahpspsprpagqfqtlvtttpaprpptpap tiasqplslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeee ggcelrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkprrknpqeglynelqkdkmaeayseigmkgerr rgkghdglyqglstatkdtydalhmqalppr (SEQ ID NO:26).

In one embodiment, the PD1 CAR comprises the amino acid sequence provided below (SEQ ID NO: 39).

pgwfldspdrpwnpptfspallvvtegdnatftcsfsntsesfvlnwyrmspsnqtdklaafpedrsqpgqdcrfrvtqlpngrdfhms vvrarrndsgtylcgaislapkaqikeslraelrvterraevptahpspsprpagqfqtlvtttpaprpptpaptiasqplslrpeacrpaagg avhtrgldfacdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeeggcelrvkfsrsadapayk qgqnqlynelnlgrreeydvldkrrgrdpemggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdglyqglstatkdt ydalhmqalppr (SEQ ID NO:39).

In one embodiment, the agent comprises a nucleic acid sequence encoding the PD1 CAR, e.g., the PD1 CAR described herein. In one embodiment, the nucleic acid sequence for the PD1 CAR is shown below, with the PD1 ECD underlined below in SEQ ID NO: 27.

atggccctccctgtcactgccctgcttctccccctcgcactcctgctccacgccgctagaccacccggatggtttctggactctccggatcgc ccgtggaatcccccaaccttctcaccggcactcttggttgtgactgagggcgataatgcgaccttcacgtgctcgttctccaacacctccgaa tcattcgtgctgaactggtaccgcatgagcccgtcaaaccagaccgacaagctcgccgcgtttccggaagatcggtcgcaaccgggacag gattgtcggttccgcgtgactcaactgccgaatggcagagacttccacatgagcgtggtccgcgctaggcgaaacgactccgggacctac ctgtgcggagccatctcgctggcgcctaaggcccaaatcaaagagagcttgagggccgaactgagagtgaccgagcgcagagctgagg tgccaactgcacatccatccccatcgcctcggcctgcggggcagtttcagaccctggtcacgaccactccggcgccgcgcccaccgactc cggccccaactatcgcgagccagcccctgtcgctgaggccggaagcatgccgccctgccgccggaggtgctgtgcatacccggggatt ggacttcgcatgcgacatctacatttgggctcctctcgccggaacttgtggcgtgctccttctgtccctggtcatcaccctgtactgcaagcgg ggtcggaaaaagcttctgtacattttcaagcagcccttcatgaggcccgtgcaaaccacccaggaggaggacggttgctcctgccggttcc ccgaagaggaagaaggaggttgcgagctgcgcgtgaagttctcccggagcgccgacgcccccgcctataagcagggccagaaccagc tgtacaacgaactgaacctgggacggcgggaagagtacgatgtgctggacaagcggcgcggccgggaccccgaaatgggcgggaag cctagaagaaagaaccctcaggaaggcctgtataacgagctgcagaaggacaagatggccgaggcctactccgaaattgggatgaagg gagagcggcggaggggaaaggggcacgacggcctgtaccaaggactgtccaccgccaccaaggacacatacgatgccctgcacatgc aggcccttcccccctcgc (SEQ ID NO: 27).

In another aspect, the present invention provides a population of CAR-expressing cells, e.g., CART cells. In some embodiments, the population of CAR-expressing cells comprises a mixture of cells expressing different CARs. For example, in one embodiment, the population of CART cells can include a first cell expressing a CAR having an antigen binding domain to a cancer associated antigen described herein, and a second cell expressing a CAR having a different antigen binding domain, e.g., an antigen binding domain to a different a cancer associated antigen described herein, e.g., an antigen binding domain to a cancer associated antigen described herein that differs from the cancer associated antigen bound by the antigen binding domain of the CAR expressed by the first cell. As another example, the population of CAR-expressing cells can include a first cell expressing a CAR that includes an antigen binding domain to a cancer associated antigen described herein, and a second cell expressing a CAR that includes an antigen binding domain to a target other than a cancer associated antigen as described herein. In one embodiment, the population of CAR-expressing cells includes, e.g., a first cell expressing a CAR that includes a primary intracellular signaling domain, and a second cell expressing a CAR that includes a secondary signaling domain.

In another aspect, the present invention provides a population of cells wherein at least one cell in the population expresses a CAR having an antigen binding domain to a cancer associated antigen described herein, and a second cell expressing another agent, e.g., an agent which enhances the activity of a CAR-expressing cell. For example, in one embodiment, the agent can be an agent which inhibits an inhibitory molecule. Inhibitory molecules, e.g., PD-1, can, in some embodiments, decrease the ability of a CAR-expressing cell to mount an immune effector response. Examples of inhibitory molecules include PD-1, PD-L1, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and TGF beta. In one embodiment, the agent which inhibits an inhibitory molecule, e.g., is a molecule described herein, e.g., an agent that comprises a first polypeptide, e.g., an inhibitory molecule, associated with a second polypeptide that provides a positive signal to the cell, e.g., an intracellular signaling domain described herein. In one embodiment, the agent comprises a first polypeptide, e.g., of an inhibitory molecule such as PD-1, PD-L1, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 or TGF beta, or a fragment of any of these, and a second polypeptide which is an intracellular signaling domain described herein (e.g., comprising

a costimulatory domain (e.g., 41BB, CD27, OX40 or CD28, e.g., as described herein) and/or a primary signaling domain (e.g., a CD3 zeta signaling domain described herein). In one embodiment, the agent comprises a first polypeptide of PD-1 or a fragment thereof, and a second polypeptide of an intracellular signaling domain described herein (e.g., a CD28 signaling domain described herein and/or a CD3 zeta signaling domain described herein).

In one aspect, the present invention provides methods comprising administering a population of CAR-expressing cells, e.g., CART cells, e.g., a mixture of cells expressing different CARs, in combination with another agent, e.g., a kinase inhibitor, such as a kinase inhibitor described herein. In another aspect, the present invention provides methods comprising administering a population of cells wherein at least one cell in the population expresses a CAR having an antigen binding domain of a cancer associated antigen described herein, and a second cell expressing another agent, e.g., an agent which enhances the activity of a CAR-expressing cell, in combination with another agent, e.g., a kinase inhibitor, such as a kinase inhibitor described herein.

Regulatable Chimeric Antigen Receptors

In some embodiments, a regulatable CAR (RCAR) where the CAR activity can be controlled is desirable to optimize the safety and efficacy of a CAR therapy. There are many ways CAR activities can be regulated. For example, inducible apoptosis using, e.g., a caspase fused to a dimerization domain (see, e.g., Di et al., N Egnl. J. Med. 2011 Nov. 3; 365(18):1673-1683), can be used as a safety switch in the CAR therapy of the instant invention. In an aspect, a RCAR comprises a set of polypeptides, typically two in the simplest embodiments, in which the components of a standard CAR described herein, e.g., an antigen binding domain and an intracellular signaling domain, are partitioned on separate polypeptides or members. In some embodiments, the set of polypeptides include a dimerization switch that, upon the presence of a dimerization molecule, can couple the polypeptides to one another, e.g., can couple an antigen binding domain to an intracellular signaling domain.

In an aspect, an RCAR comprises two polypeptides or members: 1) an intracellular signaling member comprising an intracellular signaling domain, e.g., a primary intracellular signaling domain described herein, and a first switch domain; 2) an antigen binding member comprising an antigen binding domain, e.g., that targets a tumor antigen described herein, as

described herein and a second switch domain. Optionally, the RCAR comprises a transmembrane domain described herein. In an embodiment, a transmembrane domain can be disposed on the intracellular signaling member, on the antigen binding member, or on both. (Unless otherwise indicated, when members or elements of an RCAR are described herein, the order can be as provided, but other orders are included as well. In other words, in an embodiment, the order is as set out in the text, but in other embodiments, the order can be different. E.g., the order of elements on one side of a transmembrane region can be different from the example, e.g., the placement of a switch domain relative to a intracellular signaling domain can be different, e.g., reversed).

In an embodiment, the first and second switch domains can form an intracellular or an extracellular dimerization switch. In an embodiment, the dimerization switch can be a homodimerization switch, e.g., where the first and second switch domain are the same, or a heterodimerization switch, e.g., where the first and second switch domain are different from one another.

In embodiments, an RCAR can comprise a "multi switch." A multi switch can comprise heterodimerization switch domains or homodimerization switch domains. A multi switch comprises a plurality of, e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10, switch domains, independently, on a first member, e.g., an antigen binding member, and a second member, e.g., an intracellular signaling member. In an embodiment, the first member can comprise a plurality of first switch domains, e.g., FKBP-based switch domains, and the second member can comprise a plurality of second switch domains, e.g., FRB-based switch domains. In an embodiment, the first member can comprise a first and a second switch domain, e.g., a FKBP-based switch domain and a FRB-based switch domain, and the second member can comprise a first and a second switch domain, e.g., a FKBP-based switch domain and a FRB-based switch domain.

In an embodiment, the intracellular signaling member comprises one or more intracellular signaling domains, e.g., a primary intracellular signaling domain and one or more costimulatory signaling domains.

In an embodiment, the antigen binding member may comprise one or more intracellular signaling domains, e.g., one or more costimulatory signaling domains. In an embodiment, the antigen binding member comprises a plurality, e.g., 2 or 3 costimulatory signaling domains described herein, e.g., selected from 41BB, CD28, CD27, ICOS, and OX40, and in

embodiments, no primary intracellular signaling domain. In an embodiment, the antigen binding member comprises the following costimulatory signaling domains, from the extracellular to intracellular direction: 41BB-CD27; 41BB-CD27; CD27-41BB; 41BB-CD28; CD28-41BB; OX40-CD28; CD28-OX40; CD28-41BB; or 41BB-CD28. In such embodiments, the intracellular binding member comprises a CD3zeta domain. In one such embodiment the RCAR comprises (1) an antigen binding member comprising, an antigen binding domain, a transmembrane domain, and two costimulatory domains and a first switch domain; and (2) an intracellular signaling domain comprising a transmembrane domain or membrane tethering domain and at least one primary intracellular signaling domain, and a second switch domain.

An embodiment provides RCARs wherein the antigen binding member is not tethered to the surface of the CAR cell. This allows a cell having an intracellular signaling member to be conveniently paired with one or more antigen binding domains, without transforming the cell with a sequence that encodes the antigen binding member. In such embodiments, the RCAR comprises: 1) an intracellular signaling member comprising: a first switch domain, a transmembrane domain, an intracellular signaling domain, e.g., a primary intracellular signaling domain, and a first switch domain; and 2) an antigen binding member comprising: an antigen binding domain, and a second switch domain, wherein the antigen binding member does not comprise a transmembrane domain or membrane tethering domain, and, optionally, does not comprise an intracellular signaling domain. In some embodiments, the RCAR may further comprise 3) a second antigen binding member comprising: a second antigen binding domain, e.g., a second antigen binding domain that binds a different antigen than is bound by the antigen binding domain; and a second switch domain.

Also provided herein are RCARs wherein the antigen binding member comprises bispecific activation and targeting capacity. In this embodiment, the antigen binding member can comprise a plurality, e.g., 2, 3, 4, or 5 antigen binding domains, e.g., scFvs, wherein each antigen binding domain binds to a target antigen, e.g. different antigens or the same antigen, e.g., the same or different epitopes on the same antigen. In an embodiment, the plurality of antigen binding domains are in tandem, and optionally, a linker or hinge region is disposed between each of the antigen binding domains. Suitable linkers and hinge regions are described herein.

An embodiment provides RCARs having a configuration that allows switching of proliferation. In this embodiment, the RCAR comprises: 1) an intracellular signaling member

comprising: optionally, a transmembrane domain or membrane tethering domain; one or more co-stimulatory signaling domain, e.g., selected from 41BB, CD28, CD27, ICOS, and OX40, and a switch domain; and 2) an antigen binding member comprising: an antigen binding domain, a transmembrane domain, and a primary intracellular signaling domain, e.g., a CD3zeta domain, wherein the antigen binding member does not comprise a switch domain, or does not comprise a switch domain that dimerizes with a switch domain on the intracellular signaling member. In an embodiment, the antigen binding member does not comprise a co-stimulatory signaling domain. In an embodiment, the intracellular signaling member comprises a switch domain from a homodimerization switch. In an embodiment, the intracellular signaling member comprises a first switch domain of a heterodimerization switch and the RCAR comprises a second intracellular signaling member which comprises a second switch domain of the heterodimerization switch. In such embodiments, the second intracellular signaling member comprises the same intracellular signaling domains as the intracellular signaling member. In an embodiment, the dimerization switch is intracellular. In an embodiment, the dimerization switch is extracellular.

In any of the RCAR configurations described here, the first and second switch domains comprise a FKBP-FRB based switch as described herein.

Also provided herein are cells comprising an RCAR described herein. Any cell that is engineered to express a RCAR can be used as a RCARX cell. In an embodiment the RCARX cell is a T cell, and is referred to as a RCART cell. In an embodiment the RCARX cell is an NK cell, and is referred to as a RCARN cell.

Also provided herein are nucleic acids and vectors comprising RCAR encoding sequences. Sequence encoding various elements of an RCAR can be disposed on the same nucleic acid molecule, e.g., the same plasmid or vector, e.g., viral vector, e.g., lentiviral vector. In an embodiment, (i) sequence encoding an antigen binding member and (ii) sequence encoding an intracellular signaling member, can be present on the same nucleic acid, e.g., vector. Production of the corresponding proteins can be achieved, e.g., by the use of separate promoters, or by the use of a bicistronic transcription product (which can result in the production of two proteins by cleavage of a single translation product or by the translation of two separate protein products). In an embodiment, a sequence encoding a cleavable peptide, e.g., a P2A or F2A

sequence, is disposed between (i) and (ii). Examples of peptide cleavage sites include the following, wherein the GSG residues are optional:

T2A: (GSG) E G R G S L L T C G D V E E N P G P (SEQ ID NO: 68)

P2A: (GSG) A T N F S L L K Q A G D V E E N P G P (SEQ ID NO: 69)

E2A: (GSG) Q C T N Y A L L K L A G D V E S N P G P (SEQ ID NO: 70)

F2A: (GSG) V K Q T L N F D L L K L A G D V E S N P G P (SEQ ID NO: 71)

In an embodiment, a sequence encoding an IRES, e.g., an EMCV or EV71 IRES, is disposed between (i) and (ii). In these embodiments, (i) and (ii) are transcribed as a single RNA. In an embodiment, a first promoter is operably linked to (i) and a second promoter is operably linked to (ii), such that (i) and (ii) are transcribed as separate mRNAs.

Alternatively, the sequence encoding various elements of an RCAR can be disposed on the different nucleic acid molecules, e.g., different plasmids or vectors, e.g., viral vector, e.g., lentiviral vector. E.g., the (i) sequence encoding an antigen binding member can be present on a first nucleic acid, e.g., a first vector, and the (ii) sequence encoding an intracellular signaling member can be present on the second nucleic acid, e.g., the second vector.

Dimerization switches

Dimerization switches can be non-covalent or covalent. In a non-covalent dimerization switch, the dimerization molecule promotes a non-covalent interaction between the switch domains. In a covalent dimerization switch, the dimerization molecule promotes a covalent interaction between the switch domains.

In an embodiment, the RCAR comprises a FKBP/FRAP, or FKBP/FRB,-based dimerization switch. FKBP12 (FKBP, or FK506 binding protein) is an abundant cytoplasmic protein that serves as the initial intracellular target for the natural product immunosuppressive drug, rapamycin. Rapamycin binds to FKBP and to the large PI3K homolog FRAP (RAFT, mTOR). FRB is a 93 amino acid portion of FRAP, that is sufficient for binding the FKBP-rapamycin complex (Chen, J., Zheng, X. F., Brown, E. J. & Schreiber, S. L. (1995) *Identification of an 11-kDa FKBP12-rapamycin-binding domain within the 289-kDa FKBP12-rapamycin-associated protein and characterization of a critical serine residue.* Proc Natl Acad Sci U S A 92: 4947-51.)

In embodiments, an FKBP/FRAP, e.g., an FKBP/FRB, based switch can use a dimerization molecule, e.g., rapamycin or a rapamycin analog.

The amino acid sequence of FKBP is as follows:

D V P D Y A S L G G P S S P K K K R K V S R G V Q V E T I S P G D G R T F P K R G Q T C V V H Y T G M L E D G K K F D S S R D R N K P F K F M L G K Q E V I R G W E E G V A Q M S V G Q R A K L T I S P D Y A Y G A T G H P G I I P P H A T L V F D V E L L K L E T S Y (SEQ ID NO: 54)

In embodiments, an FKBP switch domain can comprise a fragment of FKBP having the ability to bind with FRB, or a fragment or analog thereof, in the presence of rapamycin or a rapalog, e.g., the underlined portion of SEQ ID NO: 54, which is:

V Q V E T I S P G D G R T F P K R G Q T C V V H Y T G M L E D G K K F D S S R D R N K P F K F M L G K Q E V I R G W E E G V A Q M S V G Q R A K L T I S P D Y A Y G A T G H P G I I P P H A T L V F D V E L L K L E T S (SEQ ID NO:55)

The amino acid sequence of FRB is as follows:

ILWHEMWHEG LEEASRLYFG ERNVKGMFEV LEPLHAMMER GPQTLKETSF NQAYGRDLME AQEWCRKYMK SGNVKDLTQA WDLYYHVFRR ISK (SEQ ID NO: 56)

"FKBP/FRAP, e.g., an FKBP/FRB, based switch" as that term is used herein, refers to a dimerization switch comprising: a first switch domain, which comprises an FKBP fragment or analog thereof having the ability to bind with FRB, or a fragment or analog thereof, in the presence of rapamycin or a rapalog, e.g., RAD001, and has at least 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99% identity with, or differs by no more than 30, 25, 20, 15, 10, 5, 4, 3, 2, or 1 amino acid residues from, the FKBP sequence of SEQ ID NO: 54 or 55; and a second switch domain, which comprises an FRB fragment or analog thereof having the ability to bind with FRB, or a fragment or analog thereof, in the presence of rapamycin or a rapalog, and has at least 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99% identity with, or differs by no more than 30, 25, 20, 15, 10, 5, 4, 3, 2, or 1 amino acid residues from, the FRB sequence of SEQ ID NO: 56. In an embodiment, a RCAR described herein comprises one switch domain comprises amino acid residues disclosed in SEQ ID NO: 54 (or SEQ ID NO: 55), and one switch domain comprises amino acid residues disclosed in SEQ ID NO: 56.

In embodiments, the FKBP/FRB dimerization switch comprises a modified FRB switch domain that exhibits altered, e.g., enhanced, complex formation between an FRB-based switch domain, e.g., the modified FRB switch domain, a FKBP-based switch domain, and the

dimerization molecule, e.g., rapamycin or a rapalogue, e.g., RAD001. In an embodiment, the modified FRB switch domain comprises one or more mutations, e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10 or more, selected from mutations at amino acid position(s) L2031, E2032, S2035, R2036, F2039, G2040, T2098, W2101, D2102, Y2105, and F2108, where the wild-type amino acid is mutated to any other naturally-occurring amino acid. In an embodiment, a mutant FRB comprises a mutation at E2032, where E2032 is mutated to phenylalanine (E2032F), methionine (E2032M), arginine (E2032R), valine (E2032V), tyrosine (E2032Y), isoleucine (E2032I), e.g., SEQ ID NO: 57, or leucine (E2032L), e.g., SEQ ID NO: 58. In an embodiment, a mutant FRB comprises a mutation at T2098, where T2098 is mutated to phenylalanine (T2098F) or leucine (T2098L), e.g., SEQ ID NO: 59. In an embodiment, a mutant FRB comprises a mutation at E2032 and at T2098, where E2032 is mutated to any amino acid, and where T2098 is mutated to any amino acid, e.g., SEQ ID NO: 60. In an embodiment, a mutant FRB comprises an E2032I and a T2098L mutation, e.g., SEQ ID NO: 61. In an embodiment, a mutant FRB comprises an E2032L and a T2098L mutation, e.g., SEQ ID NO: 62.

Table 10. Exemplary mutant FRB having increased affinity for a dimerization molecule

FRB mutant	Amino Acid Sequence	SEQ ID NO:
E2032I mutant	ILWHEMWHEGLIEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLK ETSFNQAYGRDLMEAQEWCRKYMKSGNVKDLTQAWDLYYHVFRRIS KTS	57
E2032L mutant	ILWHEMWHEGLLEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLK ETSFNQAYGRDLMEAQEWCRKYMKSGNVKDLTQAWDLYYHVFRRIS KTS	58
T2098L mutant	ILWHEMWHEGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLK ETSFNQAYGRDLMEAQEWCRKYMKSGNVKDLLQAWDLYYHVFRRIS KTS	59
E2032, T2098 mutant	ILWHEMWHEGL**X**EASRLYFGERNVKGMFEVLEPLHAMMERGPQTLK ETSFNQAYGRDLMEAQEWCRKYMKSGNVKDL**X**QAWDLYYHVFRRIS KTS	60
E2032I, T2098L mutant	ILWHEMWHEGLIEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLK ETSFNQAYGRDLMEAQEWCRKYMKSGNVKDLLQAWDLYYHVFRRIS KTS	61
E2032L, T2098L mutant	ILWHEMWHEGLLEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLK ETSFNQAYGRDLMEAQEWCRKYMKSGNVKDLLQAWDLYYHVFRRIS KTS	62

Other suitable dimerization switches include a GyrB-GyrB based dimerization switch, a Gibberellin-based dimerization switch, a tag/binder dimerization switch, and a halo-tag/snap-tag

dimerization switch. Following the guidance provided herein, such switches and relevant dimerization molecules will be apparent to one of ordinary skill.

Dimerization molecule

Association between the switch domains is promoted by the dimerization molecule. In the presence of dimerization molecule interaction or association between switch domains allows for signal transduction between a polypeptide associated with, e.g., fused to, a first switch domain, and a polypeptide associated with, e.g., fused to, a second switch domain. In the presence of non-limiting levels of dimerization molecule signal transduction is increased by 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 5, 10, 50, 100 fold, e.g., as measured in a system described herein.

Rapamycin and rapamycin analogs (sometimes referred to as rapalogues), e.g., RAD001, can be used as dimerization molecules in a FKBP/FRB-based dimerization switch described herein. In an embodiment the dimerization molecule can be selected from rapamycin (sirolimus), RAD001 (everolimus), zotarolimus, temsirolimus, AP-23573 (ridaforolimus), biolimus and AP21967. Additional rapamycin analogs suitable for use with FKBP/FRB-based dimerization switches are further described in the section entitled "Combination Therapies", or in the subsection entitled "Exemplary mTOR inhibitors."

Split CAR

In some embodiments, the CAR-expressing cell uses a split CAR. The split CAR approach is described in more detail in publications WO2014/055442 and WO2014/055657. Briefly, a split CAR system comprises a cell expressing a first CAR having a first antigen binding domain and a costimulatory domain (e.g., 41BB), and the cell also expresses a second CAR having a second antigen binding domain and an intracellular signaling domain (e.g., CD3 zeta). When the cell encounters the first antigen, the costimulatory domain is activated, and the cell proliferates. When the cell encounters the second antigen, the intracellular signaling domain is activated and cell-killing activity begins. Thus, the CAR-expressing cell is only fully activated in the presence of both antigens.

RNA Transfection

Disclosed herein are methods for producing an in vitro transcribed RNA CAR. The present invention also includes a CAR encoding RNA construct that can be directly transfected into a cell. A method for generating mRNA for use in transfection can involve in vitro transcription (IVT) of a template with specially designed primers, followed by polyA addition, to produce a construct containing 3' and 5' untranslated sequence ("UTR"), a 5' cap and/or Internal Ribosome Entry Site (IRES), the nucleic acid to be expressed, and a polyA tail, typically 50-2000 bases in length (SEQ ID NO:32). RNA so produced can efficiently transfect different kinds of cells. In one aspect, the template includes sequences for the CAR.

In one aspect, a CAR of the present invention is encoded by a messenger RNA (mRNA). In one aspect, the mRNA encoding a CAR described herein is introduced into an immune effector cell, e.g., a T cell or a NK cell, for production of a CAR-expressing cell, e.g., a CART cell or a CAR NK cell.

In one embodiment, the *in vitro* transcribed RNA CAR can be introduced to a cell as a form of transient transfection. The RNA is produced by *in vitro* transcription using a polymerase chain reaction (PCR)-generated template. DNA of interest from any source can be directly converted by PCR into a template for in vitro mRNA synthesis using appropriate primers and RNA polymerase. The source of the DNA can be, for example, genomic DNA, plasmid DNA, phage DNA, cDNA, synthetic DNA sequence or any other appropriate source of DNA. The desired temple for *in vitro* transcription is a CAR described herein. For example, the template for the RNA CAR comprises an extracellular region comprising a single chain variable domain of an antibody to a tumor associated antigen described herein; a hinge region (e.g., a hinge region described herein), a transmembrane domain (e.g., a transmembrane domain described herein such as a transmembrane domain of CD8a); and a cytoplasmic region that includes an intracellular signaling domain, e.g., an intracellular signaling domain described herein, e.g., comprising the signaling domain of CD3-zeta and the signaling domain of 4-1BB.

In one embodiment, the DNA to be used for PCR contains an open reading frame. The DNA can be from a naturally occurring DNA sequence from the genome of an organism. In one embodiment, the nucleic acid can include some or all of the 5' and/or 3' untranslated regions (UTRs). The nucleic acid can include exons and introns. In one embodiment, the DNA to be used for PCR is a human nucleic acid sequence. In another embodiment, the DNA to be used for PCR is a human nucleic acid sequence including the 5' and 3' UTRs. The DNA can alternatively

be an artificial DNA sequence that is not normally expressed in a naturally occurring organism. An exemplary artificial DNA sequence is one that contains portions of genes that are ligated together to form an open reading frame that encodes a fusion protein. The portions of DNA that are ligated together can be from a single organism or from more than one organism.

PCR is used to generate a template for in vitro transcription of mRNA which is used for transfection. Methods for performing PCR are well known in the art. Primers for use in PCR are designed to have regions that are substantially complementary to regions of the DNA to be used as a template for the PCR. "Substantially complementary," as used herein, refers to sequences of nucleotides where a majority or all of the bases in the primer sequence are complementary, or one or more bases are non-complementary, or mismatched. Substantially complementary sequences are able to anneal or hybridize with the intended DNA target under annealing conditions used for PCR. The primers can be designed to be substantially complementary to any portion of the DNA template. For example, the primers can be designed to amplify the portion of a nucleic acid that is normally transcribed in cells (the open reading frame), including 5' and 3' UTRs. The primers can also be designed to amplify a portion of a nucleic acid that encodes a particular domain of interest. In one embodiment, the primers are designed to amplify the coding region of a human cDNA, including all or portions of the 5' and 3' UTRs. Primers useful for PCR can be generated by synthetic methods that are well known in the art. "Forward primers" are primers that contain a region of nucleotides that are substantially complementary to nucleotides on the DNA template that are upstream of the DNA sequence that is to be amplified. "Upstream" is used herein to refer to a location 5, to the DNA sequence to be amplified relative to the coding strand. "Reverse primers" are primers that contain a region of nucleotides that are substantially complementary to a double-stranded DNA template that are downstream of the DNA sequence that is to be amplified. "Downstream" is used herein to refer to a location 3' to the DNA sequence to be amplified relative to the coding strand.

Any DNA polymerase useful for PCR can be used in the methods disclosed herein. The reagents and polymerase are commercially available from a number of sources.

Chemical structures with the ability to promote stability and/or translation efficiency may also be used. The RNA preferably has 5' and 3' UTRs. In one embodiment, the 5' UTR is between one and 3000 nucleotides in length. The length of 5' and 3' UTR sequences to be added to the coding region can be altered by different methods, including, but not limited to, designing

primers for PCR that anneal to different regions of the UTRs. Using this approach, one of ordinary skill in the art can modify the 5' and 3' UTR lengths required to achieve optimal translation efficiency following transfection of the transcribed RNA.

The 5' and 3' UTRs can be the naturally occurring, endogenous 5' and 3' UTRs for the nucleic acid of interest. Alternatively, UTR sequences that are not endogenous to the nucleic acid of interest can be added by incorporating the UTR sequences into the forward and reverse primers or by any other modifications of the template. The use of UTR sequences that are not endogenous to the nucleic acid of interest can be useful for modifying the stability and/or translation efficiency of the RNA. For example, it is known that AU-rich elements in 3' UTR sequences can decrease the stability of mRNA. Therefore, 3' UTRs can be selected or designed to increase the stability of the transcribed RNA based on properties of UTRs that are well known in the art.

In one embodiment, the 5' UTR can contain the Kozak sequence of the endogenous nucleic acid. Alternatively, when a 5' UTR that is not endogenous to the nucleic acid of interest is being added by PCR as described above, a consensus Kozak sequence can be redesigned by adding the 5' UTR sequence. Kozak sequences can increase the efficiency of translation of some RNA transcripts, but does not appear to be required for all RNAs to enable efficient translation. The requirement for Kozak sequences for many mRNAs is known in the art. In other embodiments the 5' UTR can be 5'UTR of an RNA virus whose RNA genome is stable in cells. In other embodiments various nucleotide analogues can be used in the 3' or 5' UTR to impede exonuclease degradation of the mRNA.

To enable synthesis of RNA from a DNA template without the need for gene cloning, a promoter of transcription should be attached to the DNA template upstream of the sequence to be transcribed. When a sequence that functions as a promoter for an RNA polymerase is added to the 5' end of the forward primer, the RNA polymerase promoter becomes incorporated into the PCR product upstream of the open reading frame that is to be transcribed. In one preferred embodiment, the promoter is a T7 polymerase promoter, as described elsewhere herein. Other useful promoters include, but are not limited to, T3 and SP6 RNA polymerase promoters. Consensus nucleotide sequences for T7, T3 and SP6 promoters are known in the art.

In a preferred embodiment, the mRNA has both a cap on the 5' end and a 3' poly(A) tail which determine ribosome binding, initiation of translation and stability mRNA in the cell. On a

circular DNA template, for instance, plasmid DNA, RNA polymerase produces a long concatameric product which is not suitable for expression in eukaryotic cells. The transcription of plasmid DNA linearized at the end of the 3' UTR results in normal sized mRNA which is not effective in eukaryotic transfection even if it is polyadenylated after transcription.

On a linear DNA template, phage T7 RNA polymerase can extend the 3' end of the transcript beyond the last base of the template (Schenborn and Mierendorf, Nuc Acids Res., 13:6223-36 (1985); Nacheva and Berzal-Herranz, Eur. J. Biochem., 270:1485-65 (2003).

The conventional method of integration of polyA/T stretches into a DNA template is molecular cloning. However polyA/T sequence integrated into plasmid DNA can cause plasmid instability, which is why plasmid DNA templates obtained from bacterial cells are often highly contaminated with deletions and other aberrations. This makes cloning procedures not only laborious and time consuming but often not reliable. That is why a method which allows construction of DNA templates with polyA/T 3' stretch without cloning highly desirable.

The polyA/T segment of the transcriptional DNA template can be produced during PCR by using a reverse primer containing a polyT tail, such as 100T tail (SEQ ID NO: 35) (size can be 50-5000 T (SEQ ID NO: 36)), or after PCR by any other method, including, but not limited to, DNA ligation or in vitro recombination. Poly(A) tails also provide stability to RNAs and reduce their degradation. Generally, the length of a poly(A) tail positively correlates with the stability of the transcribed RNA. In one embodiment, the poly(A) tail is between 100 and 5000 adenosines (SEQ ID NO: 37).

Poly(A) tails of RNAs can be further extended following in vitro transcription with the use of a poly(A) polymerase, such as E. coli polyA polymerase (E-PAP). In one embodiment, increasing the length of a poly(A) tail from 100 nucleotides to between 300 and 400 nucleotides (SEQ ID NO: 38) results in about a two-fold increase in the translation efficiency of the RNA. Additionally, the attachment of different chemical groups to the 3' end can increase mRNA stability. Such attachment can contain modified/artificial nucleotides, aptamers and other compounds. For example, ATP analogs can be incorporated into the poly(A) tail using poly(A) polymerase. ATP analogs can further increase the stability of the RNA.

5' caps on also provide stability to RNA molecules. In a preferred embodiment, RNAs produced by the methods disclosed herein include a 5' cap. The 5' cap is provided using techniques known in the art and described herein (Cougot, et al., Trends in Biochem. Sci.,

29:436-444 (2001); Stepinski, et al., RNA, 7:1468-95 (2001); Elango, et al., Biochim. Biophys. Res. Commun., 330:958-966 (2005)).

The RNAs produced by the methods disclosed herein can also contain an internal ribosome entry site (IRES) sequence. The IRES sequence may be any viral, chromosomal or artificially designed sequence which initiates cap-independent ribosome binding to mRNA and facilitates the initiation of translation. Any solutes suitable for cell electroporation, which can contain factors facilitating cellular permeability and viability such as sugars, peptides, lipids, proteins, antioxidants, and surfactants can be included.

RNA can be introduced into target cells using any of a number of different methods, for instance, commercially available methods which include, but are not limited to, electroporation (Amaxa Nucleofector-II (Amaxa Biosystems, Cologne, Germany)), (ECM 830 (BTX) (Harvard Instruments, Boston, Mass.) or the Gene Pulser II (BioRad, Denver, Colo.), Multiporator (Eppendort, Hamburg Germany), cationic liposome mediated transfection using lipofection, polymer encapsulation, peptide mediated transfection, or biolistic particle delivery systems such as "gene guns" (see, for example, Nishikawa, et al. Hum Gene Ther., 12(8):861-70 (2001).

Non-viral delivery methods

In some aspects, non-viral methods can be used to deliver a nucleic acid encoding a CAR described herein into a cell or tissue or a subject.

In some embodiments, the non-viral method includes the use of a transposon (also called a transposable element). In some embodiments, a transposon is a piece of DNA that can insert itself at a location in a genome, for example, a piece of DNA that is capable of self-replicating and inserting its copy into a genome, or a piece of DNA that can be spliced out of a longer nucleic acid and inserted into another place in a genome. For example, a transposon comprises a DNA sequence made up of inverted repeats flanking genes for transposition.

Exemplary methods of nucleic acid delivery using a transposon include a Sleeping Beauty transposon system (SBTS) and a piggyBac (PB) transposon system. See, e.g., Aronovich et al. Hum. Mol. Genet. 20.R1(2011):R14-20; Singh et al. Cancer Res. 15(2008):2961–2971; Huang et al. Mol. Ther. 16(2008):580–589; Grabundzija et al. Mol. Ther. 18(2010):1200–1209; Kebriaei et al. Blood. 122.21(2013):166; Williams. Molecular Therapy 16.9(2008):1515–16; Bell et al. Nat. Protoc. 2.12(2007):3153-65; and Ding et al. Cell. 122.3(2005):473-83, all of

which are incorporated herein by reference.

The SBTS includes two components: 1) a transposon containing a transgene and 2) a source of transposase enzyme. The transposase can transpose the transposon from a carrier plasmid (or other donor DNA) to a target DNA, such as a host cell chromosome/genome. For example, the transposase binds to the carrier plasmid/donor DNA, cuts the transposon (including transgene(s)) out of the plasmid, and inserts it into the genome of the host cell. See, e.g., Aronovich et al. *supra.*

Exemplary transposons include a pT2-based transposon. See, e.g., Grabundzija et al. Nucleic Acids Res. 41.3(2013):1829-47; and Singh et al. Cancer Res. 68.8(2008): 2961–2971, all of which are incorporated herein by reference. Exemplary transposases include a Tc1/mariner-type transposase, e.g., the SB10 transposase or the SB11 transposase (a hyperactive transposase which can be expressed, e.g., from a cytomegalovirus promoter). See, e.g., Aronovich et al.; Kebriaei et al.; and Grabundzija et al., all of which are incorporated herein by reference.

Use of the SBTS permits efficient integration and expression of a transgene, e.g., a nucleic acid encoding a CAR described herein. Provided herein are methods of generating a cell, e.g., T cell or NK cell, that stably expresses a CAR described herein, e.g., using a transposon system such as SBTS.

In accordance with methods described herein, in some embodiments, one or more nucleic acids, e.g., plasmids, containing the SBTS components are delivered to a cell (e.g., T or NK cell). For example, the nucleic acid(s) are delivered by standard methods of nucleic acid (e.g., plasmid DNA) delivery, e.g., methods described herein, e.g., electroporation, transfection, or lipofection. In some embodiments, the nucleic acid contains a transposon comprising a transgene, e.g., a nucleic acid encoding a CAR described herein. In some embodiments, the nucleic acid contains a transposon comprising a transgene (e.g., a nucleic acid encoding a CAR described herein) as well as a nucleic acid sequence encoding a transposase enzyme. In other embodiments, a system with two nucleic acids is provided, e.g., a dual-plasmid system, e.g., where a first plasmid contains a transposon comprising a transgene, and a second plasmid contains a nucleic acid sequence encoding a transposase enzyme. For example, the first and the second nucleic acids are co-delivered into a host cell.

In some embodiments, cells, e.g., T or NK cells, are generated that express a CAR described herein by using a combination of gene insertion using the SBTS and genetic editing

using a nuclease (e.g., Zinc finger nucleases (ZFNs), Transcription Activator-Like Effector Nucleases (TALENs), the CRISPR/Cas system, or engineered meganuclease re-engineered homing endonucleases).

In some embodiments, use of a non-viral method of delivery permits reprogramming of cells, e.g., T or NK cells, and direct infusion of the cells into a subject. Advantages of non-viral vectors include but are not limited to the ease and relatively low cost of producing sufficient amounts required to meet a patient population, stability during storage, and lack of immunogenicity.

Nucleic Acid Constructs Encoding a CAR

The present invention also provides nucleic acid molecules encoding one or more CAR constructs described herein. In one aspect, the nucleic acid molecule is provided as a messenger RNA transcript. In one aspect, the nucleic acid molecule is provided as a DNA construct.

Accordingly, in one aspect, the invention pertains to a nucleic acid molecule encoding a chimeric antigen receptor (CAR), wherein the CAR comprises an antigen binding domain that binds to a tumor antigen described herein, a transmembrane domain (e.g., a transmembrane domain described herein), and an intracellular signaling domain (e.g., an intracellular signaling domain described herein) comprising a stimulatory domain, e.g., a costimulatory signaling domain (e.g., a costimulatory signaling domain described herein) and/or a primary signaling domain (e.g., a primary signaling domain described herein, e.g., a zeta chain described herein). In one embodiment, the transmembrane domain is transmembrane domain of a protein selected from the group consisting of the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 and CD154. In some embodiments, a transmembrane domain may include at least the transmembrane region(s) of, e.g., KIRDS2, OX40, CD2, CD27, LFA-1 (CD11a, CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD40, BAFFR, HVEM (LIGHTR), SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD160, CD19, IL2R beta, IL2R gamma, IL7R α, ITGA1, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100

(SEMA4D), SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, PAG/Cbp.

In one embodiment, the transmembrane domain comprises a sequence of SEQ ID NO: 12, or a sequence with 95-99% identity thereof. In one embodiment, the antigen binding domain is connected to the transmembrane domain by a hinge region, e.g., a hinge described herein. In one embodiment, the hinge region comprises SEQ ID NO:4 or SEQ ID NO:6 or SEQ ID NO:8 or SEQ ID NO:10, or a sequence with 95-99% identity thereof. In one embodiment, the isolated nucleic acid molecule further comprises a sequence encoding a costimulatory domain. In one embodiment, the costimulatory domain is a functional signaling domain of a protein selected from the group consisting of OX40, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), and 4-1BB (CD137). Further examples of such costimulatory molecules include CDS, ICAM-1, GITR, BAFFR, HVEM (LIGHTR), SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD160, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, and PAG/Cbp. In one embodiment, the costimulatory domain comprises a sequence of SEQ ID NO:16, or a sequence with 95-99% identity thereof. In one embodiment, the intracellular signaling domain comprises a functional signaling domain of 4-1BB and a functional signaling domain of CD3 zeta. In one embodiment, the intracellular signaling domain comprises the sequence of SEQ ID NO: 14 or SEQ ID NO:16, or a sequence with 95-99% identity thereof, and the sequence of SEQ ID NO: 18 or SEQ ID NO:20, or a sequence with 95-99% identity thereof, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain.

In another aspect, the invention pertains to an isolated nucleic acid molecule encoding a CAR construct comprising a leader sequence of SEQ ID NO: 2, a scFv domain as described herein, a hinge region of SEQ ID NO:4 or SEQ ID NO:6 or SEQ ID NO:8 or SEQ ID NO:10 (or a sequence with 95-99% identity thereof), a transmembrane domain having a sequence of SEQ

ID NO: 12 (or a sequence with 95-99% identity thereof), a 4-1BB costimulatory domain having a sequence of SEQ ID NO:14 or a CD27 costimulatory domain having a sequence of SEQ ID NO:16 (or a sequence with 95-99% identity thereof), and a CD3 zeta stimulatory domain having a sequence of SEQ ID NO:18 or SEQ ID NO:20 (or a sequence with 95-99% identity thereof).

In another aspect, the invention pertains to a nucleic acid molecule encoding a chimeric antigen receptor (CAR) molecule that comprises an antigen binding domain, a transmembrane domain, and an intracellular signaling domain comprising a stimulatory domain, and wherein said antigen binding domain binds to a tumor antigen selected from a group consisting of: CD19, CD123, CD22, CD30, CD171, CS-1, CLL-1 (CLECL1), CD33, EGFRvIII , GD2, GD3, BCMA, Tn Ag, PSMA, ROR1, FLT3, FAP, TAG72, CD38, CD44v6, CEA, EPCAM, B7H3, KIT, IL-13Ra2, Mesothelin, IL-11Ra, PSCA, VEGFR2, LewisY, CD24, PDGFR-beta, SSEA-4, CD20, Folate receptor alpha, ERBB2 (Her2/neu), MUC1, EGFR, NCAM, Prostase, PRSS21, PAP, ELF2M, Ephrin B2, IGF-I receptor, CAIX, LMP2, gp100, bcr-abl, tyrosinase, EphA2, Fucosyl GM1, sLe, GM3, TGS5, HMWMAA, o-acetyl-GD2, Folate receptor beta, TEM1/CD248, TEM7R, CLDN6, TSHR, GPRC5D, CXORF61, CD97, CD179a, ALK, Polysialic acid, PLAC1, GloboH, NY-BR-1, UPK2, HAVCR1, ADRB3, PANX3, GPR20, LY6K, OR51E2, TARP, WT1, NY-ESO-1, LAGE-1a, MAGE-A1, legumain, HPV E6,E7, MAGE A1, ETV6-AML, sperm protein 17, XAGE1, Tie 2, MAD-CT-1, MAD-CT-2, Fos-related antigen 1, p53, p53 mutant, prostein, survivin and telomerase, PCTA-1/Galectin 8, MelanA/MART1, Ras mutant, hTERT, sarcoma translocation breakpoints, ML-IAP, ERG (TMPRSS2 ETS fusion gene), NA17, PAX3, Androgen receptor, Cyclin B1, MYCN, RhoC, TRP-2, CYP1B1, BORIS, SART3, PAX5, OY-TES1, LCK, AKAP-4, SSX2, RAGE-1, human telomerase reverse transcriptase, RU1, RU2, intestinal carboxyl esterase, mut hsp70-2, CD79a, CD79b, CD72, LAIR1, FCAR, LILRA2, CD300LF, CLEC12A, BST2, EMR2, LY75, GPC3, FCRL5, and IGLL1.

In one embodiment, the encoded CAR molecule further comprises a sequence encoding a costimulatory domain. In one embodiment, the costimulatory domain is a functional signaling domain of a protein selected from the group consisting of OX40, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a/CD18) and 4-1BB (CD137). In one embodiment, the costimulatory domain comprises a sequence of SEQ ID NO: 14. In one embodiment, the transmembrane domain is a transmembrane domain of a protein selected from the group consisting of the alpha, beta or zeta

chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 and CD154. In one embodiment, the transmembrane domain comprises a sequence of SEQ ID NO:12. In one embodiment, the intracellular signaling domain comprises a functional signaling domain of 4-1BB and a functional signaling domain of zeta. In one embodiment, the intracellular signaling domain comprises the sequence of SEQ ID NO: 14 and the sequence of SEQ ID NO: 18, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain. In one embodiment, the anti-a cancer associated antigen as described herein binding domain is connected to the transmembrane domain by a hinge region. In one embodiment, the hinge region comprises SEQ ID NO:4. In one embodiment, the hinge region comprises SEQ ID NO:6 or SEQ ID NO:8 or SEQ ID NO:10.

The nucleic acid sequences coding for the desired molecules can be obtained using recombinant methods known in the art, such as, for example by screening libraries from cells expressing the gene, by deriving the gene from a vector known to include the same, or by isolating directly from cells and tissues containing the same, using standard techniques. Alternatively, the gene of interest can be produced synthetically, rather than cloned.

The present invention also provides vectors in which a DNA of the present invention is inserted. Vectors derived from retroviruses such as the lentivirus are suitable tools to achieve long-term gene transfer since they allow long-term, stable integration of a transgene and its propagation in daughter cells. Lentiviral vectors have the added advantage over vectors derived from onco-retroviruses such as murine leukemia viruses in that they can transduce non-proliferating cells, such as hepatocytes. They also have the added advantage of low immunogenicity. A retroviral vector may also be, e.g., a gammaretroviral vector. A gammaretroviral vector may include, e.g., a promoter, a packaging signal (ψ), a primer binding site (PBS), one or more (e.g., two) long terminal repeats (LTR), and a transgene of interest, e.g., a gene encoding a CAR. A gammaretroviral vector may lack viral structural gens such as gag, pol, and env. Exemplary gammaretroviral vectors include Murine Leukemia Virus (MLV), Spleen-Focus Forming Virus (SFFV), and Myeloproliferative Sarcoma Virus (MPSV), and vectors derived therefrom. Other gammaretroviral vectors are described, e.g., in Tobias Maetzig et al., "Gammaretroviral Vectors: Biology, Technology and Application" Viruses. 2011 Jun; 3(6): 677–713.

In another embodiment, the vector comprising the nucleic acid encoding the desired CAR of the invention is an adenoviral vector (A5/35). In another embodiment, the expression of nucleic acids encoding CARs can be accomplished using of transposons such as sleeping beauty, crisper, CAS9, and zinc finger nucleases. See below June et al. 2009*Nature Reviews Immunology* 9.10: 704-716, is incorporated herein by reference.

In brief summary, the expression of natural or synthetic nucleic acids encoding CARs is typically achieved by operably linking a nucleic acid encoding the CAR polypeptide or portions thereof to a promoter, and incorporating the construct into an expression vector. The vectors can be suitable for replication and integration eukaryotes. Typical cloning vectors contain transcription and translation terminators, initiation sequences, and promoters useful for regulation of the expression of the desired nucleic acid sequence.

The expression constructs of the present invention may also be used for nucleic acid immunization and gene therapy, using standard gene delivery protocols. Methods for gene delivery are known in the art. See, e.g., U.S. Pat. Nos. 5,399,346, 5,580,859, 5,589,466, incorporated by reference herein in their entireties. In another embodiment, the invention provides a gene therapy vector.

The nucleic acid can be cloned into a number of types of vectors. For example, the nucleic acid can be cloned into a vector including, but not limited to a plasmid, a phagemid, a phage derivative, an animal virus, and a cosmid. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors, and sequencing vectors.

Further, the expression vector may be provided to a cell in the form of a viral vector. Viral vector technology is well known in the art and is described, for example, in Sambrook et al., 2012, MOLECULAR CLONING: A LABORATORY MANUAL, volumes 1 -4, Cold Spring Harbor Press, NY), and in other virology and molecular biology manuals. Viruses, which are useful as vectors include, but are not limited to, retroviruses, adenoviruses, adeno- associated viruses, herpes viruses, and lentiviruses. In general, a suitable vector contains an origin of replication functional in at least one organism, a promoter sequence, convenient restriction endonuclease sites, and one or more selectable markers, (e.g., WO 01/96584; WO 01/29058; and U.S. Pat. No. 6,326,193).

A number of viral based systems have been developed for gene transfer into mammalian cells. For example, retroviruses provide a convenient platform for gene delivery systems. A

selected gene can be inserted into a vector and packaged in retroviral particles using techniques known in the art. The recombinant virus can then be isolated and delivered to cells of the subject either in vivo or ex vivo. A number of retroviral systems are known in the art. In some embodiments, adenovirus vectors are used. A number of adenovirus vectors are known in the art. In one embodiment, lentivirus vectors are used.

Additional promoter elements, e.g., enhancers, regulate the frequency of transcriptional initiation. Typically, these are located in the region 30-110 bp upstream of the start site, although a number of promoters have been shown to contain functional elements downstream of the start site as well. The spacing between promoter elements frequently is flexible, so that promoter function is preserved when elements are inverted or moved relative to one another. In the thymidine kinase (tk) promoter, the spacing between promoter elements can be increased to 50 bp apart before activity begins to decline. Depending on the promoter, it appears that individual elements can function either cooperatively or independently to activate transcription. Exemplary promoters include the CMV IE gene, EF-1α, ubiquitin C, or phosphoglycerokinase (PGK) promoters.

An example of a promoter that is capable of expressing a CAR encoding nucleic acid molecule in a mammalian T cell is the EF1a promoter. The native EF1a promoter drives expression of the alpha subunit of the elongation factor-1 complex, which is responsible for the enzymatic delivery of aminoacyl tRNAs to the ribosome. The EF1a promoter has been extensively used in mammalian expression plasmids and has been shown to be effective in driving CAR expression from nucleic acid molecules cloned into a lentiviral vector. See, e.g., Milone et al., Mol. Ther. 17(8): 1453–1464 (2009). In one aspect, the EF1a promoter comprises the sequence provided as SEQ ID NO: 1.

Another example of a promoter is the immediate early cytomegalovirus (CMV) promoter sequence. This promoter sequence is a strong constitutive promoter sequence capable of driving high levels of expression of any polynucleotide sequence operatively linked thereto. However, other constitutive promoter sequences may also be used, including, but not limited to the simian virus 40 (SV40) early promoter, mouse mammary tumor virus (MMTV), human immunodeficiency virus (HIV) long terminal repeat (LTR) promoter, MoMuLV promoter, an avian leukemia virus promoter, an Epstein-Barr virus immediate early promoter, a Rous sarcoma virus promoter, as well as human gene promoters such as, but not limited to, the actin promoter,

the myosin promoter, the elongation factor-1α promoter, the hemoglobin promoter, and the creatine kinase promoter. Further, the invention should not be limited to the use of constitutive promoters. Inducible promoters are also contemplated as part of the invention. The use of an inducible promoter provides a molecular switch capable of turning on expression of the polynucleotide sequence which it is operatively linked when such expression is desired, or turning off the expression when expression is not desired. Examples of inducible promoters include, but are not limited to a metallothionine promoter, a glucocorticoid promoter, a progesterone promoter, and a tetracycline promoter.

A vector may also include, e.g., a signal sequence to facilitate secretion, a polyadenylation signal and transcription terminator (e.g., from Bovine Growth Hormone (BGH) gene), an element allowing episomal replication and replication in prokaryotes (e.g. SV40 origin and ColE1 or others known in the art) and/or elements to allow selection (e.g., ampicillin resistance gene and/or zeocin marker).

In order to assess the expression of a CAR polypeptide or portions thereof, the expression vector to be introduced into a cell can also contain either a selectable marker gene or a reporter gene or both to facilitate identification and selection of expressing cells from the population of cells sought to be transfected or infected through viral vectors. In other aspects, the selectable marker may be carried on a separate piece of DNA and used in a co- transfection procedure. Both selectable markers and reporter genes may be flanked with appropriate regulatory sequences to enable expression in the host cells. Useful selectable markers include, for example, antibiotic-resistance genes, such as neo and the like.

Reporter genes are used for identifying potentially transfected cells and for evaluating the functionality of regulatory sequences. In general, a reporter gene is a gene that is not present in or expressed by the recipient organism or tissue and that encodes a polypeptide whose expression is manifested by some easily detectable property, e.g., enzymatic activity. Expression of the reporter gene is assayed at a suitable time after the DNA has been introduced into the recipient cells. Suitable reporter genes may include genes encoding luciferase, beta-galactosidase, chloramphenicol acetyl transferase, secreted alkaline phosphatase, or the green fluorescent protein gene (e.g., Ui-Tei et al., 2000 FEBS Letters 479: 79-82). Suitable expression systems are well known and may be prepared using known techniques or obtained commercially. In general, the construct with the minimal 5' flanking region showing the highest level of expression of

reporter gene is identified as the promoter. Such promoter regions may be linked to a reporter gene and used to evaluate agents for the ability to modulate promoter- driven transcription.

Methods of introducing and expressing genes into a cell are known in the art. In the context of an expression vector, the vector can be readily introduced into a host cell, e.g., mammalian, bacterial, yeast, or insect cell by any method in the art. For example, the expression vector can be transferred into a host cell by physical, chemical, or biological means.

Physical methods for introducing a polynucleotide into a host cell include calcium phosphate precipitation, lipofection, particle bombardment, microinjection, electroporation, and the like. Methods for producing cells comprising vectors and/or exogenous nucleic acids are well-known in the art. See, for example, Sambrook et al., 2012, MOLECULAR CLONING: A LABORATORY MANUAL, volumes 1 -4, Cold Spring Harbor Press, NY). A preferred method for the introduction of a polynucleotide into a host cell is calcium phosphate transfection

Biological methods for introducing a polynucleotide of interest into a host cell include the use of DNA and RNA vectors. Viral vectors, and especially retroviral vectors, have become the most widely used method for inserting genes into mammalian, e.g., human cells. Other viral vectors can be derived from lentivirus, poxviruses, herpes simplex virus I, adenoviruses and adeno-associated viruses, and the like. See, for example, U.S. Pat. Nos. 5,350,674 and 5,585,362.

Chemical means for introducing a polynucleotide into a host cell include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. An exemplary colloidal system for use as a delivery vehicle in vitro and in vivo is a liposome (e.g. , an artificial membrane vesicle). Other methods of state-of-the-art targeted delivery of nucleic acids are available, such as delivery of polynucleotides with targeted nanoparticles or other suitable sub-micron sized delivery system.

In the case where a non-viral delivery system is utilized, an exemplary delivery vehicle is a liposome. The use of lipid formulations is contemplated for the introduction of the nucleic acids into a host cell (in vitro, ex vivo or in vivo). In another aspect, the nucleic acid may be associated with a lipid. The nucleic acid associated with a lipid may be encapsulated in the aqueous interior of a liposome, interspersed within the lipid bilayer of a liposome, attached to a liposome via a linking molecule that is associated with both the liposome and the oligonucleotide, entrapped in a liposome, complexed with a liposome, dispersed in a solution

containing a lipid, mixed with a lipid, combined with a lipid, contained as a suspension in a lipid, contained or complexed with a micelle, or otherwise associated with a lipid. Lipid, lipid/DNA or lipid/expression vector associated compositions are not limited to any particular structure in solution. For example, they may be present in a bilayer structure, as micelles, or with a "collapsed" structure. They may also simply be interspersed in a solution, possibly forming aggregates that are not uniform in size or shape. Lipids are fatty substances which may be naturally occurring or synthetic lipids. For example, lipids include the fatty droplets that naturally occur in the cytoplasm as well as the class of compounds which contain long-chain aliphatic hydrocarbons and their derivatives, such as fatty acids, alcohols, amines, amino alcohols, and aldehydes.

Lipids suitable for use can be obtained from commercial sources. For example, dimyristyl phosphatidylcholine ("DMPC") can be obtained from Sigma, St. Louis, MO; dicetyl phosphate ("DCP") can be obtained from K & K Laboratories (Plainview, NY); cholesterol ("Choi") can be obtained from Calbiochem-Behring; dimyristyl phosphatidylglycerol ("DMPG") and other lipids may be obtained from Avanti Polar Lipids, Inc. (Birmingham, AL.). Stock solutions of lipids in chloroform or chloroform/methanol can be stored at about -20ºC. Chloroform is used as the only solvent since it is more readily evaporated than methanol. "Liposome" is a generic term encompassing a variety of single and multilamellar lipid vehicles formed by the generation of enclosed lipid bilayers or aggregates. Liposomes can be characterized as having vesicular structures with a phospholipid bilayer membrane and an inner aqueous medium. Multilamellar liposomes have multiple lipid layers separated by aqueous medium. They form spontaneously when phospholipids are suspended in an excess of aqueous solution. The lipid components undergo self-rearrangement before the formation of closed structures and entrap water and dissolved solutes between the lipid bilayers (Ghosh et al., 1991 Glycobiology 5: 505-10). However, compositions that have different structures in solution than the normal vesicular structure are also encompassed. For example, the lipids may assume a micellar structure or merely exist as nonuniform aggregates of lipid molecules. Also contemplated are lipofectamine-nucleic acid complexes.

Regardless of the method used to introduce exogenous nucleic acids into a host cell or otherwise expose a cell to the inhibitor of the present invention, in order to confirm the presence of the recombinant DNA sequence in the host cell, a variety of assays may be performed. Such

assays include, for example, "molecular biological" assays well known to those of skill in the art, such as Southern and Northern blotting, RT-PCR and PCR; "biochemical" assays, such as detecting the presence or absence of a particular peptide, e.g., by immunological means (ELISAs and Western blots) or by assays described herein to identify agents falling within the scope of the invention.

The present invention further provides a vector comprising a CAR encoding nucleic acid molecule. In one aspect, a CAR vector can be directly transduced into a cell, e.g., a T cell or a NK cell. In one aspect, the vector is a cloning or expression vector, e.g., a vector including, but not limited to, one or more plasmids (*e.g.*, expression plasmids, cloning vectors, minicircles, minivectors, double minute chromosomes), retroviral and lentiviral vector constructs. In one aspect, the vector is capable of expressing the CAR construct in mammalian immune effector cells (e.g., T cells, NK cells). In one aspect, the mammalian T cell is a human T cell. In one aspect, the mammalian NK cell is a human NK cell.

Sources of Cells

Prior to expansion and genetic modification or other modification, a source of cells, e.g., T cells or natural killer (NK) cells, can be obtained from a subject. The term "subject" is intended to include living organisms in which an immune response can be elicited (e.g., mammals). Examples of subjects include humans, monkeys, chimpanzees, dogs, cats, mice, rats, and transgenic species thereof. T cells can be obtained from a number of sources, including peripheral blood mononuclear cells, bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion, spleen tissue, and tumors.

In certain aspects of the present disclosure, immune effector cells, e.g., T cells, can 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. In one preferred aspect, cells from the circulating blood of an individual are obtained by apheresis. The apheresis product typically contains lymphocytes, including T cells, monocytes, granulocytes, B cells, other nucleated white blood cells, red blood cells, and platelets. In one aspect, the cells collected by apheresis may be washed to remove the plasma fraction and, optionally, to place the cells in an appropriate buffer or media for subsequent processing steps. In one embodiment, the cells are washed with

phosphate buffered saline (PBS). In an alternative embodiment, the wash solution lacks calcium and may lack magnesium or may lack many if not all divalent cations.

Initial activation steps in the absence of calcium can lead to magnified activation. As those of ordinary skill in the art would readily appreciate a washing step may be accomplished by methods known to those in the art, such as by using a semi-automated "flow-through" centrifuge (for example, the Cobe 2991 cell processor, the Baxter CytoMate, or the Haemonetics Cell Saver 5) according to the manufacturer's instructions. After washing, the cells may be resuspended in a variety of biocompatible buffers, such as, for example, Ca-free, Mg-free PBS, PlasmaLyte A, or other saline solution with or without buffer. Alternatively, the undesirable components of the apheresis sample may be removed and the cells directly resuspended in culture media.

It is recognized that the methods of the application can utilize culture media conditions comprising 5% or less, for example 2%, human AB serum, and employ known culture media conditions and compositions, for example those described in Smith et al., "Ex vivo expansion of human T cells for adoptive immunotherapy using the novel Xeno-free CTS Immune Cell Serum Replacement" *Clinical & Translational Immunology* (2015) 4, e31; doi:10.1038/cti.2014.31.

In one aspect, T cells are isolated from peripheral blood lymphocytes by lysing the red blood cells and depleting the monocytes, for example, by centrifugation through a PERCOLL™ gradient or by counterflow centrifugal elutriation.

The methods described herein can include, e.g., selection of a specific subpopulation of immune effector cells, e.g., T cells, that are a T regulatory cell-depleted population, CD25+ depleted cells, using, e.g., a negative selection technique, e.g., described herein. Preferably, the population of T regulatory depleted cells contains less than 30%, 25%, 20%, 15%, 10%, 5%, 4%, 3%, 2%, 1% of CD25+ cells.

In one embodiment, T regulatory cells, e.g., CD25+ T cells, are removed from the population using an anti-CD25 antibody, or fragment thereof, or a CD25-binding ligand, IL-2. In one embodiment, the anti-CD25 antibody, or fragment thereof, or CD25-binding ligand is conjugated to a substrate, e.g., a bead, or is otherwise coated on a substrate, e.g., a bead. In one embodiment, the anti-CD25 antibody, or fragment thereof, is conjugated to a substrate as described herein.

In one embodiment, the T regulatory cells, e.g., CD25+ T cells, are removed from the population using CD25 depletion reagent from Miltenyi™. In one embodiment, the ratio of cells to CD25 depletion reagent is 1e7 cells to 20 uL, or 1e7 cells to15 uL, or 1e7 cells to 10 uL, or 1e7 cells to 5 uL, or 1e7 cells to 2.5 uL, or 1e7 cells to 1.25 uL. In one embodiment, e.g., for T regulatory cells, e.g., CD25+ depletion, greater than 500 million cells/ml is used. In a further aspect, a concentration of cells of 600, 700, 800, or 900 million cells/ml is used.

In one embodiment, the population of immune effector cells to be depleted includes about 6 x 10^9 CD25+ T cells. In other aspects, the population of immune effector cells to be depleted include about 1 x 10^9 to 1x 10^{10} CD25+ T cell, and any integer value in between. In one embodiment, the resulting population T regulatory depleted cells has 2 x 10^9 T regulatory cells, e.g., CD25+ cells, or less (e.g., 1 x 10^9, 5 x 10^8, 1 x 10^8, 5 x 10^7, 1 x 10^7, or less CD25+ cells).

In one embodiment, the T regulatory cells, e.g., CD25+ cells, are removed from the population using the CliniMAC system with a depletion tubing set, such as, e.g., tubing 162-01. In one embodiment, the CliniMAC system is run on a depletion setting such as, e.g., DEPLETION2.1.

Without wishing to be bound by a particular theory, decreasing the level of negative regulators of immune cells (e.g., decreasing the number of unwanted immune cells, e.g., T_{REG} cells), in a subject prior to apheresis or during manufacturing of a CAR-expressing cell product can reduce the risk of subject relapse. For example, methods of depleting T_{REG} cells are known in the art. Methods of decreasing T_{REG} cells include, but are not limited to, cyclophosphamide, anti-GITR antibody (an anti-GITR antibody described herein), CD25-depletion, and combinations thereof.

In some embodiments, the manufacturing methods comprise reducing the number of (e.g., depleting) T_{REG} cells prior to manufacturing of the CAR-expressing cell. For example, manufacturing methods comprise contacting the sample, e.g., the apheresis sample, with an anti-GITR antibody and/or an anti-CD25 antibody (or fragment thereof, or a CD25-binding ligand), e.g., to deplete T_{REG} cells prior to manufacturing of the CAR-expressing cell (e.g., T cell, NK cell) product.

In an embodiment, a subject is pre-treated with one or more therapies that reduce T_{REG} cells prior to collection of cells for CAR-expressing cell product manufacturing, thereby reducing the risk of subject relapse to CAR-expressing cell treatment. In an embodiment,

methods of decreasing T_{REG} cells include, but are not limited to, administration to the subject of one or more of cyclophosphamide, anti-GITR antibody, CD25-depletion, or a combination thereof. Administration of one or more of cyclophosphamide, anti-GITR antibody, CD25-depletion, or a combination thereof, can occur before, during or after an infusion of the CAR-expressing cell product.

In an embodiment, a subject is pre-treated with cyclophosphamide prior to collection of cells for CAR-expressing cell product manufacturing, thereby reducing the risk of subject relapse to CAR-expressing cell treatment. In an embodiment, a subject is pre-treated with an anti-GITR antibody prior to collection of cells for CAR-expressing cell product manufacturing, thereby reducing the risk of subject relapse to CAR-expressing cell treatment.

In one embodiment, the population of cells to be removed are neither the regulatory T cells or tumor cells, but cells that otherwise negatively affect the expansion and/or function of CART cells, e.g. cells expressing CD14, CD11b, CD33, CD15, or other markers expressed by potentially immune suppressive cells. In one embodiment, such cells are envisioned to be removed concurrently with regulatory T cells and/or tumor cells, or following said depletion, or in another order.

The methods described herein can include more than one selection step, e.g., more than one depletion step. Enrichment of a T cell population by negative selection can be accomplished, e.g., with a combination of antibodies directed to surface markers unique to the negatively selected cells. One method is cell sorting and/or selection via negative magnetic immunoadherence or flow cytometry that uses a cocktail of monoclonal antibodies directed to cell surface markers present on the cells negatively selected. For example, to enrich for CD4+ cells by negative selection, a monoclonal antibody cocktail can include antibodies to CD14, CD20, CD11b, CD16, HLA-DR, and CD8.

The methods described herein can further include removing cells from the population which express a tumor antigen, e.g., a tumor antigen that does not comprise CD25, e.g., CD19, CD30, CD38, CD123, CD20, CD14 or CD11b, to thereby provide a population of T regulatory depleted, e.g., CD25+ depleted, and tumor antigen depleted cells that are suitable for expression of a CAR, e.g., a CAR described herein. In one embodiment, tumor antigen expressing cells are removed simultaneously with the T regulatory, e.g., CD25+ cells. For example, an anti-CD25 antibody, or fragment thereof, and an anti-tumor antigen antibody, or fragment thereof, can be

attached to the same substrate, e.g., bead, which can be used to remove the cells or an anti-CD25 antibody, or fragment thereof, or the anti-tumor antigen antibody, or fragment thereof, can be attached to separate beads, a mixture of which can be used to remove the cells. In other embodiments, the removal of T regulatory cells, e.g., CD25+ cells, and the removal of the tumor antigen expressing cells is sequential, and can occur, e.g., in either order.

Also provided are methods that include removing cells from the population which express a check point inhibitor, e.g., a check point inhibitor described herein, e.g., one or more of PD1+ cells, LAG3+ cells, and TIM3+ cells, to thereby provide a population of T regulatory depleted, e.g., CD25+ depleted cells, and check point inhibitor depleted cells, e.g., PD1+, LAG3+ and/or TIM3+ depleted cells. Exemplary check point inhibitors include B7-H1, B7-1, CD160, P1H, 2B4, PD1, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, TIGIT, CTLA-4, BTLA and LAIR1. In one embodiment, check point inhibitor expressing cells are removed simultaneously with the T regulatory, e.g., CD25+ cells. For example, an anti-CD25 antibody, or fragment thereof, and an anti-check point inhibitor antibody, or fragment thereof, can be attached to the same bead which can be used to remove the cells, or an anti-CD25 antibody, or fragment thereof, and the anti-check point inhibitor antibody, or fragment there, can be attached to separate beads, a mixture of which can be used to remove the cells. In other embodiments, the removal of T regulatory cells, e.g., CD25+ cells, and the removal of the check point inhibitor expressing cells is sequential, and can occur, e.g., in either order.

Methods described herein can include a positive selection step. For example, T cells can isolated by incubation with anti-CD3/anti-CD28 (e.g., 3x28)-conjugated beads, such as DYNABEADS® M-450 CD3/CD28 T, for a time period sufficient for positive selection of the desired T cells. In one embodiment, the time period is about 30 minutes. In a further embodiment, the time period ranges from 30 minutes to 36 hours or longer and all integer values there between. In a further embodiment, the time period is at least 1, 2, 3, 4, 5, or 6 hours. In yet another embodiment, the time period is 10 to 24 hours, e.g., 24 hours. Longer incubation times may be used to isolate T cells in any situation where there are few T cells as compared to other cell types, such in isolating tumor infiltrating lymphocytes (TIL) from tumor tissue or from immunocompromised individuals. Further, use of longer incubation times can increase the efficiency of capture of CD8+ T cells. Thus, by simply shortening or lengthening the time T cells

are allowed to bind to the CD3/CD28 beads and/or by increasing or decreasing the ratio of beads to T cells (as described further herein), subpopulations of T cells can be preferentially selected for or against at culture initiation or at other time points during the process. Additionally, by increasing or decreasing the ratio of anti-CD3 and/or anti-CD28 antibodies on the beads or other surface, subpopulations of T cells can be preferentially selected for or against at culture initiation or at other desired time points.

In one embodiment, a T cell population can be selected that expresses one or more of IFN-γ, TNFα, IL-17A, IL-2, IL-3, IL-4, GM-CSF, IL-10, IL-13, granzyme B, and perforin, or other appropriate molecules, e.g., other cytokines. Methods for screening for cell expression can be determined, e.g., by the methods described in PCT Publication No.: WO 2013/126712.

For isolation of a desired population of cells by positive or negative selection, the concentration of cells and surface (e.g., particles such as beads) can be varied. In certain aspects, it may be desirable to significantly decrease the volume in which beads and cells are mixed together (e.g., increase the concentration of cells), to ensure maximum contact of cells and beads. For example, in one aspect, a concentration of 10 billion cells/ml, 9 billion/ml, 8 billion/ml, 7 billion/ml, 6 billion/ml, or 5 billion/ml is used. In one aspect, a concentration of 1 billion cells/ml is used. In yet one aspect, a concentration of cells from 75, 80, 85, 90, 95, or 100 million cells/ml is used. In further aspects, concentrations of 125 or 150 million cells/ml can be used.

Using high concentrations can result in increased cell yield, cell activation, and cell expansion. Further, use of high cell concentrations allows more efficient capture of cells that may weakly express target antigens of interest, such as CD28-negative T cells, or from samples where there are many tumor cells present (e.g., leukemic blood, tumor tissue, etc.). Such populations of cells may have therapeutic value and would be desirable to obtain. For example, using high concentration of cells allows more efficient selection of CD8+ T cells that normally have weaker CD28 expression.

In a related aspect, it may be desirable to use lower concentrations of cells. By significantly diluting the mixture of T cells and surface (e.g., particles such as beads), interactions between the particles and cells is minimized. This selects for cells that express high amounts of desired antigens to be bound to the particles. For example, CD4+ T cells express higher levels of CD28 and are more efficiently captured than CD8+ T cells in dilute

concentrations. In one aspect, the concentration of cells used is 5 x 10^6/ml. In other aspects, the concentration used can be from about 1 x 10^5/ml to 1 x 10^6/ml, and any integer value in between.

In other aspects, the cells may be incubated on a rotator for varying lengths of time at varying speeds at either 2-10°C or at room temperature.

T cells for stimulation can also be frozen after a washing step. Wishing not to be bound by theory, the freeze and subsequent thaw step provides a more uniform product by removing granulocytes and to some extent monocytes in the cell population. After the washing step that removes plasma and platelets, the cells may be suspended in a freezing solution. While many freezing solutions and parameters are known in the art and will be useful in this context, one method involves using PBS containing 20% DMSO and 8% human serum albumin, or culture media containing 10% Dextran 40 and 5% Dextrose, 20% Human Serum Albumin and 7.5% DMSO, or 31.25% Plasmalyte-A, 31.25% Dextrose 5%, 0.45% NaCl, 10% Dextran 40 and 5% Dextrose, 20% Human Serum Albumin, and 7.5% DMSO or other suitable cell freezing media containing for example, Hespan and PlasmaLyte A, the cells then are frozen to -80°C at a rate of 1° per minute and stored in the vapor phase of a liquid nitrogen storage tank. Other methods of controlled freezing may be used as well as uncontrolled freezing immediately at -20° C or in liquid nitrogen.

In certain aspects, cryopreserved cells are thawed and washed as described herein and allowed to rest for one hour at room temperature prior to activation using the methods of the present invention.

Also contemplated in the context of the invention is the collection of blood samples or apheresis product from a subject at a time period prior to when the expanded cells as described herein might be needed. As such, the source of the cells to be expanded can be collected at any time point necessary, and desired cells, such as T cells, isolated and frozen for later use in immune effector cell therapy for any number of diseases or conditions that would benefit from immune effector cell therapy, such as those described herein. In one aspect a blood sample or an apheresis is taken from a generally healthy subject. In certain aspects, a blood sample or an apheresis is taken from a generally healthy subject who is at risk of developing a disease, but who has not yet developed a disease, and the cells of interest are isolated and frozen for later use. In certain aspects, the T cells may be expanded, frozen, and used at a later time. In certain aspects, samples are collected from a patient shortly after diagnosis of a particular disease as

described herein but prior to any treatments. In a further aspect, the cells are isolated from a blood sample or an apheresis from a subject prior to any number of relevant treatment modalities, including but not limited to treatment with agents such as natalizumab, efalizumab, antiviral agents, chemotherapy, radiation, immunosuppressive agents, such as cyclosporin, azathioprine, methotrexate, mycophenolate, and FK506, antibodies, or other immunoablative agents such as CAMPATH, anti-CD3 antibodies, cytoxan, fludarabine, cyclosporin, FK506, rapamycin, mycophenolic acid, steroids, FR901228, and irradiation.

In a further aspect of the present invention, T cells are obtained from a patient directly following treatment that leaves the subject with functional T cells. In this regard, it has been observed that following certain cancer treatments, in particular treatments with drugs that damage the immune system, shortly after treatment during the period when patients would normally be recovering from the treatment, the quality of T cells obtained may be optimal or improved for their ability to expand ex vivo. Likewise, following ex vivo manipulation using the methods described herein, these cells may be in a preferred state for enhanced engraftment and in vivo expansion. Thus, it is contemplated within the context of the present invention to collect blood cells, including T cells, dendritic cells, or other cells of the hematopoietic lineage, during this recovery phase. Further, in certain aspects, mobilization (for example, mobilization with GM-CSF) and conditioning regimens can be used to create a condition in a subject wherein repopulation, recirculation, regeneration, and/or expansion of particular cell types is favored, especially during a defined window of time following therapy. Illustrative cell types include T cells, B cells, dendritic cells, and other cells of the immune system.

In one embodiment, the immune effector cells expressing a CAR molecule, e.g., a CAR molecule described herein, are obtained from a subject that has received a low, immune enhancing dose of an mTOR inhibitor. In an embodiment, the population of immune effector cells, e.g., T cells, to be engineered to express a CAR, are harvested after a sufficient time, or after sufficient dosing of the low, immune enhancing, dose of an mTOR inhibitor, such that the level of PD1 negative immune effector cells, e.g., T cells, or the ratio of PD1 negative immune effector cells, e.g., T cells/ PD1 positive immune effector cells, e.g., T cells, in the subject or harvested from the subject has been, at least transiently, increased.

In other embodiments, population of immune effector cells, e.g., T cells, which have, or will be engineered to express a CAR, can be treated ex vivo by contact with an amount of an

mTOR inhibitor that increases the number of PD1 negative immune effector cells, e.g., T cells or increases the ratio of PD1 negative immune effector cells, e.g., T cells/ PD1 positive immune effector cells, e.g., T cells.

In one embodiment, a T cell population is diaglycerol kinase (DGK)-deficient. DGK-deficient cells include cells that do not express DGK RNA or protein, or have reduced or inhibited DGK activity. DGK-deficient cells can be generated by genetic approaches, e.g., administering RNA-interfering agents, e.g., siRNA, shRNA, miRNA, to reduce or prevent DGK expression. Alternatively, DGK-deficient cells can be generated by treatment with DGK inhibitors described herein.

In one embodiment, a T cell population is Ikaros-deficient. Ikaros-deficient cells include cells that do not express Ikaros RNA or protein, or have reduced or inhibited Ikaros activity, Ikaros-deficient cells can be generated by genetic approaches, e.g., administering RNA-interfering agents, e.g., siRNA, shRNA, miRNA, to reduce or prevent Ikaros expression. Alternatively, Ikaros-deficient cells can be generated by treatment with Ikaros inhibitors, e.g., lenalidomide.

In embodiments, a T cell population is DGK-deficient and Ikaros-deficient, e.g., does not express DGK and Ikaros, or has reduced or inhibited DGK and Ikaros activity. Such DGK and Ikaros-deficient cells can be generated by any of the methods described herein.

In an embodiment, the NK cells are obtained from the subject. In another embodiment, the NK cells are an NK cell line, e.g., NK-92 cell line (Conkwest).

Allogeneic CAR

In embodiments described herein, the immune effector cell can be an allogeneic immune effector cell, e.g., T cell or NK cell. For example, the cell can be an allogeneic T cell, e.g., an allogeneic T cell lacking expression of a functional T cell receptor (TCR) and/or human leukocyte antigen (HLA), e.g., HLA class I and/or HLA class II.

A T cell lacking a functional TCR can be, e.g., engineered such that it does not express any functional TCR on its surface, engineered such that it does not express one or more subunits that comprise a functional TCR or engineered such that it produces very little functional TCR on its surface. Alternatively, the T cell can express a substantially impaired TCR, e.g., by expression of mutated or truncated forms of one or more of the subunits of the TCR. The term

"substantially impaired TCR" means that this TCR will not elicit an adverse immune reaction in a host.

A T cell described herein can be, e.g., engineered such that it does not express a functional HLA on its surface. For example, a T cell described herein, can be engineered such that cell surface expression HLA, e.g., HLA class 1 and/or HLA class II, is downregulated.

In some embodiments, the T cell can lack a functional TCR and a functional HLA, e.g., HLA class I and/or HLA class II.

Modified T cells that lack expression of a functional TCR and/or HLA can be obtained by any suitable means, including a knock out or knock down of one or more subunit of TCR or HLA. For example, the T cell can include a knock down of TCR and/or HLA using siRNA, shRNA, clustered regularly interspaced short palindromic repeats (CRISPR) transcription-activator like effector nuclease (TALEN), or zinc finger endonuclease (ZFN).

In some embodiments, the allogeneic cell can be a cell which does not express or expresses at low levels an inhibitory molecule, e.g. by any mehod described herein. For example, the cell can be a cell that does not express or expresses at low levels an inhibitory molecule, e.g., that can decrease the ability of a CAR-expressing cell to mount an immune effector response. Examples of inhibitory molecules include PD1, PD-L1, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and TGF beta. Inhibition of an inhibitory molecule, e.g., by inhibition at the DNA, RNA or protein level, can optimize a CAR-expressing cell performance. In embodiments, an inhibitory nucleic acid, e.g., an inhibitory nucleic acid, e.g., a dsRNA, e.g., an siRNA or shRNA, a clustered regularly interspaced short palindromic repeats (CRISPR), a transcription-activator like effector nuclease (TALEN), or a zinc finger endonuclease (ZFN), e.g., as described herein, can be used.

siRNA and shRNA to inhibit TCR or HLA

In some embodiments, TCR expression and/or HLA expression can be inhibited using siRNA or shRNA that targets a nucleic acid encoding a TCR and/or HLA in a T cell.

Expression of siRNA and shRNAs in T cells can be achieved using any conventional expression system, e.g., such as a lentiviral expression system.

Exemplary shRNAs that downregulate expression of components of the TCR are described, e.g., in US Publication No.: 2012/0321667. Exemplary siRNA and shRNA that

downregulate expression of HLA class I and/or HLA class II genes are described, e.g., in U.S. publication No.: US 2007/0036773.

CRISPR to inhibit TCR or HLA

"CRISPR" or "CRISPR to TCR and/or HLA" or "CRISPR to inhibit TCR and/or HLA" as used herein refers to a set of clustered regularly interspaced short palindromic repeats, or a system comprising such a set of repeats. "Cas", as used herein, refers to a CRISPR-associated protein. A "CRISPR/Cas" system refers to a system derived from CRISPR and Cas which can be used to silence or mutate a TCR and/or HLA gene.

Naturally-occurring CRISPR/Cas systems are found in approximately 40% of sequenced eubacteria genomes and 90% of sequenced archaea. Grissa et al. (2007) BMC Bioinformatics 8: 172. This system is a type of prokaryotic immune system that confers resistance to foreign genetic elements such as plasmids and phages and provides a form of acquired immunity. Barrangou et al. (2007) Science 315: 1709-1712; Marragini et al. (2008) Science 322: 1843-1845.

The CRISPR/Cas system has been modified for use in gene editing (silencing, enhancing or changing specific genes) in eukaryotes such as mice or primates. Wiedenheft et al. (2012) Nature 482: 331-8. This is accomplished by introducing into the eukaryotic cell a plasmid containing a specifically designed CRISPR and one or more appropriate Cas.

The CRISPR sequence, sometimes called a CRISPR locus, comprises alternating repeats and spacers. In a naturally-occurring CRISPR, the spacers usually comprise sequences foreign to the bacterium such as a plasmid or phage sequence; in the TCR and/or HLA CRISPR/Cas system, the spacers are derived from the TCR or HLA gene sequence.

RNA from the CRISPR locus is constitutively expressed and processed by Cas proteins into small RNAs. These comprise a spacer flanked by a repeat sequence. The RNAs guide other Cas proteins to silence exogenous genetic elements at the RNA or DNA level. Horvath et al. (2010) *Science* 327: 167-170; Makarova et al. (2006) Biology Direct 1: 7. The spacers thus serve as templates for RNA molecules, analogously to siRNAs. Pennisi (2013) Science 341: 833-836.

As these naturally occur in many different types of bacteria, the exact arrangements of the CRISPR and structure, function and number of Cas genes and their product differ somewhat from species to species. Haft et al. (2005) PLoS Comput. Biol. 1: e60; Kunin et al. (2007)

Genome Biol. 8: R61; Mojica et al. (2005) J. Mol. Evol. 60: 174-182; Bolotin et al. (2005) Microbiol. 151: 2551-2561; Pourcel et al. (2005) Microbiol. 151: 653-663; and Stern et al. (2010) Trends. Genet. 28: 335-340. For example, the Cse (Cas subtype, E. coli) proteins (e.g., CasA) form a functional complex, Cascade, that processes CRISPR RNA transcripts into spacer-repeat units that Cascade retains. Brouns et al. (2008) *Science* 321: 960-964. In other prokaryotes, Cas6 processes the CRISPR transcript. The CRISPR-based phage inactivation in E. coli requires Cascade and Cas3, but not Cas1 or Cas2. The Cmr (Cas RAMP module) proteins in Pyrococcus furiosus and other prokaryotes form a functional complex with small CRISPR RNAs that recognizes and cleaves complementary target RNAs. A simpler CRISPR system relies on the protein Cas9, which is a nuclease with two active cutting sites, one for each strand of the double helix. Combining Cas9 and modified CRISPR locus RNA can be used in a system for gene editing. Pennisi (2013) *Science* 341: 833-836.

The CRISPR/Cas system can thus be used to edit a TCR and/or HLA gene (adding or deleting a basepair), or introducing a premature stop which thus decreases expression of a TCR and/or HLA. The CRISPR/Cas system can alternatively be used like RNA interference, turning off TCR and/or HLA gene in a reversible fashion. In a mammalian cell, for example, the RNA can guide the Cas protein to a TCR and/or HLA promoter, sterically blocking RNA polymerases.

Artificial CRISPR/Cas systems can be generated which inhibit TCR and/or HLA, using technology known in the art, e.g., that described in U.S. Publication No. 20140068797, and Cong (2013) Science 339: 819-823. Other artificial CRISPR/Cas systems that are known in the art may also be generated which inhibit TCR and/or HLA, e.g., that described in Tsai (2014) Nature Biotechnol., 32:6 569-576, U.S. Patent No.: 8,871,445; 8,865,406; 8,795,965; 8,771,945; and 8,697,359.

TALEN to inhibit TCR and/or HLA

"TALEN" or "TALEN to HLA and/or TCR" or "TALEN to inhibit HLA and/or TCR" refers to a transcription activator-like effector nuclease, an artificial nuclease which can be used to edit the HLA and/or TCR gene.

TALENs are produced artificially by fusing a TAL effector DNA binding domain to a DNA cleavage domain. Transcription activator-like effects (TALEs) can be engineered to bind any desired DNA sequence, including a portion of the HLA or TCR gene. By combining an engineered TALE with a DNA cleavage domain, a restriction enzyme can be produced which is

specific to any desired DNA sequence, including a HLA or TCR sequence. These can then be introduced into a cell, wherein they can be used for genome editing. Boch (2011) *Nature Biotech.* 29: 135-6; and Boch et al. (2009) *Science* 326: 1509-12; Moscou et al. (2009) *Science* 326: 3501.

TALEs are proteins secreted by Xanthomonas bacteria. The DNA binding domain contains a repeated, highly conserved 33-34 amino acid sequence, with the exception of the 12th and 13th amino acids. These two positions are highly variable, showing a strong correlation with specific nucleotide recognition. They can thus be engineered to bind to a desired DNA sequence.

To produce a TALEN, a TALE protein is fused to a nuclease (N), which is a wild-type or mutated FokI endonuclease. Several mutations to FokI have been made for its use in TALENs; these, for example, improve cleavage specificity or activity. Cermak et al. (2011) *Nucl. Acids Res.* 39: e82; Miller et al. (2011) *Nature Biotech.* 29: 143-8; Hockemeyer et al. (2011) *Nature Biotech.* 29: 731-734; Wood et al. (2011) *Science* 333: 307; Doyon et al. (2010) *Nature Methods* 8: 74-79; Szczepek et al. (2007) *Nature Biotech.* 25: 786-793; and Guo et al. (2010) *J. Mol. Biol.* 200: 96.

The FokI domain functions as a dimer, requiring two constructs with unique DNA binding domains for sites in the target genome with proper orientation and spacing. Both the number of amino acid residues between the TALE DNA binding domain and the FokI cleavage domain and the number of bases between the two individual TALEN binding sites appear to be important parameters for achieving high levels of activity. Miller et al. (2011) *Nature Biotech.* 29: 143-8.

A HLA or TCR TALEN can be used inside a cell to produce a double-stranded break (DSB). A mutation can be introduced at the break site if the repair mechanisms improperly repair the break via non-homologous end joining. For example, improper repair may introduce a frame shift mutation. Alternatively, foreign DNA can be introduced into the cell along with the TALEN; depending on the sequences of the foreign DNA and chromosomal sequence, this process can be used to correct a defect in the HLA or TCR gene or introduce such a defect into a wt HLA or TCR gene, thus decreasing expression of HLA or TCR.

TALENs specific to sequences in HLA or TCR can be constructed using any method known in the art, including various schemes using modular components. Zhang et al. (2011) *Nature Biotech.* 29: 149-53; Geibler et al. (2011) *PLoS ONE* 6: e19509.

Zinc finger nuclease to inhibit HLA and/or TCR

"ZFN" or "Zinc Finger Nuclease" or "ZFN to HLA and/or TCR" or "ZFN to inhibit HLA and/or TCR" refer to a zinc finger nuclease, an artificial nuclease which can be used to edit the HLA and/or TCR gene.

Like a TALEN, a ZFN comprises a FokI nuclease domain (or derivative thereof) fused to a DNA-binding domain. In the case of a ZFN, the DNA-binding domain comprises one or more zinc fingers. Carroll et al. (2011) *Genetics Society of America* 188: 773-782; and Kim et al. (1996) *Proc. Natl. Acad. Sci. USA* 93: 1156-1160.

A zinc finger is a small protein structural motif stabilized by one or more zinc ions. A zinc finger can comprise, for example, Cys2His2, and can recognize an approximately 3-bp sequence. Various zinc fingers of known specificity can be combined to produce multi-finger polypeptides which recognize about 6, 9, 12, 15 or 18-bp sequences. Various selection and modular assembly techniques are available to generate zinc fingers (and combinations thereof) recognizing specific sequences, including phage display, yeast one-hybrid systems, bacterial one-hybrid and two-hybrid systems, and mammalian cells.

Like a TALEN, a ZFN must dimerize to cleave DNA. Thus, a pair of ZFNs are required to target non-palindromic DNA sites. The two individual ZFNs must bind opposite strands of the DNA with their nucleases properly spaced apart. Bitinaite et al. (1998) *Proc. Natl. Acad. Sci. USA* 95: 10570-5.

Also like a TALEN, a ZFN can create a double-stranded break in the DNA, which can create a frame-shift mutation if improperly repaired, leading to a decrease in the expression and amount of HLA and/or TCR in a cell. ZFNs can also be used with homologous recombination to mutate in the HLA or TCR gene.

ZFNs specific to sequences in HLA AND/OR TCR can be constructed using any method known in the art. See, e.g., Provasi (2011) Nature Med. 18: 807-815; Torikai (2013) Blood 122: 1341-1349; Cathomen et al. (2008) *Mol. Ther.* 16: 1200-7; Guo et al. (2010) *J. Mol. Biol.* 400: 96; U.S. Patent Publication 2011/0158957; and U.S. Patent Publication 2012/0060230.

Telomerase expression

While not wishing to be bound by any particular theory, in some embodiments, a therapeutic T cell has short term persistence in a patient, due to shortened telomeres in the T cell; accordingly, transfection with a telomerase gene can lengthen the telomeres of the T cell and improve persistence of the T cell in the patient. See Carl June, "Adoptive T cell therapy for cancer in the clinic", Journal of Clinical Investigation, 117:1466-1476 (2007). Thus, in an embodiment, an immune effector cell, e.g., a T cell, ectopically expresses a telomerase subunit, e.g., the catalytic subunit of telomerase, e.g., TERT, e.g., hTERT. In some aspects, this disclosure provides a method of producing a CAR-expressing cell, comprising contacting a cell with a nucleic acid encoding a telomerase subunit, e.g., the catalytic subunit of telomerase, e.g., TERT, e.g., hTERT. The cell may be contacted with the nucleic acid before, simultaneous with, or after being contacted with a construct encoding a CAR.

In one aspect, the disclosure features a method of making a population of immune effector cells (e.g., T cells, NK cells). In an embodiment, the method comprises: providing a population of immune effector cells (e.g., T cells or NK cells), contacting the population of immune effector cells with a nucleic acid encoding a CAR; and contacting the population of immune effector cells with a nucleic acid encoding a telomerase subunit, e.g., hTERT, under conditions that allow for CAR and telomerase expression.

In an embodiment, the nucleic acid encoding the telomerase subunit is DNA. In an embodiment, the nucleic acid encoding the telomerase subunit comprises a promoter capable of driving expression of the telomerase subunit.

In an embodiment, hTERT has the amino acid sequence of GenBank Protein ID AAC51724.1 (Meyerson et al., "hEST2, the Putative Human Telomerase Catalytic Subunit Gene, Is Up-Regulated in Tumor Cells and during Immortalization" Cell Volume 90, Issue 4, 22 August 1997, Pages 785–795) as follows:

MPRAPRCRAVRSLLRSHYREVLPLATFVRRLGPQGWRLVQRGDPAAFRALVAQCLVCV
PWDARPPPAAPSFRQVSCLKELVARVLQRLCERGAKNVLAFGFALLDGARGGPPEAFTT
SVRSYLPNTVTDALRGSGAWGLLLRRVGDDVLVHLLARCALFVLVAPSCAYQVCGPPL
YQLGAATQARPPPHASGPRRRLGCERAWNHSVREAGVPLGLPAPGARRRGGSASRSLP
LPKRPRRGAAPEPERTPVGQGSWAHPGRTRGPSDRGFCVVSPARPAEEATSLEGALSGT
RHSHPSVGRQHHAGPPSTSRPPRPWDTPCPPVYAETKHFLYSSGDKEQLRPSFLLSSLRPS

LTGARRLVETIFLGSRPWMPGTPRRLPRLPQRYWQMRPLFLELLGNHAQCPYGVLLKTH
CPLRAAVTPAAGVCAREKPQGSVAAPEEEDTDPRRLVQLLRQHSSPWQVYGFVRACLR
RLVPPGLWGSRHNERRFLRNTKKFISLGKHAKLSLQELTWKMSVRGCAWLRRSPGVGC
VPAAEHRLREEILAKFLHWLMSVYVVELLRSFFYVTETTFQKNRLFFYRKSVWSKLQSI
GIRQHLKRVQLRELSEAEVRQHREARPALLTSRLRFIPKPDGLRPIVNMDYVVGARTFRR
EKRAERLTSRVKALFSVLNYERARRPGLLGASVLGLDDIHRAWRTFVLRVRAQDPPPEL
YFVKVDVTGAYDTIPQDRLTEVIASIIKPQNTYCVRRYAVVQKAAHGHVRKAFKSHVST
LTDLQPYMRQFVAHLQETSPLRDAVVIEQSSSLNEASSGLFDVFLRFMCHHAVRIRGKS
YVQCQGIPQGSILSTLLCSLCYGDMENKLFAGIRRDGLLLRLVDDFLLVTPHLTHAKTFL
RTLVRGVPEYGCVVNLRKTVVNFPVEDEALGGTAFVQMPAHGLFPWCGLLLDTRTLEV
QSDYSSYARTSIRASLTFNRGFKAGRNMRRKLFGVLRLKCHSLFLDLQVNSLQTVCTNI
YKILLLQAYRFHACVLQLPFHQQVWKNPTFFLRVISDTASLCYSILKAKNAGMSLGAKG
AAGPLPSEAVQWLCHQAFLLKLTRHRVTYVPLLGSLRTAQTQLSRKLPGTTLTALEAAA
NPALPSDFKTILD (SEQ ID NO: 63)

In an embodiment, the hTERT has a sequence at least 80%, 85%, 90%, 95%, 96^, 97%, 98%, or 99% identical to the sequence of SEQ ID NO: 63. In an embodiment, the hTERT has a sequence of SEQ ID NO: 63. In an embodiment, the hTERT comprises a deletion (e.g., of no more than 5, 10, 15, 20, or 30 amino acids) at the N-terminus, the C-terminus, or both. In an embodiment, the hTERT comprises a transgenic amino acid sequence (e.g., of no more than 5, 10, 15, 20, or 30 amino acids) at the N-terminus, the C-terminus, or both.

In an embodiment, the hTERT is encoded by the nucleic acid sequence of GenBank Accession No. AF018167 (Meyerson et al., "hEST2, the Putative Human Telomerase Catalytic Subunit Gene, Is Up-Regulated in Tumor Cells and during Immortalization" Cell Volume 90, Issue 4, 22 August 1997, Pages 785–795):

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   1 caggcagcgt ggtcctgctg cgcacgtggg aagccctggc cccggccacc cccgcgatgc
  61 cgcgcgctcc ccgctgccga gccgtgcgct ccctgctgcg cagccactac cgcgaggtgc
 121 tgccgctggc cacgttcgtg cggcgcctgg ggccccaggg ctggcggctg gtgcagcgcg
 181 gggacccggc ggctttccgc gcgctggtgg cccagtgcct ggtgtgcgtg ccctgggacg
 241 cacggccgcc ccccgccgcc ccctccttcc gccaggtgtc ctgcctgaag gagctggtgg
 301 cccgagtgct gcagaggctg tgcgagcgcg gcgcgaagaa cgtgctggcc ttcggcttcg
 361 cgctgctgga cggggcccgc ggggggcccc ccgaggcctt caccaccagc gtgcgcagct
 421 acctgcccaa cacggtgacc gacgcactgc gggggagcgg ggcgtggggg ctgctgttgc
 481 gccgcgtggg cgacgacgtg ctggttcacc tgctggcacg ctgcgcgctc tttgtgctgg
 541 tggctcccag ctgcgcctac caggtgtgcg ggccgccgct gtaccagctc ggcgctgcca
 601 ctcaggcccg gcccccgcca cacgctagtg gaccccgaag gcgtctggga tgcgaacggg
 661 cctggaacca tagcgtcagg gaggccgggg tccccctggg cctgccagcc ccgggtgcga
 721 ggaggcgcgg gggcagtgcc agccgaagtc tgccgttgcc caagaggccc aggcgtggcg
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781 ctgcccctga gccggagcgg acgcccgttg ggcaggggtc ctgggcccac ccgggcagga
841 cgcgtggacc gagtgaccgt ggtttctgtg tggtgtcacc tgccagaccc gccgaagaag
901 ccacctcttt ggagggtgcg ctctctggca cgcgccactc ccacccatcc gtgggccgcc
961 agcaccacgc gggcccccca tccacatcgc ggccaccacg tccctgggac acgccttgtc
1021 ccccggtgta cgccgagacc aagcacttcc tctactcctc aggcgacaag gagcagctgc
1081 ggccctcctt cctactcagc tctctgaggc ccagcctgac tggcgctcgg aggctcgtgg
1141 agaccatctt tctgggttcc aggccctgga tgccagggac tccccgcagg ttgccccgcc
1201 tgccccagcg ctactggcaa atgcggcccc tgtttctgga gctgcttggg aaccacgcgc
1261 agtgccccta cggggtgctc ctcaagacgc actgcccgct gcgagctgcg gtcaccccag
1321 cagccggtgt ctgtgcccgg gagaagcccc agggctctgt ggcggccccc gaggaggagg
1381 acacagaccc ccgtcgcctg gtgcagctgc tccgccagca cagcagcccc tggcaggtgt
1441 acggcttcgt gcgggcctgc ctgcgccggc tggtgccccc aggcctctgg ggctccaggc
1501 acaacgaacg ccgcttcctc aggaacacca agaagttcat ctccctgggg aagcatgcca
1561 agctctcgct gcaggagctg acgtggaaga tgagcgtgcg gggctgcgct tggctgcgca
1621 ggagcccagg ggttggctgt gttccggccg cagagcaccg tctgcgtgag gagatcctgg
1681 ccaagttcct gcactggctg atgagtgtgt acgtcgtcga gctgctcagg tctttctttt
1741 atgtcacgga gaccacgttt caaaagaaca ggctcttttt ctaccggaag agtgtctgga
1801 gcaagttgca aagcattgga atcagacagc acttgaagag ggtgcagctg cgggagctgt
1861 cggaagcaga ggtcaggcag catcgggaag ccaggcccgc cctgctgacg tccagactcc
1921 gcttcatccc caagcctgac gggctgcggc cgattgtgaa catggactac gtcgtgggag
1981 ccagaacgtt ccgcagagaa aagagggccg agcgtctcac ctcgagggtg aaggcactgt
2041 tcagcgtgct caactacgag cgggcgcggc gccccggcct cctgggcgcc tctgtgctgg
2101 gcctggacga tatccacagg gcctggcgca ccttcgtgct gcgtgtgcgg gcccaggacc
2161 cgccgcctga gctgtacttt gtcaaggtgg atgtgacggg cgcgtacgac accatccccc
2221 aggacaggct cacggaggtc atcgccagca tcatcaaacc ccagaacacg tactgcgtgc
2281 gtcggtatgc cgtggtccag aaggccgccc atgggcacgt ccgcaaggcc ttcaagagcc
2341 acgtctctac cttgacagac ctccagccgt acatgcgaca gttcgtggct cacctgcagg
2401 agaccagccc gctgagggat gccgtcgtca tcgagcagag ctcctccctg aatgaggcca
2461 gcagtggcct cttcgacgtc ttcctacgct tcatgtgcca ccacgccgtg cgcatcaggg
2521 gcaagtccta cgtccagtgc caggggatcc cgcagggctc catcctctcc acgctgctct
2581 gcagcctgtg ctacggcgac atggagaaca agctgtttgc ggggattcgg cgggacgggc
2641 tgctcctgcg tttggtggat gatttcttgt tggtgacacc tcacctcacc cacgcgaaaa
2701 ccttcctcag gaccctggtc cgaggtgtcc ctgagtatgg ctgcgtggtg aacttgcgga
2761 agacagtggt gaacttccct gtagaagacg aggccctggg tggcacggct tttgttcaga
2821 tgccggccca cggcctattc ccctggtgcg gcctgctgct ggatacccgg accctggagg
2881 tgcagagcga ctactccagc tatgcccgga cctccatcag agccagtctc accttcaacc
2941 gcggcttcaa ggctgggagg aacatgcgtc gcaaactctt tggggtcttg cggctgaagt
3001 gtcacagcct gtttctggat ttgcaggtga acagcctcca gacggtgtgc accaacatct
3061 acaagatcct cctgctgcag gcgtacaggt ttcacgcatg tgtgctgcag ctcccatttc
3121 atcagcaagt ttggaagaac cccacatttt tcctgcgcgt catctctgac acggcctccc
3181 tctgctactc catcctgaaa gccaagaacg cagggatgtc gctgggggcc aagggcgccg
3241 ccggccctct gccctccgag gccgtgcagt ggctgtgcca ccaagcattc ctgctcaagc
3301 tgactcgaca ccgtgtcacc tacgtgccac tcctggggtc actcaggaca gcccagacgc
3361 agctgagtcg gaagctcccg gggacgacgc tgactgccct ggaggccgca gccaacccgg
3421 cactgccctc agacttcaag accatcctgg actgatggcc acccgcccac agccaggccg
3481 agagcagaca ccagcagccc tgtcacgccg ggctctacgt cccagggagg gaggggcggc
3541 ccacacccag gcccgcaccg ctgggagtct gaggcctgag tgagtgtttg gccgaggcct
3601 gcatgtccgg ctgaaggctg agtgtccggc tgaggcctga gcgagtgtcc agccaagggc
3661 tgagtgtcca gcacacctgc cgtcttcact tccccacagg ctggcgctcg gctccacccc
3721 agggccagct tttcctcacc aggagcccgg cttccactcc ccacatagga atagtccatc
3781 cccagattcg ccattgttca cccctcgccc tgccctcctt tgccttccac ccccaccatc
3841 caggtggaga ccctgagaag gaccctggga gctctgggaa tttggagtga ccaaaggtgt
3901 gccctgtaca caggcgagga ccctgcacct ggatgggggt ccctgtgggt caaattgggg
3961 ggaggtgctg tgggagtaaa atactgaata tatgagtttt tcagttttga aaaaaaaaaa
4021 aaaaaaa (SEQ ID NO: 64)

In an embodiment, the hTERT is encoded by a nucleic acid having a sequence at least 80%, 85%, 90%, 95%, 96, 97%, 98%, or 99% identical to the sequence of SEQ ID NO: 64. In an embodiment, the hTERT is encoded by a nucleic acid of SEQ ID NO: 64.

Activation and Expansion of Immune Effector Cells (e.g., T Cells)

Immune effector cells such as T cells may be activated and expanded generally using methods as described, for example, in U.S. Patents 6,352,694; 6,534,055; 6,905,680; 6,692,964; 5,858,358; 6,887,466; 6,905,681; 7,144,575; 7,067,318; 7,172,869; 7,232,566; 7,175,843; 5,883,223; 6,905,874; 6,797,514; 6,867,041; and U.S. Patent Application Publication No. 20060121005.

Generally, a population of immune effector cells e.g., T regulatory cell depleted cells, may be expanded by contact with a surface having attached thereto an agent that stimulates a CD3/TCR complex associated signal and a ligand that stimulates a costimulatory molecule on the surface of the T cells. In particular, T cell populations may be stimulated as described herein, such as by contact with an anti-CD3 antibody, or antigen-binding fragment thereof, or an anti-CD2 antibody immobilized on a surface, or by contact with a protein kinase C activator (e.g., bryostatin) in conjunction with a calcium ionophore. For co-stimulation of an accessory molecule on the surface of the T cells, a ligand that binds the accessory molecule is used. For example, a population of T cells can be contacted with an anti-CD3 antibody and an anti-CD28 antibody, under conditions appropriate for stimulating proliferation of the T cells. To stimulate proliferation of either CD4+ T cells or CD8+ T cells, an anti-CD3 antibody and an anti-CD28 antibody can be used. Examples of an anti-CD28 antibody include 9.3, B-T3, XR-CD28 (Diaclone, Besançon, France) can be used as can other methods commonly known in the art (Berg et al., Transplant Proc. 30(8):3975-3977, 1998; Haanen et al., J. Exp. Med. 190(9):13191328, 1999; Garland et al., J. Immunol Meth. 227(1-2):53-63, 1999).

In certain aspects, the primary stimulatory signal and the costimulatory signal for the T cell may be provided by different protocols. For example, the agents providing each signal may be in solution or coupled to a surface. When coupled to a surface, the agents may be coupled to the same surface (i.e., in "cis" formation) or to separate surfaces (i.e., in "trans" formation). Alternatively, one agent may be coupled to a surface and the other agent in solution. In one aspect, the agent providing the costimulatory signal is bound to a cell surface and the agent

providing the primary activation signal is in solution or coupled to a surface. In certain aspects, both agents can be in solution. In one aspect, the agents may be in soluble form, and then cross-linked to a surface, such as a cell expressing Fc receptors or an antibody or other binding agent which will bind to the agents. In this regard, see for example, U.S. Patent Application Publication Nos. 20040101519 and 20060034810 for artificial antigen presenting cells (aAPCs) that are contemplated for use in activating and expanding T cells in the present invention.

In one aspect, the two agents are immobilized on beads, either on the same bead, i.e., "cis," or to separate beads, i.e., "trans." By way of example, the agent providing the primary activation signal is an anti-CD3 antibody or an antigen-binding fragment thereof and the agent providing the costimulatory signal is an anti-CD28 antibody or antigen-binding fragment thereof; and both agents are co-immobilized to the same bead in equivalent molecular amounts. In one aspect, a 1:1 ratio of each antibody bound to the beads for CD4+ T cell expansion and T cell growth is used. In certain aspects of the present invention, a ratio of anti CD3:CD28 antibodies bound to the beads is used such that an increase in T cell expansion is observed as compared to the expansion observed using a ratio of 1:1. In one particular aspect an increase of from about 1 to about 3 fold is observed as compared to the expansion observed using a ratio of 1:1. In one aspect, the ratio of CD3:CD28 antibody bound to the beads ranges from 100:1 to 1:100 and all integer values there between. In one aspect, more anti-CD28 antibody is bound to the particles than anti-CD3 antibody, i.e., the ratio of CD3:CD28 is less than one. In certain aspects, the ratio of anti CD28 antibody to anti CD3 antibody bound to the beads is greater than 2:1. In one particular aspect, a 1:100 CD3:CD28 ratio of antibody bound to beads is used. In one aspect, a 1:75 CD3:CD28 ratio of antibody bound to beads is used. In a further aspect, a 1:50 CD3:CD28 ratio of antibody bound to beads is used. In one aspect, a 1:30 CD3:CD28 ratio of antibody bound to beads is used. In one preferred aspect, a 1:10 CD3:CD28 ratio of antibody bound to beads is used. In one aspect, a 1:3 CD3:CD28 ratio of antibody bound to the beads is used. In yet one aspect, a 3:1 CD3:CD28 ratio of antibody bound to the beads is used.

Ratios of particles to cells from 1:500 to 500:1 and any integer values in between may be used to stimulate T cells or other target cells. As those of ordinary skill in the art can readily appreciate, the ratio of particles to cells may depend on particle size relative to the target cell. For example, small sized beads could only bind a few cells, while larger beads could bind many. In certain aspects the ratio of cells to particles ranges from 1:100 to 100:1 and any integer values

in-between and in further aspects the ratio comprises 1:9 to 9:1 and any integer values in between, can also be used to stimulate T cells. The ratio of anti-CD3- and anti-CD28-coupled particles to T cells that result in T cell stimulation can vary as noted above, however certain preferred values include 1:100, 1:50, 1:40, 1:30, 1:20, 1:10, 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, and 15:1 with one preferred ratio being at least 1:1 particles per T cell. In one aspect, a ratio of particles to cells of 1:1 or less is used. In one particular aspect, a preferred particle: cell ratio is 1:5. In further aspects, the ratio of particles to cells can be varied depending on the day of stimulation. For example, in one aspect, the ratio of particles to cells is from 1:1 to 10:1 on the first day and additional particles are added to the cells every day or every other day thereafter for up to 10 days, at final ratios of from 1:1 to 1:10 (based on cell counts on the day of addition). In one particular aspect, the ratio of particles to cells is 1:1 on the first day of stimulation and adjusted to 1:5 on the third and fifth days of stimulation. In one aspect, particles are added on a daily or every other day basis to a final ratio of 1:1 on the first day, and 1:5 on the third and fifth days of stimulation. In one aspect, the ratio of particles to cells is 2:1 on the first day of stimulation and adjusted to 1:10 on the third and fifth days of stimulation. In one aspect, particles are added on a daily or every other day basis to a final ratio of 1:1 on the first day, and 1:10 on the third and fifth days of stimulation. One of skill in the art will appreciate that a variety of other ratios may be suitable for use in the present invention. In particular, ratios will vary depending on particle size and on cell size and type. In one aspect, the most typical ratios for use are in the neighborhood of 1:1, 2:1 and 3:1 on the first day.

In further aspects, the cells, such as T cells, are combined with agent-coated beads, the beads and the cells are subsequently separated, and then the cells are cultured. In an alternative aspect, prior to culture, the agent-coated beads and cells are not separated but are cultured together. In a further aspect, the beads and cells are first concentrated by application of a force, such as a magnetic force, resulting in increased ligation of cell surface markers, thereby inducing cell stimulation.

By way of example, cell surface proteins may be ligated by allowing paramagnetic beads to which anti-CD3 and anti-CD28 are attached (3x28 beads) to contact the T cells. In one aspect the cells (for example, 10^4 to 10^9 T cells) and beads (for example, DYNABEADS® M-450 CD3/CD28 T paramagnetic beads at a ratio of 1:1) are combined in a buffer, for example PBS

(without divalent cations such as, calcium and magnesium). Again, those of ordinary skill in the art can readily appreciate any cell concentration may be used. For example, the target cell may be very rare in the sample and comprise only 0.01% of the sample or the entire sample (i.e., 100%) may comprise the target cell of interest. Accordingly, any cell number is within the context of the present invention. In certain aspects, it may be desirable to significantly decrease the volume in which particles and cells are mixed together (i.e., increase the concentration of cells), to ensure maximum contact of cells and particles. For example, in one aspect, a concentration of about 10 billion cells/ml, 9 billion/ml, 8 billion/ml, 7 billion/ml, 6 billion/ml, 5 billion/ml, or 2 billion cells/ml is used. In one aspect, greater than 100 million cells/ml is used. In a further aspect, a concentration of cells of 10, 15, 20, 25, 30, 35, 40, 45, or 50 million cells/ml is used. In yet one aspect, a concentration of cells from 75, 80, 85, 90, 95, or 100 million cells/ml is used. In further aspects, concentrations of 125 or 150 million cells/ml can be used. Using high concentrations can result in increased cell yield, cell activation, and cell expansion. Further, use of high cell concentrations allows more efficient capture of cells that may weakly express target antigens of interest, such as CD28-negative T cells. Such populations of cells may have therapeutic value and would be desirable to obtain in certain aspects. For example, using high concentration of cells allows more efficient selection of CD8+ T cells that normally have weaker CD28 expression.

In one embodiment, cells transduced with a nucleic acid encoding a CAR, e.g., a CAR described herein, are expanded, e.g., by a method described herein. In one embodiment, the cells are expanded in culture for a period of several hours (e.g., about 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 18, 21 hours) to about 14 days (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 days). In one embodiment, the cells are expanded for a period of 4 to 9 days. In one embodiment, the cells are expanded for a period of 8 days or less, e.g., 7, 6 or 5 days. In one embodiment, the cells, e.g., a CD19 CAR cell described herein, are expanded in culture for 5 days, and the resulting cells are more potent than the same cells expanded in culture for 9 days under the same culture conditions. Potency can be defined, e.g., by various T cell functions, e.g. proliferation, target cell killing, cytokine production, activation, migration, or combinations thereof. In one embodiment, the cells, e.g., a CD19 CAR cell described herein, expanded for 5 days show at least a one, two, three or four fold increase in cells doublings upon antigen stimulation as compared to the same cells expanded in culture for 9 days under the same culture conditions. In one embodiment, the

cells, e.g., the cells expressing a CD19 CAR described herein, are expanded in culture for 5 days, and the resulting cells exhibit higher proinflammatory cytokine production, e.g., IFN-γ and/or GM-CSF levels, as compared to the same cells expanded in culture for 9 days under the same culture conditions. In one embodiment, the cells, e.g., a CD19 CAR cell described herein, expanded for 5 days show at least a one, two, three, four, five, ten fold or more increase in pg/ml of proinflammatory cytokine production, e.g., IFN-γ and/or GM-CSF levels, as compared to the same cells expanded in culture for 9 days under the same culture conditions.

Several cycles of stimulation may also be desired such that culture time of T cells can be 60 days or more. Conditions appropriate for T cell culture include an appropriate media (e.g., Minimal Essential Media or RPMI Media 1640 or, X-vivo 15, (Lonza)) that may contain factors necessary for proliferation and viability, including serum (e.g., fetal bovine or human serum), interleukin-2 (IL-2), insulin, IFN-γ, IL-4, IL-7, GM-CSF, IL-10, IL-12, IL-15, TGFβ, and TNF-α or any other additives for the growth of cells known to the skilled artisan. Other additives for the growth of cells include, but are not limited to, surfactant, plasmanate, and reducing agents such as N-acetyl-cysteine and 2-mercaptoethanol. Media can include RPMI 1640, AIM-V, DMEM, MEM, α-MEM, F-12, X-Vivo 15, and X-Vivo 20, Optimizer, with added amino acids, sodium pyruvate, and vitamins, either serum-free or supplemented with an appropriate amount of serum (or plasma) or a defined set of hormones, and/or an amount of cytokine(s) sufficient for the growth and expansion of T cells. Antibiotics, e.g., penicillin and streptomycin, are included only in experimental cultures, not in cultures of cells that are to be infused into a subject. The target cells are maintained under conditions necessary to support growth, for example, an appropriate temperature (e.g., 37° C) and atmosphere (e.g., air plus 5% CO_2).

In one embodiment, the cells are expanded in an appropriate media (e.g., media described herein) that includes one or more interleukin that result in at least a 200-fold (e.g., 200-fold, 250-fold, 300-fold, 350-fold) increase in cells over a 14 day expansion period, e.g., as measured by a method described herein such as flow cytometry. In one embodiment, the cells are expanded in the presence of IL-15 and/or IL-7 (e.g., IL-15 and IL-7).

In embodiments, methods described herein, e.g., CAR-expressing cell manufacturing methods, comprise removing T regulatory cells, e.g., CD25+ T cells, from a cell population, e.g., using an anti-CD25 antibody, or fragment thereof, or a CD25-binding ligand, IL-2. Methods of removing T regulatory cells, e.g., CD25+ T cells, from a cell population are described herein. In

embodiments, the methods, e.g., manufacturing methods, further comprise contacting a cell population (e.g., a cell population in which T regulatory cells, such as CD25+ T cells, have been depleted; or a cell population that has previously contacted an anti-CD25 antibody, fragment thereof, or CD25-binding ligand) with IL-15 and/or IL-7. For example, the cell population (e.g., that has previously contacted an anti-CD25 antibody, fragment thereof, or CD25-binding ligand) is expanded in the presence of IL-15 and/or IL-7.

In some embodiments a CAR-expressing cell described herein is contacted with a composition comprising a interleukin-15 (IL-15) polypeptide, a interleukin-15 receptor alpha (IL-15Ra) polypeptide, or a combination of both a IL-15 polypeptide and a IL-15Ra polypeptide e.g., hetIL-15, during the manufacturing of the CAR-expressing cell, e.g., ex vivo. In embodiments, a CAR-expressing cell described herein is contacted with a composition comprising a IL-15 polypeptide during the manufacturing of the CAR-expressing cell, e.g., ex vivo. In embodiments, a CAR-expressing cell described herein is contacted with a composition comprising a combination of both a IL-15 polypeptide and a IL-15 Ra polypeptide during the manufacturing of the CAR-expressing cell, e.g., ex vivo. In embodiments, a CAR-expressing cell described herein is contacted with a composition comprising hetIL-15 during the manufacturing of the CAR-expressing cell, e.g., ex vivo.

In one embodiment the CAR-expressing cell described herein is contacted with a composition comprising hetIL-15 during ex vivo expansion. In an embodiment, the CAR-expressing cell described herein is contacted with a composition comprising an IL-15 polypeptide during ex vivo expansion. In an embodiment, the CAR-expressing cell described herein is contacted with a composition comprising both an IL-15 polypeptide and an IL-15Ra polypeptide during ex vivo expansion. In one embodiment the contacting results in the survival and proliferation of a lymphocyte subpopulation, e.g., CD8+ T cells.

T cells that have been exposed to varied stimulation times may exhibit different characteristics. For example, typical blood or apheresed peripheral blood mononuclear cell products have a helper T cell population (TH, CD4+) that is greater than the cytotoxic or suppressor T cell population (TC, CD8+). Ex vivo expansion of T cells by stimulating CD3 and CD28 receptors produces a population of T cells that prior to about days 8-9 consists predominately of TH cells, while after about days 8-9, the population of T cells comprises an increasingly greater population of TC cells. Accordingly, depending on the purpose of treatment,

infusing a subject with a T cell population comprising predominately of TH cells may be advantageous. Similarly, if an antigen-specific subset of TC cells has been isolated it may be beneficial to expand this subset to a greater degree.

Further, in addition to CD4 and CD8 markers, other phenotypic markers vary significantly, but in large part, reproducibly during the course of the cell expansion process. Thus, such reproducibility enables the ability to tailor an activated T cell product for specific purposes.

Once a CAR described herein is constructed, various assays can be used to evaluate the activity of the molecule, such as but not limited to, the ability to expand T cells following antigen stimulation, sustain T cell expansion in the absence of re-stimulation, and anti-cancer activities in appropriate in vitro and animal models. Assays to evaluate the effects of a cars of the present invention are described in further detail below

Western blot analysis of CAR expression in primary T cells can be used to detect the presence of monomers and dimers. See, *e.g.*, Milone et al., Molecular Therapy 17(8): 1453-1464 (2009). Very briefly, T cells (1:1 mixture of $CD4^+$ and $CD8^+$ T cells) expressing the CARs are expanded *in vitro* for more than 10 days followed by lysis and SDS-PAGE under reducing conditions. CARs containing the full length TCR-ζ cytoplasmic domain and the endogenous TCR-ζ chain are detected by western blotting using an antibody to the TCR-ζ chain. The same T cell subsets are used for SDS-PAGE analysis under non-reducing conditions to permit evaluation of covalent dimer formation.

In vitro expansion of CAR^+ T cells following antigen stimulation can be measured by flow cytometry. For example, a mixture of $CD4^+$ and $CD8^+$ T cells are stimulated with αCD3/αCD28 aAPCs followed by transduction with lentiviral vectors expressing GFP under the control of the promoters to be analyzed. Exemplary promoters include the CMV IE gene, EF-1α, ubiquitin C, or phosphoglycerokinase (PGK) promoters. GFP fluorescence is evaluated on day 6 of culture in the $CD4^+$ and/or $CD8^+$ T cell subsets by flow cytometry. See, *e.g.*, Milone et al., Molecular Therapy 17(8): 1453-1464 (2009). Alternatively, a mixture of $CD4^+$ and $CD8^+$ T cells are stimulated with αCD3/αCD28 coated magnetic beads on day 0, and transduced with CAR on day 1 using a bicistronic lentiviral vector expressing CAR along with eGFP using a 2A ribosomal skipping sequence. Cultures are re-stimulated with either a cancer associated antigen as described herein$^+$ K562 cells (K562 expressing a cancer associated antigen as described

herein), wild-type K562 cells (K562 wild type) or K562 cells expressing hCD32 and 4-1BBL in the presence of antiCD3 and anti-CD28 antibody (K562-BBL-3/28) following washing. Exogenous IL-2 is added to the cultures every other day at 100 IU/ml. GFP^+ T cells are enumerated by flow cytometry using bead-based counting. See, *e.g.*, Milone et al., Molecular Therapy 17(8): 1453-1464 (2009).

Sustained CAR^+ T cell expansion in the absence of re-stimulation can also be measured. See, e.g., Milone et al., Molecular Therapy 17(8): 1453-1464 (2009). Briefly, mean T cell volume (fl) is measured on day 8 of culture using a Coulter Multisizer III particle counter, a Nexcelom Cellometer Vision or Millipore Scepter, following stimulation with αCD3/αCD28 coated magnetic beads on day 0, and transduction with the indicated CAR on day 1.

Animal models can also be used to measure a CART activity. For example, xenograft model using human a cancer associated antigen described herein-specific CAR^+ T cells to treat a primary human pre-B ALL in immunodeficient mice can be used. See, e.g., Milone et al., Molecular Therapy 17(8): 1453-1464 (2009). Very briefly, after establishment of ALL, mice are randomized as to treatment groups. Different numbers of a cancer associated antigen -specific CARengineered T cells are coinjected at a 1:1 ratio into NOD-SCID-$\gamma^{-/-}$ mice bearing B-ALL. The number of copies of a cancer associated antigen -specific CAR vector in spleen DNA from mice is evaluated at various times following T cell injection. Animals are assessed for leukemia at weekly intervals. Peripheral blood a cancer associate antigen as described herein$^+$ B-ALL blast cell counts are measured in mice that are injected with a cancer associated antigen described herein-ζ CAR^+ T cells or mock-transduced T cells. Survival curves for the groups are compared using the log-rank test. In addition, absolute peripheral blood $CD4^+$ and $CD8^+$ T cell counts 4 weeks following T cell injection in NOD-SCID-$\gamma^{-/-}$ mice can also be analyzed. Mice are injected with leukemic cells and 3 weeks later are injected with T cells engineered to express CAR by a bicistronic lentiviral vector that encodes the CAR linked to eGFP. T cells are normalized to 45–50% input GFP^+ T cells by mixing with mock-transduced cells prior to injection, and confirmed by flow cytometry. Animals are assessed for leukemia at 1-week intervals. Survival curves for the CAR^+ T cell groups are compared using the log-rank test.

Dose dependent CAR treatment response can be evaluated. See, *e.g.*, Milone et al., Molecular Therapy 17(8): 1453-1464 (2009). For example, peripheral blood is obtained 35–70 days after establishing leukemia in mice injected on day 21 with CAR T cells, an equivalent

number of mock-transduced T cells, or no T cells. Mice from each group are randomly bled for determination of peripheral blood a cancer associate antigen as described herein$^+$ ALL blast counts and then killed on days 35 and 49. The remaining animals are evaluated on days 57 and 70.

Assessment of cell proliferation and cytokine production has been previously described, *e.g.*, at Milone et al., Molecular Therapy 17(8): 1453-1464 (2009). Briefly, assessment of CAR-mediated proliferation is performed in microtiter plates by mixing washed T cells with K562 cells expressing a cancer associated antigen described herein (K19) or CD32 and CD137 (KT32-BBL) for a final T-cell:K562 ratio of 2:1. K562 cells are irradiated with gamma-radiation prior to use. Anti-CD3 (clone OKT3) and anti- CD28 (clone 9.3) monoclonal antibodies are added to cultures with KT32-BBL cells to serve as a positive control for stimulating T-cell proliferation since these signals support long-term CD8$^+$ T cell expansion *ex vivo*. T cells are enumerated in cultures using CountBright™ fluorescent beads (Invitrogen, Carlsbad, CA) and flow cytometry as described by the manufacturer. CAR$^+$ T cells are identified by GFP expression using T cells that are engineered with eGFP-2A linked CAR-expressing lentiviral vectors. For CAR+ T cells not expressing GFP, the CAR+ T cells are detected with biotinylated recombinant a cancer associate antigen as described herein protein and a secondary avidin-PE conjugate. CD4+ and CD8$^+$ expression on T cells are also simultaneously detected with specific monoclonal antibodies (BD Biosciences). Cytokine measurements are performed on supernatants collected 24 hours following re-stimulation using the human TH1/TH2 cytokine cytometric bead array kit (BD Biosciences, San Diego, CA) according the manufacturer's instructions. Fluorescence is assessed using a FACScalibur flow cytometer, and data is analyzed according to the manufacturer's instructions.

Cytotoxicity can be assessed by a standard 51Cr-release assay. See, e.g., Milone et al., Molecular Therapy 17(8): 1453-1464 (2009). Briefly, target cells (K562 lines and primary pro-B-ALL cells) are loaded with 51Cr (as NaCrO4, New England Nuclear, Boston, MA) at 37°C for 2 hours with frequent agitation, washed twice in complete RPMI and plated into microtiter plates. Effector T cells are mixed with target cells in the wells in complete RPMI at varying ratios of effector cell:target cell (E:T). Additional wells containing media only (spontaneous release, SR) or a 1% solution of triton-X 100 detergent (total release, TR) are also prepared. After 4 hours of incubation at 37°C, supernatant from each well is harvested. Released 51Cr is

then measured using a gamma particle counter (Packard Instrument Co., Waltham, MA). Each condition is performed in at least triplicate, and the percentage of lysis is calculated using the formula: % Lysis = (ER– SR) / (TR – SR), where ER represents the average 51Cr released for each experimental condition.

Imaging technologies can be used to evaluate specific trafficking and proliferation of CARs in tumor-bearing animal models. Such assays have been described, for example, in Barrett et al., Human Gene Therapy 22:1575-1586 (2011). Briefly, NOD/SCID/$\gamma c^{-/-}$ (NSG) mice are injected IV with Nalm-6 cells followed 7 days later with T cells 4 hour after electroporation with the CAR constructs. The T cells are stably transfected with a lentiviral construct to express firefly luciferase, and mice are imaged for bioluminescence. Alternatively, therapeutic efficacy and specificity of a single injection of CAR^+ T cells in Nalm-6 xenograft model can be measured as the following: NSG mice are injected with Nalm-6 transduced to stably express firefly luciferase, followed by a single tail-vein injection of T cells electroporated with cars of the present invention 7 days later. Animals are imaged at various time points post injection. For example, photon-density heat maps of firefly luciferasepositive leukemia in representative mice at day 5 (2 days before treatment) and day 8 (24 hr post CAR^+ PBLs) can be generated.

Other assays, including those described in the Example section herein as well as those that are known in the art can also be used to evaluate the CARs described herein.

Therapeutic Application

In one aspect, the invention provides methods for treating a disease associated with expression of a cancer associated antigen described herein.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express an XCAR, wherein X represents a tumor antigen as described herein, and wherein the cancer cells express said X tumor antigen.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a XCAR described herein, wherein the cancer cells express X. In one embodiment, X is expressed on both normal cells and cancers cells, but is expressed at lower levels on normal

cells. In one embodiment, the method further comprises selecting a CAR that binds X with an affinity that allows the XCAR to bind and kill the cancer cells expressing X but less than 30%, 25%, 20%, 15%, 10%, 5% or less of the normal cells expressing X are killed, e.g., as determined by an assay described herein. For example, the assay described in FIGS. 13A and 13B can be used or a killing assay such as flow cytometry based on Cr51 CTL. In one embodiment, the selected CAR has an antigen binding domain that has a binding affinity KD of 10^{-4} M to 10^{-8} M, e.g., 10^{-5} M to 10^{-7} M, e.g., 10^{-6} M or 10^{-7} M, for the target antigen. In one embodiment, the selected antigen binding domain has a binding affinity that is at least five-fold, 10-fold, 20-fold, 30-fold, 50-fold, 100-fold or 1,000-fold less than a reference antibody, e.g., an antibody described herein.

In one embodiment, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express CD19 CAR, wherein the cancer cells express CD19. In one embodiment, the cancer to be treated is ALL (acute lymphoblastic leukemia), CLL (chronic lymphocytic leukemia), DLBCL (diffuse large B-cell lymphoma), MCL (Mantle cell lymphoma, or MM (multiple myeloma).

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express an EGFRvIIICAR, wherein the cancer cells express EGFRvIII. In one embodiment, the cancer to be treated is glioblastoma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a mesothelinCAR, wherein the cancer cells express mesothelin. In one embodiment, the cancer to be treated is mesothelioma, pancreatic cancer, or ovarian cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a CD123CAR, wherein the cancer cells express CD123. In one embodiment, the cancer to be treated is AML.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to

express a CD22CAR, wherein the cancer cells express CD22. In one embodiment, the cancer to be treated is B cell malignancies.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a CS-1CAR, wherein the cancer cells express CS-1. In one embodiment, the cancer to be treated is multiple myeloma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a CLL-1CAR, wherein the cancer cells express CLL-1. In one embodiment, the cancer to be treated is AML.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a CD33CAR, wherein the cancer cells express CD33. In one embodiment, the cancer to be treated is AML.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a GD2CAR, wherein the cancer cells express GD2. In one embodiment, the cancer to be treated is neuroblastoma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a BCMACAR, wherein the cancer cells express BCMA. In one embodiment, the cancer to be treated is multiple myeloma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a TnCAR, wherein the cancer cells express Tn antigen. In one embodiment, the cancer to be treated is ovarian cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a PSMACAR, wherein the cancer cells express PSMA. In one embodiment, the cancer to be treated is prostate cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a ROR1CAR, wherein the cancer cells express ROR1. In one embodiment, the cancer to be treated is B cell malignancies.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a FLT3 CAR, wherein the cancer cells express FLT3. In one embodiment, the cancer to be treated is AML.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a TAG72CAR, wherein the cancer cells express TAG72. In one embodiment, the cancer to be treated is gastrointestinal cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a CD38CAR, wherein the cancer cells express CD38. In one embodiment, the cancer to be treated is multiple myeloma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a CD44v6CAR, wherein the cancer cells express CD44v6. In one embodiment, the cancer to be treated is cervical cancer, AML, or MM.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a CEACAR, wherein the cancer cells express CEA. In one embodiment, the cancer to be treated is pastrointestinal cancer, or pancreatic cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express an EPCAMCAR, wherein the cancer cells express EPCAM. In one embodiment, the cancer to be treated is gastrointestinal cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a B7H3CAR, wherein the cancer cells express B7H3.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a KITCAR, wherein the cancer cells express KIT. In one embodiment, the cancer to be treated is gastrointestinal cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express an IL-13Ra2CAR, wherein the cancer cells express IL-13Ra2. In one embodiment, the cancer to be treated is glioblastoma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a PRSS21CAR, wherein the cancer cells express PRSS21. In one embodiment, the cancer to be treated is selected from ovarian, pancreatic, lung and breast cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a CD30CAR, wherein the cancer cells express CD30. In one embodiment, the cancer to be treated is lymphomas, or leukemias.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a GD3CAR, wherein the cancer cells express GD3. In one embodiment, the cancer to be treated is melanoma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a CD171CAR, wherein the cancer cells express CD171. In one embodiment, the cancer to be treated is neuroblastoma, ovarian cancer, melanoma, breast cancer, pancreatic cancer, colon cancers, or NSCLC (non-small cell lung cancer).

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express an IL-11RaCAR, wherein the cancer cells express IL-11Ra. In one embodiment, the cancer to be treated is osteosarcoma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to

express a PSCACAR, wherein the cancer cells express PSCA. In one embodiment, the cancer to be treated is prostate cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a VEGFR2CAR, wherein the cancer cells express VEGFR2. In one embodiment, the cancer to be treated is a solid tumor.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a LewisYCAR, wherein the cancer cells express LewisY. In one embodiment, the cancer to be treated is ovarian cancer, or AML.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a CD24CAR, wherein the cancer cells express CD24. In one embodiment, the cancer to be treated is pancreatic cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a PDGFR-betaCAR, wherein the cancer cells express PDGFR-beta. In one embodiment, the cancer to be treated is breast cancer, prostate cancer, GIST (gastrointestinal stromal tumor), CML, DFSP (dermatofibrosarcoma protuberans), or glioma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a SSEA-4CAR, wherein the cancer cells express SSEA-4. In one embodiment, the cancer to be treated is glioblastoma, breast cancer, lung cancer, or stem cell cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a CD20CAR, wherein the cancer cells express CD20. In one embodiment, the cancer to be treated is B cell malignancies.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a Folate receptor alphaCAR, wherein the cancer cells express folate receptor alpha. In

one embodiment, the cancer to be treated is ovarian cancer, NSCLC, endometrial cancer, renal cancer, or other solid tumors.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express an ERBB2CAR, wherein the cancer cells express ERBB2 (Her2/neu). In one embodiment, the cancer to be treated is breast cancer, gastric cancer, colorectal cancer, lung cancer, or other solid tumors.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a MUC1CAR, wherein the cancer cells express MUC1. In one embodiment, the cancer to be treated is breast cancer, lung cancer, or other solid tumors.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express an EGFRCAR, wherein the cancer cells express EGFR. In one embodiment, the cancer to be treated is glioblastoma, SCLC (small cell lung cancer), SCCHN (squamous cell carcinoma of the head and neck), NSCLC, or other solid tumors.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a NCAMCAR, wherein the cancer cells express NCAM. In one embodiment, the cancer to be treated is neuroblastoma, or other solid tumors.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a CAIXCAR, wherein the cancer cells express CAIX. In one embodiment, the cancer to be treated is renal cancer, CRC, cervical cancer, or other solid tumors.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express an EphA2CAR, wherein the cancer cells express EphA2. In one embodiment, the cancer to be treated is GBM.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to

express a GD3CAR, wherein the cancer cells express GD3. In one embodiment, the cancer to be treated is melanoma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a Fucosyl GM1CAR, wherein the cancer cells express Fucosyl GM

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a sLeCAR, wherein the cancer cells express sLe. In one embodiment, the cancer to be treated is NSCLC, or AML.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a GM3CAR, wherein the cancer cells express GM3.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a TGS5CAR, wherein the cancer cells express TGS5.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a HMWMAACAR, wherein the cancer cells express HMWMAA. In one embodiment, the cancer to be treated is melanoma, glioblastoma, or breast cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express an o-acetyl-GD2CAR, wherein the cancer cells express o-acetyl-GD2. In one embodiment, the cancer to be treated is neuroblastoma, or melanoma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a CD19CAR, wherein the cancer cells express CD19. In one embodiment, the cancer to be treated isFolate receptor beta AML, myeloma

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a TEM1/CD248CAR, wherein the cancer cells express TEM1/CD248. In one embodiment, the cancer to be treated is a solid tumor.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a TEM7RCAR, wherein the cancer cells express TEM7R. In one embodiment, the cancer to be treated is solid tumor.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a CLDN6CAR, wherein the cancer cells express CLDN6. In one embodiment, the cancer to be treated is ovarian cancer, lung cancer, or breast cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a TSHRCAR, wherein the cancer cells express TSHR. In one embodiment, the cancer to be treated is thyroid cancer, or multiple myeloma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a GPRC5DCAR, wherein the cancer cells express GPRC5D. In one embodiment, the cancer to be treated is multiple myeloma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a CXORF61CAR, wherein the cancer cells express CXORF61.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a CD97CAR, wherein the cancer cells express CD97. In one embodiment, the cancer to be treated is B cell malignancies, gastric cancer, pancreatic cancer, esophageal cancer, glioblastoma, breast cancer, or colorectal cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a CD179aCAR, wherein the cancer cells express CD179a. In one embodiment, the cancer to be treated is B cell malignancies.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express an ALK CAR, wherein the cancer cells express ALK. In one embodiment, the cancer to

be treated is NSCLC, ALCL (anaplastic large cell lymphoma), IMT (inflammatory myofibroblastic tumor), or neuroblastoma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a Polysialic acid CAR, wherein the cancer cells express Polysialic acid. In one embodiment, the cancer to be treated is small cell lung cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a PLAC1CAR, wherein the cancer cells express PLAC1. In one embodiment, the cancer to be treated is HCC (hepatocellular carcinoma).

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a GloboHCAR, wherein the cancer cells express GloboH. In one embodiment, the cancer to be treated is ovarian cancer, gastric cancer, prostate cancer, lung cancer, breast cancer, or pancreatic cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a NY-BR-1CAR, wherein the cancer cells express NY-BR-1. In one embodiment, the cancer to be treated is breast cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a UPK2CAR, wherein the cancer cells express UPK2. In one embodiment, the cancer to be treated is bladder cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a HAVCR1CAR, wherein the cancer cells express HAVCR1. In one embodiment, the cancer to be treated is renal cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a ADRB3CAR, wherein the cancer cells express ADRB3. In one embodiment, the cancer to be treated is Ewing sarcoma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a PANX3CAR, wherein the cancer cells express PANX3. In one embodiment, the cancer to be treated is osteosarcoma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a GPR20CAR, wherein the cancer cells express GPR20. In one embodiment, the cancer to be treated is GIST.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a LY6KCAR, wherein the cancer cells express LY6K. In one embodiment, the cancer to be treated is breast cancer, lung cancer, ovary caner, or cervix cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a OR51E2CAR, wherein the cancer cells express OR51E2. In one embodiment, the cancer to be treated is prostate cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a TARPCAR, wherein the cancer cells express TARP. In one embodiment, the cancer to be treated is prostate cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a WT1CAR, wherein the cancer cells express WT1.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a NY-ESO-1CAR, wherein the cancer cells express NY-ESO-1.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a LAGE-1a CAR, wherein the cancer cells express LAGE-1a.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to

express a MAGE-A1CAR, wherein the cancer cells express MAGE-A1. In one embodiment, the cancer to be treated is melanoma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a MAGE A1CAR, wherein the cancer cells express MAGE A1.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a ETV6-AML CAR, wherein the cancer cells express ETV6-AML.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a sperm protein 17 CAR, wherein the cancer cells express sperm protein 17. In one embodiment, the cancer to be treated is ovarian cancer, HCC, or NSCLC.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a XAGE1CAR, wherein the cancer cells express XAGE1. In one embodiment, the cancer to be treated is Ewings, or rhabdo cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a Tie 2 CAR, wherein the cancer cells express Tie 2. In one embodiment, the cancer to be treated is a solid tumor.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a MAD-CT-1CAR, wherein the cancer cells express MAD-CT-1. In one embodiment, the cancer to be treated is prostate cancer, or melanoma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a MAD-CT-2CAR, wherein the cancer cells express MAD-CT-2. In one embodiment, the cancer to be treated is prostate cancer, melanoma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to

express a Fos-related antigen 1 CAR, wherein the cancer cells express Fos-related antigen 1. In one embodiment, the cancer to be treated is glioma, squamous cell cancer, or pancreatic cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a p53CAR, wherein the cancer cells express p53.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a prostein CAR, wherein the cancer cells express prostein.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a survivin and telomerase CAR, wherein the cancer cells express survivin and telomerase.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a PCTA-1/Galectin 8 CAR, wherein the cancer cells express PCTA-1/Galectin 8.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a MelanA/MART1CAR, wherein the cancer cells express MelanA/MART1.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a Ras mutant CAR, wherein the cancer cells express Ras mutant.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a p53 mutant CAR, wherein the cancer cells express p53 mutant.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a hTERT CAR, wherein the cancer cells express hTERT.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a sarcoma translocation breakpoints CAR, wherein the cancer cells express sarcoma translocation breakpoints. In one embodiment, the cancer to be treated is sarcoma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a ML-IAP CAR, wherein the cancer cells express ML-IAP. In one embodiment, the cancer to be treated is melanoma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express an ERGCAR, wherein the cancer cells express ERG (TMPRSS2 ETS fusion gene).

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a NA17CAR, wherein the cancer cells express NA17. In one embodiment, the cancer to be treated is melanoma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a PAX3CAR, wherein the cancer cells express PAX3. In one embodiment, the cancer to be treated is alveolar rhabdomyosarcoma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express an androgen receptor CAR, wherein the cancer cells express androgen receptor. In one embodiment, the cancer to be treated is metastatic prostate cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a Cyclin B1CAR, wherein the cancer cells express Cyclin B1.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a MYCNCAR, wherein the cancer cells express MYCN.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a RhoC CAR, wherein the cancer cells express RhoC.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to

express a TRP-2CAR, wherein the cancer cells express TRP-2. In one embodiment, the cancer to be treated is melanoma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a CYP1B1CAR, wherein the cancer cells express CYP1B1. In one embodiment, the cancer to be treated is breast cancer, colon cancer, lung cancer, esophagus cancer, skin cancer, lymph node cancer, brain cancer, or testis cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a BORIS CAR, wherein the cancer cells express BORIS. In one embodiment, the cancer to be treated is lung cancer.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a SART3CAR, wherein the cancer cells express SART3

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a PAX5CAR, wherein the cancer cells express PAX5.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a OY-TES1CAR, wherein the cancer cells express OY-TES1.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a LCK CAR, wherein the cancer cells express LCK.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a AKAP-4CAR, wherein the cancer cells express AKAP-4.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a SSX2CAR, wherein the cancer cells express SSX2.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to

express a RAGE-1CAR, wherein the cancer cells express RAGE-1. In one embodiment, the cancer to be treated is RCC (renal cell cancer), or other solid tumors

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a human telomerase reverse transcriptase CAR, wherein the cancer cells express human telomerase reverse transcriptase. In one embodiment, the cancer to be treated is solid tumors.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a RU1CAR, wherein the cancer cells express RU1.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a RU2CAR, wherein the cancer cells express RU2.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express an intestinal carboxyl esterase CAR, wherein the cancer cells express intestinal carboxyl esterase. In one embodiment, the cancer to be treated is thyroid cancer, RCC, CRC (colorectal cancer), breast cancer, or other solid tumors.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a Prostase CAR, wherein the cancer cells express Prostase.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a PAPCAR, wherein the cancer cells express PAP.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express an IGF-I receptor CAR, wherein the cancer cells express IGF-I receptor.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a gp100 CAR, wherein the cancer cells express gp100.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a bcr-abl CAR, wherein the cancer cells express bcr-abl.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a tyrosinase CAR, wherein the cancer cells express tyrosinase.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a Fucosyl GM1CAR, wherein the cancer cells express Fucosyl GM1.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a mut hsp70-2CAR, wherein the cancer cells express mut hsp70-2. In one embodiment, the cancer to be treated is melanoma.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a CD79a CAR, wherein the cancer cells express CD79a.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a CD79b CAR, wherein the cancer cells express CD79b.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a CD72 CAR, wherein the cancer cells express CD72.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a LAIR1 CAR, wherein the cancer cells express LAIR1.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a FCAR CAR, wherein the cancer cells express FCAR.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a LILRA2 CAR, wherein the cancer cells express LILRA2.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a CD300LF CAR, wherein the cancer cells express CD300LF.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a CLEC12A CAR, wherein the cancer cells express CLEC12A.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a BST2 CAR, wherein the cancer cells express BST2.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express an EMR2 CAR, wherein the cancer cells express EMR2.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a LY75 CAR, wherein the cancer cells express LY75.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a GPC3 CAR, wherein the cancer cells express GPC3.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express a FCRL5 CAR, wherein the cancer cells express FCRL5.

In one aspect, the present invention provides methods of treating cancer by providing to the subject in need thereof immune effector cells (e.g., T cells, NK cells) that are engineered to express an IGLL1 CAR, wherein the cancer cells express IGLL1.

In one aspect, the present invention relates to treatment of a subject in vivo using an PD1 CAR such that growth of cancerous tumors is inhibited. A PD1 CAR may be used alone to inhibit the growth of cancerous tumors. Alternatively, PD1 CAR may be used in conjunction with other CARs, immunogenic agents, standard cancer treatments, or other antibodies. In one embodiment, the subject is treated with a PD1 CAR and an XCAR described herein. In an embodiment, a PD1 CAR is used in conjunction with another CAR, e.g., a CAR described herein, and a kinase inhibitor, e.g., a kinase inhibitor described herein.

In another aspect, a method of treating a subject, e.g., reducing or ameliorating, a hyperproliferative condition or disorder (e.g., a cancer), e.g., solid tumor, a soft tissue tumor, or a metastatic lesion, in a subject is provided. As used herein, the term "cancer" is meant to include all types of cancerous growths or oncogenic processes, metastatic tissues or malignantly transformed cells, tissues, or organs, irrespective of histopathologic type or stage of invasiveness. Examples of solid tumors include malignancies, e.g., sarcomas, adenocarcinomas, and carcinomas, of the various organ systems, such as those affecting liver, lung, breast, lymphoid, gastrointestinal (e.g., colon), genitourinary tract (e.g., renal, urothelial cells), prostate and pharynx. Adenocarcinomas include malignancies such as most colon cancers, rectal cancer, renal-cell carcinoma, liver cancer, non-small cell carcinoma of the lung, cancer of the small intestine and cancer of the esophagus. In one embodiment, the cancer is a melanoma, e.g., an advanced stage melanoma. Metastatic lesions of the aforementioned cancers can also be treated or prevented using the methods and compositions of the invention. Examples of other cancers that can be treated include 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, Hodgkin Disease, non-Hodgkin lymphoma, 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 leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, 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, and combinations of said cancers. Treatment of metastatic cancers, e.g., metastatic cancers that express PD-L1 (Iwai et al. (2005) Int. Immunol. 17:133-144) can be effected using the antibody molecules described herein.

Exemplary cancers whose growth can be inhibited include cancers typically responsive to immunotherapy. Non-limiting examples of cancers for treatment include melanoma (e.g.,

metastatic malignant melanoma), renal cancer (e.g. clear cell carcinoma), prostate cancer (e.g. hormone refractory prostate adenocarcinoma), breast cancer, colon cancer and lung cancer (e.g. non-small cell lung cancer). Additionally, refractory or recurrent malignancies can be treated using the molecules described herein.

In one aspect, the invention pertains to a vector comprising a CAR operably linked to promoter for expression in mammalian immune effector cells (e.g., T cells, NK cells). In one aspect, the invention provides a recombinant immune effector cell expressing a CAR of the present invention for use in treating cancer expressing a cancer associate antigen as described herein. In one aspect, CAR-expressing cells of the invention is capable of contacting a tumor cell with at least one cancer associated antigen expressed on its surface such that the CAR-expressing cell targets the cancer cell and growth of the cancer is inhibited.

In one aspect, the invention pertains to a method of inhibiting growth of a cancer, comprising contacting the cancer cell with a CAR-expressing cell of the present invention such that the CART is activated in response to the antigen and targets the cancer cell, wherein the growth of the tumor is inhibited.

In one aspect, the invention pertains to a method of treating cancer in a subject. The method comprises administering to the subject CAR-expressing cell of the present invention such that the cancer is treated in the subject. In one aspect, the cancer associated with expression of a cancer associate antigen as described herein is a hematological cancer. In one aspect, the hematological cancer is a leukemia or a lymphoma. In one aspect, a cancer associated with expression of a cancer associate antigen as described herein includes cancers and malignancies including, but not limited to, e.g., one or more acute leukemias including but not limited to, e.g., B-cell acute lymphoblastic Leukemia ("BALL"), T-cell acute lymphoblastic Leukemia ("TALL"), acute lymphocytic leukemia (ALL); one or more chronic leukemias including but not limited to, e.g., chronic myelogenous leukemia (CML), Chronic Lymphoid Leukemia (CLL). Additional cancers or hematologic conditions associated with expression of a cancer associate antigen as described herein include, but are not limited to, e.g., 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 lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-

Hodgkin lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, and "preleukemia" which are a diverse collection of hematological conditions united by ineffective production (or dysplasia) of myeloid blood cells, and the like. Further a disease associated with a cancer associate antigen as described herein expression include, but not limited to, e.g., atypical and/or non-classical cancers, malignancies, precancerous conditions or proliferative diseases associated with expression of a cancer associate antigen as described herein.

In some embodiments, a cancer that can be treated with CAR-expressing cell of the present invention is multiple myeloma. Multiple myeloma is a cancer of the blood, characterized by accumulation of a plasma cell clone in the bone marrow. Current therapies for multiple myeloma include, but are not limited to, treatment with lenalidomide, which is an analog of thalidomide. Lenalidomide has activities which include anti-tumor activity, angiogenesis inhibition, and immunomodulation. Generally, myeloma cells are thought to be negative for a cancer associate antigen as described herein expression by flow cytometry. Thus, in some embodiments, a CD19 CAR, e.g., as described herein, may be used to target myeloma cells. In some embodiments, cars of the present invention therapy can be used in combination with one or more additional therapies, e.g., lenalidomide treatment.

The invention includes a type of cellular therapy where immune effector cells (e.g., T cells, NK cells) are genetically modified to express a chimeric antigen receptor (CAR) and the CAR-expressing T cell or NK cell is infused to a recipient in need thereof. The infused cell is able to kill tumor cells in the recipient. Unlike antibody therapies, CAR-modified immune effector cells (e.g., T cells, NK cells) are able to replicate in vivo resulting in long-term persistence that can lead to sustained tumor control. In various aspects, the immune effector cells (e.g., T cells, NK cells) administered to the patient, or their progeny, persist in the patient for at least four months, five months, six months, seven months, eight months, nine months, ten months, eleven months, twelve months, thirteen months, fourteen month, fifteen months, sixteen months, seventeen months, eighteen months, nineteen months, twenty months, twenty-one months, twenty-two months, twenty-three months, two years, three years, four years, or five years after administration of the T cell or NK cell to the patient.

The invention also includes a type of cellular therapy where immune effector cells (e.g., T cells, NK cells) are modified, e.g., by in vitro transcribed RNA, to transiently express a

chimeric antigen receptor (CAR) and the CAR T cell or NK cell is infused to a recipient in need thereof. The infused cell is able to kill tumor cells in the recipient. Thus, in various aspects, the immune effector cells (e.g., T cells, NK cells) administered to the patient, is present for less than one month, e.g., three weeks, two weeks, one week, after administration of the T cell or NK cell to the patient.

Without wishing to be bound by any particular theory, the anti-tumor immunity response elicited by the CAR-modified immune effector cells (e.g., T cells, NK cells) may be an active or a passive immune response, or alternatively may be due to a direct vs indirect immune response. In one aspect, the CAR transduced immune effector cells (e.g., T cells, NK cells) exhibit specific proinflammatory cytokine secretion and potent cytolytic activity in response to human cancer cells expressing the a cancer associate antigen as described herein, resist soluble a cancer associate antigen as described herein inhibition, mediate bystander killing and mediate regression of an established human tumor. For example, antigen-less tumor cells within a heterogeneous field of a cancer associate antigen as described herein-expressing tumor may be susceptible to indirect destruction by a cancer associate antigen as described herein-redirected immune effector cells (e.g., T cells, NK cells) that has previously reacted against adjacent antigen-positive cancer cells.

In one aspect, the fully-human CAR-modified immune effector cells (e.g., T cells, NK cells) of the invention may be a type of vaccine for ex vivo immunization and/or in vivo therapy in a mammal. In one aspect, the mammal is a human.

With respect to ex vivo immunization, at least one of the following occurs in vitro prior to administering the cell into a mammal: i) expansion of the cells, ii) introducing a nucleic acid encoding a CAR to the cells or iii) cryopreservation of the cells.

Ex vivo procedures are well known in the art and are discussed more fully below. Briefly, cells are isolated from a mammal (e.g., a human) and genetically modified (i.e., transduced or transfected in vitro) with a vector expressing a CAR disclosed herein. The CAR-modified cell can be administered to a mammalian recipient to provide a therapeutic benefit. The mammalian recipient may be a human and the CAR-modified cell can be autologous with respect to the recipient. Alternatively, the cells can be allogeneic, syngeneic or xenogeneic with respect to the recipient.

The procedure for ex vivo expansion of hematopoietic stem and progenitor cells is described in U.S. Pat. No. 5,199,942, incorporated herein by reference, can be applied to the cells of the present invention. Other suitable methods are known in the art, therefore the present invention is not limited to any particular method of ex vivo expansion of the cells. Briefly, ex vivo culture and expansion of immune effector cells (e.g., T cells, NK cells) comprises: (1) collecting CD34+ hematopoietic stem and progenitor cells from a mammal from peripheral blood harvest or bone marrow explants; and (2) expanding such cells ex vivo. In addition to the cellular growth factors described in U.S. Pat. No. 5,199,942, other factors such as flt3-L, IL-1, IL-3 and c-kit ligand, can be used for culturing and expansion of the cells.

In addition to using a cell-based vaccine in terms of ex vivo immunization, the present invention also provides compositions and methods for in vivo immunization to elicit an immune response directed against an antigen in a patient.

Generally, the cells activated and expanded as described herein may be utilized in the treatment and prevention of diseases that arise in individuals who are immunocompromised. In particular, the CAR-modified immune effector cells (e.g., T cells, NK cells) of the invention are used in the treatment of diseases, disorders and conditions associated with expression of a cancer associate antigen as described herein. In certain aspects, the cells of the invention are used in the treatment of patients at risk for developing diseases, disorders and conditions associated with expression of a cancer associate antigen as described herein. Thus, the present invention provides methods for the treatment or prevention of diseases, disorders and conditions associated with expression of a cancer associate antigen as described herein comprising administering to a subject in need thereof, a therapeutically effective amount of the CAR-modified immune effector cells (e.g., T cells, NK cells) of the invention.

In one aspect the CAR-expressing cells of the inventions may be used to treat a proliferative disease such as a cancer or malignancy or is a precancerous condition such as a myelodysplasia, a myelodysplastic syndrome or a preleukemia. Further a disease associated with a cancer associate antigen as described herein expression include, but not limited to, e.g., atypical and/or non-classical cancers, malignancies, precancerous conditions or proliferative diseases expressing a cancer associated antigen as described herein. Non-cancer related indications associated with expression of a cancer associate antigen as described herein include,

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but are not limited to, e.g., autoimmune disease, (e.g., lupus), inflammatory disorders (allergy and asthma) and transplantation.

The CAR-modified immune effector cells (e.g., T cells, NK cells) of the present invention may be administered either alone, or as a pharmaceutical composition in combination with diluents and/or with other components such as IL-2 or other cytokines or cell populations.

Hematologic Cancer

Hematological cancer conditions are the types of cancer such as leukemia, lymphoma, and malignant lymphoproliferative conditions that affect blood, bone marrow and the lymphatic system.

Leukemia can be classified as acute leukemia and chronic leukemia. Acute leukemia can be further classified as acute myelogenous leukemia (AML) and acute lymphocytic leukemia (ALL). Chronic leukemia includes chronic myelogenous leukemia (CML) and chronic lymphoid leukemia (CLL). Other related conditions include myelodysplastic syndromes (MDS, formerly known as "preleukemia") which are a diverse collection of hematological conditions united by ineffective production (or dysplasia) of myeloid blood cells and risk of transformation to AML.

Lymphoma is a group of blood cell tumors that develop from lymphocytes. Exemplary lymphomas include non-Hodgkin lymphoma and Hodgkin lymphoma.

The present invention provides for compositions and methods for treating cancer. In one aspect, the cancer is a hematologic cancer including but is not limited to hematolical cancer is a leukemia or a lymphoma. In one aspect, the CAR-expressing cells of the invention may be used to treat cancers and malignancies such as, but not limited to, e.g., acute leukemias including but not limited to, e.g., B-cell acute lymphoblastic leukemia ("BALL"), T-cell acute lymphoblastic leukemia ("TALL"), acute lymphocytic leukemia (ALL); one or more chronic leukemias including but not limited to, e.g., chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL); additional hematologic cancers or hematologic conditions including, but not limited to, e.g., 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 lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, and "preleukemia" which are a

diverse collection of hematological conditions united by ineffective production (or dysplasia) of myeloid blood cells, and the like. Further a disease associated with a cancer associate antigen as described herein expression includes, but not limited to, e.g., atypical and/or non-classical cancers, malignancies, precancerous conditions or proliferative diseases expressing a cancer associate antigen as described herein.

The present invention also provides methods for inhibiting the proliferation or reducing a cancer associated antigen as described herein-expressing cell population, the methods comprising contacting a population of cells comprising a cancer associated antigen as described herein-expressing cell with a CAR-expressing T cell or NK cell of the invention that binds to the a cancer associate antigen as described herein-expressing cell. In a specific aspect, the present invention provides methods for inhibiting the proliferation or reducing the population of cancer cells expressing a cancer associated antigen as described herein, the methods comprising contacting a cancer associate antigen as described herein-expressing cancer cell population with a CAR-expressing T cell or NK cell of the invention that binds to a cancer associated antigen as described herein-expressing cell. In one aspect, the present invention provides methods for inhibiting the proliferation or reducing the population of cancer cells expressing a cancer associated antigen as described herein, the methods comprising contacting a cancer associated antigen as described herein-expressing cancer cell population with a CAR-expressing T cell or NK cell of the invention that binds to a cancer associated antigen as described herein-expressing cell. In certain aspects, a CAR-expressing T cell or NK cell of the invention reduces the quantity, number, amount or percentage of cells and/or cancer cells by at least 25%, at least 30%, at least 40%, at least 50%, at least 65%, at least 75%, at least 85%, at least 95%, or at least 99% in a subject with or animal model for myeloid leukemia or another cancer associated with a cancer associated antigen as described herein-expressing cells relative to a negative control. In one aspect, the subject is a human.

The present invention also provides methods for preventing, treating and/or managing a disease associated with a cancer associated antigen as described herein-expressing cells (e.g., a hematologic cancer or atypical cancer expessing a cancer associated antigen as described herein), the methods comprising administering to a subject in need a CAR T cell or NK cell of the invention that binds to a cancer associated antigen as described herein-expressing cell. In one aspect, the subject is a human. Non-limiting examples of disorders associated with a cancer

associated antigen as described herein-expressing cells include autoimmune disorders (such as lupus), inflammatory disorders (such as allergies and asthma) and cancers (such as hematological cancers or atypical cancers expessing a cancer associated antigen as described herein).

The present invention also provides methods for preventing, treating and/or managing a disease associated with a cancer associated antigen as described herein-expressing cells, the methods comprising administering to a subject in need a CAR T cell or NK cell of the invention that binds to a cancer associated antigen as described herein-expressing cell. In one aspect, the subject is a human.

The present invention provides methods for preventing relapse of cancer associated with a cancer associated antigen as described herein-expressing cells, the methods comprising administering to a subject in need thereof aCAR T cell or NK cell of the invention that binds to a cancer associated antigen as described herein-expressing cell. In one aspect, the methods comprise administering to the subject in need thereof an effective amount of a CAR-expressingT cell or NK cell described herein that binds to a cancer associated antigen as described herein-expressing cell in combination with an effective amount of another therapy.

Combination Therapies

A CAR-expressing cell described herein may be used in combination with other known agents and therapies. Administered "in combination", as used herein, means that two (or more) different treatments are delivered to the subject during the course of the subject's affliction with the disorder, e.g., the two or more treatments are delivered after the subject has been diagnosed with the disorder and before the disorder has been cured or eliminated or treatment has ceased for other reasons. In some embodiments, the delivery of one treatment is still occurring when the delivery of the second begins, so that there is overlap in terms of administration. This is sometimes referred to herein as "simultaneous" or "concurrent delivery". In other embodiments, the delivery of one treatment ends before the delivery of the other treatment begins. In some embodiments of either case, the treatment is more effective because of combined administration. For example, the second treatment is more effective, e.g., an equivalent effect is seen with less of the second treatment, or the second treatment reduces symptoms to a greater extent, than would be seen if the second treatment were administered in the absence of the first treatment, or the analogous situation is seen with the first treatment. In some embodiments, delivery is such that

the reduction in a symptom, or other parameter related to the disorder is greater than what would be observed with one treatment delivered in the absence of the other. The effect of the two treatments can be partially additive, wholly additive, or greater than additive. The delivery can be such that an effect of the first treatment delivered is still detectable when the second is delivered.

A CAR-expressing cell described herein and the at least one additional therapeutic agent can be administered simultaneously, in the same or in separate compositions, or sequentially. For sequential administration, the CAR-expressing cell described herein can be administered first, and the additional agent can be administered second, or the order of administration can be reversed.

The CAR therapy and/or other therapeutic agents, procedures or modalities can be administered during periods of active disorder, or during a period of remission or less active disease. The CAR therapy can be administered before the other treatment, concurrently with the treatment, post-treatment, or during remission of the disorder.

When administered in combination, the CAR therapy and the additional agent (e.g., second or third agent), or all, can be administered in an amount or dose that is higher, lower or the same than the amount or dosage of each agent used individually, e.g., as a monotherapy. In certain embodiments, the administered amount or dosage of the CAR therapy, the additional agent (e.g., second or third agent), or all, is lower (e.g., at least 20%, at least 30%, at least 40%, or at least 50%) than the amount or dosage of each agent used individually, e.g., as a monotherapy. In other embodiments, the amount or dosage of the CAR therapy, the additional agent (e.g., second or third agent), or all, that results in a desired effect (e.g., treatment of cancer) is lower (e.g., at least 20%, at least 30%, at least 40%, or at least 50% lower) than the amount or dosage of each agent used individually, e.g., as a monotherapy, required to achieve the same therapeutic effect.

In further aspects, a CAR-expressing cell described herein may be used in a treatment regimen in combination with surgery, chemotherapy, radiation, immunosuppressive agents, such as cyclosporin, azathioprine, methotrexate, mycophenolate, and FK506, antibodies, or other immunoablative agents such as CAMPATH, anti-CD3 antibodies or other antibody therapies, cytoxin, fludarabine, cyclosporin, FK506, rapamycin, mycophenolic acid, steroids, FR901228,

cytokines, and irradiation. peptide vaccine, such as that described in Izumoto et al. 2008 J Neurosurg 108:963-971.

In one embodiment, a CAR-expressing cell described herein can be used in combination with a chemotherapeutic agent. Exemplary chemotherapeutic agents include an anthracycline (e.g., doxorubicin (e.g., liposomal doxorubicin)). a vinca alkaloid (e.g., vinblastine, vincristine, vindesine, vinorelbine), an alkylating agent (e.g., cyclophosphamide, decarbazine, melphalan, ifosfamide, temozolomide), an immune cell antibody (e.g., alemtuzamab, gemtuzumab, rituximab, ofatumumab, tositumomab, brentuximab), an antimetabolite (including, e.g., folic acid antagonists, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors (e.g., fludarabine)), an mTOR inhibitor, a TNFR glucocorticoid induced TNFR related protein (GITR) agonist, a proteasome inhibitor (e.g., aclacinomycin A, gliotoxin or bortezomib), an immunomodulator such as thalidomide or a thalidomide derivative (e.g., lenalidomide).

General Chemotherapeutic agents considered for use in combination therapies include anastrozole (Arimidex®), bicalutamide (Casodex®), bleomycin sulfate (Blenoxane®), busulfan (Myleran®), busulfan injection (Busulfex®), capecitabine (Xeloda®), N4-pentoxycarbonyl-5-deoxy-5-fluorocytidine, carboplatin (Paraplatin®), carmustine (BiCNU®), chlorambucil (Leukeran®), cisplatin (Platinol®), cladribine (Leustatin®), cyclophosphamide (Cytoxan® or Neosar®), cytarabine, cytosine arabinoside (Cytosar-U®), cytarabine liposome injection (DepoCyt®), dacarbazine (DTIC-Dome®), dactinomycin (Actinomycin D, Cosmegan), daunorubicin hydrochloride (Cerubidine®), daunorubicin citrate liposome injection (DaunoXome®), dexamethasone, docetaxel (Taxotere®), doxorubicin hydrochloride (Adriamycin®, Rubex®), etoposide (Vepesid®), fludarabine phosphate (Fludara®), 5-fluorouracil (Adrucil®, Efudex®), flutamide (Eulexin®), tezacitibine, Gemcitabine (difluorodeoxycitidine), hydroxyurea (Hydrea®), Idarubicin (Idamycin®), ifosfamide (IFEX®), irinotecan (Camptosar®), L-asparaginase (ELSPAR®), leucovorin calcium, melphalan (Alkeran®), 6-mercaptopurine (Purinethol®), methotrexate (Folex®), mitoxantrone (Novantrone®), mylotarg, paclitaxel (Taxol®), phoenix (Yttrium90/MX-DTPA), pentostatin, polifeprosan 20 with carmustine implant (Gliadel®), tamoxifen citrate (Nolvadex®), teniposide (Vumon®), 6-thioguanine, thiotepa, tirapazamine (Tirazone®), topotecan hydrochloride for injection (Hycamptin®), vinblastine (Velban®), vincristine (Oncovin®), and vinorelbine (Navelbine®).

Exemplary alkylating agents include, without limitation, nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes): uracil mustard (Aminouracil Mustard®, Chlorethaminacil®, Demethyldopan®, Desmethyldopan®, Haemanthamine®, Nordopan®, Uracil nitrogen mustard®, Uracillost®, Uracilmostaza®, Uramustin®, Uramustine®), chlormethine (Mustargen®), cyclophosphamide (Cytoxan®, Neosar®, Clafen®, Endoxan®, Procytox®, Revimmune™), ifosfamide (Mitoxana®), melphalan (Alkeran®), Chlorambucil (Leukeran®), pipobroman (Amedel®, Vercyte®), triethylenemelamine (Hemel®, Hexalen®, Hexastat®), triethylenethiophosphoramine, Temozolomide (Temodar®), thiotepa (Thioplex®), busulfan (Busilvex®, Myleran®), carmustine (BiCNU®), lomustine (CeeNU®), streptozocin (Zanosar®), and Dacarbazine (DTIC-Dome®). Additional exemplary alkylating agents include, without limitation, Oxaliplatin (Eloxatin®); Temozolomide (Temodar® and Temodal®); Dactinomycin (also known as actinomycin-D, Cosmegen®); Melphalan (also known as L-PAM, L-sarcolysin, and phenylalanine mustard, Alkeran®); Altretamine (also known as hexamethylmelamine (HMM), Hexalen®); Carmustine (BiCNU®); Bendamustine (Treanda®); Busulfan (Busulfex® and Myleran®); Carboplatin (Paraplatin®); Lomustine (also known as CCNU, CeeNU®); Cisplatin (also known as CDDP, Platinol® and Platinol®-AQ); Chlorambucil (Leukeran®); Cyclophosphamide (Cytoxan® and Neosar®); Dacarbazine (also known as DTIC, DIC and imidazole carboxamide, DTIC-Dome®); Altretamine (also known as hexamethylmelamine (HMM), Hexalen®); Ifosfamide (Ifex®); Prednumustine; Procarbazine (Matulane®); Mechlorethamine (also known as nitrogen mustard, mustine and mechloroethamine hydrochloride, Mustargen®); Streptozocin (Zanosar®); Thiotepa (also known as thiophosphoamide, TESPA and TSPA, Thioplex®); Cyclophosphamide (Endoxan®, Cytoxan®, Neosar®, Procytox®, Revimmune®); and Bendamustine HCl (Treanda®).

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with fludarabine, cyclophosphamide, and/or rituximab. In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with fludarabine, cyclophosphamide, and rituximab (FCR). In embodiments, the subject has CLL. For example, the subject has a deletion in the short arm of chromosome 17 (del(17p), e.g., in a leukemic cell). In other examples, the subject does not have a del(17p). In embodiments, the subject comprises a leukemic cell comprising a mutation in the immunoglobulin heavy-chain variable-region (IgV_H) gene. In other embodiments, the subject does not comprise a leukemic cell comprising a

mutation in the immunoglobulin heavy-chain variable-region (IgV_H) gene. In embodiments, the fludarabine is administered at a dosage of about 10-50 mg/m^2 (e.g., about 10-15, 15-20, 20-25, 25-30, 30-35, 35-40, 40-45, or 45-50 mg/m^2), e.g., intravenously. In embodiments, the cyclophosphamide is administered at a dosage of about 200-300 mg/m^2 (e.g., about 200-225, 225-250, 250-275, or 275-300 mg/m^2), e.g., intravenously. In embodiments, the rituximab is administered at a dosage of about 400-600 mg/m2 (e.g., 400-450, 450-500, 500-550, or 550-600 mg/m^2), e.g., intravenously.

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with bendamustine and rituximab. In embodiments, the subject has CLL. For example, the subject has a deletion in the short arm of chromosome 17 (del(17p), e.g., in a leukemic cell). In other examples, the subject does not have a del(17p). In embodiments, the subject comprises a leukemic cell comprising a mutation in the immunoglobulin heavy-chain variable-region (IgV_H) gene. In other embodiments, the subject does not comprise a leukemic cell comprising a mutation in the immunoglobulin heavy-chain variable-region (IgV_H) gene. In embodiments, the bendamustine is administered at a dosage of about 70-110 mg/m2 (e.g., 70-80, 80-90, 90-100, or 100-110 mg/m2), e.g., intravenously. In embodiments, the rituximab is administered at a dosage of about 400-600 mg/m2 (e.g., 400-450, 450-500, 500-550, or 550-600 mg/m^2), e.g., intravenously.

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with rituximab, cyclophosphamide, doxorubicine, vincristine, and/or a corticosteroid (e.g., prednisone). In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with rituximab, cyclophosphamide, doxorubicine, vincristine, and prednisone (R-CHOP). In embodiments, the subject has diffuse large B-cell lymphoma (DLBCL). In embodiments, the subject has nonbulky limited-stage DLBCL (e.g., comprises a tumor having a size/diameter of less than 7 cm). In embodiments, the subject is treated with radiation in combination with the R-CHOP. For example, the subject is administered R-CHOP (e.g., 1-6 cycles, e.g., 1, 2, 3, 4, 5, or 6 cycles of R-CHOP), followed by radiation. In some cases, the subject is administered R-CHOP (e.g., 1-6 cycles, e.g., 1, 2, 3, 4, 5, or 6 cycles of R-CHOP) following radiation.

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and/or

rituximab. In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (EPOCH-R). In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with dose-adjusted EPOCH-R (DA-EPOCH-R). In embodiments, the subject has a B cell lymphoma, e.g., a Myc-rearranged aggressive B cell lymphoma.

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with rituximab and/or lenalidomide. Lenalidomide ((*RS*)-3-(4-Amino-1-oxo 1,3-dihydro-2*H*-isoindol- 2-yl)piperidine-2,6-dione) is an immunomodulator. In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with rituximab and lenalidomide. In embodiments, the subject has follicular lymphoma (FL) or mantle cell lymphoma (MCL). In embodiments, the subject has FL and has not previously been treated with a cancer therapy. In embodiments, lenalidomide is administered at a dosage of about 10-20 mg (e.g., 10-15 or 15-20 mg), e.g., daily. In embodiments, rituximab is administered at a dosage of about 350-550 mg/m^2 (e.g., 350-375, 375-400, 400-425, 425-450, 450-475, or 475-500 mg/m^2), e.g., intravenously.

Exemplary mTOR inhibitors include, e.g., temsirolimus; ridaforolimus (formally known as deferolimus, (1*R*,2*R*,4*S*)-4-[(2*R*)-2 [(1*R*,9*S*,12*S*,15*R*,16*E*,18*R*,19*R*,21*R*, 23*S*,24*E*,26*E*,28*Z*,30*S*,32*S*,35*R*)-1,18-dihydroxy-19,30-dimethoxy-15,17,21,23, 29,35-hexamethyl-2,3,10,14,20-pentaoxo-11,36-dioxa-4-azatricyclo[30.3.1.0^{4,9}] hexatriaconta-16,24,26,28-tetraen-12-yl]propyl]-2-methoxycyclohexyl dimethylphosphinate, also known as AP23573 and MK8669, and described in PCT Publication No. WO 03/064383); everolimus (Afinitor® or RAD001); rapamycin (AY22989, Sirolimus®); simapimod (CAS 164301-51-3); emsirolimus, (5-{2,4-Bis[(3*S*)-3-methylmorpholin-4-yl]pyrido[2,3-*d*]pyrimidin-7-yl}-2-methoxyphenyl)methanol (AZD8055); 2-Amino-8-[*trans*-4-(2-hydroxyethoxy)cyclohexyl]-6-(6-methoxy-3-pyridinyl)-4-methyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (PF04691502, CAS 1013101-36-4); and N^2-[1,4-dioxo-4-[[4-(4-oxo-8-phenyl-4*H*-1-benzopyran-2-yl)morpholinium-4-yl]methoxy]butyl]-L-arginylglycyl-L-α-aspartylL-serine-, inner salt (SF1126, CAS 936487-67-1) (SEQ ID NO: 1262), and XL765.

Exemplary immunomodulators include, e.g., afutuzumab (available from Roche®); pegfilgrastim (Neulasta®); lenalidomide (CC-5013, Revlimid®); thalidomide (Thalomid®),

actimid (CC4047); and IRX-2 (mixture of human cytokines including interleukin 1, interleukin 2, and interferon γ, CAS 951209-71-5, available from IRX Therapeutics).

Exemplary anthracyclines include, e.g., doxorubicin (Adriamycin® and Rubex®); bleomycin (lenoxane®); daunorubicin (dauorubicin hydrochloride, daunomycin, and rubidomycin hydrochloride, Cerubidine®); daunorubicin liposomal (daunorubicin citrate liposome, DaunoXome®); mitoxantrone (DHAD, Novantrone®); epirubicin (Ellence™); idarubicin (Idamycin®, Idamycin PFS®); mitomycin C (Mutamycin®); geldanamycin; herbimycin; ravidomycin; and desacetylravidomycin.

Exemplary vinca alkaloids include, e.g., vinorelbine tartrate (Navelbine®), Vincristine (Oncovin®), and Vindesine (Eldisine®)); vinblastine (also known as vinblastine sulfate, vincaleukoblastine and VLB, Alkaban-AQ® and Velban®); and vinorelbine (Navelbine®).

Exemplary proteosome inhibitors include bortezomib (Velcade®); carfilzomib (PX-171-007, (*S*)-4-Methyl-*N*-((*S*)-1-(((*S*)-4-methyl-1-((*R*)-2-methyloxiran-2-yl)-1-oxopentan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)-2-((*S*)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-pentanamide); marizomib (NPI-0052); ixazomib citrate (MLN-9708); delanzomib (CEP-18770); and *O*-Methyl-*N*-[(2-methyl-5-thiazolyl)carbonyl]-L-seryl-*O*-methyl-*N*-[(1*S*)-2-[(2*R*)-2-methyl-2-oxiranyl]-2-oxo-1-(phenylmethyl)ethyl]- L-serinamide (ONX-0912).

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with brentuximab. Brentuximab is an antibody-drug conjugate of anti-CD30 antibody and monomethyl auristatin E. In embodiments, the subject has Hodgkin's lymphoma (HL), e.g., relapsed or refractory HL. In embodiments, the subject comprises CD30+ HL. In embodiments, the subject has undergone an autologous stem cell transplant (ASCT). In embodiments, the subject has not undergone an ASCT. In embodiments, brentuximab is administered at a dosage of about 1-3 mg/kg (e.g., about 1-1.5, 1.5-2, 2-2.5, or 2.5-3 mg/kg), e.g., intravenously, e.g., every 3 weeks.

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with brentuximab and dacarbazine or in combination with brentuximab and bendamustine. Dacarbazine is an alkylating agent with a chemical name of 5-(3,3-Dimethyl-1-triazenyl)imidazole-4-carboxamide. Bendamustine is an alkylating agent with a chemical name of 4-[5-[Bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid. In embodiments, the subject has Hodgkin's lymphoma (HL). In embodiments, the subject has not previously been

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treated with a cancer therapy. In embodiments, the subject is at least 60 years of age, e.g., 60, 65, 70, 75, 80, 85, or older. In embodiments, dacarbazine is administered at a dosage of about 300-450 mg/m^2 (e.g., about 300-325, 325-350, 350-375, 375-400, 400-425, or 425-450 mg/m^2), e.g., intravenously. In embodiments, bendamustine is administered at a dosage of about 75-125 mg/m2 (e.g., 75-100 or 100-125 mg/m 2 , e.g., about 90 mg/m 2), e.g., intravenously. In embodiments, brentuximab is administered at a dosage of about 1-3 mg/kg (e.g., about 1-1.5, 1.5-2, 2-2.5, or 2.5-3 mg/kg), e.g., intravenously, e.g., every 3 weeks.

In some embodiments, a CAR-expressing cell described herein is administered to a subject in combination with a CD20 inhibitor, e.g., an anti-CD20 antibody (e.g., an anti-CD20 mono- or bispecific antibody) or a fragment thereof. Exemplary anti-CD20 antibodies include but are not limited to rituximab, ofatumumab, ocrelizumab, veltuzumab, obinutuzumab, TRU-015 (Trubion Pharmaceuticals), ocaratuzumab, and Prol31921 (Genentech). See, e.g., Lim et al. Haematologica. 95.1 (2010) : 135-43.

In some embodiments, the anti-CD20 antibody comprises rituximab. Rituximab is a chimeric mouse/human monoclonal antibody IgGl kappa that binds to CD20 and causes cytolysis of a CD20 expressing cell, e.g., as described in www.accessdata.fda.gov/drugsatfda_docs/label/2010/103705s53111bl.pdf. In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with rituximab. In embodiments, the subject has CLL or small lymphocytic lymphoma (SLL).

In some embodiments, rituximab is administered intravenously, e.g., as an intravenous infusion. For example, each infusion provides about 500-2000 mg (e.g., about 500-550, 550-600, 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 900-950, 950-1000, 1000-1100, 1100-1200, 1200-1300, 1300-1400, 1400-1500, 1500-1600, 1600-1700, 1700-1800, 1800-1900, or 1900-2000 mg) of rituximab. In some embodiments, rituximab is administered at a dose of 150 mg/m^2 to 750 mg/m^2, e.g., about 150-175 mg/m^2, 175-200 mg/m^2, 200-225 mg/m^2, 225-250 mg/m^2, 250-300 mg/m^2, 300-325 mg/m^2, 325-350 mg/m^2, 350-375 mg/m^2, 375-400 mg/m^2, 400-425 mg/m^2, 425-450 mg/m^2, 450-475 mg/m^2, 475-500 mg/m^2, 500-525 mg/m^2, 525-550 mg/m^2, 550-575 mg/m^2, 575-600 mg/m^2, 600-625 mg/m^2, 625-650 mg/m^2, 650-675 mg/m^2, or 675-700 mg/m 2 , where m 2 indicates the body surface area of the subject. In some embodiments, rituximab is administered at a dosing interval of at least 4 days, e.g., 4, 7, 14, 21, 28, 35 days, or more. For example, rituximab is administered at a dosing interval of at least 0.5 weeks, e.g., 0.5,

1, 2, 3, 4, 5, 6, 7, 8 weeks, or more. In some embodiments, rituximab is administered at a dose and dosing interval described herein for a period of time, e.g., at least 2 weeks, e.g., at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 weeks, or greater. For example, rituximab is administered at a dose and dosing interval described herein for a total of at least 4 doses per treatment cycle (e.g., at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or more doses per treatment cycle).

In some embodiments, the anti-CD20 antibody comprises ofatumumab. Ofatumumab is an anti-CD20 IgG1κ human monoclonal antibody with a molecular weight of approximately 149 kDa. For example, ofatumumab is generated using transgenic mouse and hybridoma technology and is expressed and purified from a recombinant murine cell line (NS0). See, e.g., www.accessdata.fda.gov/drugsatfda_docs/label/2009/125326lbl.pdf; and Clinical Trial Identifier number NCT01363128, NCT01515176, NCT01626352, and NCT01397591. In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with ofatumumab. In embodiments, the subject has CLL or SLL.

In some embodiments, ofatumumab is administered as an intravenous infusion. For example, each infusion provides about 150-3000 mg (e.g., about 150-200, 200-250, 250-300, 300-350, 350-400, 400-450, 450-500, 500-550, 550-600, 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 900-950, 950-1000, 1000-1200, 1200-1400, 1400-1600, 1600-1800, 1800-2000, 2000-2200, 2200-2400, 2400-2600, 2600-2800, or 2800-3000 mg) of ofatumumab. In embodiments, ofatumumab is administered at a starting dosage of about 300 mg, followed by 2000 mg, e.g., for about 11 doses, e.g., for 24 weeks. In some embodiments, ofatumumab is administered at a dosing interval of at least 4 days, e.g., 4, 7, 14, 21, 28, 35 days, or more. For example, ofatumumab is administered at a dosing interval of at least 1 week, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 24, 26, 28, 20, 22, 24, 26, 28, 30 weeks, or more. In some embodiments, ofatumumab is administered at a dose and dosing interval described herein for a period of time, e.g., at least 1 week, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 24, 26, 28, 30, 40, 50, 60 weeks or greater, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months or greater, or 1, 2, 3, 4, 5 years or greater. For example, ofatumumab is administered at a dose and dosing interval described herein for a total of at least 2 doses per treatment cycle (e.g., at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 20, or more doses per treatment cycle).

In some cases, the anti-CD20 antibody comprises ocrelizumab. Ocrelizumab is a humanized anti-CD20 monoclonal antibody, e.g., as described in Clinical Trials Identifier Nos. NCT00077870, NCT01412333, NCT00779220, NCT00673920, NCT01194570, and Kappos et al. Lancet. 19.378(2011):1779-87.

In some cases, the anti-CD20 antibody comprises veltuzumab. Veltuzumab is a humanized monoclonal antibody against CD20. See, e.g., Clinical Trial Identifier No. NCT00547066, NCT00546793, NCT01101581, and Goldenberg et al. Leuk Lymphoma. 51(5)(2010):747-55.

In some cases, the anti-CD20 antibody comprises GA101. GA101 (also called obinutuzumab or RO5072759) is a humanized and glyco-engineered anti-CD20 monoclonal antibody. See, e.g., Robak. Curr. Opin. Investig. Drugs. 10.6(2009):588-96; Clinical Trial Identifier Numbers: NCT01995669, NCT01889797, NCT02229422, and NCT01414205; and www.accessdata.fda.gov/drugsatfda_docs/label/2013/125486s000lbl.pdf.

In some cases, the anti-CD20 antibody comprises AME-133v. AME-133v (also called LY2469298 or ocaratuzumab) is a humanized IgG1 monoclonal antibody against CD20 with increased affinity for the FcγRIIIa receptor and an enhanced antibody dependent cellular cytotoxicity (ADCC) activity compared with rituximab. See, e.g., Robak et al. BioDrugs 25.1(2011):13-25; and Forero-Torres et al. Clin Cancer Res. 18.5(2012):1395-403.

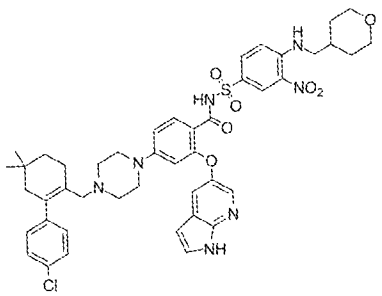
In some cases, the anti-CD20 antibody comprises PRO131921. PRO131921 is a humanized anti-CD20 monoclonal antibody engineered to have better binding to FcγRIIIa and enhanced ADCC compared with rituximab. See, e.g., Robak et al. BioDrugs 25.1(2011):13-25; and Casulo et al. Clin Immunol. 154.1(2014):37-46; and Clinical Trial Identifier No. NCT00452127.

In some cases, the anti-CD20 antibody comprises TRU-015. TRU-015 is an anti-CD20 fusion protein derived from domains of an antibody against CD20. TRU-015 is smaller than monoclonal antibodies, but retains Fc-mediated effector functions. See, e.g., Robak et al. BioDrugs 25.1(2011):13-25. TRU-015 contains an anti-CD20 single-chain variable fragment (scFv) linked to human IgG1 hinge, CH2, and CH3 domains but lacks CH1 and CL domains.

In some embodiments, an anti-CD20 antibody described herein is conjugated or otherwise bound to a therapeutic agent, e.g., a chemotherapeutic agent (e.g., cytoxan, fludarabine, histone deacetylase inhibitor, demethylating agent, peptide vaccine, anti-tumor

antibiotic, tyrosine kinase inhibitor, alkylating agent, anti-microtubule or anti-mitotic agent), anti-allergic agent, anti-nausea agent (or anti-emetic), pain reliever, or cytoprotective agent described herein.

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with a B-cell lymphoma 2 (BCL-2) inhibitor (e.g., venetoclax, also called ABT-199 or GDC-0199;) and/or rituximab. In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with venetoclax and rituximab. Venetoclax is a small molecule that inhibits the anti-apoptotic protein, BCL-2. The structure of venetoclax (4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-({3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzamide) is shown below.



In embodiments, the subject has CLL. In embodiments, the subject has relapsed CLL, e.g., the subject has previously been administered a cancer therapy. In embodiments, venetoclax is administered at a dosage of about 15-600 mg (e.g., 15-20, 20-50, 50-75, 75-100, 100-200, 200-300, 300-400, 400-500, or 500-600 mg), e.g., daily. In embodiments, rituximab is administered at a dosage of about 350-550 mg/m2 (e.g., 350-375, 375-400, 400-425, 425-450, 450-475, or 475-500 mg/m2), e.g., intravenously, e.g., monthly

In an embodiment, cells expressing a CAR described herein are administered to a subject in combination with a molecule that decreases the Treg cell population. Methods that decrease the number of (e.g., deplete) Treg cells are known in the art and include, e.g., CD25 depletion, cyclophosphamide administration, modulating GITR function. Without wishing to be bound by theory, it is believed that reducing the number of Treg cells in a subject prior to apheresis or prior to administration of a CAR-expressing cell described herein reduces the number of unwanted immune cells (e.g., Tregs) in the tumor microenvironment and reduces the subject's risk of relapse. In one embodiment, cells expressing a CAR described herein are administered to

a subject in combination with a molecule targeting GITR and/or modulating GITR functions, such as a GITR agonist and/or a GITR antibody that depletes regulatory T cells (Tregs). In embodiments, cells expressing a CAR described herein are administered to a subject in combination with cyclophosphamide. In one embodiment, the GITR binding molecules and/or molecules modulating GITR functions (e.g., GITR agonist and/or Treg depleting GITR antibodies) are administered prior to administration of the CAR-expressing cell. For example, in one embodiment, the GITR agonist can be administered prior to apheresis of the cells. In embodiments, cyclophosphamide is administered to the subject prior to administration (e.g., infusion or re-infusion) of the CAR-expressing cell or prior to aphersis of the cells. In embodiments, cyclophosphamide and an anti-GITR antibody are administered to the subject prior to administration (e.g., infusion or re-infusion) of the CAR-expressing cell or prior to apheresis of the cells. In one embodiment, the subject has cancer (e.g., a solid cancer or a hematological cancer such as ALL or CLL). In an embodiment, the subject has CLL. In embodiments, the subject has ALL. In embodiments, the subject has a solid cancer, e.g., a solid cancer described herein. Exemplary GITR agonists include, e.g., GITR fusion proteins and anti-GITR antibodies (e.g., bivalent anti-GITR antibodies) such as, e.g., a GITR fusion protein described in U.S. Patent No.: 6,111,090, European Patent No.: 090505B1, U.S Patent No.: 8,586,023, PCT Publication Nos.: WO 2010/003118 and 2011/090754, or an anti-GITR antibody described, e.g., in U.S. Patent No.: 7,025,962, European Patent No.: 1947183B1, U.S. Patent No.: 7,812,135, U.S. Patent No.: 8,388,967, U.S. Patent No.: 8,591,886, European Patent No.: EP 1866339, PCT Publication No.: WO 2011/028683, PCT Publication No.:WO 2013/039954, PCT Publication No.: WO2005/007190, PCT Publication No.: WO 2007/133822, PCT Publication No.: WO2005/055808, PCT Publication No.: WO 99/40196, PCT Publication No.: WO 2001/03720, PCT Publication No.: WO99/20758, PCT Publication No.: WO2006/083289, PCT Publication No.: WO 2005/115451, U.S. Patent No.: 7,618,632, and PCT Publication No.: WO 2011/051726.

In one embodiment, a CAR expressing cell described herein is administered to a subject in combination with an mTOR inhibitor, e.g., an mTOR inhibitor described herein, e.g., a rapalog such as everolimus. In one embodiment, the mTOR inhibitor is administered prior to the CAR-expressing cell. For example, in one embodiment, the mTOR inhibitor can be administered prior to apheresis of the cells. In one embodiment, the subject has CLL.

In one embodiment, a CAR expressing cell described herein is administered to a subject in combination with a GITR agonist, e.g., a GITR agonist described herein. In one embodiment, the GITR agonist is administered prior to the CAR-expressing cell. For example, in one embodiment, the GITR agonist can be administered prior to apheresis of the cells. In one embodiment, the subject has CLL.

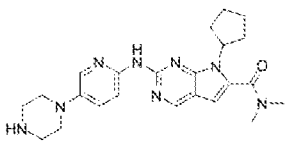
In one embodiment, a CAR-expressing cell described herein can be used in combination with a kinase inhibitor. In one embodiment, the kinase inhibitor is a CDK4 inhibitor, e.g., a CDK4 inhibitor described herein, e.g., a CD4/6 inhibitor, such as, e.g., 6-Acetyl-8-cyclopentyl-5-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one, hydrochloride (also referred to as palbociclib or PD0332991). In one embodiment, the kinase inhibitor is a BTK inhibitor, e.g., a BTK inhibitor described herein, such as, e.g., ibrutinib. In one embodiment, the kinase inhibitor is an mTOR inhibitor, e.g., an mTOR inhibitor described herein, such as, e.g., rapamycin, a rapamycin analog, OSI-027. The mTOR inhibitor can be, e.g., an mTORC1 inhibitor and/or an mTORC2 inhibitor, e.g., an mTORC1 inhibitor and/or mTORC2 inhibitor described herein. In one embodiment, the kinase inhibitor is a MNK inhibitor, e.g., a MNK inhibitor described herein, such as, e.g., 4-amino-5-(4-fluoroanilino)-pyrazolo [3,4-*d*] pyrimidine. The MNK inhibitor can be, e.g., a MNK1a, MNK1b, MNK2a and/or MNK2b inhibitor. In one embodiment, the kinase inhibitor is a dual PI3K/mTOR inhibitor described herein, such as, e.g., PF-04695102.

In one embodiment, the kinase inhibitor is a CDK4 inhibitor selected from aloisine A; flavopiridol or HMR-1275, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-4-chromenone; crizotinib (PF-02341066; 2-(2-Chlorophenyl)-5,7-dihydroxy-8-[(2*R*,3*S*)-2-(hydroxymethyl)-1-methyl-3-pyrrolidinyl]- 4*H*-1-benzopyran-4-one, hydrochloride (P276-00); 1-methyl-5-[[2-[5-(trifluoromethyl)-1*H*-imidazol-2-yl]-4-pyridinyl]oxy]-*N*-[4-(trifluoromethyl)phenyl]-1*H*-benzimidazol-2-amine (RAF265); indisulam (E7070); roscovitine (CYC202); palbociclib (PD0332991); dinaciclib (SCH727965); N-[5-[[(5-*tert*-butyloxazol-2-yl)methyl]thio]thiazol-2-yl]piperidine-4-carboxamide (BMS 387032); 4-[[9-chloro-7-(2,6-difluorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepin-2-yl]amino]-benzoic acid (MLN8054); 5-[3-(4,6-difluoro-1H-benzimidazol-2-yl)-1H-indazol-5-yl]-N-ethyl-4-methyl-3-pyridinemethanamine (AG-024322); 4-(2,6-dichlorobenzoylamino)-1H-pyrazole-3-carboxylic

acid N-(piperidin-4-yl)amide (AT7519); 4-[2-methyl-1-(1-methylethyl)-1*H*-imidazol-5-yl]-*N*-[4-(methylsulfonyl)phenyl]- 2-pyrimidinamine (AZD5438); and XL281 (BMS908662).

In one embodiment, the kinase inhibitor is a CDK4 inhibitor, e.g., palbociclib (PD0332991), and the palbociclib is administered at a dose of about 50 mg, 60 mg, 70 mg, 75 mg, 80 mg, 90 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg (e.g., 75 mg, 100 mg or 125 mg) daily for a period of time, e.g., daily for 14-21 days of a 28 day cycle, or daily for 7-12 days of a 21 day cycle. In one embodiment, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or more cycles of palbociclib are administered.

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with a cyclin-dependent kinase (CDK) 4 or 6 inhibitor, e.g., a CDK4 inhibitor or a CDK6 inhibitor described herein. In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with a CDK4/6 inhibitor (e.g., an inhibitor that targets both CDK4 and CDK6), e.g., a CDK4/6 inhibitor described herein. In an embodiment, the subject has MCL. MCL is an aggressive cancer that is poorly responsive to currently available therapies, i.e., essentially incurable. In many cases of MCL, cyclin D1 (a regulator of CDK4/6) is expressed (e.g., due to chromosomal translocation involving immunoglobulin and Cyclin D1 genes) in MCL cells. Thus, without being bound by theory, it is thought that MCL cells are highly sensitive to CDK4/6 inhibition with high specificity (i.e., minimal effect on normal immune cells). CDK4/6 inhibitors alone have had some efficacy in treating MCL, but have only achieved partial remission with a high relapse rate. An exemplary CDK4/6 inhibitor is LEE011 (also called ribociclib), the structure of which is shown below.

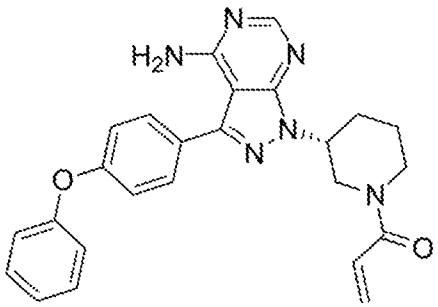


Without being bound by theory, it is believed that administration of a CAR-expressing cell described herein with a CDK4/6 inhibitor (e.g., LEE011 or other CDK4/6 inhibitor described herein) can achieve higher responsiveness, e.g., with higher remission rates and/or lower relapse rates, e.g., compared to a CDK4/6 inhibitor alone.

In one embodiment, the kinase inhibitor is a BTK inhibitor selected from ibrutinib (PCI-32765); GDC-0834; RN-486; CGI-560; CGI-1764; HM-71224; CC-292; ONO-4059; CNX-774;

and LFM-A13. In a preferred embodiment, the BTK inhibitor does not reduce or inhibit the kinase activity of interleukin-2-inducible kinase (ITK), and is selected from GDC-0834; RN-486; CGI-560; CGI-1764; HM-71224; CC-292; ONO-4059; CNX-774; and LFM-A13.

In one embodiment, the kinase inhibitor is a BTK inhibitor, e.g., ibrutinib (PCI-32765). In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with a BTK inhibitor (e.g., ibrutinib). In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with ibrutinib (also called PCI-32765). The structure of ibrutinib (1-[(3*R*)-3-[4-Amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one) is shown below.



In embodiments, the subject has CLL, mantle cell lymphoma (MCL), or small lymphocytic lymphoma (SLL). For example, the subject has a deletion in the short arm of chromosome 17 (del(17p), e.g., in a leukemic cell). In other examples, the subject does not have a del(17p). In embodiments, the subject has relapsed CLL or SLL, e.g., the subject has previously been administered a cancer therapy (e.g., previously been administered one, two, three, or four prior cancer therapies). In embodiments, the subject has refractory CLL or SLL. In other embodiments, the subject has follicular lymphoma, e.g., relapse or refractory follicular lymphoma. In some embodiments, ibrutinib is administered at a dosage of about 300-600 mg/day (e.g., about 300-350, 350-400, 400-450, 450-500, 500-550, or 550-600 mg/day, e.g., about 420 mg/day or about 560 mg/day), e.g., orally. In embodiments, the ibrutinib is administered at a dose of about 250 mg, 300 mg, 350 mg, 400 mg, 420 mg, 440 mg, 460 mg, 480 mg, 500 mg, 520 mg, 540 mg, 560 mg, 580 mg, 600 mg (e.g., 250 mg, 420 mg or 560 mg) daily for a period of time, e.g., daily for 21 day cycle cycle, or daily for 28 day cycle. In one embodiment, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or more cycles of ibrutinib are administered. Without being bound by theory, it is thought that the addition of ibrutinib enhances the T cell proliferative response and may shift T cells from a T-helper-2 (Th2) to T-helper-1 (Th1)

phenotype. Th1 and Th2 are phenotypes of helper T cells, with Th1 versus Th2 directing different immune response pathways. A Th1 phenotype is associated with proinflammatory responses, e.g., for killing cells, such as intracellular pathogens/viruses or cancerous cells, or perpetuating autoimmune responses. A Th2 phenotype is associated with eosinophil accumulation and anti-inflammatory responses.

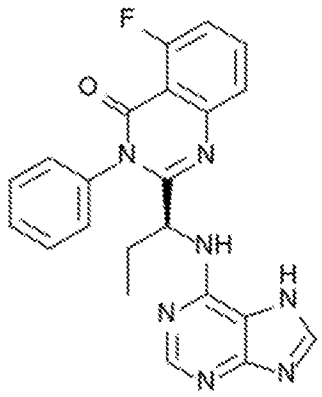
In one embodiment, the kinase inhibitor is an mTOR inhibitor selected from temsirolimus; ridaforolimus (1*R*,2*R*,4*S*)-4-[(2*R*)-2 [(1*R*,9*S*,12*S*,15*R*,16*E*,18*R*,19*R*,21*R*, 23*S*,24*E*,26*E*,28*Z*,30*S*,32*S*,35*R*)-1,18-dihydroxy-19,30-dimethoxy-15,17,21,23, 29,35-hexamethyl-2,3,10,14,20-pentaoxo-11,36-dioxa-4-azatricyclo[30.3.1.$0^{4,9}$] hexatriaconta-16,24,26,28-tetraen-12-yl]propyl]-2-methoxycyclohexyl dimethylphosphinate, also known as AP23573 and MK8669; everolimus (RAD001); rapamycin (AY22989); simapimod; (5-{2,4-bis[(3*S*)-3-methylmorpholin-4-yl]pyrido[2,3-*d*]pyrimidin-7-yl}-2-methoxyphenyl)methanol (AZD8055); 2-amino-8-[*trans*-4-(2-hydroxyethoxy)cyclohexyl]-6-(6-methoxy-3-pyridinyl)-4-methyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (PF04691502); and N^2-[1,4-dioxo-4-[[4-(4-oxo-8-phenyl-4*H*-1-benzopyran-2-yl)morpholinium-4-yl]methoxy]butyl]-L-arginylglycyl-L-α-aspartylL-serine-, inner salt (SF1126) (SEQ ID NO: 1262); and XL765.

In one embodiment, the kinase inhibitor is an mTOR inhibitor, e.g., rapamycin, and the rapamycin is administered at a dose of about 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg (e.g., 6 mg) daily for a period of time, e.g., daily for 21 day cycle cycle, or daily for 28 day cycle. In one embodiment, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or more cycles of rapamycin are administered. In one embodiment, the kinase inhibitor is an mTOR inhibitor, e.g., everolimus and the everolimus is administered at a dose of about 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg (e.g., 10 mg) daily for a period of time, e.g., daily for 28 day cycle. In one embodiment, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or more cycles of everolimus are administered.

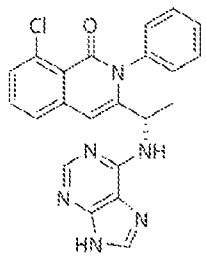
In one embodiment, the kinase inhibitor is an MNK inhibitor selected from CGP052088; 4-amino-3-(p-fluorophenylamino)-pyrazolo [3,4-*d*] pyrimidine (CGP57380); cercosporamide; ETC-1780445-2; and 4-amino-5-(4-fluoroanilino)-pyrazolo [3,4-*d*] pyrimidine.

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with a phosphoinositide 3-kinase (PI3K) inhibitor (e.g., a PI3K inhibitor described herein, e.g., idelalisib or duvelisib) and/or rituximab. In embodiments, a CAR-expressing cell

described herein is administered to a subject in combination with idelalisib and rituximab. In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with duvelisib and rituximab. Idelalisib (also called GS-1101 or CAL-101; Gilead) is a small molecule that blocks the delta isoform of PI3K. The structure of idelalisib (5-Fluoro-3-phenyl-2-[(1*S*)-1-(7*H*-purin-6-ylamino)propyl]-4(3*H*)-quinazolinone) is shown below.



Duvelisib (also called IPI-145; Infinity Pharmaceuticals and Abbvie) is a small molecule that blocks PI3K-δ,γ. The structure of duvelisib (8-Chloro-2-phenyl-3-[(1S)-1-(9H-purin-6-ylamino)ethyl]-1(2H)-isoquinolinone) is shown below.



In embodiments, the subject has CLL. In embodiments, the subject has relapsed CLL, e.g., the subject has previously been administered a cancer therapy (e.g., previously been administered an anti-CD20 antibody or previously been administered ibrutinib). For example, the subject has a deletion in the short arm of chromosome 17 (del(17p), e.g., in a leukemic cell). In other examples, the subject does not have a del(17p). In embodiments, the subject comprises a leukemic cell comprising a mutation in the immunoglobulin heavy-chain variable-region (IgV_H) gene. In other embodiments, the subject does not comprise a leukemic cell comprising a mutation in the immunoglobulin heavy-chain variable-region (IgV_H) gene. In embodiments, the subject has a deletion in the long arm of chromosome 11 (del(11q)). In other embodiments, the

subject does not have a del(11q). In embodiments, idelalisib is administered at a dosage of about 100-400 mg (e.g., 100-125, 125-150, 150-175, 175-200, 200-225, 225-250, 250-275, 275-300, 325-350, 350-375, or 375-400 mg), e.g., BID. In embodiments, duvelisib is administered at a dosage of about 15-100 mg (e.g., about 15-25, 25-50, 50-75, or 75-100 mg), e.g., twice a day. In embodiments, rituximab is administered at a dosage of about 350-550 mg/m^2 (e.g., 350-375, 375-400, 400-425, 425-450, 450-475, or 475-500 mg/m^2), e.g., intravenously.

In one embodiment, the kinase inhibitor is a dual phosphatidylinositol 3-kinase (PI3K) and mTOR inhibitor selected from 2-Amino-8-[*trans*-4-(2-hydroxyethoxy)cyclohexyl]-6-(6-methoxy-3-pyridinyl)-4-methyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (PF-04691502); *N*-[4-[[4-(Dimethylamino)-1-piperidinyl]carbonyl]phenyl]-*N*'-[4-(4,6-di-4-morpholinyl-1,3,5-triazin-2-yl)phenyl]urea (PF-05212384, PKI-587); 2-Methyl-2-{4-[3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-1*H*-imidazo[4,5-c]quinolin-1-yl]phenyl}propanenitrile (BEZ-235); apitolisib (GDC-0980, RG7422); 2,4-Difluoro-N-{2-(methyloxy)-5-[4-(4-pyridazinyl)-6-quinolinyl]-3-pyridinyl}benzenesulfonamide (GSK2126458); 8-(6-methoxypyridin-3-yl)-3-methyl-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)-1H-imidazo[4,5-c]quinolin-2(3H)-one Maleic acid (NVP-BGT226); 3-[4-(4-Morpholinylpyrido[3',2':4,5]furo[3,2-d]pyrimidin-2-yl]phenol (PI-103); 5-(9-isopropyl-8-methyl-2-morpholino-9H-purin-6-yl)pyrimidin-2-amine (VS-5584, SB2343); and N-[2-[(3,5-Dimethoxyphenyl)amino]quinoxalin-3-yl]-4-[(4-methyl-3-methoxyphenyl)carbonyl]aminophenylsulfonamide (XL765).

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with an anaplastic lymphoma kinase (ALK) inhibitor. Exemplary ALK kinases include but are not limited to crizotinib (Pfizer), ceritinib (Novartis), alectinib (Chugai), brigatinib (also called AP26113; Ariad), entrectinib (Ignyta), PF-06463922 (Pfizer), TSR-011 (Tesaro) (see, e.g., Clinical Trial Identifier No. NCT02048488), CEP-37440 (Teva), and X-396 (Xcovery). In some embodiments, the subject has a solid cancer, e.g., a solid cancer described herein, e.g., lung cancer.

The chemical name of crizotinib is 3-[(1*R*)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]-5-(1-piperidin-4-ylpyrazol-4-yl)pyridin-2-amine. The chemical name of ceritinib is 5-Chloro-N^2-[2-isopropoxy-5-methyl-4-(4-piperidinyl)phenyl]-N^4-[2-(isopropylsulfonyl)phenyl]-2,4-pyrimidinediamine. The chemical name of alectinib is 9-ethyl-6,6-dimethyl-8-(4-morpholinopiperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile. The

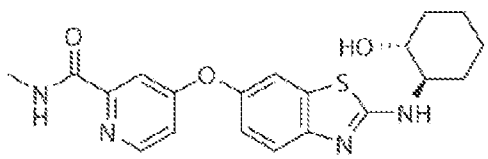
chemical name of brigatinib is 5-Chloro-N^2-{4-[4-(dimethylamino)-1-piperidinyl]-2-methoxyphenyl}-N^4-[2-(dimethylphosphoryl)phenyl]-2,4-pyrimidinediamine. The chemical name of entrectinib is N-(5-(3,5-difluorobenzyl)-1H-indazol-3-yl)-4-(4-methylpiperazin-1-yl)-2-((tetrahydro-2H-pyran-4-yl)amino)benzamide. The chemical name of PF-06463922 is (10R)-7-Amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]-benzoxadiazacyclotetradecine-3-carbonitrile. The chemical structure of CEP-37440 is (S)-2-((5-chloro-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-1-methoxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-2-yl)amino)pyrimidin-4-yl)amino)-N-methylbenzamide. The chemical name of X-396 is (R)-6-amino-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)-N-(4-(4-methylpiperazine-1-carbonyl)phenyl)pyridazine-3-carboxamide.

Drugs that inhibit either the calcium dependent phosphatase calcineurin (cyclosporine and FK506) or inhibit the p70S6 kinase that is important for growth factor induced signaling (rapamycin). (Liu et al., Cell 66:807-815, 1991; Henderson et al., Immun. 73:316-321, 1991; Bierer et al., Curr. Opin. Immun. 5:763-773, 1993) can also be used. In a further aspect, the cell compositions of the present invention may be administered to a patient in conjunction with (e.g., before, simultaneously or following) bone marrow transplantation, T cell ablative therapy using chemotherapy agents such as, fludarabine, external-beam radiation therapy (XRT), cyclophosphamide, and/or antibodies such as OKT3 or CAMPATH. In one aspect, the cell compositions of the present invention are administered following B-cell ablative therapy such as agents that react with CD20, e.g., Rituxan. For example, in one embodiment, subjects may undergo standard treatment with high dose chemotherapy followed by peripheral blood stem cell transplantation. In certain embodiments, following the transplant, subjects receive an infusion of the expanded immune cells of the present invention. In an additional embodiment, expanded cells are administered before or following surgery.

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with an indoleamine 2,3-dioxygenase (IDO) inhibitor. IDO is an enzyme that catalyzes the degradation of the amino acid, L-tryptophan, to kynurenine. Many cancers overexpress IDO, e.g., prostatic, colorectal, pancreatic, cervical, gastric, ovarian, head, and lung cancer. pDCs, macrophages, and dendritic cells (DCs) can express IDO. Without being bound by theory, it is thought that a decrease in L-tryptophan (e.g., catalyzed by IDO) results in an immunosuppressive milieu by inducing T-cell anergy and apoptosis. Thus, without being bound

by theory, it is thought that an IDO inhibitor can enhance the efficacy of a CAR-expressing cell described herein, e.g., by decreasing the suppression or death of a CAR-expressing immune cell. In embodiments, the subject has a solid tumor, e.g., a solid tumor described herein, e.g., prostatic, colorectal, pancreatic, cervical, gastric, ovarian, head, or lung cancer. Exemplary inhibitors of IDO include but are not limited to 1-methyl-tryptophan, indoximod (NewLink Genetics) (see, e.g., Clinical Trial Identifier Nos. NCT01191216; NCT01792050), and INCB024360 (Incyte Corp.) (see, e.g., Clinical Trial Identifier Nos. NCT01604889; NCT01685255)

In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with a modulator of myeloid-derived suppressor cells (MDSCs). MDSCs accumulate in the periphery and at the tumor site of many solid tumors. These cells suppress T cell responses, thereby hindering the efficacy of CAR-expressing cell therapy. Without being bound by theory, it is thought that administration of a MDSC modulator enhances the efficacy of a CAR-expressing cell described herein. In an embodiment, the subject has a solid tumor, e.g., a solid tumor described herein, e.g., glioblastoma. Exemplary modulators of MDSCs include but are not limited to MCS110 and BLZ945. MCS110 is a monoclonal antibody (mAb) against macrophage colony-stimulating factor (M-CSF). See, e.g., Clinical Trial Identifier No. NCT00757757. BLZ945 is a small molecule inhibitor of colony stimulating factor 1 receptor (CSF1R). See, e.g., Pyonteck et al. Nat. Med. 19(2013):1264-72. The structure of BLZ945 is shown below.



In embodiments, a CAR-expressing cell described herein is administered to a subject in combination with a CD19 CART cell (e.g., CTL019, e.g., as described in WO2012/079000, incorporated herein by reference). In embodiments, the subject has a CD19+ lymphoma, e.g., a CD19+ Non-Hodgkin's Lymphoma (NHL), a CD19+ FL, or a CD19+ DLBCL. In embodiments, the subject has a relapsed or refractory CD19+ lymphoma. In embodiments, a

lymphodepleting chemotherapy is administered to the subject prior to, concurrently with, or after administration (e.g., infusion) of CD19 CART cells. In an example, the lymphodepleting chemotherapy is administered to the subject prior to administration of CD19 CART cells. For example, the lymphodepleting chemotherapy ends 1-4 days (e.g,. 1, 2, 3, or 4 days) prior to CD19 CART cell infusion. In embodiments, multiple doses of CD19 CART cells are administered, e.g., as described herein. For example, a single dose comprises about 5 x 10^8 CD19 CART cells. In embodiments, a lymphodepleting chemotherapy is administered to the subject prior to, concurrently with, or after administration (e.g., infusion) of a CAR-expressing cell described herein, e.g., a non-CD19 CAR-expresing cell. In embodiments, a CD19 CART is administered to the subject prior to, concurrently with, or after administration (e.g., infusion) of a non-CD19 CAR-expressing cell, e.g., a non-CD19 CAR-expressing cell described herein.

In some embodiments , a CAR-expressing cell described herein is administered to a subject in combination with a interleukin-15 (IL-15) polypeptide, a interleukin-15 receptor alpha (IL-15Ra) polypeptide, or a combination of both a IL-15 polypeptide and a IL-15Ra polypeptide e.g., hetIL-15 (Admune Therapeutics, LLC). hetIL-15 is a heterodimeric non-covalent complex of IL-15 and IL-15Ra. hetIL-15 is described in, e.g., U.S. 8,124,084, U.S. 2012/0177598, U.S. 2009/0082299, U.S. 2012/0141413, and U.S. 2011/0081311, incorporated herein by reference. In embodiments, het-IL-15 is administered subcutaneously. In embodiments, the subject has a cancer, e.g., solid cancer, e.g., melanoma or colon cancer. In embodiments, the subject has a metastatic cancer.

In one embodiment, the subject can be administered an agent which reduces or ameliorates a side effect associated with the administration of a CAR-expressing cell. Side effects associated with the administration of a CAR-expressing cell include, but are not limited to CRS, and hemophagocytic lymphohistiocytosis (HLH), also termed Macrophage Activation Syndrome (MAS). Symptoms of CRS include high fevers, nausea, transient hypotension, hypoxia, and the like. CRS may include clinical constitutional signs and symptoms such as fever, fatigue, anorexia, myalgias, arthalgias, nausea, vomiting, and headache. CRS may include clinical skin signs and symptoms such as rash. CRS may include clinical gastrointestinal signs and symsptoms such as nausea, vomiting and diarrhea. CRS may include clinical respiratory signs and symptoms such as tachypnea and hypoxemia. CRS may include clinical cardiovascular signs and symptoms such as tachycardia, widened pulse pressure, hypotension,

increased cardac output (early) and potentially diminished cardiac output (late). CRS may include clinical coagulation signs and symptoms such as elevated d-dimer, hypofibrinogenemia with or without bleeding. CRS may include clinical renal signs and symptoms such as azotemia. CRS may include clinical hepatic signs and symptoms such as transaminitis and hyperbilirubinemia. CRS may include clinical neurologic signs and symptoms such as headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dymetria, altered gait, and seizures.

Accordingly, the methods described herein can comprise administering a CAR-expressing cell described herein to a subject and further administering one or more agents to manage elevated levels of a soluble factor resulting from treatment with a CAR-expressing cell. In one embodiment, the soluble factor elevated in the subject is one or more of IFN-γ, TNFα, IL-2 and IL-6. In an embodiment, the factor elevated in the subject is one or more of IL-1, GM-CSF, IL-10, IL-8, IL-5 and fraktalkine. Therefore, an agent administered to treat this side effect can be an agent that neutralizes one or more of these soluble factors. In one embodiment, the agent that neutralizes one or more of these soluble forms is an antibody or antigen binding fragment thereof. Examples of such agents include, but are not limited to a steroid (e.g., corticosteroid), an inhibitor of TNFα, and an inhibitor of IL-6. An example of a TNFα inhibitor is an anti-TNFα antibody molecule such as, infliximab, adalimumab, certolizumab pegol, and golimumab. Another example of a TNFα inhibitor is a fusion protein such as entanercept. Small molecule inhibitors of TNFα include, but are not limited to, xanthine derivatives (e.g. pentoxifylline) and bupropion. An example of an IL-6 inhibitor is an anti-IL-6 antibody molecule or an anti-IL-6 receptor antibody molecule such as tocilizumab (toc), sarilumab, elsilimomab, CNTO 328, ALD518/BMS-945429, CNTO 136, CPSI-2364, CDP6038, VX30, ARGX-109, FE301, and FM101. In one embodiment, the anti-IL-6 receptor antibody molecule is tocilizumab. An example of an IL-1R based inhibitor is anakinra.

In one embodiment, the subject can be administered an agent which enhances the activity of a CAR-expressing cell. For example, in one embodiment, the agent can be an agent which inhibits an inhibitory molecule. Inhibitory molecules, e.g., Programmed Death 1 (PD-1), can, in some embodiments, decrease the ability of a CAR-expressing cell to mount an immune effector response. Examples of inhibitory molecules include PD-1, PD-L1, CTLA-4, TIM-3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG-3, VISTA, BTLA, TIGIT, LAIR1,

CD160, 2B4 and TGF beta. Inhibition of an inhibitory molecule, e.g., by inhibition at the DNA, RNA or protein level, can optimize a CAR-expressing cell performance. In embodiments, an inhibitory nucleic acid, e.g., an inhibitory nucleic acid, e.g., a dsRNA, e.g., an siRNA or shRNA, a clustered regularly interspaced short palindromic repeats (CRISPR), a transcription-activator like effector nuclease (TALEN), or a zinc finger endonuclease (ZFN), e.g., as described herein, can be used to inhibit expression of an inhibitory molecule in the CAR-expressing cell. In an embodiment the inhibitor is an shRNA. In an embodiment, the inhibitory molecule is inhibited within a CAR-expressing cell. In these embodiments, a dsRNA molecule that inhibits expression of the inhibitory molecule is linked to the nucleic acid that encodes a component, e.g., all of the components, of the CAR. In one embodiment, the inhibitor of an inhibitory signal can be, e.g., an antibody or antibody fragment that binds to an inhibitory molecule. For example, the agent can be an antibody or antibody fragment that binds to PD-1, PD-L1, PD-L2 or CTLA4 (e.g., ipilimumab (also referred to as MDX-010 and MDX-101, and marketed as Yervoy®; Bristol-Myers Squibb; Tremelimumab (IgG2 monoclonal antibody available from Pfizer, formerly known as ticilimumab, CP-675,206).). In an embodiment, the agent is an antibody or antibody fragment that binds to TIM3. In an embodiment, the agent is an antibody or antibody fragment that binds to CEACAM (CEACAM-1, CEACAM-3, and/or CEACAM-5). In an embodiment, the agent is an antibody or antibody fragment that binds to LAG3.

PD-1 is an inhibitory member of the CD28 family of receptors that also includes CD28, CTLA-4, ICOS, and BTLA. PD-1 is expressed on activated B cells, T cells and myeloid cells (Agata et al. 1996 Int. Immunol 8:765-75). Two ligands for PD-1, PD-L1 and PD-L2 have been shown to downregulate T cell activation upon binding to PD-1 (Freeman et a. 2000 J Exp Med 192:1027-34; Latchman et al. 2001 Nat Immunol 2:261-8; Carter et al. 2002 Eur J Immunol 32:634-43). PD-L1 is abundant in human cancers (Dong et al. 2003 J Mol Med 81:281-7; Blank et al. 2005 Cancer Immunol. Immunother 54:307-314; Konishi et al. 2004 Clin Cancer Res 10:5094). Immune suppression can be reversed by inhibiting the local interaction of PD-1 with PD-L1. Antibodies, antibody fragments, and other inhibitors of PD-1, PD-L1 and PD-L2 are available in the art and may be used combination with a cars of the present invention described herein. For example, nivolumab (also referred to as BMS-936558 or MDX1106; Bristol-Myers Squibb) is a fully human IgG4 monoclonal antibody which specifically blocks PD-1. Nivolumab (clone 5C4) and other human monoclonal antibodies that specifically bind to PD-1 are disclosed

in US 8,008,449 and WO2006/121168. Pidilizumab (CT-011; Cure Tech) is a humanized IgG1k monoclonal antibody that binds to PD-1. Pidilizumab and other humanized anti-PD-1 monoclonal antibodies are disclosed in WO2009/101611. Pembrolizumab (formerly known as lambrolizumab, and also referred to as MK03475; Merck) is a humanized IgG4 monoclonal antibody that binds to PD-1. Pembrolizumab and other humanized anti-PD-1 antibodies are disclosed in US 8,354,509 and WO2009/114335. MEDI4736 (Medimmune) is a human monoclonal antibody that binds to PDL1, and inhibits interaction of the ligand with PD1. MDPL3280A (Genentech / Roche) is a human Fc optimized IgG1 monoclonal antibody that binds to PD-L1. MDPL3280A and other human monoclonal antibodies to PD-L1 are disclosed in U.S. Patent No.: 7,943,743 and U.S Publication No.: 20120039906. Other anti-PD-L1 binding agents include YW243.55.S70 (heavy and light chain variable regions are shown in SEQ ID NOs 20 and 21 in WO2010/077634) and MDX-1 105 (also referred to as BMS-936559, and, e.g., anti-PD-L1 binding agents disclosed in WO2007/005874). AMP-224 (B7-DCIg; Amplimmune; e.g., disclosed in WO2010/027827 and WO2011/066342), is a PD-L2 Fc fusion soluble receptor that blocks the interaction between PD-1 and B7-H1. Other anti-PD-1 antibodies include AMP 514 (Amplimmune), among others, e.g., anti-PD-1 antibodies disclosed in US 8,609,089, US 2010028330, and/or US 20120114649.

TIM-3 (T cell immunoglobulin-3) also negatively regulates T cell function, particularly in IFN-g-secreting CD4+ T helper 1 and CD8+ T cytotoxic 1 cells, and plays a critical role in T cell exhaustion. Inhibition of the interaction between TIM3 and its ligands, e.g., galectin-9 (Gal9), phosphotidylserine (PS), and HMGB1, can increase immune response. Antibodies, antibody fragments, and other inhibitors of TIM3 and its ligands are available in the art and may be used combination with a CD19 CAR described herein. For example, antibodies, antibody fragments, small molecules, or peptide inhibitors that target TIM3 binds to the IgV domain of TIM3 to inhibit interaction with its ligands. Antibodies and peptides that inhibit TIM3 are disclosed in WO2013/006490 and US20100247521. Other anti-TIM3 antibodies include humanized versions of RMT3-23 (disclosed in Ngiow et al., 2011, Cancer Res, 71:3540-3551), and clone 8B.2C12 (disclosed in Monney et al., 2002, Nature, 415:536-541). Bi-specific antibodies that inhibit TIM3 and PD-1 are disclosed in US20130156774.

In other embodiments, the agent that enhances the activity of a CAR-expressing cell is a CEACAM inhibitor (*e.g.*, CEACAM-1, CEACAM-3, and/or CEACAM-5 inhibitor). In one

embodiment, the inhibitor of CEACAM is an anti-CEACAM antibody molecule. Exemplary anti-CEACAM-1 antibodies are described in WO 2010/125571, WO 2013/082366 WO 2014/059251 and WO 2014/022332, e.g., a monoclonal antibody 34B1, 26H7, and 5F4; or a recombinant form thereof, as described in, *e.g.*, US 2004/0047858, US 7,132,255 and WO 99/052552. In other embodiments, the anti-CEACAM antibody binds to CEACAM-5 as described in, *e.g.*, Zheng et al. *PLoS One*. 2010 Sep 2;5(9). pii: e12529 (DOI:10:1371/journal.pone.0021146), or crossreacts with CEACAM-1 and CEACAM-5 as described in, *e.g.*, WO 2013/054331 and US 2014/0271618.

Without wishing to be bound by theory, carcinoembryonic antigen cell adhesion molecules (CEACAM), such as CEACAM-1 and CEACAM-5, are believed to mediate, at least in part, inhibition of an anti-tumor immune response (see e.g., Markel et al. J Immunol. 2002 Mar 15;168(6):2803-10; Markel et al. J Immunol. 2006 Nov 1;177(9):6062-71; Markel et al. Immunology. 2009 Feb;126(2):186-200; Markel et al. Cancer Immunol Immunother. 2010 Feb;59(2):215-30; Ortenberg et al. Mol Cancer Ther. 2012 Jun;11(6):1300-10; Stern et al. J Immunol. 2005 Jun 1;174(11):6692-701; Zheng et al. PLoS One. 2010 Sep 2;5(9). pii: e12529). For example, CEACAM-1 has been described as a heterophilic ligand for TIM-3 and as playing a role in TIM-3-mediated T cell tolerance and exhaustion (see e.g., WO 2014/022332; Huang, et al. (2014) Nature doi:10.1038/nature13848). In embodiments, co-blockade of CEACAM-1 and TIM-3 has been shown to enhance an anti-tumor immune response in xenograft colorectal cancer models (see e.g., WO 2014/022332; Huang, et al. (2014), *supra*). In other embodiments, co-blockade of CEACAM-1 and PD-1 reduce T cell tolerance as described, *e.g.*, in WO 2014/059251. Thus, CEACAM inhibitors can be used with the other immunomodulators described herein (e.g., anti-PD-1 and/or anti-TIM-3 inhibitors) to enhance an immune response against a cancer, *e.g.*, a melanoma, a lung cancer (e.g., NSCLC), a bladder cancer, a colon cancer an ovarian cancer, and other cancers as described herein.

LAG-3 (lymphocyte activation gene-3 or CD223) is a cell surface molecule expressed on activated T cells and B cells that has been shown to play a role in CD8+ T cell exhaustion. Antibodies, antibody fragments, and other inhibitors of LAG-3 and its ligands are available in the art and may be used combination with a CD19 CAR described herein. For example, BMS-986016 (Bristol-Myers Squib) is a monoclonal antibody that targets LAG3. IMP701 (Immutep) is an antagonist LAG-3 antibody and IMP731 (Immutep and GlaxoSmithKline) is a depleting

LAG-3 antibody. Other LAG-3 inhibitors include IMP321 (Immutep), which is a recombinant fusion protein of a soluble portion of LAG3 and Ig that binds to MHC class II molecules and activates antigen presenting cells (APC). Other antibodies are disclosed, e.g., in WO2010/019570.

In some embodiments, the agent which enhances the activity of a CAR-expressing cell can be, e.g., a fusion protein comprising a first domain and a second domain, wherein the first domain is an inhibitory molecule, or fragment thereof, and the second domain is a polypeptide that is associated with a positive signal, e.g., a polypeptide comrpsing an antracellular signaling domain as described herein. In some embodiments, the polypeptide that is associated with a positive signal can include a costimulatory domain of CD28, CD27, ICOS, e.g., an intracellular signaling domain of CD28, CD27 and/or ICOS, and/or a primary signaling domain, e.g., of CD3 zeta, e.g., described herein. In one embodiment, the fusion protein is expressed by the same cell that expressed the CAR. In another embodiment, the fusion protein is expressed by a cell, e.g., a T cell that does not express a CAR of the present invention.

In one embodiment, the agent which enhances activity of a CAR-expressing cell described herein is miR-17-92.

In one embodiment, the agent which enhances activity of a CAR-described herein is a cytokine. Cytokines have important functions related to T cell expansion, differentiation, survival, and homeostatis. Cytokines that can be administered to the subject receiving a CAR-expressing cell described herein include: IL-2, IL-4, IL-7, IL-9, IL-15, IL-18, and IL-21, or a combination thereof. In preferred embodiments, the cytokine administered is IL-7, IL-15, or IL-21, or a combination thereof. The cytokine can be administered once a day or more than once a day, e.g., twice a day, three times a day, or four times a day. The cytokine can be administered for more than one day, e.g. the cytokine is administered for 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, or 4 weeks. For example, the cytokine is administered once a day for 7 days.

In embodiments, the cytokine is administered in combination with CAR-expressing T cells. The cytokine can be administered simultaneously or concurrently with the CAR-expressing T cells, e.g., administered on the same day. The cytokine may be prepared in the same pharmaceutical composition as the CAR-expressing T cells, or may be prepared in a separate pharmaceutical composition. Alternatively, the cytokine can be administered shortly

after administration of the CAR-expressing T cells, e.g., 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, or 7 days after administration of the CAR-expressing T cells. In embodiments where the cytokine is administered in a dosing regimen that occurs over more than one day, the first day of the cytokine dosing regimen can be on the same day as administration with the CAR-expressing T cells, or the first day of the cytokine dosing regimen can be 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, or 7 days after administration of the CAR-expressing T cells. In one embodiment, on the first day, the CAR-expressing T cells are administered to the subject, and on the second day, a cytokine is administered once a day for the next 7 days. In a preferred embodiment, the cytokine to be administered in combination with CAR-expressing T cells is IL-7, IL-15, or IL-21.

In other embodiments, the cytokine is administered a period of time after administration of CAR-expressing cells, e.g., at least 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or 1 year or more after administration of CAR-expressing cells. In one embodiment, the cytokine is administered after assessment of the subject's response to the CAR-expressing cells. For example, the subject is administered CAR-expressing cells according to the dosage and regimens described herein. The response of the subject to CAR-expressing cell therapy is assessed at 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or 1 year or more after administration of CAR-expressing cells, using any of the methods described herein, including inhibition of tumor growth, reduction of circulating tumor cells, or tumor regression. Subjects that do not exhibit a sufficient response to CAR-expressing cell therapy can be administered a cytokine. Administration of the cytokine to the subject that has sub-optimal response to the CAR-expressing cell therapy improves CAR-expressing cell efficacy or anti-cancer activity. In a preferred embodiment, the cytokine administered after administration of CAR-expressing cells is IL-7.

Combination with a low dose of an mTOR inhibitor

In one embodiment, the cells expressing a CAR molecule, e.g., a CAR molecule described herein, are administered in combination with a low, immune enhancing dose of an mTOR inhibitor.

In an embodiment, a dose of an mTOR inhibitor is associated with, or provides, mTOR inhibition of at least 5 but no more than 90%, at least 10 but no more than 90%, at least 15, but no more than 90%, at least 20 but no more than 90%, at least 30 but no more than 90%, at least 40 but no more than 90%, at least 50 but no more than 90%, at least 60 but no more than 90%, or at least 70 but no more than 90%.

In an embodiment, a dose of an mTOR inhibitor is associated with, or provides, mTOR inhibition of at least 5 but no more than 80%, at least 10 but no more than 80%, at least 15, but no more than 80%, at least 20 but no more than 80%, at least 30 but no more than 80%, at least 40 but no more than 80%, at least 50 but no more than 80%, or at least 60 but no more than 80%.

In an embodiment, a dose of an mTOR inhibitor is associated with, or provides, mTOR inhibition of at least 5 but no more than 70%, at least 10 but no more than 70%, at least 15, but no more than 70%, at least 20 but no more than 70%, at least 30 but no more than 70%, at least 40 but no more than 70%, or at least 50 but no more than 70%.

In an embodiment, a dose of an mTOR inhibitor is associated with, or provides, mTOR inhibition of at least 5 but no more than 60%, at least 10 but no more than 60%, at least 15, but no more than 60%, at least 20 but no more than 60%, at least 30 but no more than 60%, or at least 40 but no more than 60%.

In an embodiment, a dose of an mTOR inhibitor is associated with, or provides, mTOR inhibition of at least 5 but no more than 50%, at least 10 but no more than 50%, at least 15, but no more than 50%, at least 20 but no more than 50%, at least 30 but no more than 50%, or at least 40 but no more than 50%.

In an embodiment, a dose of an mTOR inhibitor is associated with, or provides, mTOR inhibition of at least 5 but no more than 40%, at least 10 but no more than 40%, at least 15, but no more than 40%, at least 20 but no more than 40%, at least 30 but no more than 40%, or at least 35 but no more than 40%.

In an embodiment, a dose of an mTOR inhibitor is associated with, or provides, mTOR inhibition of at least 5 but no more than 30%, at least 10 but no more than 30%, at least 15, but no more than 30%, at least 20 but no more than 30%, or at least 25 but no more than 30%.

In an embodiment, a dose of an mTOR inhibitor is associated with, or provides, mTOR inhibition of at least 1, 2, 3, 4 or 5 but no more than 20%, at least 1, 2, 3, 4 or 5 but no more than

30%, at least 1, 2, 3, 4 or 5, but no more than 35, at least 1, 2, 3, 4 or 5 but no more than 40%, or at least 1, 2, 3, 4 or 5 but no more than 45%.

In an embodiment, a dose of an mTOR inhibitor is associated with, or provides, mTOR inhibition of at least 1, 2, 3, 4 or 5 but no more than 90%.

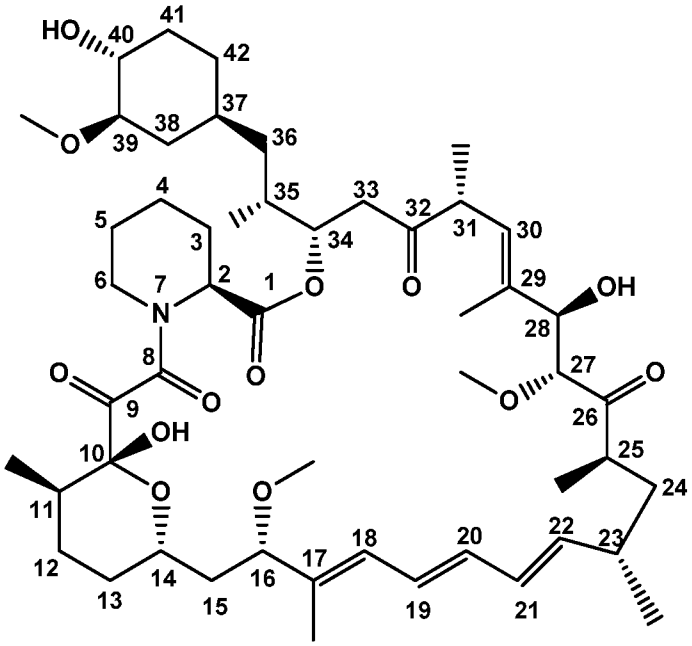
As is discussed herein, the extent of mTOR inhibition can be expressed as the extent of P70 S6 kinase inhibition, e.g., the extent of mTOR inhibition can be determined by the level of decrease in P70 S6 kinase activity, e.g., by the decrease in phosphorylation of a P70 S6 kinase substrate. The level of mTOR inhibition can be evaluated by a method described herein, e.g. by the Boulay assay, or measurement of phosphorylated S6 levels by western blot.

Exemplary mTOR Inhibitors

As used herein, the term "mTOR inhibitor" refers to a compound or ligand, or a pharmaceutically acceptable salt thereof, which inhibits the mTOR kinase in a cell. In an embodiment an mTOR inhibitor is an allosteric inhibitor. In an embodiment an mTOR inhibitor is a catalytic inhibitor.

Allosteric mTOR inhibitors include the neutral tricyclic compound rapamycin (sirolimus), rapamycin-related compounds, that is compounds having structural and functional similarity to rapamycin including, e.g., rapamycin derivatives, rapamycin analogs (also referred to as rapalogs) and other macrolide compounds that inhibit mTOR activity.

Rapamycin is a known macrolide antibiotic produced by Streptomyces hygroscopicus having the structure shown in Formula A.



(A)

See, e.g., McAlpine, J.B., et al., J. Antibiotics (1991) 44: 688; Schreiber, S.L., et al., J. Am. Chem. Soc. (1991) 113: 7433; U.S. Patent No. 3,929,992. There are various numbering schemes proposed for rapamycin. To avoid confusion, when specific rapamycin analogs are named herein, the names are given with reference to rapamycin using the numbering scheme of formula A.

Rapamycin analogs useful in the invention are, for example, O-substituted analogs in which the hydroxyl group on the cyclohexyl ring of rapamycin is replaced by OR_1 in which R_1 is hydroxyalkyl, hydroxyalkoxyalkyl, acylaminoalkyl, or aminoalkyl; e.g. RAD001, also known as, everolimus as described in US 5,665,772 and WO94/09010 the contents of which are incorporated by reference. Other suitable rapamycin analogs include those substituted at the 26- or 28-position. The rapamycin analog may be an epimer of an analog mentioned above, particularly an epimer of an analog substituted in position 40, 28 or 26, and may optionally be further hydrogenated, e.g. as described in US 6,015,815, WO95/14023 and WO99/15530 the contents of which are incorporated by reference, e.g. ABT578 also known as zotarolimus or a rapamycin analog described in US 7,091,213, WO98/02441 and WO01/14387 the contents of which are incorporated by reference, e.g. AP23573 also known as ridaforolimus.

Examples of rapamycin analogs suitable for use in the present invention from US 5,665,772 include, but are not limited to, 40-O-benzyl-rapamycin, 40-O-(4'-hydroxymethyl)benzyl-rapamycin, 40-O-[4'-(1,2-dihydroxyethyl)]benzyl-rapamycin, 40-O-allyl-rapamycin, 40-O-[3'-(2,2-dimethyl-1,3-dioxolan-4(S)-yl)-prop-2'-en-1'-yl]-rapamycin, (2'E,4'S)-40-O-(4',5'-dihydroxypent-2'-en-1'-yl)-rapamycin, 40-O-(2-hydroxy)ethoxycarbonylmethyl-rapamycin, 40-O-(2-hydroxy)ethyl-rapamycin , 40-O-(3-hydroxy)propyl-rapamycin, 40-O-(6-hydroxy)hexyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, 40-O-[(3S)-2,2-dimethyldioxolan-3-yl]methyl-rapamycin, 40-O-[(2S)-2,3-dihydroxyprop-1-yl]-rapamycin, 40-O-(2-acetoxy)ethyl-rapamycin, 40-O-(2-nicotinoyloxy)ethyl-rapamycin, 40-O-[2-(N-morpholino)acetoxy]ethyl-rapamycin, 40-O-(2-N-imidazolylacetoxy)ethyl-rapamycin, 40-O-[2-(N-methyl-N'-piperazinyl)acetoxy]ethyl-rapamycin, 39-O-desmethyl-39,40-O,O-ethylene-rapamycin, (26R)-26-dihydro-40-O-(2-hydroxy)ethyl-rapamycin, 40-O-(2-aminoethyl)-rapamycin, 40-O-(2-acetaminoethyl)-rapamycin, 40-O-(2-nicotinamidoethyl)-rapamycin, 40-O-(2-(N-methyl-imidazo-2'-ylcarbethoxamido)ethyl)-rapamycin, 40-O-(2-ethoxycarbonylaminoethyl)-rapamycin, 40-O-(2-tolylsulfonamidoethyl)-rapamycin and 40-O-[2-(4',5'-dicarboethoxy-1',2',3'-triazol-1'-yl)-ethyl]-rapamycin.

Other rapamycin analogs useful in the present invention are analogs where the hydroxyl group on the cyclohexyl ring of rapamycin and/or the hydroxy group at the 28 position is replaced with an hydroxyester group are known, for example, rapamycin analogs found in US RE44,768, e.g. temsirolimus.

Other rapamycin analogs useful in the preset invention include those wherein the methoxy group at the 16 position is replaced with another substituent, preferably (optionally hydroxy-substituted) alkynyloxy, benzyl, orthomethoxybenzyl or chlorobenzyl and/or wherein the mexthoxy group at the 39 position is deleted together with the 39 carbon so that the cyclohexyl ring of rapamycin becomes a cyclopentyl ring lacking the 39 position methyoxy group; e.g. as described in WO95/16691 and WO96/41807 the contents of which are incorporated by reference. The analogs can be further modified such that the hydroxy at the 40-position of rapamycin is alkylated and/or the 32-carbonyl is reduced.

Rapamycin analogs from WO95/16691 include, but are not limited to, 16-demthoxy-16-(pent-2-ynyl)oxy-rapamycin, 16-demthoxy-16-(but-2-ynyl)oxy-rapamycin, 16-demthoxy-16-

(propargyl)oxy-rapamycin, 16-demethoxy-16-(4-hydroxy-but-2-ynyl)oxy-rapamycin, 16-demthoxy-16-benzyloxy-40-O-(2-hydroxyethyl)-rapamycin, 16-demthoxy-16-benzyloxy-rapamycin, 16-demethoxy-16-ortho-methoxybenzyl-rapamycin, 16-demethoxy-40-O-(2-methoxyethyl)-16-pent-2-ynyl)oxy-rapamycin, 39-demethoxy-40-desoxy-39-formyl-42-nor-rapamycin, 39-demethoxy-40-desoxy-39-hydroxymethyl-42-nor-rapamycin, 39-demethoxy-40-desoxy-39-carboxy-42-nor-rapamycin, 39-demethoxy-40-desoxy-39-(4-methyl-piperazin-1-yl)carbonyl-42-nor-rapamycin, 39-demethoxy-40-desoxy-39-(morpholin-4-yl)carbonyl-42-nor-rapamycin, 39-demethoxy-40-desoxy-39-[N-methyl, N-(2-pyridin-2-yl-ethyl)]carbamoyl-42-nor-rapamycin and 39-demethoxy-40-desoxy-39-(p-toluenesulfonylhydrazonomethyl)-42-nor-rapamycin.

Rapamycin analogs from WO96/41807 include, but are not limited to, 32-deoxo-rapamycin, 16-O-pent-2-ynyl-32-deoxo-rapamycin, 16-O-pent-2-ynyl-32-deoxo-40-O-(2-hydroxy-ethyl)-rapamycin, 16-O-pent-2-ynyl-32-(S)-dihydro-40-O-(2-hydroxyethyl)-rapamycin, 32(S)-dihydro-40-O-(2-methoxy)ethyl-rapamycin and 32(S)-dihydro-40-O-(2-hydroxyethyl)-rapamycin.

Another suitable rapamycin analog is umirolimus as described in US2005/0101624 the contents of which are incorporated by reference.

RAD001, otherwise known as everolimus (Afinitor®), has the chemical name (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.04,9]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone

Further examples of allosteric mTOR inhibitors include sirolimus (rapamycin, AY-22989), 40-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate]-rapamycin (also called temsirolimus or CCI-779) and ridaforolimus (AP-23573/MK-8669). Other examples of allosteric mTor inhibtors include zotarolimus (ABT578) and umirolimus.

Alternatively or additionally, catalytic, ATP-competitive mTOR inhibitors have been found to target the mTOR kinase domain directly and target both mTORC1 and mTORC2. These are also more effective inhibitors of mTORC1 than such allosteric mTOR inhibitors as rapamycin, because they modulate rapamycin-resistant mTORC1 outputs such as 4EBP1-T37/46 phosphorylation and cap-dependent translation.

Catalytic inhibitors include: BEZ235 or 2-methyl-2-[4-(3-methyl-2-oxo-8-quinolin-3-yl-2,3-dihydro-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile, or the monotosylate salt form. the synthesis of BEZ235 is described in WO2006/122806; CCG168 (otherwise known as AZD-8055, Chresta, C.M., et al., Cancer Res, 2010, 70(1), 288-298) which has the chemical name {5-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3d]pyrimidin-7-yl]-2-methoxy-phenyl}-methanol; 3-[2,4-bis[(3S)-3-methylmorpholin-4-yl]pyrido[2,3-d]pyrimidin-7-yl]-N-methylbenzamide (WO09104019); 3-(2-aminobenzo[d]oxazol-5-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (WO10051043 and WO2013023184); A N-(3-(N-(3-((3,5-dimethoxyphenyl)amino)quinoxaline-2-yl)sulfamoyl)phenyl)-3-methoxy-4-methylbenzamide (WO07044729 and WO12006552); PKI-587 (Venkatesan, A.M., J. Med.Chem., 2010, 53, 2636-2645) which has the chemical name 1-[4-[4-(dimethylamino)piperidine-1-carbonyl]phenyl]-3-[4-(4,6-dimorpholino-1,3,5-triazin-2-yl)phenyl]urea; GSK-2126458 (ACS Med. Chem. Lett., 2010, 1, 39-43) which has the chemical name 2,4-difluoro-N-{2-methoxy-5-[4-(4-pyridazinyl)-6-quinolinyl]-3-pyridinyl}benzenesulfonamide; ; 5-(9-isopropyl-8-methyl-2-morpholino-9H-purin-6-yl)pyrimidin-2-amine (WO10114484); (E)-N-(8-(6-amino-5-(trifluoromethyl)pyridin-3-yl)-1-(6-(2-cyanopropan-2-yl)pyridin-3-yl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-ylidene)cyanamide (WO12007926).

Further examples of catalytic mTOR inhibitors include 8-(6-methoxy-pyridin-3-yl)-3-methyl-1-(4-piperazin-1-yl-3-trifluoromethyl-phenyl)-1,3-dihydro-imidazo[4,5-c]quinolin-2-one (WO2006/122806) and Ku-0063794 (Garcia-Martinez JM, et al.,Biochem J., 2009, 421(1), 29-42.. Ku-0063794 is a specific inhibitor of the mammalian target of rapamycin (mTOR).) WYE-354 is another example of a catalytic mTor inhibitor (Yu K, et al. (2009). Biochemical, Cellular, and In vivo Activity of Novel ATP-Competitive and Selective Inhibitors of the Mammalian Target of Rapamycin. Cancer Res. 69(15): 6232-6240).

mTOR inhibitors useful according to the present invention also include prodrugs, derivatives, pharmaceutically acceptable salts, or analogs thereof of any of the foregoing.

mTOR inhibitors, such as RAD001, may be formulated for delivery based on well-established methods in the art based on the particular dosages described herein. In particular, US Patent 6,004,973 (incorporated herein by reference) provides examples of formulations useable with the mTOR inhibitors described herein.

Evaluation of mTOR Inhibition

mTOR phosphorylates the kinase P70 S6, thereby activating P70 S6 kinase and allowing it to phosphorylate its substrate. The extent of mTOR inhibition can be expressed as the extent of P70 S6 kinase inhibition, e.g., the extent of mTOR inhibition can be determined by the level of decrease in P70 S6 kinase activity, e.g., by the decrease in phosphorylation of a P70 S6 kinase substrate. One can determine the level of mTOR inhibition, by measuring P70 S6 kinase activity (the ability of P70 S6 kinase to phsophorylate a substrate), in the absence of inhibitor, e.g., prior to administration of inhibitor, and in the presences of inhibitor, or after the administration of inhibitor. The level of inhibition of P70 S6 kinase gives the level of mTOR inhibition. Thus, if P70 S6 kinase is inhibited by 40%, mTOR activity, as measured by P70 S6 kinase activity, is inhibited by 40%. The extent or level of inhibition referred to herein is the average level of inhibition over the dosage interval. By way of example, if the inhibitor is given once per week, the level of inhibition is given by the average level of inhibition over that interval, namely a week.

Boulay et al., *Cancer Res*, 2004, 64:252-61, hereby incorporated by reference, teaches an assay that can be used to assess the level of mTOR inhibition (referred to herein as the Boulay assay). In an embodiment, the assay relies on the measurement of P70 S6 kinase activity from biological samples before and after administration of an mTOR inhibitor, e.g., RAD001. Samples can be taken at preselected times after treatment with an mTOR ihibitor, e.g., 24, 48, and 72 hours after treatment. Biological samples, e.g., from skin or peripheral blood mononuclear cells (PBMCs) can be used. Total protein extracts are prepared from the samples. P70 S6 kinase is isolated from the protein extracts by immunoprecipitation using an antibody that specifically recognizes the P70 S6 kinase. Activity of the isolated P70 S6 kinase can be measured in an in vitro kinase assay. The isolated kinase can be incubated with 40S ribosomal subunit substrates (which is an endogenous substrate of P70 S6 kinase) and gamma-^{32}P under conditions that allow phosphorylation of the substrate. Then the reaction mixture can be resolved on an SDS-PAGE gel, and ^{32}P signal analyzed using a PhosphorImager. A ^{32}P signal corresponding to the size of the 40S ribosomal subunit indicates phosphorylated substrate and the activity of P70 S6 kinase. Increases and decreases in kinase activity can be calculated by quantifying the area and intensity of the ^{32}P signal of the phosphorylated substrate (e.g., using ImageQuant, Molecular Dynamics), assigning arbitrary unit values to the quantified signal, and

comparing the values from after administration with values from before administration or with a reference value. For example, percent inhibition of kinase activity can be calculated with the following formula: 1-(value obtained after administration/value obtained before administration) X 100. As described above, the extent or level of inhibition referred to herein is the average level of inhibition over the dosage interval.

Methods for the evaluation of kinase activity, e.g., P70 S6 kinase activity, are also provided in US 7,727,950, hereby incorporated by reference.

The level of mTOR inhibition can also be evaluated by a change in the ration of PD1 negative to PD1 positive T cells. T cells from peripheral blood can be identified as PD1 negative or positive by art-known methods.

Low-Dose mTOR Inhibitors

Methods described herein use low, immune enhancing, dose mTOR inhibitors, doses of mTOR inhibitors, e.g., allosteric mTOR inhibitors, including rapalogs such as RAD001. In contrast, levels of inhibitor that fully or near fully inhibit the mTOR pathway are immunosuppressive and are used, e.g., to prevent organ transplant rejection. In addition, high doses of rapalogs that fully inhibit mTOR also inhibit tumor cell growth and are used to treat a variety of cancers (See, e.g., Antineoplastic effects of mammalian target of rapamycine inhibitors. Salvadori M. World J Transplant. 2012 Oct 24;2(5):74-83; Current and Future Treatment Strategies for Patients with Advanced Hepatocellular Carcinoma: Role of mTOR Inhibition. Finn RS. Liver Cancer. 2012 Nov;1(3-4):247-256; Emerging Signaling Pathways in Hepatocellular Carcinoma. Moeini A, Cornellà H, Villanueva A. Liver Cancer. 2012 Sep;1(2):83-93; Targeted cancer therapy - Are the days of systemic chemotherapy numbered? Joo WD, Visintin I, Mor G. Maturitas. 2013 Sep 20.; *Role of natural and adaptive immunity in renal cell carcinoma response to VEGFR-TKIs and mTOR inhibitor.* Santoni M, Berardi R, Amantini C, Burattini L, Santini D, Santoni G, Cascinu S. Int J Cancer. 2013 Oct 2).

The present invention is based, at least in part, on the surprising finding that doses of mTOR inhibitors well below those used in current clinical settings had a superior effect in increasing an immune response in a subject and increasing the ratio of PD-1 negative T cells/PD-1 positive T cells. It was surprising that low doses of mTOR inhibitors, producing only partial

inhibition of mTOR activity, were able to effectively improve immune responses in human human subjects and increase the ratio of PD-1 negative T cells/PD-1 positive T cells.

Alternatively, or in addition, without wishing to be bound by any theory, it is believed that low, a low, immune enhancing, dose of an mTOR inhibitor can increase naive T cell numbers, e.g., at least transiently, e.g., as compared to a non-treated subject. Alternatively or additionally, again while not wishing to be bound by theory, it is believed that treatment with an mTOR inhibitor after a sufficient amount of time or sufficient dosing results in one or more of the following:

an increase in the expression of one or more of the following markers: $CD62L^{high}$, $CD127^{high}$, $CD27^{+}$, and BCL2, e.g., on memory T cells, e.g., memory T cell precursors;

a decrease in the expression of KLRG1, e.g., on memory T cells, e.g., memory T cell precursors; and

an increase in the number of memory T cell precursors, e.g., cells with any one or combination of the following characteristics: increased $CD62L^{high}$, increased $CD127^{high}$, increased $CD27^{+}$, decreased KLRG1, and increased BCL2;

and wherein any of the changes described above occurs, e.g., at least transiently, e.g., as compared to a non-treated subject (Araki, K et al. (2009) *Nature* 460:108-112). Memory T cell precursors are memory T cells that are early in the differentiation program. For example, memory T cells have one or more of the following characteristics: increased $CD62L^{high}$, increased $CD127^{high}$, increased $CD27^{+}$, decreased KLRG1, and/or increased BCL2.

In an embodiment, the invention relates to a composition, or dosage form, of an mTOR inhibitor, e.g., an allosteric mTOR inhibitor, e.g., a rapalog, rapamycin, or RAD001, or a catalytic mTOR inhibitor, which, when administered on a selected dosing regimen, e.g., once daily or once weekly, is associated with: a level of mTOR inhibition that is not associated with complete, or significant immune suppression, but is associated with enhancement of the immune response.

An mTOR inhibitor, e.g., an allosteric mTOR inhibitor, e.g., a rapalog, rapamycin, or RAD001, or a catalytic mTOR inhibitor, can be provided in a sustained relase formulation. Any of the compositions or unit dosage forms described herein can be provided in a sustained release formulation. In some embodiments, a sustained release formulation will have lower

bioavailability than an immediate release formulation. E.g., in embodiments, to attain a similar therapeutic effect of an immediate release forlation a sustained release formulation will have from about 2 to about 5, about 2.5 to about 3.5, or about 3 times the amount of inhibitor provided in the immediate release formulation.

In an embodiment, immediate release forms, e.g., of RAD001, typically used for one administration per week, having 0.1 to 20, 0.5 to 10, 2.5 to 7.5, 3 to 6, or about 5, mgs per unit dosage form, are provided. For once per week administrations, these immediate release formulations correspond to sustained release forms, having, respectively, 0.3 to 60, 1.5 to 30, 7.5 to 22.5, 9 to 18, or about 15 mgs of an mTOR inhibitor, e.g., an allosteric mTOR inhibitor, e.g., rapamycin or RAD001. In embodiments both forms are administered on a once/week basis.

In an embodiment, immediate release forms, e.g., of RAD001, typically used for one administration per day, having having 0.005 to 1.5, 0.01 to 1.5, 0.1 to 1.5, 0.2 to 1.5, 0.3 to 1.5, 0.4 to 1.5, 0.5 to 1.5, 0.6 to 1.5, 0.7 to 1.5, 0.8 to 1.5, 1.0 to 1.5, 0.3 to 0.6, or about 0.5 mgs per unit dosage form, are provided. For once per day administrations, these immediate release forms correspond to sustained release forms, having, respectively, 0.015 to 4.5, 0.03 to 4.5, 0.3 to 4.5, 0.6 to 4.5, 0.9 to 4.5, 1.2 to 4.5, 1.5 to 4.5, 1.8 to 4.5, 2.1 to 4.5, 2.4 to 4.5, 3.0 to 4.5, 0.9 to 1.8, or about 1.5 mgs of an mTOR inhibitor, e.g., an allosteric mTOR inhibitor, e.g., rapamycin or RAD001. For once per week administrations, these immediate release forms correspond to sustained release forms, having, respectively, 0.1 to 30, 0.2 to 30, 2 to 30, 4 to 30, 6 to 30, 8 to 30, 10 to 30, 1.2 to 30, 14 to 30, 16 to 30, 20 to 30, 6 to 12, or about 10 mgs of an mTOR inhibitor, e.g., an allosteric mTOR inhibitor, e.g., rapamycin or RAD001.

In an embodiment, immediate release forms, e.g., of RAD001, typically used for one administration per day, having having 0.01 to 1.0 mgs per unit dosage form, are provided. For once per day administrations, these immediate release forms correspond to sustained release forms, having, respectively, 0.03 to 3 mgs of an mTOR inhibitor, e.g., an allosteric mTOR inhibitor, e.g., rapamycin or RAD001.For once per week administrations, these immediate release forms correspond to sustained release forms, having, respectively, 0.2 to 20 mgs of an mTOR inhibitor, e.g., an allosteric mTOR inhibitor, e.g., rapamycin or RAD001.

In an embodiment, immediate release forms, e.g., of RAD001, typically used for one administration per week, having having 0.5 to 5.0 mgs per unit dosage form, are provided. For once per week administrations, these immediate release forms correspond to sustained release

forms, having, respectively, 1.5 to 15 mgs of an mTOR inhibitor, e.g., an allosteric mTOR inhibitor, e.g., rapamycin or RAD001.

As described above, one target of the mTOR pathway is the P70 S6 kinase. Thus, doses of mTOR inhibitors which are useful in the methods and compositions described herein are those which are sufficient to achieve no greater than 80% inhibition of P70 S6 kinase activity relative to the activity of the P70 S6 kinase in the absence of an mTOR inhibitor, e.g., as measured by an assay described herein, e.g., the Boulay assay. In a further aspect, the invention provides an amount of an mTOR inhibitor sufficient to achieve no greater than 38% inhibition of P70 S6 kinase activity relative to P70 S6 kinase activity in the absence of an mTOR inhibitor.

In one aspect the dose of mTOR inhibitor useful in the methods and compositions of the invention is sufficient to achieve, e.g., when administered to a human subject, 90 +/-5 % (i.e., 85-95%), 89+/-5 %, 88+/-5 %, 87+/-5 %, 86+/-5 %, 85+/-5 %, 84+/-5 %, 83+/-5 %, 82+/-5 %, 81+/-5 %, 80+/-5 %, 79+/-5 %, 78+/-5 %, 77+/-5 %, 76+/-5 %, 75+/-5 %, 74+/-5 %, 73+/-5 %, 72 +/-5%, 71 +/-5%, 70 +/-5%, 69 +/-5%, 68 +/-5%, 67 +/-5%, 66 +/-5%, 65 +/-5%, 64 +/-5%, 63 +/-5%, 62 +/-5%, 61 +/-5%, 60 +/-5%, 59 +/-5%, 58 +/-5%, 57 +/-5%, 56 +/-5%, 55 +/-5%, 54 +/-5%, 54 +/-5%, 53 +/-5%, 52 +/-5%, 51 +/-5%, 50 +/-5%, 49 +/-5%, 48 +/-5%, 47 +/-5%, 46 +/-5%, 45 +/-5%, 44 +/-5%, 43 +/-5%, 42 +/-5%, 41 +/-5%, 40 +/-5%, 39 +/-5%, 38 +/-5%, 37 +/-5%, 36 +/-5%, 35 +/-5%, 34 +/-5%, 33 +/-5%, 32 +/-5%, 31 +/-5%, 30 +/-5%, 29 +/-5%, 28 +/-5%, 27 +/-5%, 26 +/-5%, 25 +/-5%, 24 +/-5%, 23 +/-5%, 22 +/-5%, 21 +/-5%, 20 +/-5%, 19 +/-5%, 18 +/-5%, 17 +/-5%, 16 +/-5%, 15 +/-5%, 14 +/-5%, 13 +/-5%, 12 +/-5%, 11 +/-5%, or 10 +/-5%, inhibition of P70 S6 kinase activity , e.g., as measured by an assay described herein, e.g., the Boulay assay.

P70 S6 kinase activity in a subject may be measured using methods known in the art, such as, for example, according to the methods described in U.S. Pat. 7,727,950, by immunoblot analysis of phosphoP70 S6K levels and/or phosphoP70 S6 levels or by in vitro kinase activity assays.

As used herein, the term "about" in reference to a dose of mTOR inhibitor refers to up to a +/- 10% variability in the amount of mTOR inhibitor, but can include no variability around the stated dose.

In some embodiments, the invention provides methods comprising administering to a subject an mTOR inhibitor, e.g., an allosteric inhibitor, e.g., RAD001, at a dosage within a target

trough level. In some embodiments, the trough level is significantly lower than trough levels associated with dosing regimens used in organ transplant and cancer patients. In an embodiment mTOR inhibitor, e.g., RAD001, or rapamycin, is administerd to result in a trough level that is less than ½, 1/4, 1/10, or 1/20 of the trough level that results in immunosuppression or an anticancer effect. In an embodiment mTOR inhibitor, e.g., RAD001, or rapamycin, is administerd to result in a trough level that is less than ½, 1/4, 1/10, or 1/20 of the trough level provided on the FDA approved packaging insert for use in immunosuppression or an anticancer indications.

In an embodiment a method disclosed herein comprises administering to a subject an mTOR inhibitor, e.g., an allosteric inhibitor, e.g., RAD001, at a dosage that provides a target trough level of 0.1 to 10 ng/ml, 0.1 to 5 ng/ml, 0.1 to 3ng/ml, 0.1 to 2 ng/ml, or 0.1 to 1 ng/ml.

In an embodiment a method disclosed herein comprises administering to a subject an mTOR inhibitor, e.g., an allosteric inhibitor, e.g., RAD001, at a dosage that provides a target trough level of 0.2 to 10 ng/ml, 0.2 to 5 ng/ml, 0.2 to 3ng/ml, 0.2 to 2 ng/ml, or 0.2 to 1 ng/ml.

In an embodiment a method disclosed herein comprises administering to a subject an mTOR inhibitor, e.g. an, allosteric inhibitor, e.g., RAD001, at a dosage that provides a target trough level of 0.3 to 10 ng/ml, 0.3 to 5 ng/ml, 0.3 to 3ng/ml, 0.3 to 2 ng/ml, or 0.3 to 1 ng/ml.

In an embodiment a method disclosed herein comprises administering to a subject an mTOR inhibitor, e.g., an allosteric inhibitor, e.g., RAD001, at a dosage that provides a target trough level of 0.4 to 10 ng/ml, 0.4 to 5 ng/ml, 0.4 to 3ng/ml, 0.4 to 2 ng/ml, or 0.4 to 1 ng/ml.

In an embodiment a method disclosed herein comprises administering to a subject an mTOR inhibitor, e.g., an allosteric inhibitor, e.g., RAD001, at a dosage that provides a target trough level of 0.5 to 10 ng/ml, 0.5 to 5 ng/ml, 0.5 to 3ng/ml, 0.5 to 2 ng/ml, or 0.5 to 1 ng/ml.

In an embodiment a method disclosed herein comprises administering to a subject an mTOR inhibitor, e.g., an allosteric inhibitor, e.g., RAD001, at a dosage that provides a target trough level of 1 to 10 ng/ml, 1 to 5 ng/ml, 1 to 3ng/ml, or 1 to 2 ng/ml.

As used herein, the term "trough level" refers to the concentration of a drug in plasma just before the next dose, or the minimum drug conce ntration between two doses.

In some embodiments, a target trough level of RAD001 is in a range of between about 0.1 and 4.9 ng/ml. In an embodiment, the target trough level is below 3ng/ml, e.g., is between

0.3 or less and 3 ng/ml. In an embodiment, the target trough level is below 3ng/ml, e.g., is between 0.3 or less and 1 ng/ml.

In a further aspect, the invention can utilize an mTOR inhibitor other than RAD001 in an amount that is associated with a target trough level that is bioequivalent to the specified target trough level for RAD001. In an embodiment, the target trough level for an mTOR inhibitor other than RAD001, is a level that gives the same level of mTOR inhibition (e.g., as measured by a method described herein, e.g., the inhibition of P70 S6) as does a trough level of RAD001 described herein.

Pharmaceutical compositions: mTOR Inhibitors

In one aspect, the present invention relates to pharmaceutical compositions comprising an mTOR inhibitor, e.g., an mTOR inhibitor as described herein, formulated for use in combination with CAR cells described herein.

In some embodiments, the mTOR inhibitor is formulated for administration in combination with an additional, e.g., as described herein.

In general, compounds of the invention will be administered in therapeutically effective amounts as described above via any of the usual and acceptable modes known in the art, either singly or in combination with one or more therapeutic agents.

The pharmaceutical formulations may be prepared using conventional dissolution and mixing procedures. For example, the bulk drug substance (e.g., an mTOR inhibitor or stabilized form of the compound (e.g., complex with a cyclodextrin derivative or other known complexation agent) is dissolved in a suitable solvent in the presence of one or more of the excipients described herein. The mTOR inhibitor is typically formulated into pharmaceutical dosage forms to provide an easily controllable dosage of the drug and to give the patient an elegant and easily handleable product.

Compounds of the invention can be administered as pharmaceutical compositions by any conventional route, in particular enterally, e.g., orally, e.g., in the form of tablets or capsules, or parenterally, e.g., in the form of injectable solutions or suspensions, topically, e.g., in the form of lotions, gels, ointments or creams, or in a nasal or suppository form. Where an mTOR inhibitor is administered in combination with (either simultaneously with or separately from) another agent as described herein, in one aspect, both components can be administered by the same route

(e.g., parenterally). Alternatively, another agent may be administered by a different route relative to the mTOR inhibitor. For example, an mTOR inhibitor may be administered orally and the other agent may be administered parenterally.

SUSTAINED RELEASE

mTOR inhibitors, e.g., allosteric mTOR inhibitors or catalytic mTOR inhibitors, disclosed herein can be provided as pharmaceutical formulations in form of oral solid dosage forms comprising an mTOR inhibitor disclosed herein, e.g., rapamycin or RAD001, which satisfy product stability requirements and/or have favorable pharmacokinetic properties over the immediate release (IR) tablets, such as reduced average plasma peak concentrations, reduced inter- and intra-patient variability in the extent of drug absorption and in the plasma peak concentration, reduced C_{max} / C_{min} ratio and/or reduced food effects. Provided pharmaceutical formulations may allow for more precise dose adjustment and/or reduce frequency of adverse events thus providing safer treatments for patients with an mTOR inhibitor disclosed herein, e.g., rapamycin or RAD001.

In some embodiments, the present disclosure provides stable extended release formulations of an mTOR inhibitor disclosed herein, e.g., rapamycin or RAD001, which are multi-particulate systems and may have functional layers and coatings.

The term "extended release, multi-particulate formulation as used herein refers to a formulation which enables release of an mTOR inhibitor disclosed herein, e.g., rapamycin or RAD001, over an extended period of time e.g. over at least 1, 2, 3, 4, 5 or 6 hours. The extended release formulation may contain matrices and coatings made of special excipients, e.g., as described herein, which are formulated in a manner as to make the active ingredient available over an extended period of time following ingestion.

The term "extended release" can be interchangeably used with the terms "sustained release" (SR) or "prolonged release". The term "extended release" relates to a pharmaceutical formulation that does not release active drug substance immediately after oral dosing but over an extended in accordance with the definition in the pharmacopoeias Ph. Eur. (7^{th} edition) mongraph for tablets and capsules and USP general chapter <1151> for pharmaceutical dosage forms. The term "Immediate Release" (IR) as used herein refers to a pharmaceutical formulation which releases 85% of the active drug substance within less than 60 minutes in accordance with the definition of "Guidance for Industry: "Dissolution Testing of Immediate Release Solid Oral

Dosage Forms" (FDA CDER, 1997). In some embodiments, the term "immediate release" means release of everolismus from tablets within the time of 30 minutes, e.g., as measured in the dissolution assay described herein.

Stable extended release formulations of an mTOR inhibitor disclosed herein, e.g., rapamycin or RAD001, can be characterized by an in-vitro release profile using assays known in the art, such as a dissolution assay as described herein: a dissolution vessel filled with 900 mL phosphate buffer pH 6.8 containing sodium dodecyl sulfate 0.2% at 37°C and the dissolution is performed using a paddle method at 75 rpm according to USP by according to USP testing monograph 711, and Ph.Eur. testing monograph 2.9.3. respectively.

In some embodiments, stable extended release formulations of an mTOR inhibitor disclosed herein, e.g., rapamycin or RAD001, release the mTOR inhibitor in the in-vitro release assay according to following release specifications:

0.5h: <45%, or <40, e.g., <30%

1h: 20-80%, e.g., 30-60%

2h: >50%, or >70%, e.g., >75%

3h: >60%, or >65%, e.g., >85%, e.g., >90%.

In some embodiments, stable extended release formulations of an mTOR inhibitor disclosed herein, e.g., rapamycin or RAD001, release 50% of the mTOR inhibitor not earlier than 45, 60, 75, 90, 105 min or 120 min in the in-vitro dissolution assay.

Biopolymer delivery methods

In some embodiments, one or more CAR-expressing cells as disclosed herein can be administered or delivered to the subject via a biopolymer scaffold, e.g., a biopolymer implant. Biopolymer scaffolds can support or enhance the delivery, expansion, and/or dispersion of the CAR-expressing cells described herein. A biopolymer scaffold comprises a biocompatible (e.g., does not substantially induce an inflammatory or immune response) and/or a biodegradable polymer that can be naturally occurring or synthetic.

Examples of suitable biopolymers include, but are not limited to, agar, agarose, alginate, alginate/calcium phosphate cement (CPC), beta-galactosidase (β-GAL), (1 ,2,3,4,6-pentaacetyl a-D-galactose), cellulose, chitin, chitosan, collagen, elastin, gelatin, hyaluronic acid collagen, hydroxyapatite, poly(3-hydroxybutyrate-co-3-hydroxy-hexanoate) (PHBHHx), poly(lactide),

poly(caprolactone) (PCL), poly(lactide-co-glycolide) (PLG), polyethylene oxide (PEO), poly(lactic-co-glycolic acid) (PLGA), polypropylene oxide (PPO), polyvinyl alcohol) (PVA), silk, soy protein, and soy protein isolate, alone or in combination with any other polymer composition, in any concentration and in any ratio. The biopolymer can be augmented or modified with adhesion- or migration-promoting molecules, e.g., collagen-mimetic peptides that bind to the collagen receptor of lymphocytes, and/or stimulatory molecules to enhance the delivery, expansion, or function, e.g., anti-cancer activity, of the cells to be delivered. The biopolymer scaffold can be an injectable, e.g., a gel or a semi-solid, or a solid composition.

In some embodiments, CAR-expressing cells described herein are seeded onto the biopolymer scaffold prior to delivery to the subject. In embodiments, the biopolymer scaffold further comprises one or more additional therapeutic agents described herein (e.g., another CAR-expressing cell, an antibody, or a small molecule) or agents that enhance the activity of a CAR-expressing cell, e.g., incorporated or conjugated to the biopolymers of the scaffold. In embodiments, the biopolymer scaffold is injected, e.g., intratumorally, or surgically implanted at the tumor or within a proximity of the tumor sufficient to mediate an anti-tumor effect. Additional examples of biopolymer compositions and methods for their delivery are described in Stephan et al., *Nature Biotechnology*, 2015, 33:97-101; and WO2014/110591.

Pharmaceutical compositions and treatments

Pharmaceutical compositions of the present invention may comprise a CAR-expressing cell, e.g., a plurality of CAR-expressing cells, as described herein, in combination with one or more pharmaceutically or physiologically acceptable carriers, diluents or excipients. Such compositions may comprise buffers such as neutral buffered saline, phosphate buffered saline and the like; carbohydrates such as glucose, mannose, sucrose or dextrans, mannitol; proteins; polypeptides or amino acids such as glycine; antioxidants; chelating agents such as EDTA or glutathione; adjuvants (e.g., aluminum hydroxide); and preservatives. Compositions of the present invention are in one aspect formulated for intravenous administration.

Pharmaceutical compositions of the present invention may be administered in a manner appropriate to the disease to be treated (or prevented). The quantity and frequency of administration will be determined by such factors as the condition of the patient, and the type

and severity of the patient's disease, although appropriate dosages may be determined by clinical trials.

In one embodiment, the pharmaceutical composition is substantially free of, e.g., there are no detectable levels of a contaminant, e.g., selected from the group consisting of endotoxin, mycoplasma, replication competent lentivirus (RCL), p24, VSV-G nucleic acid, HIV gag, residual anti-CD3/anti-CD28 coated beads, mouse antibodies, pooled human serum, bovine serum albumin, bovine serum, culture media components, vector packaging cell or plasmid components, a bacterium and a fungus. In one embodiment, the bacterium is at least one selected from the group consisting of Alcaligenes faecalis, Candida albicans, Escherichia coli, Haemophilus influenza, Neisseria meningitides, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pneumonia, and Streptococcus pyogenes group A.

When "an immunologically effective amount," "an anti-tumor effective amount," "a tumor-inhibiting effective amount," or "therapeutic amount" is indicated, the precise amount of the compositions of the present invention to be administered can be determined by a physician with consideration of individual differences in age, weight, tumor size, extent of infection or metastasis, and condition of the patient (subject). It can generally be stated that a pharmaceutical composition comprising the immune effector cells (e.g., T cells, NK cells) described herein may be administered at a dosage of 10^4 to 10^9 cells/kg body weight, in some instances 10^5 to 10^6 cells/kg body weight, including all integer values within those ranges. T cell compositions may also be administered multiple times at these dosages. The cells can be administered by using infusion techniques that are commonly known in immunotherapy (see, e.g., Rosenberg et al., New Eng. J. of Med. 319:1676, 1988).

In certain aspects, it may be desired to administer activated immune effector cells (e.g., T cells, NK cells) to a subject and then subsequently redraw blood (or have an apheresis performed), activate immune effector cells (e.g., T cells, NK cells) therefrom according to the present invention, and reinfuse the patient with these activated and expanded immune effector cells (e.g., T cells, NK cells). This process can be carried out multiple times every few weeks. In certain aspects, immune effector cells (e.g., T cells, NK cells) can be activated from blood draws of from 10cc to 400cc. In certain aspects, immune effector cells (e.g., T cells, NK cells) are activated from blood draws of 20cc, 30cc, 40cc, 50cc, 60cc, 70cc, 80cc, 90cc, or 100cc.

The administration of the subject compositions may be carried out in any convenient manner, including by aerosol inhalation, injection, ingestion, transfusion, implantation or transplantation. The compositions described herein may be administered to a patient trans arterially, subcutaneously, intradermally, intratumorally, intranodally, intramedullary, intramuscularly, by intravenous (i.v.) injection, or intraperitoneally. In one aspect, the T cell compositions of the present invention are administered to a patient by intradermal or subcutaneous injection. In one aspect, the T cell compositions of the present invention are administered by i.v. injection. The compositions of immune effector cells (e.g., T cells, NK cells) may be injected directly into a tumor, lymph node, or site of infection.

In a particular exemplary aspect, subjects may undergo leukapheresis, wherein leukocytes are collected, enriched, or depleted ex vivo to select and/or isolate the cells of interest, e.g., T cells. These T cell isolates may be expanded by methods known in the art and treated such that one or more CAR constructs of the invention may be introduced, thereby creating a CAR T cell of the invention. Subjects in need thereof may subsequently undergo standard treatment with high dose chemotherapy followed by peripheral blood stem cell transplantation. In certain aspects, following or concurrent with the transplant, subjects receive an infusion of the expanded CAR T cells of the present invention. In an additional aspect, expanded cells are administered before or following surgery.

The dosage of the above treatments to be administered to a patient will vary with the precise nature of the condition being treated and the recipient of the treatment. The scaling of dosages for human administration can be performed according to art-accepted practices. The dose for CAMPATH, for example, will generally be in the range 1 to about 100 mg for an adult patient, usually administered daily for a period between 1 and 30 days. The preferred daily dose is 1 to 10 mg per day although in some instances larger doses of up to 40 mg per day may be used (described in U.S. Patent No. 6,120,766).

In one embodiment, the CAR is introduced into immune effector cells (e.g., T cells, NK cells), e.g., using in vitro transcription, and the subject (e.g., human) receives an initial administration of CAR immune effector cells (e.g., T cells, NK cells) of the invention, and one or more subsequent administrations of the CAR immune effector cells (e.g., T cells, NK cells) of the invention, wherein the one or more subsequent administrations are administered less than 15 days, e.g., 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, or 2 days after the previous administration. In one

embodiment, more than one administration of the CAR immune effector cells (e.g., T cells, NK cells) of the invention are administered to the subject (e.g., human) per week, e.g., 2, 3, or 4 administrations of the CAR immune effector cells (e.g., T cells, NK cells) of the invention are administered per week. In one embodiment, the subject (e.g., human subject) receives more than one administration of the CAR immune effector cells (e.g., T cells, NK cells) per week (e.g., 2, 3 or 4 administrations per week) (also referred to herein as a cycle), followed by a week of no CAR immune effector cells (e.g., T cells, NK cells) administrations, and then one or more additional administration of the CAR immune effector cells (e.g., T cells, NK cells) (e.g., more than one administration of the CAR immune effector cells (e.g., T cells, NK cells) per week) is administered to the subject. In another embodiment, the subject (e.g., human subject) receives more than one cycle of CAR immune effector cells (e.g., T cells, NK cells), and the time between each cycle is less than 10, 9, 8, 7, 6, 5, 4, or 3 days. In one embodiment, the CAR immune effector cells (e.g., T cells, NK cells) are administered every other day for 3 administrations per week. In one embodiment, the CAR immune effector cells (e.g., T cells, NK cells) of the invention are administered for at least two, three, four, five, six, seven, eight or more weeks.

In one aspect, CAR-expressing cells of the present inventions are generated using lentiviral viral vectors, such as lentivirus. Cells, e.g., CARTs, generated that way will have stable CAR expression.

In one aspect, CAR-expressing cells, e.g., CARTs, are generated using a viral vector such as a gammaretroviral vector, e.g., a gammaretroviral vector described herein. CARTs generated using these vectors can have stable CAR expression.

In one aspect, CARTs transiently express CAR vectors for 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 days after transduction. Transient expression of CARs can be effected by RNA CAR vector delivery. In one aspect, the CAR RNA is transduced into the T cell by electroporation.

A potential issue that can arise in patients being treated using transiently expressing CAR immune effector cells (e.g., T cells, NK cells) (particularly with murine scFv bearing CARTs) is anaphylaxis after multiple treatments.

Without being bound by this theory, it is believed that such an anaphylactic response might be caused by a patient developing humoral anti-CAR response, i.e., anti-CAR antibodies having an anti-IgE isotype. It is thought that a patient's antibody producing cells undergo a class

switch from IgG isotype (that does not cause anaphylaxis) to IgE isotype when there is a ten to fourteen day break in exposure to antigen.

If a patient is at high risk of generating an anti-CAR antibody response during the course of transient CAR therapy (such as those generated by RNA transductions), CART infusion breaks should not last more than ten to fourteen days.

EXAMPLES

The invention is further described in detail by reference to the following experimental examples. These examples are provided for purposes of illustration only, and are not intended to be limiting unless otherwise specified. Thus, the invention should in no way be construed as being limited to the following examples, but rather, should be construed to encompass any and all variations which become evident as a result of the teaching provided herein.

Treatment of Patient with CLL with CART19

Patient UPCC04409-10 was treated with autologous CART19 T cells for CLL. The treatment led to complete remission of the CLL.

Analysis of CART cell population

As shown in FIG. 1, CART cells in patient UPCC04409-10 were monitored over time by sampling blood. The amount of BBZ expression in cells was determined (red). The number of copies of sequence from the Vbeta5.1 TCR family was determined (blue). Both measurements were made from samples collected on the indicated days after the second infusion of CART cells. As shown in FIG2, the T-cell receptor repertoire from patient UPCC04409-10 was determined from a sample collected on day 28 (FIG. 2A) or day 51 (FIG. 2B) after CART infusion. This demonstrates the abundance of the TCRBV05-01 family of T-cell receptors at day 51 indicating clonal expansion over time. As shown in FIG. 3, The T-cells isolated from patient UPCC04409-10 were analyzed for the simultaneous expression of CAR19 and 2 different TCR family genes over time (day 50 and day 51) and compared to the input dosed material (product): upper panel is TCR family Vb13.1; the lower panel shows TCR family Vb5.1. The data demonstrate that the CAR19 positive cells contain a single TCR family gene (Vb5.1) that becomes rapidly enriched between days 50 and 51. As shown in FIG. 4, the T-cell receptor

repertoire of CD8 positive cells from patient UPCC04409-10 was determined from a sample collected on day 51 after CART infusion. This demonstrates the abundance of the TCRBV05-01 family of T-cell receptors at day 51 indicating clonal expansion of CD8 positive cells over time.

Analysis of Persisting CART Clone

As shown in FIG. 6, sonically fragmented DNA was generated from T-cells from Patient #. This material was used to amplify genomic sequences adjacent to the CAR19 insertion. The genes indicated were identified as being enriched relative to the infused product (D0) adjacent to CAR19 in the genome. At the different time points after CART infusion indicated (d=day; m=month), a different relative abundance of adjacent genes was seen, with Tet2 abundance peaking in both peripheral blood (PBMC) and CAR+CD8+ T-cells samples at day 51.

As shown in FIG. 7, the site of insertion of the CAR19 gene was mapped to the Tet2 gene. More specifically, the insertion occurred between exons 9 and 10 of the Tet2 gene. The catalytic domain for Tet2 resides in exon 11. The insertion at this location may lead to expression of aberrant mRNA transcripts or decrease the expression of functional (wild-type) Tet2.

As shown in FIG. 8, transcripts of the Tet2 gene from mRNA isolated from patient UPCC04409-10 were evaluated by RTPCR using primers spanning the indicated regions of Tet2 or CAR19 or both as indicated in the right hand side of the figure. Rxn 3 contains primers designed to amplify the region of the Tet2 transcript spanning exons 9 and 10. Rxn, 6, 7, 8, 9, and 10 are primers designed to amplify the indicated portions of the CAR19 lentivirus. Rxn 12-16 are pairs of primers that contain exon 9 sequence of the Tet2 transcript as well as sequence from the CAR19 lentiviral construct. These data show that transcripts are made from the Tet2 locus that contains both Tet2 sequence as well as CAR19 sequence.

Analysis of Tet2 Function

As shown in FIG. 10, the enzymatic activity of Tet2 is schematized (FIG. 10A). Tet family protein convert 5-methylcytosine (5-mc) to 5-hydroxymethylcytosine (5-hmc) and then into 5-formylcytosine (5-fmc) resulting in demethylated cytosine. Methylated DNA is an epigenetic state that is known to affect transcriptional profiles. The methylation state of the T-cells from patient UPCC04409-10 was evaluated (FIG. 10B). The patient's T-cells were stained

for TCRVb5.1 (which contain the CAR19 insertion at Tet2) and the 5-hmc and 5-fmc were evaluated in TCRVb5.1 positive (red) and TCRVb5.1 negative (blue) populations by flow cytometry. This data indicates that the cells containing the insertion of CAR19 in the Tet2 gene are defective in demethylation.

Treatment of T cells with shRNA Tet2 Inhibitors

Materials and methods

Lenti-viral preparation and infection to the Jurkat cells

Lenti-viruses were prepared from 15cm 293T cells. Briefly, 10 million 293T cells were seeded onto collagen coated 15cm dishes at day -1. At day 0, 15ug shRNA vector (i.e., vector comprising sequence encoding the TET2-targeting or control shRNA), 15ug Gag/pol vector, and 5ug VSV-G vector were transfected using Lipofectamin 2000 (Invitrogen). 24 hours later (day 1), media was changed. After changing media, viral supernants were harvested at day 2 and day 3. Viruses were concentrated with Lenti-X concentrator (3:1 volume ratio, Clonetech, Cat#: 631231). 100ul of viruses were added into either 0.5 million jurkat cells in the presence of 6 ug/ml of polybrene. The cells were spin-infected at 2000 rpm, 90 min at 32°C. After 1 hour incubation at 37 degree incubator, fresh RPMI 1640 media were added and transferred into 24-well plate. At day 6, cells were transferred into 6-well plate in the presence of final concentration 2 ug/ml of puromycin for 6 days.

Antibodies

Antibodies used for western blotting were as follows: β-actin (clone#: 8H10D10, Cell Signaling); TET2 (clone#: hT2H21F11, Millipore); mouse IgG(H+L) (HRP conjugated, Cat#: 115-035-166, Jackson ImmunoResearch); rabbit IgG(H+L) (HRP conjugated, Cat#: 111-035-114, Jackson ImmunoResearch).

Western blotting

To examine TET2 shRNA knockdown efficiency at protein level in jurkat cells, cell lysates were prepared in protease inhibitor cocktails (Sigma) containing RIPA buffer. Protein concentration was measured by BCA protein assay kits (Pierce, Item#: 3603904). 20ug of protein was subjected to SDS-PAGE followed by transferring protein onto nitrocellulose membrane using iBot transfer system (Invitrogen, 20V, 11min 30sec). The membrane was blocked in 5% BSA containing TBST for 30min at room temperature. Antibodies were overnight

incubated with membranes at 1:000 dilution at 4°C. After incubation with HRP conjugated secondary antibodies, signal was detected using chemiluminescence detection machine (Chemidoc; Bio-Rad).

Quantitative RT-PCR

To examine TET2 shRNA knock-down efficiency at DNA level in jurkat cells, quantitative reverse transcription polymerase chain reaction (qRT-PCR) was performed. A RNeasy Micro Kit (Qiagen) was used to extract RNA. mRNA was reverse transcribed to single-strand complementary DNA (cDNA) with SuperScript III First-Strand Synthesis System for RT-PCR (Invitrogen). Real-time PCR was performed with C1000 Touch Thermal Cycler (Biorad). A SYBR-based protocol was used to detect gene expression (SsoAdvanced Universal SYBR Green Supermix, Biorad). The PCR reactions were done in 96-well plates and run using the manufacture's recommended cycling parameters with triplicate (95°C for 3 minutes, followed by 40 cycles of 95°C for 15 seconds and 60°C for 30 seconds). Cycle threshold (Ct) values for the genes of interest were normalized to the Ct for β-actin. Primers used for qRT-PCR were as follows: β-actin #1 (fowrard primer: CAT GTA CGT TGC TAT CCA GGC (SEQ ID NO: 1263), reverse primer: CTC CTT AAT GTC ACG CAC GAT (SEQ ID NO: 1264); product size 250 bp); β-actin #2 (fowrard primer: CTC ACC ATG GAT GAT GAT ATC GC (SEQ ID NO: 1265), reverse primer: CCA CAT AGG AAT CCT TCT GAC CC (SEQ ID NO: 1266); product size 169 bp); TET1 (forward primer: CAG AAC CTA AAC CAC CCG TG (SEQ ID NO: 1267), reverse primer: TGC TTC GTA GCG CCA TTG TAA (SEQ ID NO: 1268); product size 141 bp); TET2 (forward primer: ATA CCC TGT ATG AAG GGA AGC C (SEQ ID NO: 1269), reverse primer: CTT ACC CCG AAG TTA CGT CTT TC (SEQ ID NO: 1270); product size 197 bp); TET3 (forward primer: CAC CCG GCT CTA TGA AAC CTT (SEQ ID NO: 1271), reverse primer: CCA GCC ACT CGA GGT AGT CA (SEQ ID NO: 1272); product size 209 bp); RPLP1 (Cat#: PPH17813G-200, Qiagen).

Flow cytometry

The cells were acquired on a FACS Fortessa (BD). Data processing for presentation was done using FlowJo (Treestar Inc.) program.

Results

Validation of Knockdown Efficiency of Tet2 shRNAs

As shown in FIG. 27, the validation of knockdown efficiency of TET2 shRNAs is schematized. TET2 and scramble control shRNA constructs expressing Red Fluorescence Protein (RPF) and puromycin resistant gene were introduced into jurkat cells to validate knockdown efficiency of TET2 shRNAs by qRT-PCR and western blot experiments.

As shown in FIG. 28, shRNA infected jurkat cells express RFP. RFP expression was determined by FACS on day 6 after puromycin treatment. Based on RFP expression, greater than 99% shRNA introduced jurkat cells were selected by puromycin treatment. Of note, TET2 shRNA #3 and #4 infected jurkat cells did not grow in the presence of puromycin. Therefore, TET2 shRNA #3 and #4 infected jurkat cells were not processed further. This data indicates that puromycin is effective to select shRNA infected jurkat cells.

As shown in FIG. 29, knockdown efficiency of *tet2* depends on shRNAs. To determine mRNA expression level of *tet1* and *tet2* and *tet3* in TET2 shRNAs infected jurkat cells, qRT-PCR experiment was performed. Compared to scramble shRNA, TET2 shRNA #1, #2, #8, and #9 knockdown *tet2* gene at 35.6%, 22.7%, 21.6%, and 76.7% respectively. Surprisingly, while TET2 shRNA #9 knocks down *tet2* efficiently, it also down-regulates *tet1* and *tet3* expression at 43.4% and 67.3% respectively. β-actin serves as an internal control to quantify relative gene expression among samples tested. To increase reliability of qRT-PCR, two β-actin primers and one RPLP1 primer were used in this experiment. This data indicates that several TET2-targeting shRNA are capable of reducing mRNA levels of TET2, with shRNA#9 showing the most robust knockdown effect of *tet2,* while also affecting levels of TET1 and TET2.

As shown in FIG. 30, knockdown of TET2 protein in response to shRNAs correlates with knockdown of TET2 mRNA levels. To determine protein expression level of TET2 in TET2 shRNAs infected jurkat cells, a western blot experiment was performed. Similar to qRT-PCR data as shown in FIG.29, TET2 shRNA #1, #2, #8, and #9 reduce TET2 protein level compared to scramble shRNA, while β-actin is constitutively expressed in all samples tested. This data indicates that several TET2-targeting shRNA are capable of reducing TET2 protein levels in Jurkat cells, with shRNA#9 showing the most robust knockdown effect of Tet2.

Treatment of primary T cells with shRNA Tet2 Inhibitors

As shown in FIG. 11, TET2 shRNAs reduce 5-hmc levels in normal human T cells. TET2 and scramble control shRNA constructs expressing mCherry were introduced into normal human T cells. 5-hmc levels were determined by intracellular staining by FACS on day 6 following expansion with anti-CD3/CD28 beads. Knockdown of TET2 reduced overall 5-hmc levels.

As shown in FIG. 12, TET2 shRNAs expand Tscm T cells. TET2 and scramble control shRNA constructs expressing mCherry were introduced into normal human T cells. CD45RA+CD62L+CCR7+CD27+CD95+ Tscm T cells were determined by FACS staining on day 11 following expansion with anti-CD3/CD28 beads. Knockdown of TET2 promoted the expansion of T cells with a Tscm phenotype.

Tet2 Inhibition in CAR T Cells Using CRISPR/Cas Gene Editing Systems

In this example, inhibiton of TET2 was explored in chimeric antigen receptor (CAR)-expressing T cells.

Methods

Guide RNA molecules

gRNA molecules comprising the targeting sequences listed in Table 5 were used for the experiments described in this subexample. Unless otherwise indicated, all gRNA molecules were tested as dual gRNA molecules comprising the tracr and crRNA sequences described in this subexample.

Table 5

Target Region	TET2 gRNA targeting sequence	guide reference
Exon 9	CAGAGCACCAGAGUGCCGUC (SEQ ID NO: 1273)	9_1 (also referred to as Tet2_E9_1_Tet2)
Exon 9	AGAGCACCAGAGUGCCGUCU (SEQ ID NO: 1274)	9_2 (also referred to as Tet2_E9_2_Tet2)
Exon 9	UUCAGACCCAGACGGCACUC (SEQ ID NO: 1275)	9_3 (also referred to as Tet2_E9_3_Tet2)
Exon 9	AUGGCAGCACAUUGGUAAGU (SEQ ID NO: 1276)	9_4 (also referred to as Tet2_E9_4_Tet2)
Exon 9	CACAUUGGUAAGUUGGGCUG (SEQ ID NO: 1277)	9_5 (also referred to as Tet2_E9_5_Tet2)
Exon 9	GACUUGCACAACAUGCAGAA (SEQ ID NO: 1278)	9_6 (also referred to as Tet2_E9_5_Tet2, Ex9-3 or crEx9-3)

exon 7	UCAUGGAGCAUGUACUACAA (SEQ ID NO: 1279)	7_1
exon 7	AACUUGCGCCUGUCAGGGGC (SEQ ID NO: 1280)	7_2
exon 7	CCAAGGAAGUUUAAGCUGCU (SEQ ID NO: 1281)	7_3
exon 7	CCAAGCAGCUUAAACUUCCU (SEQ ID NO: 1282)	7_4
exon 8	UUGGUGCCAUAAGAGUGGAC (SEQ ID NO: 1283)	8_1
exon 8	GCAAAACCUGUCCACUCUUA (SEQ ID NO: 1284)	8_2
exon 8	AUAUGUUGGUGCCAUAAGAG (SEQ ID NO: 1285)	8_3
exon 10	AAAACGGAGUGGUGCCAUUC (SEQ ID NO: 1286)	10_1
exon 10	GUCUCUGACGUGGAUGAGUU (SEQ ID NO: 1287)	10_2
exon 10	UUUAUACAAAGUCUCUGACG (SEQ ID NO: 1288)	10_3
exon 10	AGAGAAGACAAUCGAGAAUU (SEQ ID NO: 1289)	10_4
exon 10	ACGUCAGAGACUUUGUAUAA (SEQ ID NO: 1290)	10_5
exon 3	GGAUAGAACCAACCAUGUUG (SEQ ID NO: 1291)	3_1 (also referred to as Tet2_E3_1_Tet2)
exon 3	UUGUAGCCAGAGGUUCUGUC (SEQ ID NO: 1292)	3_2 (also referred to as Tet2_E3_2_Tet2)
exon 3	UCUGUUGCCCUCAACAUGGU (SEQ ID NO: 1293)	3_3 (also referred to as Tet2_E3_3_Tet2, Ex3-3 or crEx3-3)
exon 3	GAUAGAACCAACCAUGUUGA (SEQ ID NO: 1294)	3_4 (also referred to as Tet2_E3_4_Tet2)
exon 3	UUCUGGAGCUUUGUAGCCAG (SEQ ID NO: 1295)	3_5 (also referred to as Tet2_E3_5_Tet2)

Generation of CRISPR CAR T cells

Isolated and frozen Pan T cells were thawed and activated with CD3/CD28 beads (CD3/CD28 CTS Dynabeads® 43205D) on day 0. Activated T cells were transduced with lentivirus encoding either a BCMA CAR (BCMA-10 (139109) as described in WO2016/0046724; referred to herein as BCMA-10 CAR) or CD19 CAR (the CD19 CAR having the amino acid sequence of SEQ ID NO: 12 of WO2012/079000; referred to herein as CD19

CAR) on day 1. On day 3, transduced CAR T cells were electroporated to introduce CRISPR/Cas systems in the form of pre-complexed gRNA/Cas9 ribonuclear protein ("RNP"). To form RNP, all RNA samples were heated at 95C. *S. pyogenes* CAS9 Protein (NLS CAS9 iPROT106154, 37μM) was diluted in buffer before tracrRNA (having the sequence: AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAACUUGAAAAAGUGGC ACCGAGUCGGUGUUUUUUU (SEQ ID NO: 1296); AXO Labs) was added to it. After mixing CAS9 Protein with tracrRNA, the CRISPR RNA was added (in each case, each crRNA comprised the sequence nnnnnnnnnnnnnnnnnnnnGUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO: 40), where the n residues represent the 20 ribonucleic acid residues of the indicated targeting sequence). The precomplexed RNPs were then added to a total of 1 million cells, RNP concentration was 3.2μM. Electroporation was done by neon electroporator using *Neon® Transfection System 100 μL Kit (MPK10096)* at 1600V, 10ms, 3 pulses. The cells were kept in culture for 7 more days. Cells were then divided, with some used to perform flow cytometry: Staining for CAR (PE), CD3 (PerCP-Cy5.5), CD4 (V450) and CD8 (APC). Remaining T cells were frozen and used for functional assays and next generation sequencing (NGS) sample generation.

Next Generation Sequencing (NGS) sample generation

Frozen edited cell pellets (described above) were thawed and processed using *DNeasy Blood & Tissue Kit (Qiagen, 69506)* to isolate genomic DNA. Eluted DNA was used to run PCR using *Titanium Taq PCR kit (Clontech Laboratories, 639211)* and TET2 primers (primers designed to flank the expected target site of the gRNA). PCR product was purified using *QIAquick PCR Purification Kit (Qiagen, 28104).* Purified PCR product was then used for T7E1 assay to detect base pair mismatches and confirm gene editing. PCR amplicons were subjected to standard Nextera NGS library prep (Illumina) and sequenced with paired-end reads on an Illumina MiSeq sequencer. Sequencing reads were aligned to the reference genome and variants were called.

Cytokine Production assay

Effector cells (CAR T cells) are thawed on the day of the assay and counted on Cellometer (Nexelcom). These cells are then co cultured with different target cells at Effector:Target cell ratio of 2:1. 100ul of co-culture supernatant is harvested after 20h. These supernatants are then used measure the cytokines IL-2 and IFN-g released using Meso Scale

Discovery, Proinflammatory Panel 1 catalog # N05049A-1 system according to the manufacturer's protocol.

T cell Proliferation Assay

CAR T cell proliferation in response to BCMA- or CD19-expressing target cells was evaluated. Target cell lines were: BCMA positive multiple myeloma cell lines, NCI-H929-luc, KMS-11-luc, and BCMA-negative Nalm6luc (CD19-positive cell line). CAR T cells were thawed incubated for 2 hours in T cell medium to recover. Cells were counted on a Cellometer. Target cells were irradiated at 10,000 rad. After irradiation, target cells were washed twice in complete T cell medium and counted. 30,000 Irradiated target cells were then co cultured with CART cells at 1:1 ratio. As a negative control, medium alone was added to CAR T cells.

The co-culture was incubated for 4 days at 37°C. On Day 4, coculture cells were stained for 20 mins on ice with CD3-percp cy5.5(Ebioscience:45-0037), CD4-eflor450(Ebioscience:48-0047), and CD8-APC(Ebioscience 17-0087and measured by flow cytometry relative to CountBright Absolute Counting Beads (Life Technologies) to determine relative cell counts.). CAR expression was measured by two step incubation of 20 mins each on ice: Biotinylated-Protein L + Streptavidin-PE(Jackson immuno research). Flow cytometry data was acquired using BD 5 laser Fortessa and analyzed by FlowJo software.

Results

FIGS. 13A and 13B show CAR expression in cells electroporated with and without Tet2 CRISPR. FIG. 13A shows the gating strategy for determining CAR+ T cells. Lymphocytes were selected using forward scatter (FSC-A) and side scatter (SSC-A) as encircled. CD3-expressing cells were then selected (middle panel). CAR positive (PE positive cells using CAR detection by biotinylated protein and streptavitin-PE) cells indicated by the bar were then determined by gating relative to the negative control peak. FIG. 13B shows the quantitation of the percentage of CAR positive cells. Cells were transduced with either the BCMA-10 CAR of the CD19 CAR as indicated. Cells were electroporated with RNP containing Cas9 protein, tracer RNA, and the indicated guide RNA targeting Tet2 (Ex3-3 targeting exon 3 or Ex9-6 targeting exon 9), or with no electroporation. CAR expression was determined 10 days after cell activation with beads. These data indicate that editing of Tet2 does not impact CAR expression in T cells.

FIG. 14 shows quantitation of CD4 and CD8 positive cells after CAR transduction and Tet2 editing. Cells were stained for CD3, CD4, CD8, and CAR expression at the end of the 10 day bead expansion. The left panel indicates the percentage of CD4 and CD8 positive cells in the total population of CD3+ cells. The right panel indicates the percentage of CD4 and CD8 positive cells in the population of CD3+ cells that are also CAR+. Cells were transduced with either the BCMA-10 CAR of the CD19 CAR or left untransduced (UTD) as indicated. Cells were electroporated with RNP containing Cas9 protein, tracer RNA, and the indicated guide RNA targeting Tet2 (Ex3-3 targeting exon 3 and Ex9-6 targeting exon 9), or with no electroporation. These data indicated that editing of Tet2 causes a small but consistent decrease in the percentage of CD8 cells and increase in the percentage of CD4 during the window of time of the bead-based expansion process.

FIG. 15 shows cell yield and viability after bead expansion for 10 days. The number of cells per mL (left panel) and the viability of cells (right panel) were measured by Cellometer after the 10 day bead expansion process. Cells were transduced with either the BCMA-10 CAR of the CD19 CAR or left untransduced (UTD) as indicated. Cells were electroporated with RNP containing Cas9 protein, tracer RNA, and the indicated guide RNA targeting Tet2 (Ex3-3 targeting exon 3 and Ex9-6 targeting exon 9), or with no electroporation. These data indicate that Tet2 editing causes an increase in cell number and viability relative to cells with no CRISPR/Cas9, with the Exon 9 targeting guide (ex9-6) showing the greatest impact in untransduced as well as CAR transduced cells.

FIG. 16 shows IL-2 production in response to cells either positive or negative for the antigen recognized by the CAR. CART cells or untransduced cells (UTD) were co-cultured with BCMA-positive/ CD19-negative cells (KMS11 and NCIH929) or BCMA-negative/CD19-positive cells (NALM6) and cytokine secretion into the media was measured. IL-2 (pg/ml) levels are shown. Cells were prepared as described above. These data indicated that Tet2 editing causes an increase in IL-2 production by T cells in response to antigen with the Exon 9 targeting guide (Ex9-6) showing the greatest effect.

FIG. 17 shows interferon gamma production. CART cells or untransduced cells (UTD) were co-cultured with BCMA-positive/ CD19-negative cells (KMS11 and NCIH929) or BCMA-negative/ CD19-positive cells (NALM6) and cytokine secretion into the media was measured. Interferon gamma (IFN-g) (pg/ml) levels are shown. Cells were prepared as described above.

These data indicated that Tet2 editing causes an increase in Interferon gamma production by T cells in response to antigen, with the Exon 9 targeting guide (Ex9-6) showing the greatest effect.

FIG. 18 shows antigen-driven CAR-T cell proliferation. CART cells or untransduced cells (UTD) were co-cultured with BCMA-positive/ CD19-negative cells (KMS11 and NCIH929) or BCMA-negative/CD19-positive cells (NALM6) or no target cells (media) and proliferation of CAR positive T cells was measured. Cells were prepared as described above. These data indicated that Tet2 editing causes an increase in CAR+ T cell proliferation in response to antigen, with the Exon 9 targeting guide (CrEx9-6) showing the greatest effect.

FIG. 19 shows antigen-driven total T cell proliferation. CART cells or untransduced cells (UTD) were co-cultured with BCMA-positive/CD19-negative cells (KMS11 and NCIH929) or BCMA-negative/CD19-positive cells (NALM6) or no target cells (media) and proliferation of all CD3+ T cells was measured. Cells were prepared as described above. These data indicated that Tet2 editing causes an increase in CD3+ T cell proliferation in response to antigen, with the Exon 9 targeting guide (CrEx9-6) showing the greatest effect.

FIG. 20 shows antigen-driven CAR+ T cell proliferation. CART cells or untransduced cells (UTD) were co-cultured with BCMA-positive/CD19-negative cells (KMS11 and NCIH929) or BCMA-negative/CD19-positive cells (NALM6) or no target cells (media) and proliferation of all CD4+ CD3+ T cells was measured. Cells were prepared as described above. These data indicated that Tet2 editing causes an increase in CD4+ T cell proliferation in response to antigen, with the Exon 9 targeting guide (CrEx9-6) showing the greatest effect.

FIG. 21 shows antigen-driven CAR+ CD4+ T cell proliferation. CART cells or untransduced cells (UTD) were co-cultured with BCMA-positive/CD19-negative cells (KMS11 and NCIH929) or BCMA-negative/CD19-positive cells (NALM6) or no target cells (media) and proliferation of all CAR+CD4+ CD3+ T cells was measured. Cells were prepared as described above. These data indicated that Tet2 editing causes an increase in CAR+CD4+ T cell proliferation in response to antigen, with the Exon 9 targeting guide (CrEx9-6) showing the greatest effect.

FIG. 22 shows antigen-driven CD8+ T cell proliferation. CART cells or untransduced cells (UTD) were co-cultured with BCMA-positive/CD19-negative cells (KMS11 and NCIH929) or BCMA-negative/CD19-positive cells (NALM6) or no target cells (media) and proliferation of all CD8+ CD3+ T cells was measured. Cells were prepared as described above. These data

indicated that Tet2 editing causes an increase in CD8+ T cell proliferation in response to antigen, with the Exon 9 targeting guide (CrEx9-6) showing the greatest effect.

FIG. 23 shows antigen-driven CAR+ CD8+ T cell proliferation. CART cells or untransduced cells (UTD) were co-cultured with BCMA-positive/CD19-negative cells (KMS11 and NCIH929) or BCMA-negative/CD19-positive cells (NALM6) or no target cells (media) and proliferation of all CAR+CD8+ CD3+ T cells was measured. Cells were prepared as described above. These data indicated that Tet2 editing causes an increase in CAR+CD8+ T cell proliferation in response to antigen, with the Exon 9 targeting guide (CrEx9-6) showing the greatest effect.

FIG. 24 shows % editing, and % frameshift edit by introduction of Tet2 targeting CRISPR/Cas systems. The level of editing in primary T cells after electroporation of RNP containing Cas9 protein, tracer RNA, and the indicated guide RNAs targeting either exon 3 or exon 9 of Tet2 is shown. The percentage of observed insertions or deletions of nucleotides relative to a reference genome is shown in the middle column (average % insertion/deletion). Editing that results in a shift in the open reading frame is shown in the far right column (average % frameshift). These data are the average of triplicates. These data indicate highly efficient genome editing in primary T cells with these guide RNA sequences.

The insertion and deletion pattern present at or near the target site for each gRNA was assessed by next generation sequencing. Briefly, T cells were electroporated with an RNP containing the indicated guide RNAs. After 48 hours, DNA was isolated and processed for sequencing. FIG. 25 shows the 5 most common indels (insertions and/or deletions) observed in primary T cells for the guides RNAs targeting exon 3 of Tet2. FIG. 26 shows the 5 most common indels (insertions and/or deletions) observed in primary T cells for the guides RNAs targeting exon 9 of Tet2. The percentages indicate the frequency with which a given editing pattern was observed. Insertions are shown by lowercase nucleotide letters ("a," "g," "c" or "t"), while deletions are shown by a dash ("-").

ATAC-Seq Experiments

CD8+ T cells with and without the Tet2 insertion were expanded from a patient's post-infusion sample. Chromatin accessibility was assessed using Assay for Transposase-Accessible Chromatin with high throughput sequencing (ATAC-seq). This is essentially a technique for

global chromatin mapping based on the transposition of "barcoded" DNA fragments. These DNA fragments get incorporated into regions of open chromatin, which allow for determination of which chromatin regions are opened versus closed. Based on the location of open or closed regions, pathway analyses can be done under the assumption that "open" equals to "expressed" and "closed" equals to "repressed." FIG. 30A shows Venn diagrams of ATAC peaks in the CAR+CD8+ T cells from a patient with a Tet2 disruption compared to CAR-CD8+ T cells from the same patient at the matched time point without the Tet2 disruption. FIG. 28B show GO terms associated with ATAC peaks more closed in the cell population with the Tet2 disruption, compared to its counterpart. The significance of FIG. 30B is, at least in part, that the chromatin landscape of the CD8+ T cells with the Tet2 disruption is possibly in line with a less differentiated cell that may be more "early memory-like" and less "effector-like." These are the sort of cells that are thought to persist to provide robust and long-term anti-tumor activity.

ShRNA Studies

T cells from healthy donors were activated for 24 hours via CD3/CD28-coated beads, followed by lentiviral transduction with either the non-targeting (control) shRNA or the Tet2 shRNA. As shown in FIG. 32A, knock-down efficiency was assessed by qPCR and shown to be 50% (may mirror what happened in the patient in which Tet2 was disrupted via lentiviral integration). The differentiation phenotype was examined at day 14 by examining CCR7, CD45RO. Central memory cells are defined as CCR7+CD45RO+, whereas effector cells are CCR7-CD45RO-. To examine the differentiation phenotype specifically in cells with the 50% Tet2 knockdown, a GFP indicator was used in the shRNA constructs. The results are shown in FIGS. 32B and 32C.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. The following working examples specifically point out various aspects of the present invention, and are not to be construed as limiting in any way the remainder of the disclosure.

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EQUIVALENTS

The disclosures of each and every patent, patent application, and publication cited herein are hereby incorporated herein by reference in their entirety. While this invention has been disclosed with reference to specific aspects, it is apparent that other aspects and variations of this invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The appended claims are intended to be construed to include all such aspects and equivalent variations.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A cell or a population of cells engineered to express a chimeric antigen receptor (CAR), wherein the CAR comprises an antigen-binding domain (e.g., an antibody or antibody fragment), a transmembrane domain, and an intracellular signaling domain, and wherein the cell or population of cells comprises:
   (a) an inhibitor of Tet1, Tet2 and/or Tet3, wherein said inhibitor is:
      (i) an siRNA or shRNA specific for Tet1, Tet2 and/or Tet3, or a nucleic acid encoding said siRNA or shRNA;
      (ii) a gene editing system targeted to one or more sites within the gene encoding Tet1, Tet2 and/or Tet3 or its regulatory elements (e.g., Tet2 or its regulatory elements),
      (iii) a nucleic acid encoding said gene editing system of (ii);
      (iv) combinations of (ii) and (iii); or
      (v) a protein that is a dominant negative binding partner of Tet1, Tet2 and/or Tet3, or a nucleic acid encoding said dominant negative binding partner of Tet1, Tet2 and/or Tet3; or
   (b) a disruption in a Tet1, Tet2 and/or Tet3 gene.

2. The cell or population of cells of claim 1, wherein the antigen-binding domain binds to a tumor antigen is selected from a group consisting of: CD19, TSHR, CD123, CD22, CD30, CD171, CS-1, CLL-1, CD33, EGFRvIII , GD2, GD3, BCMA, Tn Ag, PSMA, RORl, FLT3, FAP, TAG72, CD38, CD44v6, CEA, EPCAM, B7H3, KIT, IL-13Ra2, Mesothelin, IL-l lRa, PSCA, PRSS21, VEGFR2, LewisY, CD24, PDGFR-beta, SSEA-4, CD20, Folate receptor alpha, ERBB2 (Her2/neu), MUC1, EGFR, NCAM, Prostase, PAP, ELF2M, Ephrin B2, IGF-I receptor, CAIX, LMP2, gplOO, bcr-abl, tyrosinase, EphA2, Fucosyl GMl, sLe, GM3, TGS5, HMWMAA, o-acetyl-GD2, Folate receptor beta, TEM1/CD248, TEM7R, CLDN6, GPRC5D, CXORF61, CD97, CD179a, ALK, Polysialic acid, PLAC1, GloboH, NY-BR-1, UPK2, HAVCR1, ADRB3, PANX3, GPR20, LY6K, OR51E2, TARP, WT1, NY-ESO-1, LAGE-la, MAGE-A1, legumain, HPV E6,E7, MAGE Al, ETV6-AML, sperm protein 17, XAGE1, Tie 2, MAD-CT-1, MAD-CT-2, Fos-related antigen 1, p53, p53 mutant, prostein, survivin and telomerase,

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PCTA-l/Galectin 8, MelanA/MARTl, Ras mutant, hTERT, sarcoma translocation breakpoints, ML-IAP, ERG (TMPRSS2 ETS fusion gene), NA17, PAX3, Androgen receptor, Cyclin Bl, MYCN, RhoC, TRP-2, CYP1B1, BORIS, SART3, PAX5, OY-TES1, LCK, AKAP-4, SSX2, RAGE-1, human telomerase reverse transcriptase, RUl, RU2, intestinal carboxyl esterase, mut hsp70-2, CD79a, CD79b, CD72, LAIRl, FCAR, LILRA2, CD300LF, CLEC12A, BST2, EMR2, LY75, GPC3, FCRL5, and IGLL1.

3. The cell or population of cells of claim 1 or claim 2, wherein:
   (a) the transmembrane domain comprises:
      (i) an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO: 12, or a sequence with 95-99% identity to the amino acid sequence of SEQ ID NO: 12; or
      (ii) the sequence of SEQ ID NO: 12:
   (b) the antigen binding domain is connected to the transmembrane domain by a hinge region, wherein said hinge region comprises SEQ ID NO: 4 or SEQ ID NO: 6, or a sequence with 95-99% identity thereto; and/or
   (c) the CAR comprises a leader sequence comprising the sequence of SEQ ID NO: 2.

4. The cell or population of cells of any one of claims 1 to 3, wherein the intracellular signaling domain comprises a costimulatory signalling domain, a primary signaling domain, or a primary signalling domain and a costimulatory signaling domain, wherein:
   (a) the primary signaling domain comprises:
      (i) a functional signaling domain of a protein selected from the group consisting of CD3 zeta, CD3 gamma, CD3 delta, CD3 epsilon, common FcR gamma (FCERIG), FcR beta (Fc Epsilon Rib), CD79a, CD79b, Fcgamma Rlla, DAP10 and DAP12;
      (ii) an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO: 18 or SEQ ID NO: 20, or a

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sequence with 95-99% identity to an amino acid sequence of SEQ ID NO: 18 or SEQ ID NO: 20; or

(iii) the amino acid sequence of SEQ ID NO: 18 or SEQ ID NO: 20;

(b) the costimulatory domain comprises:

(i) a functional signaling domain of a protein selected from the group consisting of CD27, CD28, 4-lBB (CD137), OX40, CD30, CD40, PD-1, ICOS, lymphocyte function- associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, B7-H3, a ligand that specifically binds with CD83, CDS, ICAM-1, GITR, BAFFR, HVEM (LIGHTR), SLAMF7, NKp80 (KLRF1), CD160, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Lyl08), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, NKp44, NKp30, NKp46 and NKG2D;

(ii) an amino acid sequence having at least one, two or three modifications but not more than 20, 10 or 5 modifications of an amino acid sequence of SEQ ID NO: 14 or SEQ ID NO: 16, or a sequence with 95-99% identity to an amino acid sequence of SEQ ID NO: 14 or SEQ ID NO: 16; or

(iii) the sequence of SEQ ID NO: 14 or SEQ ID NO: 16; or

(c) the intracellular domain comprises the sequence of SEQ ID NO: 14 or SEQ ID NO: 16, and the sequence of SEQ ID NO: 18 or SEQ ID NO: 20, wherein the sequences comprising the intracellular signaling domain are expressed in the same frame and as a single polypeptide chain.

5. The cell or population of cells of any one of claims 1 to 4, wherein the cell or population of cells is an immune effector cell or a population of immune effector

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cells.

6. The cell or population of cells of claim 5, wherein the immune effector cell, e.g., a human immune effector cell, is a T cell, e.g., a CD4+ T cell, a CD8+ T cell, or a combination thereof.

7. The cell of claim 5, wherein the immune effector cell, e.g., a human immune effector cell, is an NK cell.

8. The cell or population of cells of any one of claims 1 to 7, wherein:
   (i) the protein that is a dominant negative binding partner of Tet1, Tet2 and/or Tet3 is a histone deacetylase (HDAC) that interacts with Tet1, Tet2 and/or Tet3; or
   (ii) the siRNA or shRNA comprises a sequence complementary to a sequence of a Tet2 mRNA, e.g., comprises a target sequence of shRNA of any one of SEQ ID NOs: 1244 to 1252.

9. The cell or population of cells of any one of claims 1 to 8, wherein the gene editing system:
   (a) is selected from the group consisting of: a CRISPR/Cas9 system, a zinc finger nuclease system, a TALEN system and a meganuclease system;
   (b) binds to a target sequence in an early exon or intron of a gene encoding Tet1, Tet2 and/or Tet3, e.g., Tet2;
   (c) binds to a target sequence in a late exon or intron of a gene encoding Tet1, Tet2 and/or Tet3, e.g., Tet2;
   (d) binds a target sequence of a gene encoding tet2, and the target sequence is downstream of exon 8, e.g., is in exon 9, exon 10, or exon 11; and/or
   (e) is a CRISPR/Cas system comprising a gRNA molecule comprising a targeting sequence which hybridizes to a target sequence of a Tet2 gene, e.g., a targeting sequence of any one of SEQ ID NOs: 73 to 1243 or SEQ ID NOs: 1273 to 1295.

10. The cell or population of cells of claim 9, wherein the gene editing system binds a

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target sequence of a gene encoding tet2, and the target sequence is upstream of exon 4, e.g., in exon 1, exon 2, or exon 3.

11. A method of increasing the therapeutic efficacy of a CAR-expressing cell, e.g., a cell of any one of claims 1 to 10, comprising a step of contacting said cell *in vivo* with a composition comprising a Tet inhibitor, e.g., a Tet1, Tet2 and/or Tet3 inhibitor.

12. A method of treating a disease associated with expression of a tumor antigen, e.g., a proliferative disease, a precancerous condition, a cancer, and a non-cancer related indication associated with expression of the tumor antigen, in a subject in need thereof, the method comprising:
    (a) providing a cell or population of cells obtained from the subject;
    (b) reducing the expression and/or function of Tet1, Tet2 and/or Tet3 in said cell or population of cells by contacting said cell or population of cells *ex vivo* with a Tet1, Tet2 and/or Tet3 inhibitor, wherein the contacting is done prior to, simultaneously with, or after said cell is modified to express a CAR; and
    (c) administering said cell or population of cells to the subject.

13. A method for the treatment of a disease associated with expression of a tumor antigen, e.g., a proliferative disease, a precancerous condition, a cancer, and a non-cancer related indication associated with expression of the tumor antigen, in a subject in need thereof, the method comprising administering to said subject an effective amount of the cell or population of cells of any one of claims 1 to 10.

14. The method of claim 13, wherein said Tet inhibitor is a Tet2 inhibitor.

15. A method for the treatment of a disease associated with expression of a tumor antigen, e.g., a proliferative disease, a precancerous condition, a cancer, and a non-cancer related indication associated with expression of the tumor antigen, in a subject in need thereof, the method comprising administering to said subject a CAR-expressing cell therapy and a Tet1, Tet2 and/or Tet3 inhibitor.

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16. The method of claim 15, wherein:

(a) the subject receives a pre-treatment of the Tet1, Tet2 and/or Tet3 inhibitor, prior to the initiation of the CAR-expressing cell therapy;

(b) the subject receives concurrent treatment with a Tet1, Tet2, and/or Tet3 inhibitor and the CAR expressing cell therapy; or

(c) the subject receives treatment with a Tet1, Tet2, and/or Tet3 inhibitor post-CAR-expressing cell therapy.

17. The method of any one of claims 12 to 16, wherein the disease associated with expression of a tumor antigen is:

(a) a hematologic cancer selected from the group consisting of chronic lymphocytic leukemia (CLL), acute leukemias, acute lymphocytic leukemia (ALL), B-cell acute lymphocytic leukemia (B-ALL), T-cell acute lymphocytic leukemia (T-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 lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, pre-leukemia, and combinations of said hematologic cancers; or

(b) a cancer selected from the group consisting of colon cancer, rectal cancer, renal-cell carcinoma, liver cancer, non-small cell carcinoma of the lung, cancer of the small intestine, cancer of the esophagus, melanoma, 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, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the

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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, solid tumors of childhood, 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, combinations of said cancers, and metastatic lesions of said cancers.

18. A method of manufacturing a CAR-expressing cell, comprising:
    (a) introducing nucleic acid encoding a CAR into a cell such that said nucleic acid (or CAR-encoding portion thereof) integrates into the genome of the cell within a Tet1, Tet2 and/or Tet3 gene (e.g., within an intron or exon of a Tet1, Tet2 and/or Tet3 gene), such that Tet1, Tet2 and/or Tet3 expression and/or function is reduced or eliminated; or
    (b) providing a cell obtained from a subject, and contacting the cell *ex vivo* with a Tet1, Tet2 and/or Tet3 inhibitor, wherein the contacting is done prior to, simultaneous with, or after said cell is modified to express a CAR.

19. A vector comprising a sequence encoding a CAR and a sequence encoding a Tet inhibitor, e.g., a Tet1, Tet2 and/or Tet3 inhibitor.

20. The vector of claim 19, wherein:
    (a) the Tet inhibitor is a (i) a gene editing system targeted to one or more sites within the gene encoding Tet1, Tet2, or Tet3, or its corresponding regulatory elements; (ii) a nucleic acid (e.g., an siRNA or shRNA) that inhibits expression of Tet1, Tet2, or Tet3; (iii) a protein (e.g., a dominant negative, e.g., catalytically inactive) Tet1, Tet2, or Tet3, or a binding partner of Tet1, Tet2, or Tet3; and (iv) a nucleic acid encoding any of (i)-(iii), or combinations thereof; and/or
    (b) the sequence encoding a CAR and the sequence encoding a Tet inhibitor are separated by a 2A site.

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21. Use of a composition for the *ex vivo* manufacture of a CAR-expressing cell, the composition comprising a Tet inhibitor, e.g., a Tet1, Tet2, and/or Tet3 inhibitor, e.g., a Tet2 inhibitor.

22. Use of the cell or population of cells of any one of claims 1 to 10 in the manufacture of a medicament for the treatment of a disease associated with expression of a tumor antigen, e.g., a proliferative disease, a precancerous condition, a cancer, and a non-cancer related indication associated with expression of the tumor antigen.

23. Use of a CAR-expressing cell therapy and a Tet1, Tet2 and/or Tet3 inhibitor in the manufacture of a medicament for the treatment of a disease associated with expression of a tumor antigen, e.g., a proliferative disease, a precancerous condition, a cancer, and a non-cancer related indication associated with expression of the tumor antigen.

24. The method of any one of claims 11 to 18, or the use of any one of claims 21 to 23, wherein:

(a) the Tet inhibitor is a Tet2 inhibitor; or

(b) the Tet inhibitor is selected from the group consisting of:

(i) a gene editing system targeted to one or more sites within the gene encoding Tet1, Tet2, or Tet3, or its corresponding regulatory elements;

(ii) a nucleic acid (e.g., an siRNA or shRNA) that inhibits expression of Tet1, Tet2, or Tet3;

(iii) a protein (e.g., a dominant negative, e.g., catalytically inactive) Tet1, Tet2, or Tet3, or a binding partner of Tet1, Tet2, or Tet3 (e.g., a dominant negative binding partner of Tet1, Tet2, and/or Tet3);

(iv) a small molecule that inhibits expression and/or function of Tet1, Tet2, or Tet3;

(v) a nucleic acid encoding any of (i) - (iii); and

(vi) any combination of (i) - (v).

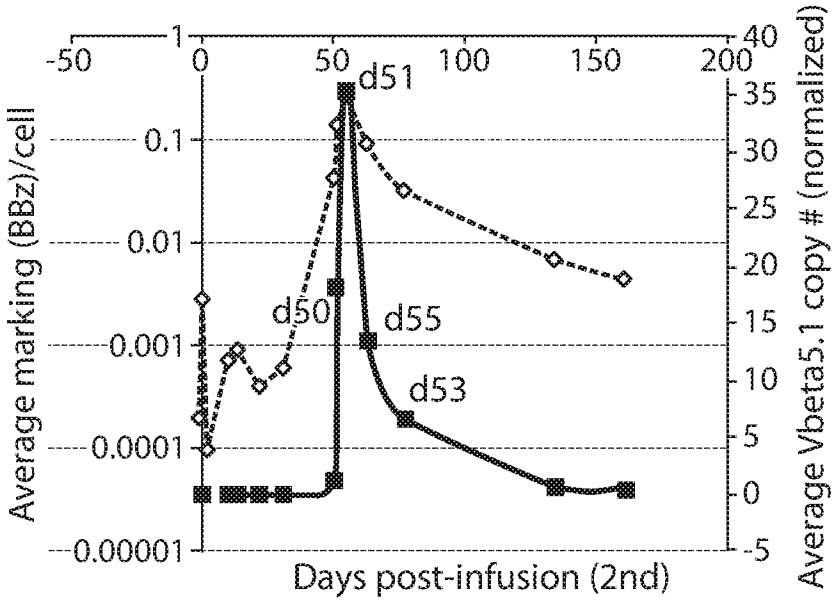

Average marking (BBz)/cell
1
0.1
0.01
0.001
0.0001
0.00001
-50
0
50
100
150
200
d51
d50
d55
d53
Days post-infusion (2nd)
Average Vbeta5.1 copy # (normalized)
40
35
30
25
20
15
10
5
0
-5

FIG. 1

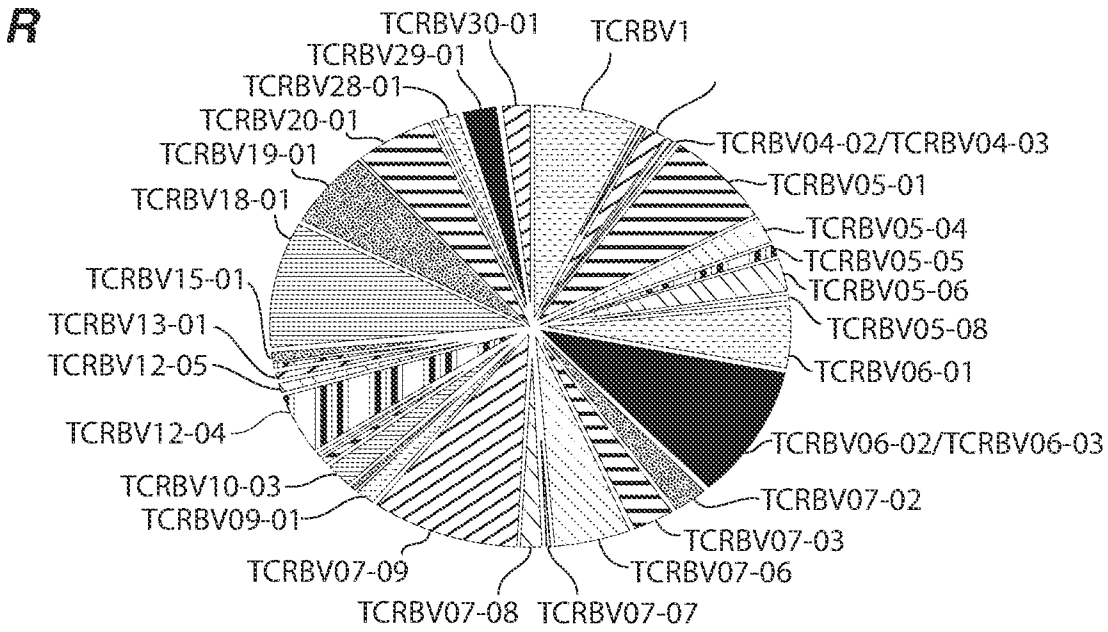

R
TCRBV30-01
TCRBV1
TCRBV29-01
TCRBV28-01
TCRBV20-01
TCRBV04-02/TCRBV04-03
TCRBV19-01
TCRBV05-01
TCRBV18-01
TCRBV05-04
TCRBV05-05
TCRBV15-01
TCRBV05-06
TCRBV13-01
TCRBV05-08
TCRBV12-05
TCRBV06-01
TCRBV12-04
TCRBV06-02/TCRBV06-03
TCRBV10-03
TCRBV07-02
TCRBV09-01
TCRBV07-03
TCRBV07-09
TCRBV07-06
TCRBV07-08
TCRBV07-07

FIG. 2A

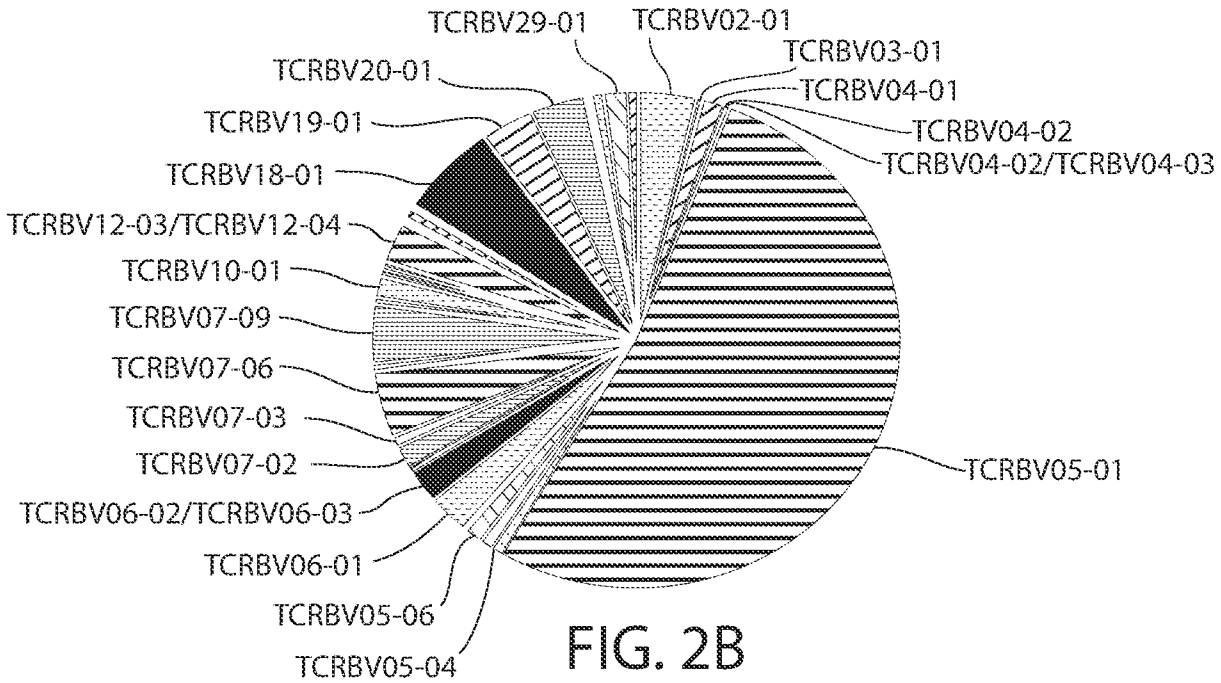

TCRBV29-01
TCRBV02-01
TCRBV03-01
TCRBV20-01
TCRBV04-01
TCRBV19-01
TCRBV04-02
TCRBV04-02/TCRBV04-03
TCRBV18-01
TCRBV12-03/TCRBV12-04
TCRBV10-01
TCRBV07-09
TCRBV07-06
TCRBV07-03
TCRBV05-01
TCRBV07-02
TCRBV06-02/TCRBV06-03
TCRBV06-01
TCRBV05-06
TCRBV05-04

FIG. 2B

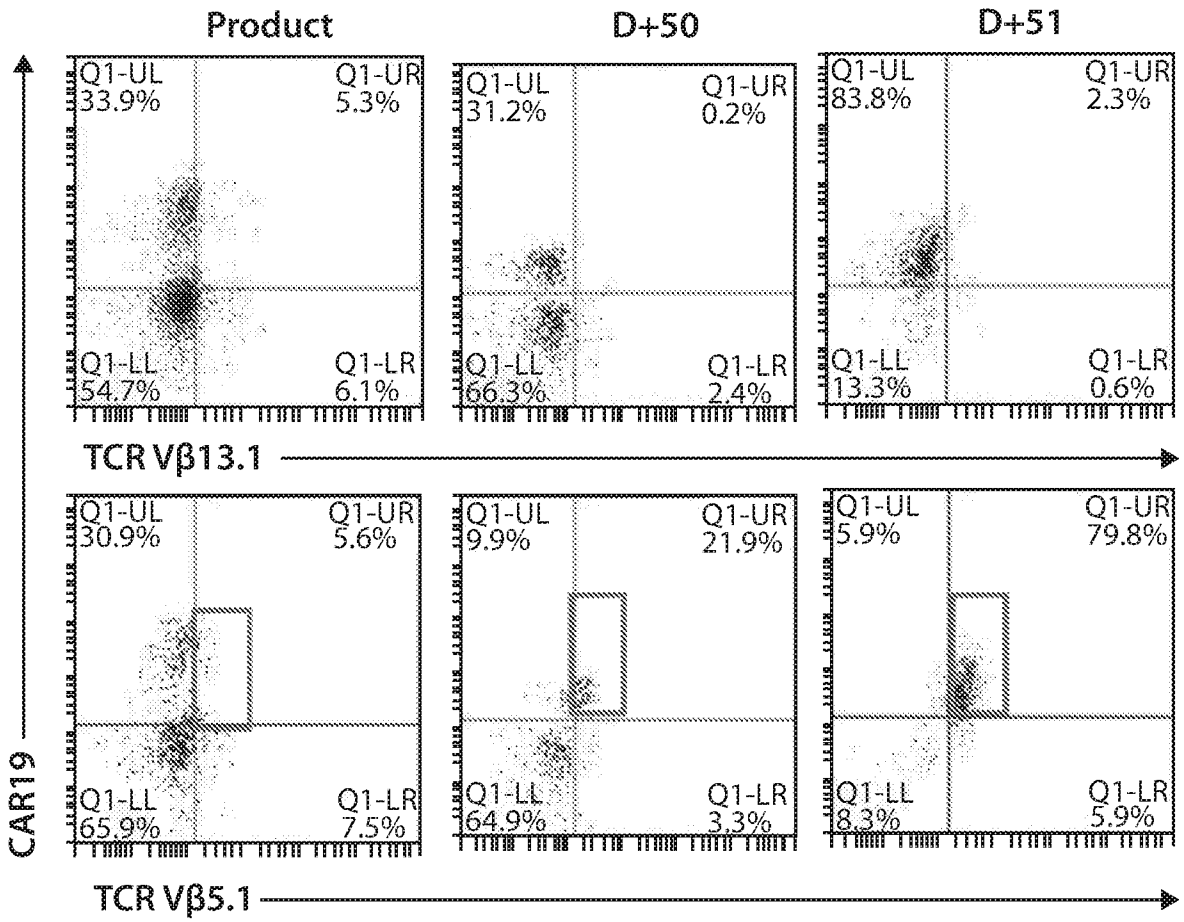

Product
D+50
D+51
Q1-UL
33.9%
Q1-UR
5.3%
Q1-LL
54.7%
Q1-LR
6.1%
Q1-UL
31.2%
Q1-UR
0.2%
Q1-LL
66.3%
Q1-LR
2.4%
Q1-UL
83.8%
Q1-UR
2.3%
Q1-LL
13.3%
Q1-LR
0.6%
TCR Vβ13.1
Q1-UL
30.9%
Q1-UR
5.6%
Q1-LL
65.9%
Q1-LR
7.5%
Q1-UL
9.9%
Q1-UR
21.9%
Q1-LL
64.9%
Q1-LR
3.3%
Q1-UL
5.9%
Q1-UR
79.8%
Q1-LL
8.3%
Q1-LR
5.9%
CAR19
TCR Vβ5.1

FIG. 3

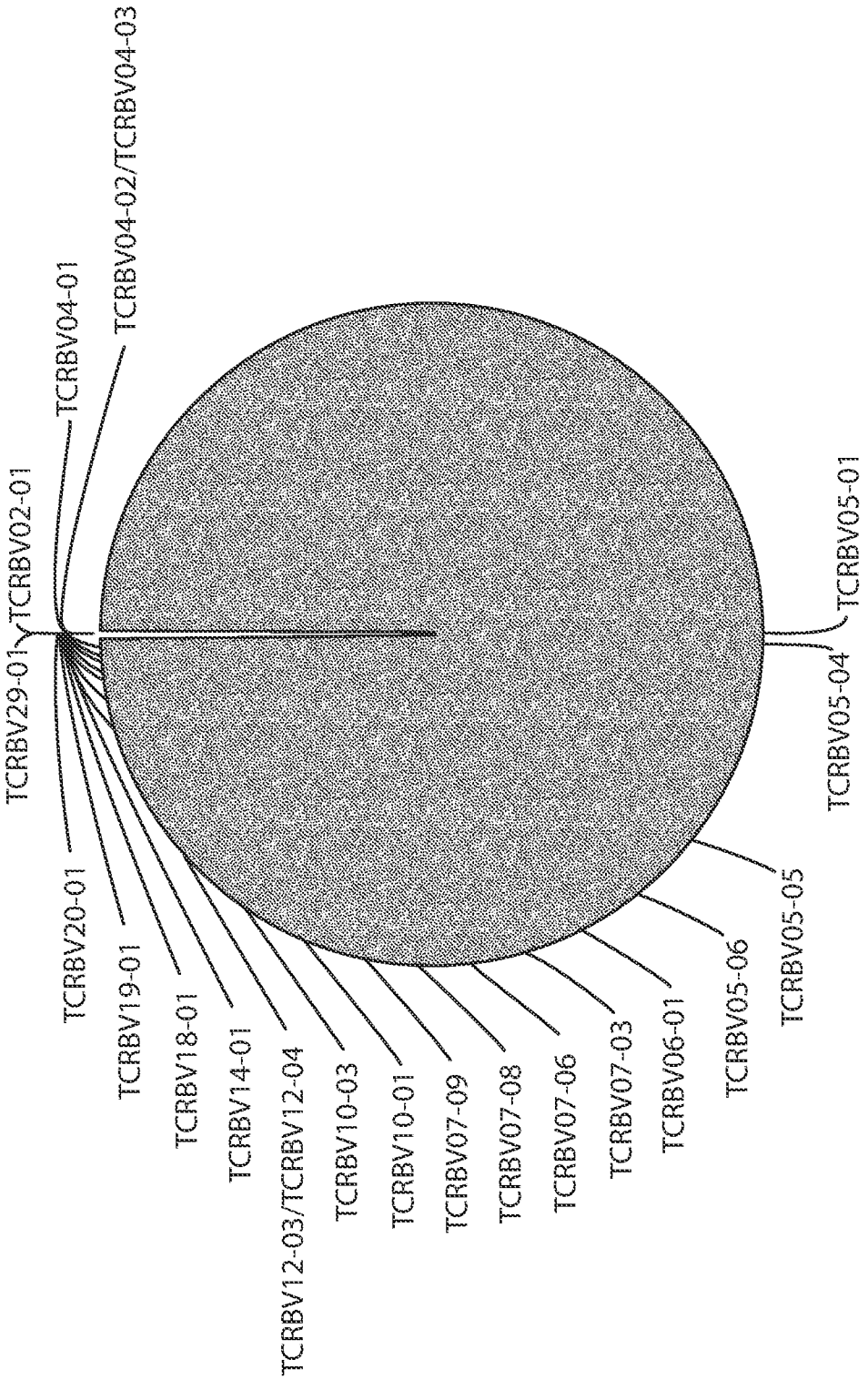

TCRBV29-01
TCRBV02-01
TCRBV04-01
TCRBV04-02/TCRBV04-03
TCRBV05-01
TCRBV05-04
TCRBV05-05
TCRBV05-06
TCRBV06-01
TCRBV07-03
TCRBV07-06
TCRBV07-08
TCRBV07-09
TCRBV10-01
TCRBV10-03
TCRBV12-03/TCRBV12-04
TCRBV14-01
TCRBV18-01
TCRBV19-01
TCRBV20-01

FIG. 4

V	D	J	Amino acid	Nucleotide
TCRAV13-01	TCRDD01-01	TCRAJ34-01*01		TGTGCAGCAAGTAGCGGAGGCGACACCGACAAGCTCATCTTT
TCRAV04-01*01	unresolved	TCRAJ30-01*01	CLVGANRDDKIIF	TGCCTCGTGGGTGCGAACAGAGATGACAAGATCATCTTT
TCRBV05-01	TCRBD01-01	TCRBJ01-02	CASSLDGSGQGSDYGYTF	GCGCCAGCAGCTTGGACGGTTCGGGACAGGGATCGGACTATGGCTA

Non-templated insertions

D gene

FIG. 5

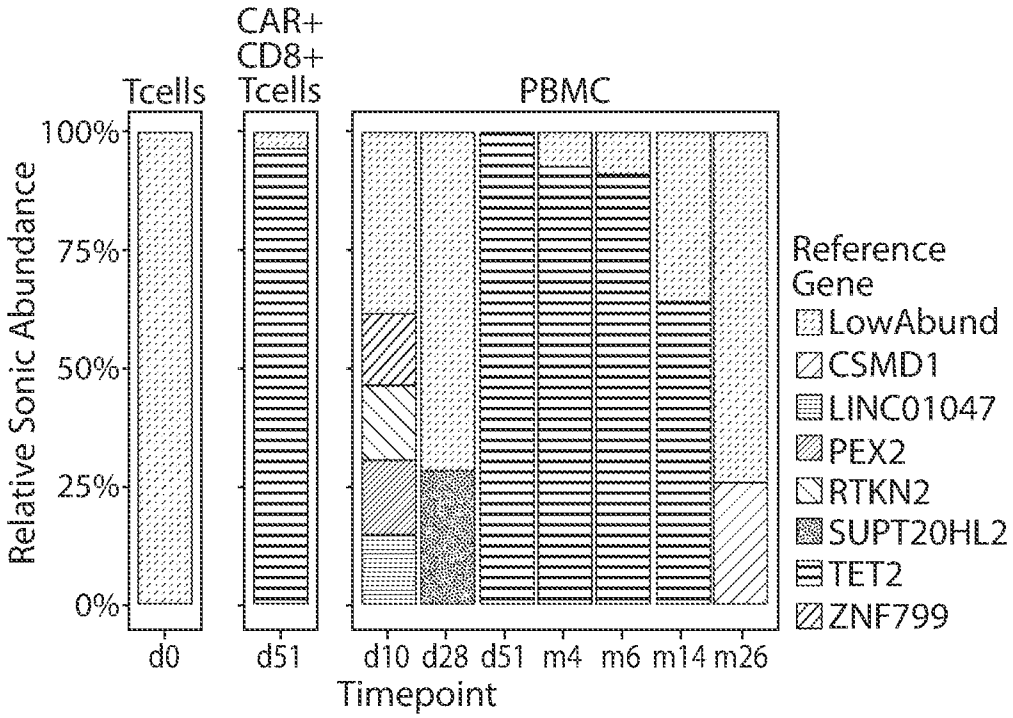

Tcells
CAR+ CD8+ Tcells
PBMC
100%
75%
50%
25%
0%
Relative Sonic Abundance
d0
d51
d10 d28 d51 m4 m6 m14 m26
Timepoint
Reference Gene
LowAbund
CSMD1
LINC01047
PEX2
RTKN2
SUPT20HL2
TET2
ZNF799

FIG. 6

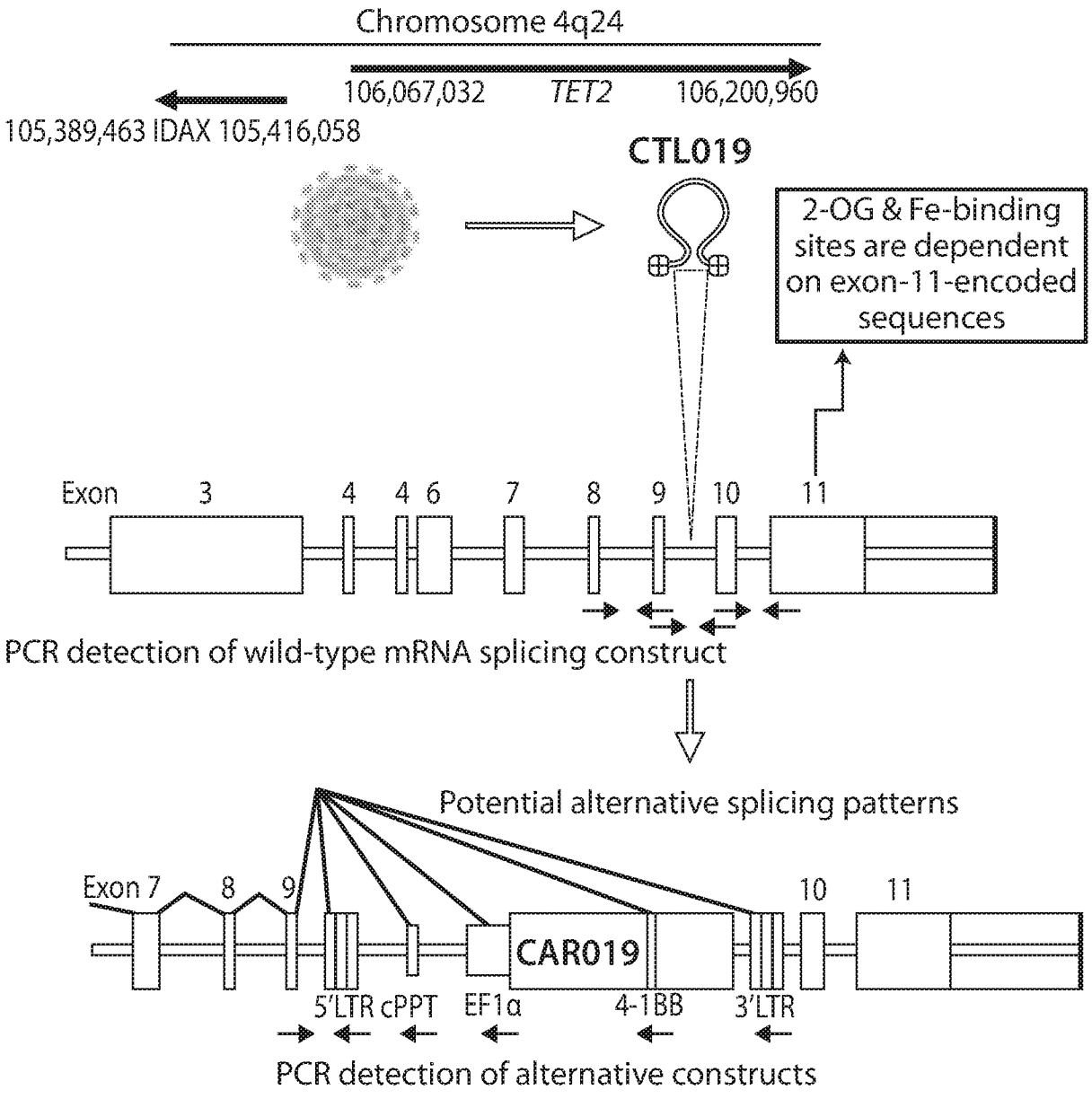
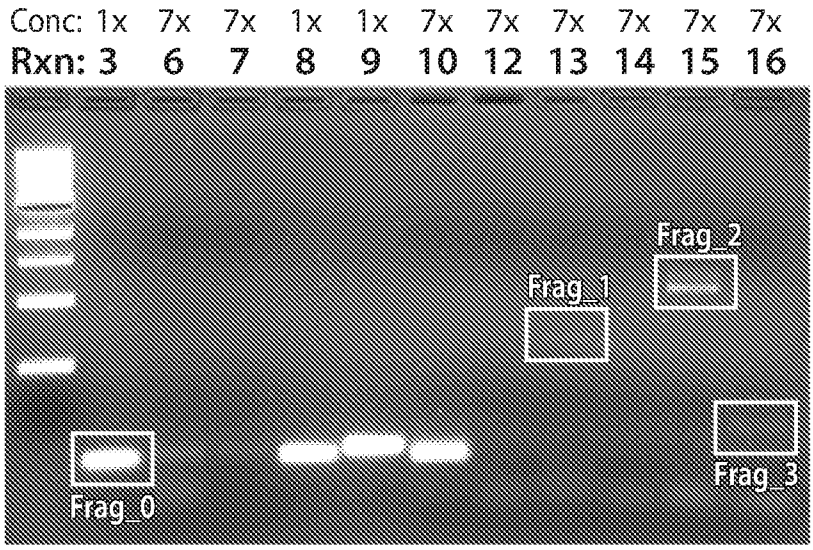

Chromosome 4q24
106,067,032
TET2
106,200,960
105,389,463 IDAX 105,416,058
CTL019
2-OG & Fe-binding sites are dependent on exon-11-encoded sequences
Exon 3 4 4 6 7 8 9 10 11
PCR detection of wild-type mRNA splicing construct
Potential alternative splicing patterns
Exon 7 8 9 10 11
CAR019
5'LTR cPPT EF1α 4-1BB 3'LTR
PCR detection of alternative constructs

FIG. 7

CTL019



Rxn:	Target:	FwdP:	RevP:
3...	E9-10	3	6
6...	cPPT	19	10
7...	EF1a	20	11
8...	4-1BB	21	12
9...	3'U5	22	13
10...	3'R	22	9
12...	E9-R	5.2	9
13...	E9-cPPT	5.2	10
14...	E9-EF1a	5.2	11
15...	E9-4-1BB	5.2	12
16...	E9-R	5.2	13

FIG. 8

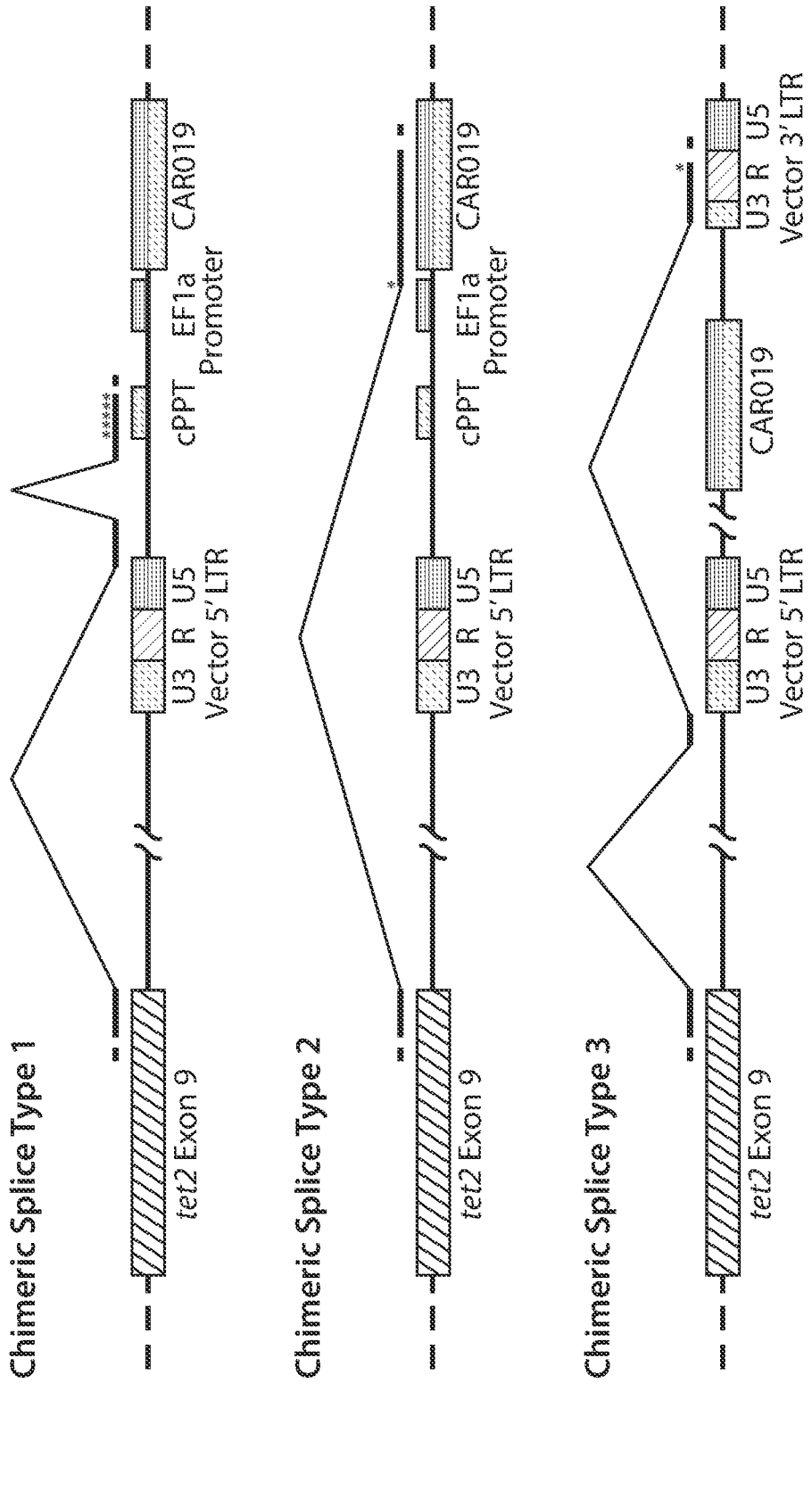

Chimeric Splice Type 1
tet2 Exon 9
U3 R U5
Vector 5'LTR
cPPT
EF1a Promoter
CAR019
Chimeric Splice Type 2
tet2 Exon 9
U3 R U5
Vector 5'LTR
cPPT
EF1a Promoter
CAR019
Chimeric Splice Type 3
tet2 Exon 9
U3 R U5
Vector 5'LTR
CAR019
U3 R U5
Vector 3'LTR
* = in-frame stop codon

FIG. 9

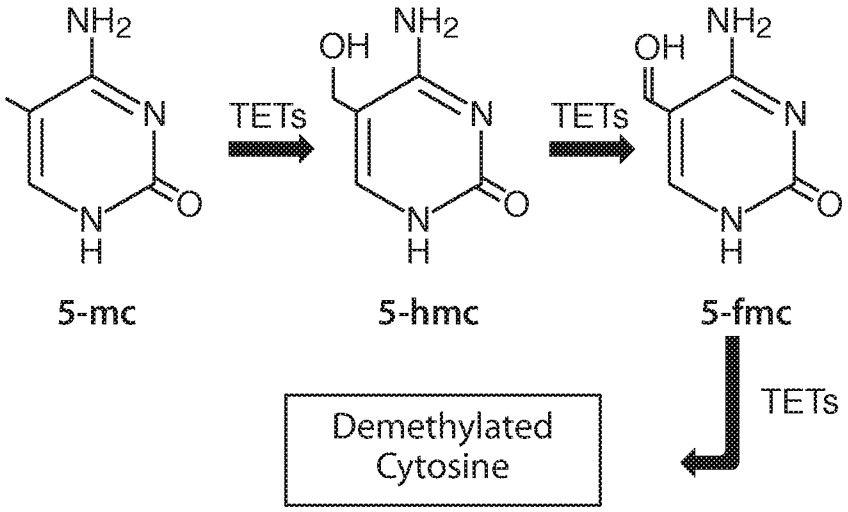


FIG. 10A

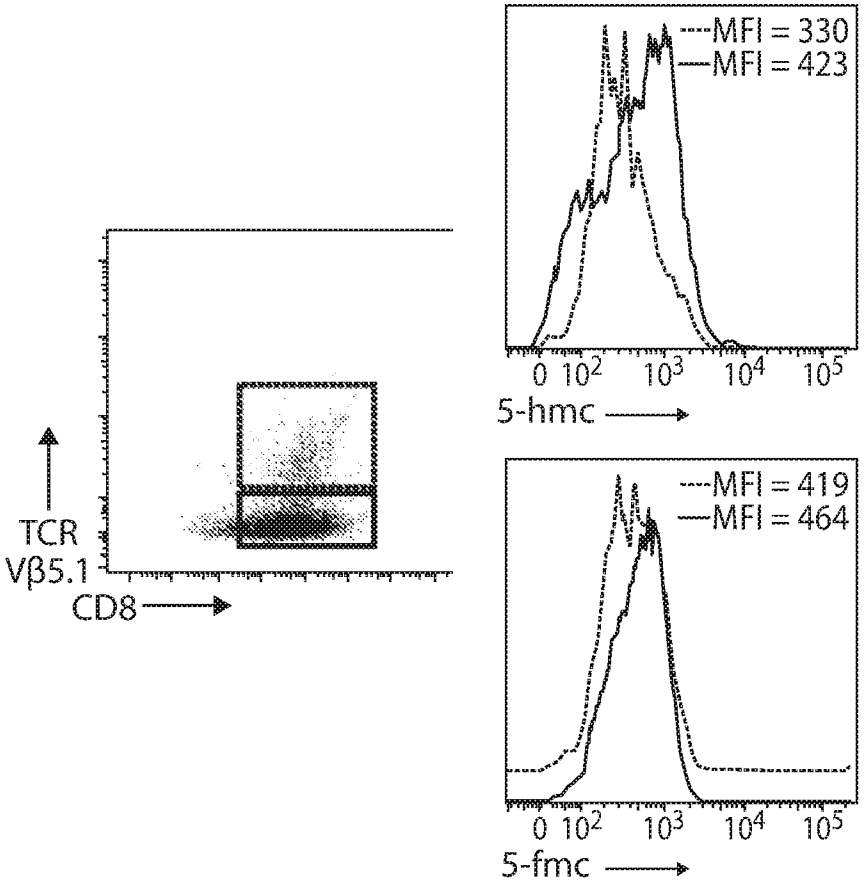


FIG. 10B

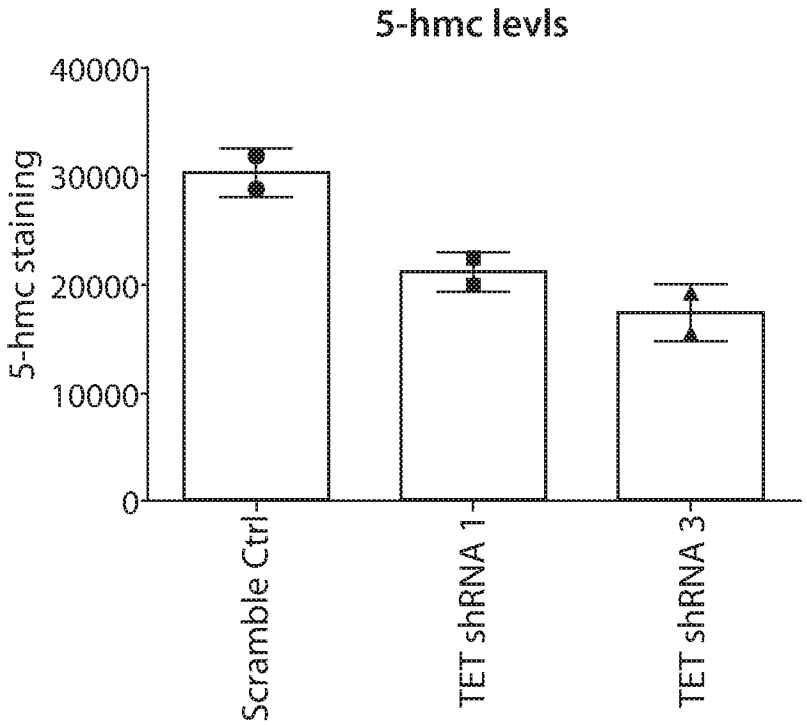

5-hmc levls
40000
30000
20000
10000
0
5-hmc staining
Scramble Ctrl
TET shRNA 1
TET shRNA 3

FIG. 11

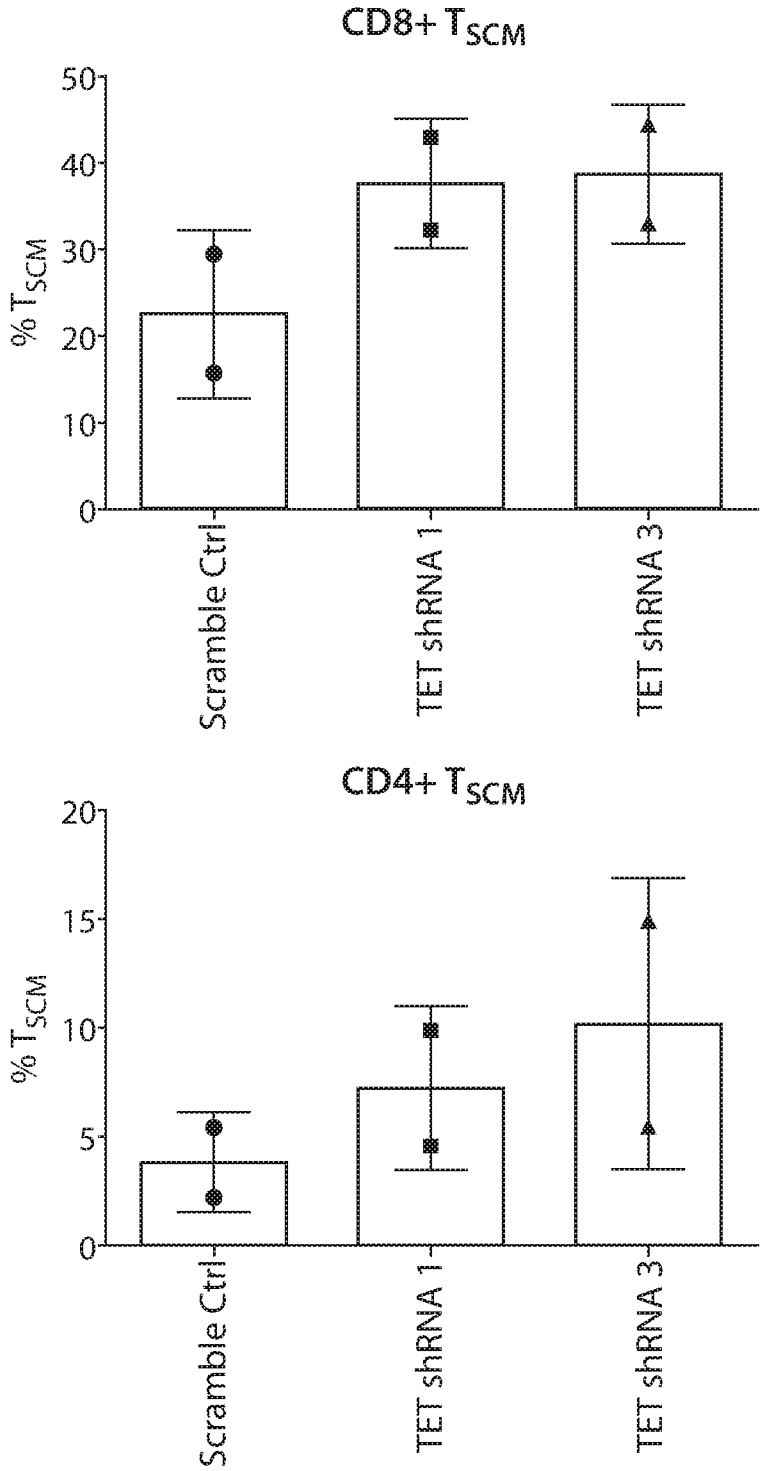

CD8+ T_{SCM}
% T_{SCM}
50
40
30
20
10
0
Scramble Ctrl
TET shRNA 1
TET shRNA 3
CD4+ T_{SCM}
% T_{SCM}
20
15
10
5
0
Scramble Ctrl
TET shRNA 1
TET shRNA 3

FIG. 12

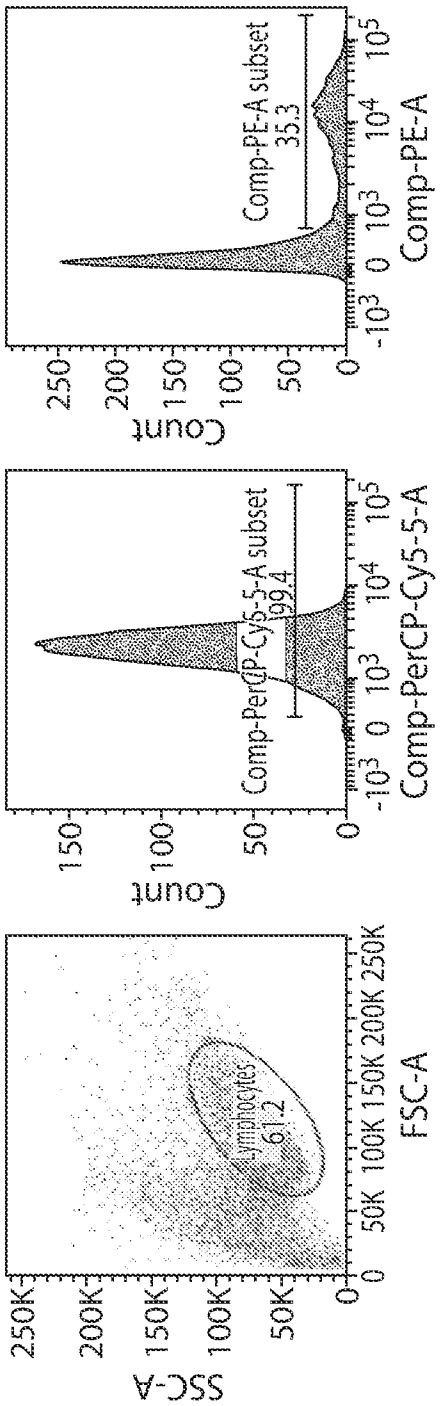


FIG. 13A

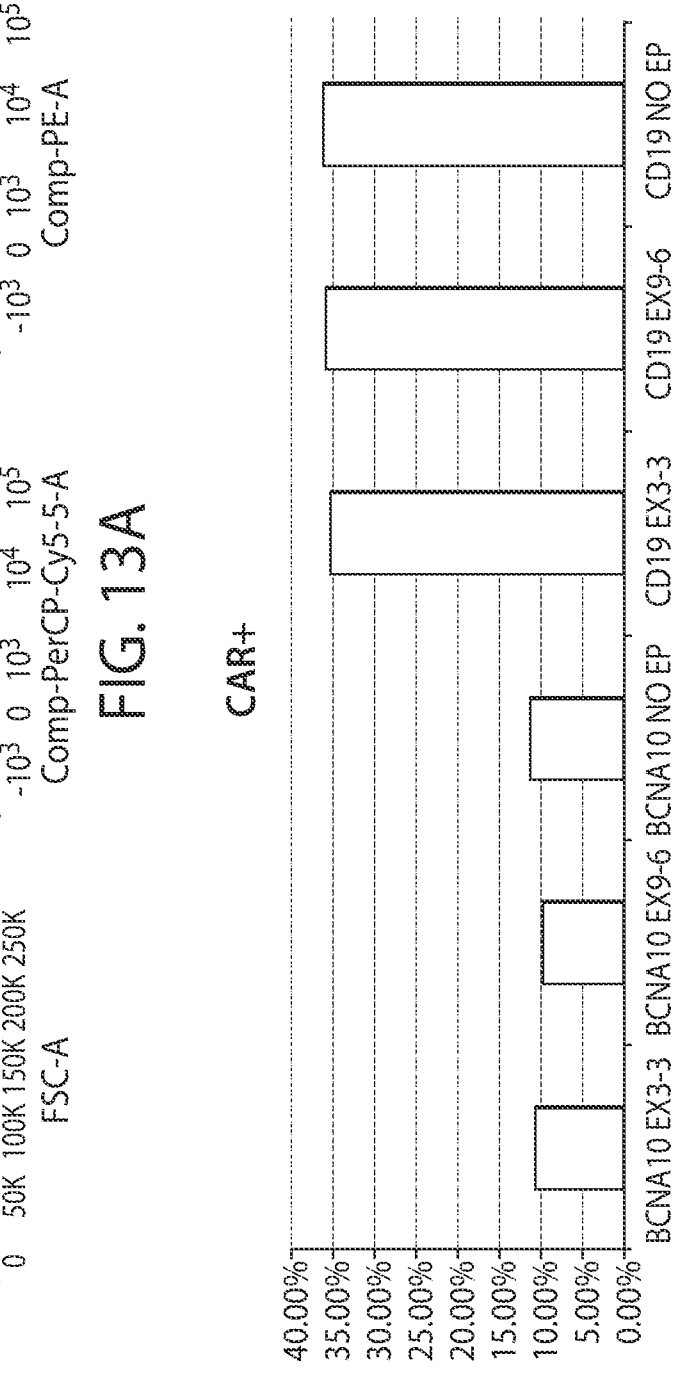


FIG. 13B

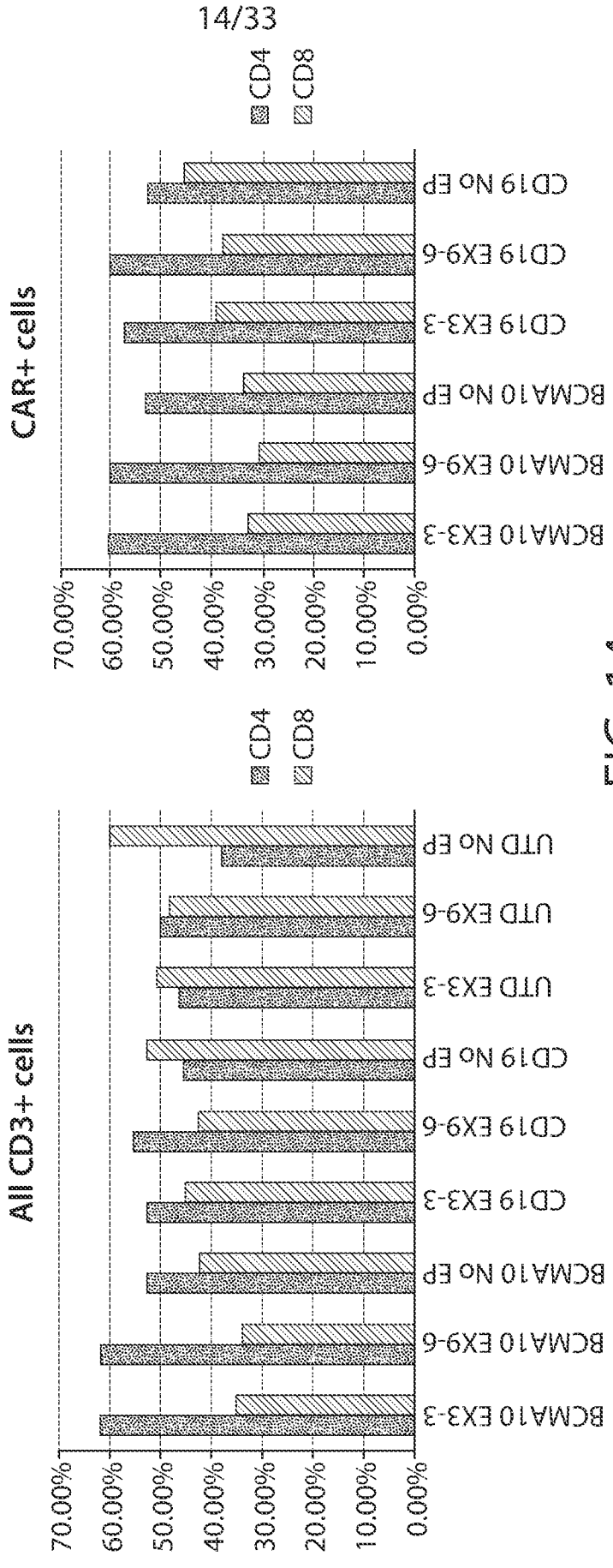
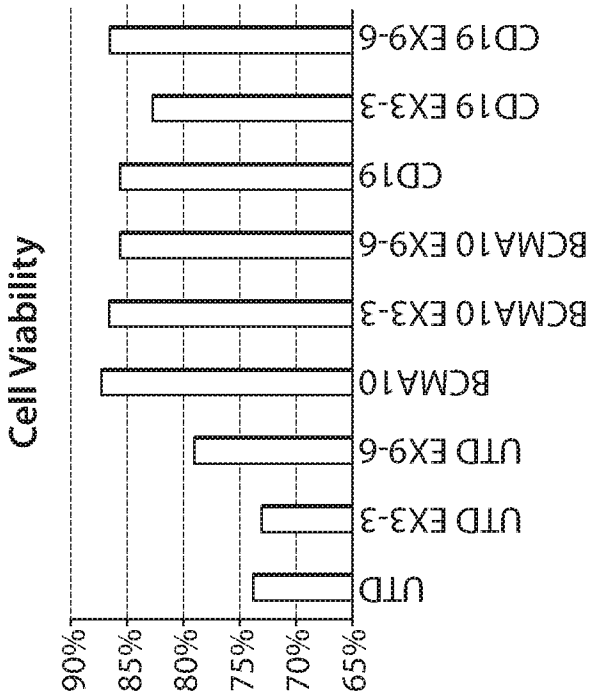
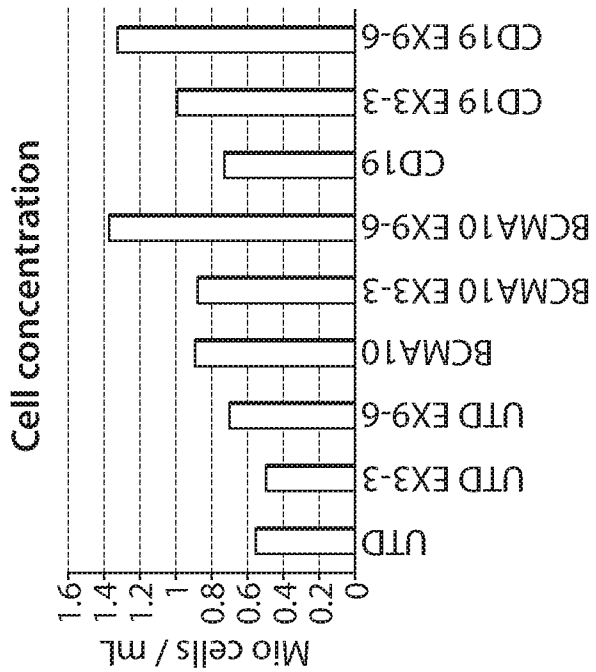

CD4
CD8
CAR+ cells
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
BCMA10 EX3-3
BCMA10 EX9-6
BCMA10 No EP
CD19 EX3-3
CD19 EX9-6
CD19 No EP
CD4
CD8
All CD3+ cells
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
BCMA10 EX3-3
BCMA10 EX9-6
BCMA10 No EP
CD19 EX3-3
CD19 EX9-6
CD19 No EP
UTD EX3-3
UTD EX9-6
UTD No EP

FIG. 14





	Size	Conc [*E6]	Viability	Yield [*E6]
UTD	10.4	0.56	74%	11.2
UTD EX3-3	9.8	0.5	73%	10
UTD EX9-6	9.3	0.71	79%	14.2
BCMA10	9.2	0.9	87%	18
BCMA10 EX3-3	9.5	0.88	87%	17.6
BCMA10 EX9-6	9.6	1.37	86%	27.4
CD19	9.7	0.74	86%	14.8
CD19 EX3-3	10.1	0.99	83%	19.8
CD19 EX9-6	10	1.33	87%	26.6

FIG. 15

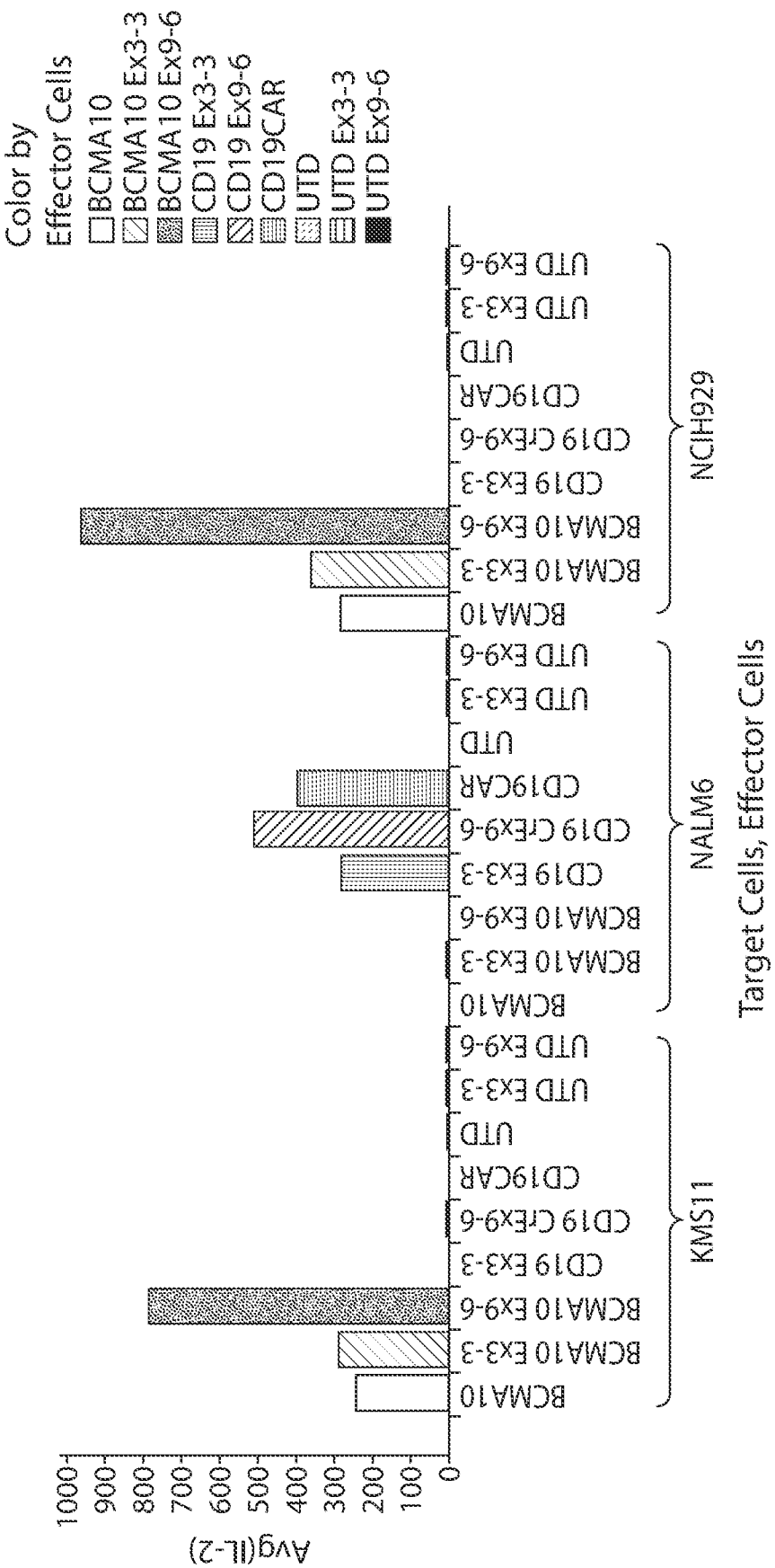

Color by
Effector Cells
BCMA10
BCMA10 Ex3-3
BCMA10 Ex9-6
CD19 Ex3-3
CD19 Ex9-6
CD19CAR
UTD
UTD Ex3-3
UTD Ex9-6
Avg(IL-2)
1000
900
800
700
600
500
400
300
200
100
0
KMS11
NALM6
NCIH929
Target Cells, Effector Cells

FIG. 16

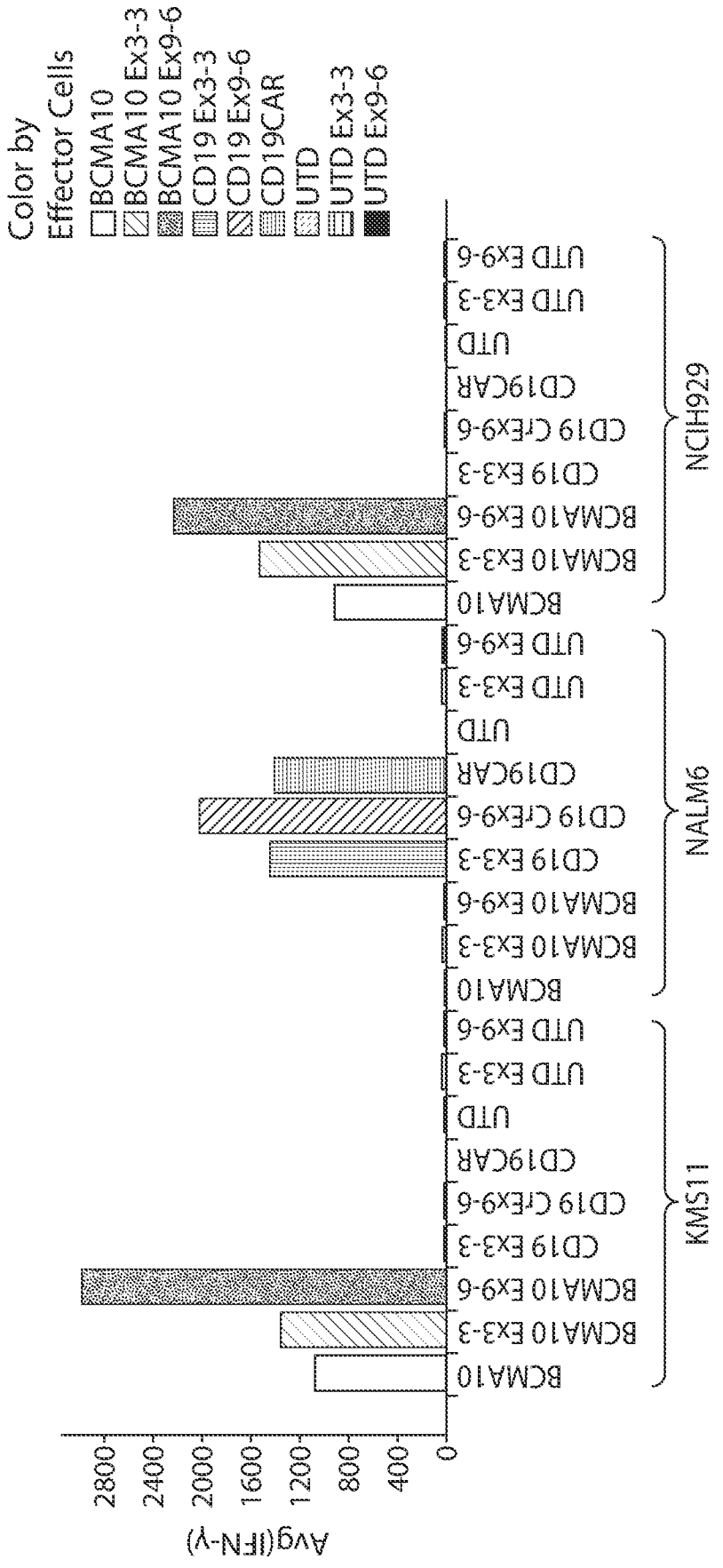

Color by
Effector Cells
BCMA10
BCMA10 Ex3-3
BCMA10 Ex9-6
CD19 Ex3-3
CD19 Ex9-6
CD19CAR
UTD
UTD Ex3-3
UTD Ex9-6
Avg(IFN-γ)
0
400
800
1200
1600
2000
2400
2800
KMS11
NALM6
NCIH929
Target Cells, Effector Cells

FIG. 17

Color by
Effector(CART)
BCMA10
BCMA10 CrEx3-3
BCMA10 CrEx9-6
CD19
CD19 CrEx3-3
CD19 CrEx9-6
UTD
UTD CrEx3-3
UTD CrEx9-6
Avg(CD3+CAR+)
8000
7000
6000
5000
4000
3000
2000
1000
0
KMS11
Media
Nalm6
NCIH929
Target, Effector(CART)

FIG. 18

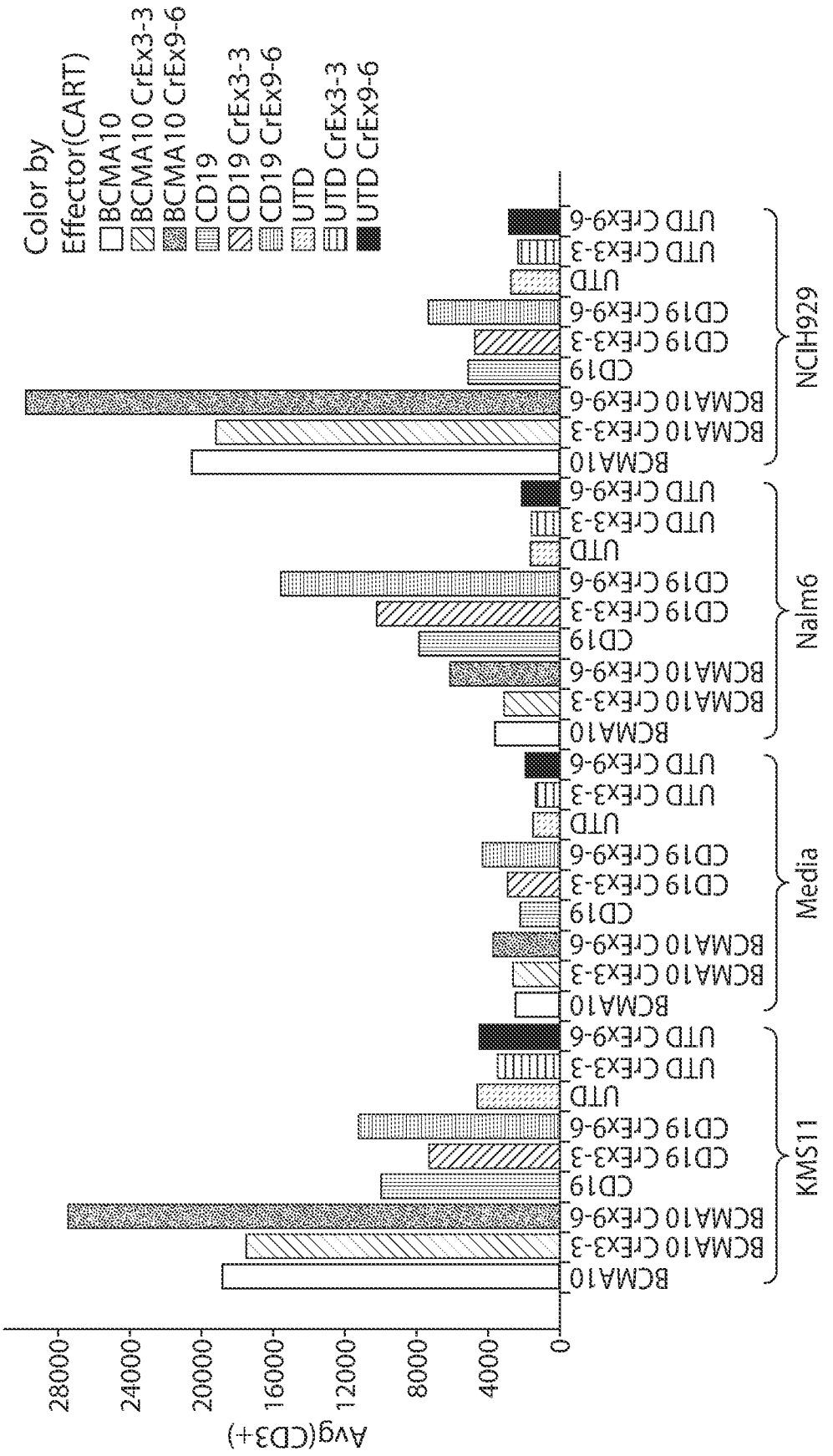

Color by
Effector(CART)
BCMA10
BCMA10 CrEx3-3
BCMA10 CrEx9-6
CD19
CD19 CrEx3-3
CD19 CrEx9-6
UTD
UTD CrEx3-3
UTD CrEx9-6
Avg(CD3+)
28000
24000
20000
16000
12000
8000
4000
0
KMS11
Media
Nalm6
NCIH929
Target, Effector(CART)

FIG. 19

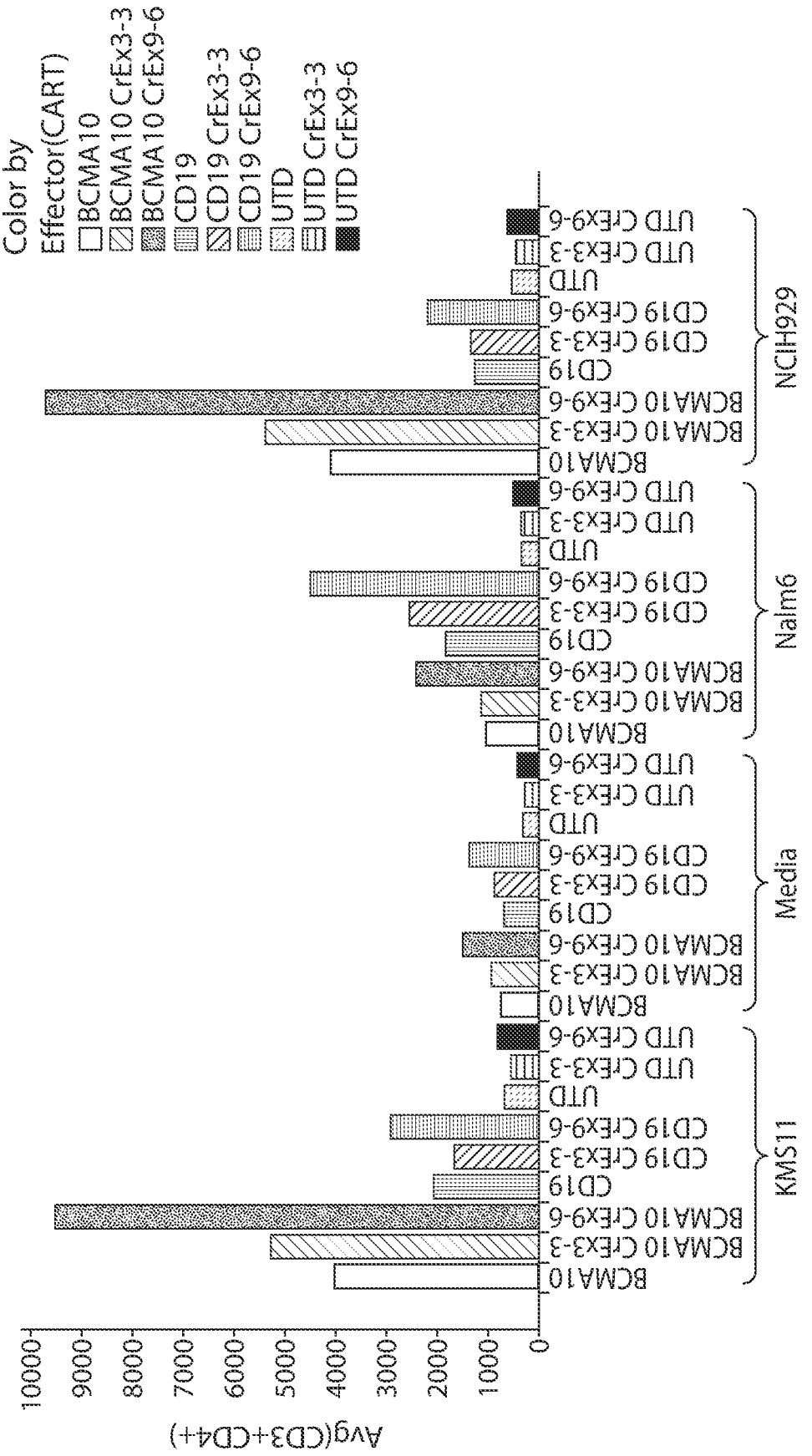

Color by
Effector(CART)
BCMA10
BCMA10 CrEx3-3
BCMA10 CrEx9-6
CD19
CD19 CrEx3-3
CD19 CrEx9-6
UTD
UTD CrEx3-3
UTD CrEx9-6
Avg(CD3+CD4+)
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
KMS11
Media
Nalm6
NCIH929
Target, Effector(CART)

FIG. 20

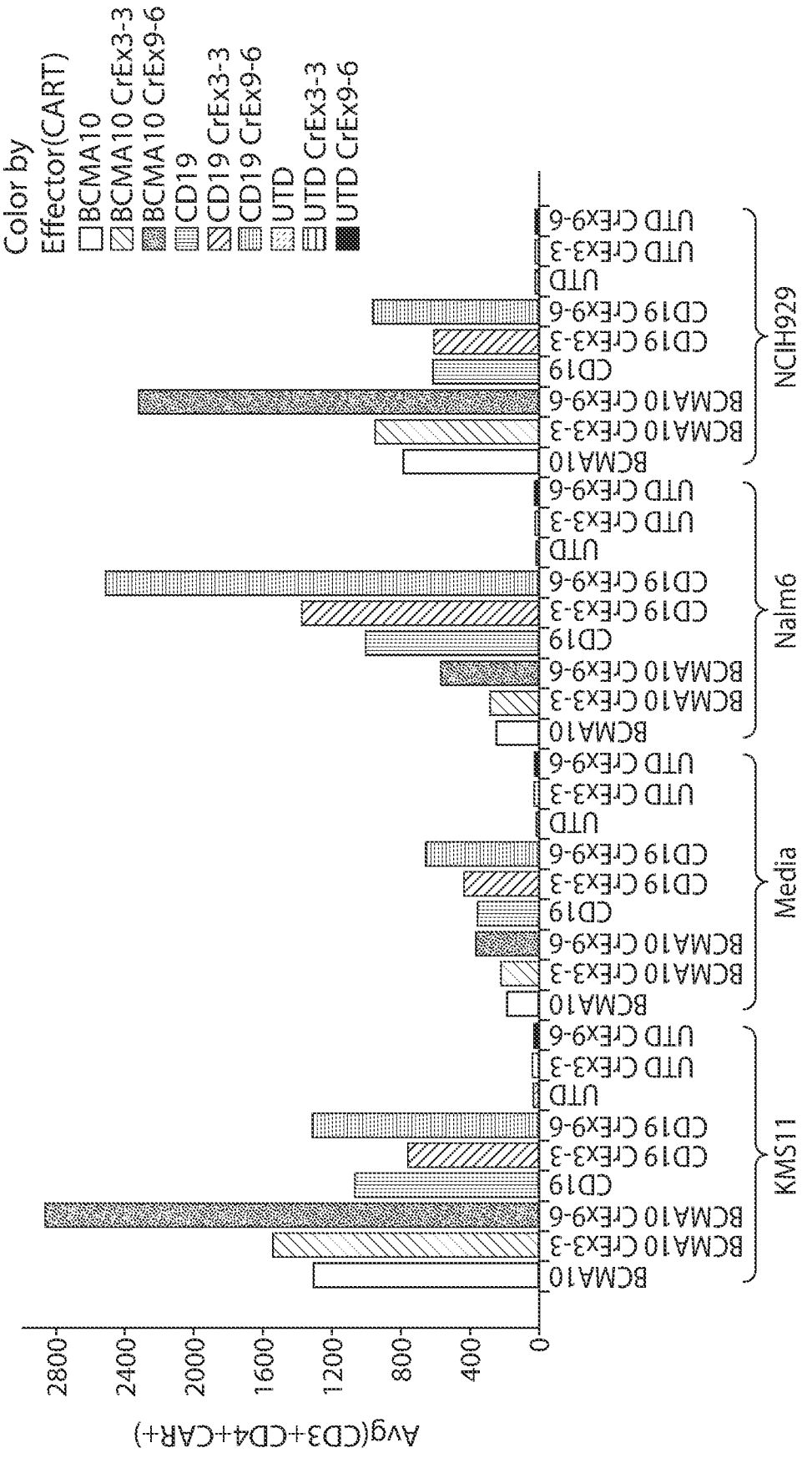

Color by
Effector(CART)
BCMA10
BCMA10 CrEx3-3
BCMA10 CrEx9-6
CD19
CD19 CrEx3-3
CD19 CrEx9-6
UTD
UTD CrEx3-3
UTD CrEx9-6
Avg(CD3+CD4+CAR+)
2800
2400
2000
1600
1200
800
400
0
KMS11
Media
Nalm6
NCIH929
Target, Effector(CART)

FIG. 21

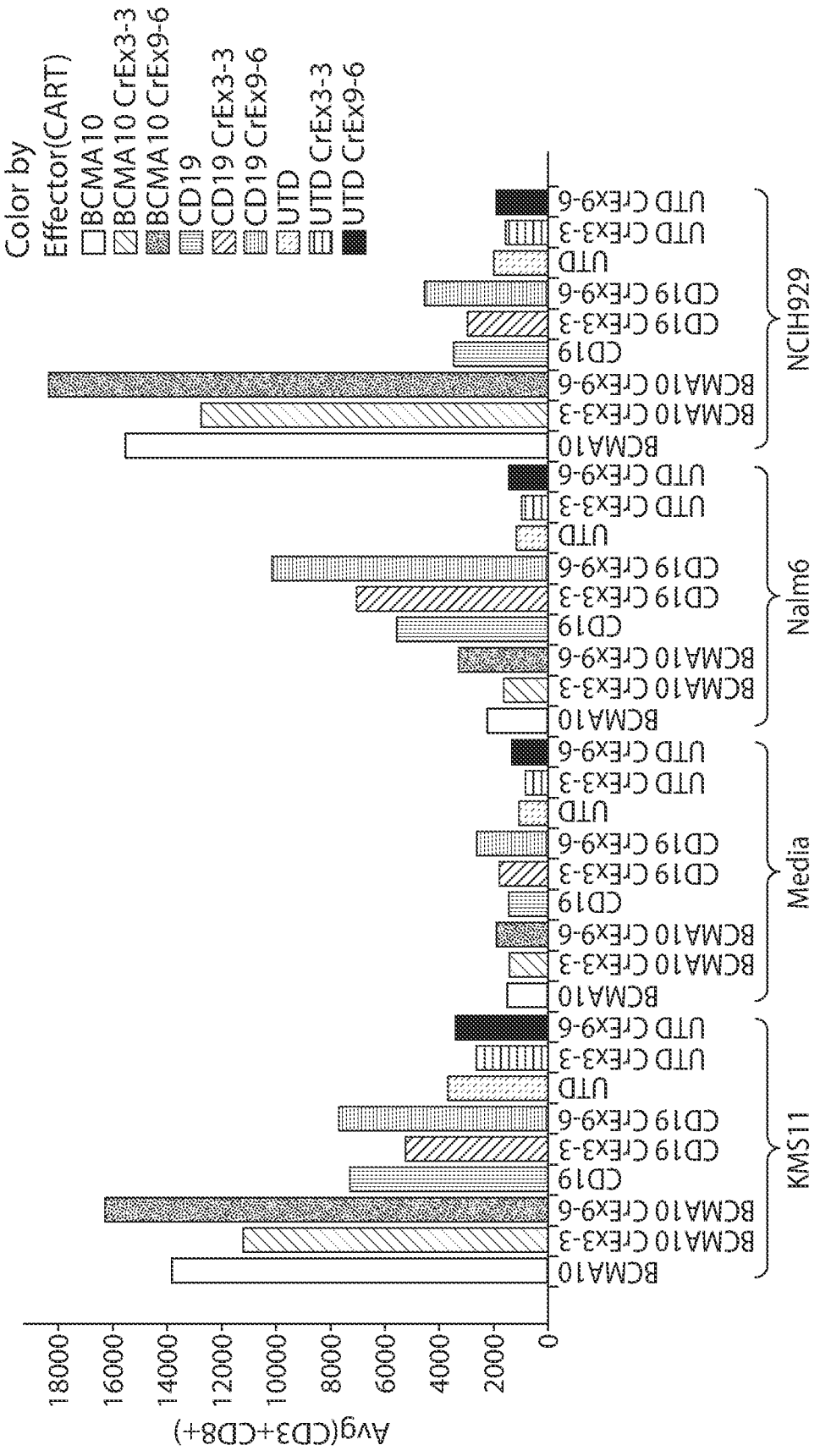

Color by
Effector(CART)
BCMA10
BCMA10 CrEx3-3
BCMA10 CrEx9-6
CD19
CD19 CrEx3-3
CD19 CrEx9-6
UTD
UTD CrEx3-3
UTD CrEx9-6
Avg(CD3+CD8+)
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
KMS11
Media
Nalm6
NCIH929
Target, Effector(CART)

FIG. 22

Color by
Effector(CART)
BCMA10
BCMA10 CrEx3-3
BCMA10 CrEx9-6
CD19
CD19 CrEx3-3
CD19 CrEx9-6
UTD
UTD CrEx3-3
UTD CrEx9-6
Avg(CD3+CD8+CAR+)
0
500
1000
1500
2000
2500
3000
3500
4000
4500
5000
KMS11
Media
Nalm6
NCIH929
Target, Effector(CART)

FIG. 23

Guide RNA	Average % insertion/ deletion	Average % frameshift
Tet2 Exon 3-1	80.78	38.86
Tet2 Exon 3-2	32.22	22.63
Tet2 Exon 3-3	92.30	56.14
Tet2 Exon 3-4	92.26	54.02
Tet2 Exon 3-5	42.66	23.00
Tet2 Exon 9-1	6.07	3.86
Tet2 Exon 9-2	47.16	23.82
Tet2 Exon 9-3	88.38	52.48
Tet2 Exon 9-4	57.17	30.75
Tet2 Exon 9-5	28.70	13.31
Tet2 Exon 9-6	95.79	69.59

FIG. 24

TET2_E3_1__TET2	AAGCAAGCCTGATGGAACAG----------ACTAAGTCCATTCCTGATACCATCACCTCCC	7.60 %
	AAGCAAGCCTGATGGAACAGGATAGAACCAAC----------AGACTAAGTCCATTCCTGATACCATCACCTCCC	7.03 %
	AAGCAAGCCTGATGGAACAGGATAGAACCAACCAT--TGAGGGCAACAGACTAAGTCCATTCCTGATACCATCACCTCCC	3.08 %
	AAGCAAGCCTGATGGAACAGGATAGAACCAACCATG---AGGGCAACAGACTAAGTCCATTCCTGATACCATCACCTCCC	2.67 %
	AAGCAAGCCTGATGGAACAGGATAGAAC----------AGACTAAGTCCATTCCTGATACCATCACCTCCC	2.54 %
TET2_E3_2__TET2	ACTAAGTCCATTCCTGATACCATCACCTCCCATTTGCCAGACAGAACgTCTGGCTACAAAGCTCCAGAATGGAAGCCCAC	31.72 %
	ACTAAGTCCATTCCTGATACCATCACCTCCCATTTGCCAGACAaGAACCTCTGGCTACAAAGCTCCAGAATGGAAGCCC.	12.87 %
	ACTAAGTCCATTCCTGATACCATCACCTCCCATTTGCCAGACAaGAACGTCTGGCTACAAAGCTCCAGAATGGAAGCCC.	8.09 %
	ACTAAGTCCATTCCTGATACCATCACCTCCCATTTGCC----------TCTGGCTACAAAGCTCCAGAATGGAAGCCCAC	1.54 %
	ACTAAGTCCATTCCTGATACCATCACCTCCCATTTGCCAGAC-----CTCTGGCTACAAAGCTCCAGAATGGAAGCCCAC	0.86 %
TET2_E3_3__TET2	ATGGCCCCCGAAGCAAGCCTGATGGAACAGGATAGAACCAACCAaTGTTGAGGGCAACAGACTAAGTCCATTCCTGATAC.	12.88 %
	ATGGCCCCCGAAGCAAGCCTGATGGAACAGGATAGAACCAACC-TGTTGAGGGCAACAGACTAAGTCCATTCCTGATACCA	9.16 %
	ATGGCCCCCGAAGCAAGCCTGATGGAACAG----------ACTAAGTCCATTCCTGATACCA	7.15 %
	ATGGCCCCCGAAGCAAGCCTGATGGAACAGGATAGAACCAACC--GTTGAGGGCAACAGACTAAGTCCATTCCTGATACCA	4.55 %
	ATGGCCCCCGAAGCAAGCCTGATGGAACAGGATAGAACCAAC----------AGACTAAGTCCATTCCTGATACCA	2.20 %
TET2_E3_4__TET2	AGCAAGCCTGATGGAACAGGATAGAACCAACCATGTT+GAGGGCAACAGACTAAGTCCATTCCTGATACCATCACCTCC.	21.79 %
	AGCAAGCCTGATGGAACAGGATAGAACCAACCATGT-GAGGGCAACAGACTAAGTCCATTCCTGATACCATCACCTCCCA	7.57 %
	AGCAAGCCTGATGGAACAG----------ACTAAGTCCATTCCTGATACCATCACCTCCCA	4.50 %
	AGCAAGCCTGATGGAACAGGATAGAACCAAC----------AGACTAAGTCCATTCCTGATACCATCACCTCCCA	4.25 %
	AGCAAGCCTGATGGAACAGGATAGAACCAACCATG---AGGGCAACAGACTAAGTCCATTCCTGATACCATCACCTCCCA	2.81 %
TET2_E3_5__TET2	TTCCTGATACCATCACCTCCCATTTGCCAGACAGAACgTCTGGCTACAAAGCTCCAGAATGGAAGCCCACTGCCTGAGAG	40.20 %
	TTCCTGATACCATCACCTCCCATTTGCCAGACAGAACCTCTGGgCTACAAAGCTCCAGAATGGAAGCCCACTGCCTGAG.	6.29 %
	TTCCTGATACCATCACCTCCCATTTGCCAGACAGAACCTCTG-CTACAAAGCTCCAGAATGGAAGCCCACTGCCTGAGAG	3.12 %
	TTCCTGATACCATCACCTCCCATTTGCCAGACAGAA----------TGGAAGCCCACTGCCTGAGAG	3.06 %
	TTCCTGATACCATCACCTCCCATTTGCCAGACAGAACCTC----------CAGAATGGAAGCCCACTGCCTGAGAG	2.18 %

FIG. 25

TET2_E9_1__TET2
TTCAGATTGAATATGAACACAGAGCACCAGAGTGC-GTCTGGGTCTGAAGGAAGGCCGTCCATTCTCAGGGGTCACTGCA 1.87 %
TTCAGATTGAATATGAACACAGAGCACCAGAGTGCCcGTCTGGGTCTGAAGGAAGGCCGTCCATTCTCAGGGGTCACTG. 1.53 %
TTCAGATTGAATATGAACACAGAGCACCAGAGTGCCGTCTGGGTCcGAAGGAAGGCCGTCCATTCTCAGGGGTCACTGCA 0.33 %
TTCAGATTGAATATGAgCACAGAGCACCAGAGTGCCGTCTGGGTCTGAAGGAAGGCCGTCCATTCTCAGGGGTCACTGCA 0.27 %
TTCAGATTGAATATGAACACAGAGCACCAGAGTGCCGTCTGGGTCTGAAGGAgGGCCGTCCATTCTCAGGGGTCACTGCA 0.25 %
TET2_E9_2__TET2
TCAGATTGAATATGAACACAGAGCACCAGAGTGCC-TCTGGGTCTGAAGGAAGGCCGTCCATTCTCAGGGGTCACTGCAT 2.40 %
TCAGATTGAATATGAACACAGAGCACCAGAGTG--------GGTCTGAAGGAAGGCCGTCCATTCTCAGGGGTCACTGCAT 2.29 %
TCAGATTGAATATGAACACAGAGCACCAGAGT----------CTGAAGGAAGGCCGTCCATTCTCAGGGGTCACTGCAT 2.28 %
TCAGATTGAATATGAACACAGAGCACCAGAGTGC-----TGGGTCTGAAGGAAGGCCGTCCATTCTCAGGGGTCACTGCAT 1.59 %
TCAGATTGAATATGAACACAGAGCACCAGAGTGC----------TGAAGGAAGGCCGTCCATTCTCAGGGGTCACTGCAT 1.31 %
TET2_E9_3__TET2
ACTTTTATTTTTCAGATTGAATATGAACACAGAGCACC---------GTCTGGGTCTGAAGGAAGGCCGTCCATTCTCAGG 9.13 %
ACTTTTATTTTTCAGATTGAATATGAACACAGAGCACCAGAGTtGCCGTCTGGGTCTGAAGGAAGGCCGTCCATTCTCA. 7.17 %
ACTTTTATTTTTCAGATTGAATATGAACACAGAGC----------CGTCTGGGTCTGAAGGAAGGCCGTCCATTCTCAGG 4.18 %
ACTTTTATTTTTCAGATTGAATATGAACACAGAGCACCAGAG--CCGTCTGGGTCTGAAGGAAGGCCGTCCATTCTCAGG 3.47 %
ACTTTTATTTTTCAGATTGAATATGAACACAGAGCACCAG--TGCCGTCTGGGTCTGAAGGAAGGCCGTCCATTCTCAGG 3.04 %
TET2_E9_4__TET2
GACTTGCACAACATGCAGAATGGCAGCACATTGG---------GCTGAGGACAGCTTAGCAGCTGTTGAGTCTGTTCTCAC 11.67 %
GACTTGCACAACATGCAGAATGGCAGCACATTGGT-----TGGGCTGAGGACAGCTTAGCAGCTGTTGAGTCTGTTCTCAC 3.68 %
GACTTGCACAACATGCAGAATGGCAGCACATTGGTA-GTTGGGCTGAGGACAGCTTAGCAGCTGTTGAGTCTGTTCTCAC 3.16 %
GACTTGCACAACATGCAGAATGGCAGC----------TTAGCAGCTGTTGAGTCTGTTCTCAC 2.38 %
GACTTGCACAACATGCAGAATGGCAGCACATTGG----------CTGAGGACAGCTTAGCAGCTGTTGAGTCTGTTCTCAC 1.13 %
TET2_E9_5__TET2
ACAACATGCAGAATGGCAGCACATTGGTAAGTTGG-CTGAGGACAGCTTAGCAGCTGTTGAGTCTGTTCTCACACTGCTA 1.31 %
ACAACATGCAGAATGGCAGCACATTGGTAAGTTGGG--GAGGACAGCTTAGCAGCTGTTGAGTCTGTTCTCACACTGCTA 1.29 %
ACAACATGCAGAATGGCAGCACATTGGTAAGT----------CTGTTCTCACACTGCTA 1.18 %
ACAACATGCAGAATGGCAGCACATTGGTAAGTTGGG-------ACAGCTTAGCAGCTGTTGAGTCTGTTCTCACACTGCTA 1.08 %
ACAACATGCAGAATGGCAGCACATTGGTAAG----------CTTAGCAGCTGTTGAGTCTGTTCTCACACTGCTA 1.06 %
TET2_E9_6__TET2
CTGTGCTCATGCCCACAGAGACTTGCACAACATGCAaGAATGGCAGCACATTGGTAAGTTGGGCTGAGGACAGCTTAGC. 43.24 %
CTGTGCTCATGCCCACAGAGACTTGCACA----------TTGGTAAGTTGGGCTGAGGACAGCTTAGCAG 5.53 %
CTGTGCTCATGCCCACAGAGACTTGCACAACATG--------GCAGCACATTGGTAAGTTGGGCTGAGGACAGCTTAGCAG 2.03 %
CTGTGCTCATGCCCACAGAGACTTGCA----------GCACATTGGTAAGTTGGGCTGAGGACAGCTTAGCAG 1.79 %
CTGTGCTCATGCCCACAGAGACTTGCACAACAT--AGAATGGCAGCACATTGGTAAGTTGGGCTGAGGACAGCTTAGCAG 1.44 %

FIG. 26

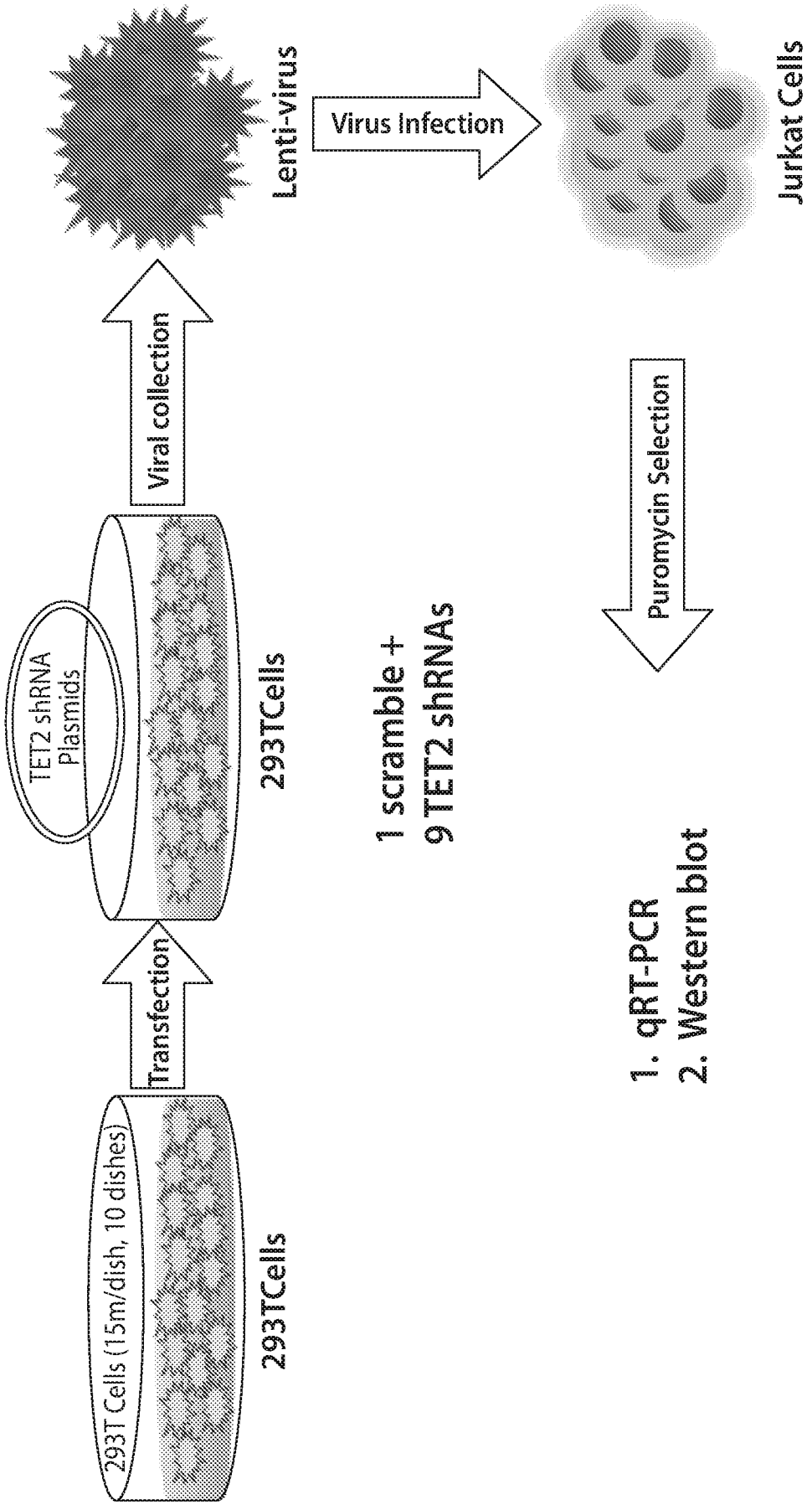

293T Cells (15m/dish, 10 dishes)
293TCells
Transfection
TET2 shRNA Plasmids
293TCells
Viral collection
Lenti-virus
Virus Infection
Jurkat Cells
1 scramble +
9 TET2 shRNAs
Puromycin Selection
1. qRT-PCR
2. Western blot

FIG. 27

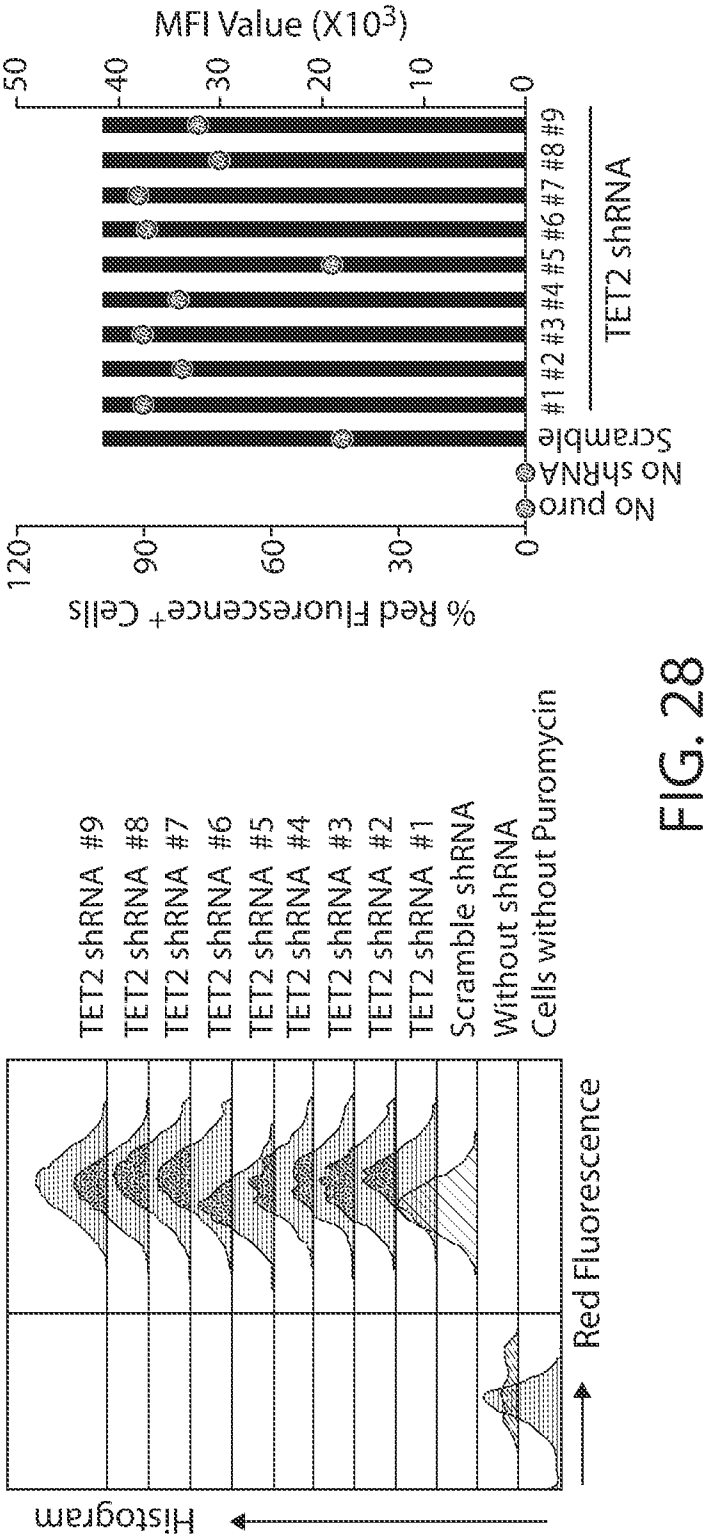

MFI Value (X10^3)
50
40
30
20
10
0
#1 #2 #3 #4 #5 #6 #7 #8 #9
TET2 shRNA
Scramble
No shRNA
No puro
% Red Fluorescence$^+$ Cells
120
90
60
30
0
TET2 shRNA #9
TET2 shRNA #8
TET2 shRNA #7
TET2 shRNA #6
TET2 shRNA #5
TET2 shRNA #4
TET2 shRNA #3
TET2 shRNA #2
TET2 shRNA #1
Scramble shRNA
Without shRNA
Cells without Puromycin
Histogram
Red Fluorescence

FIG. 28

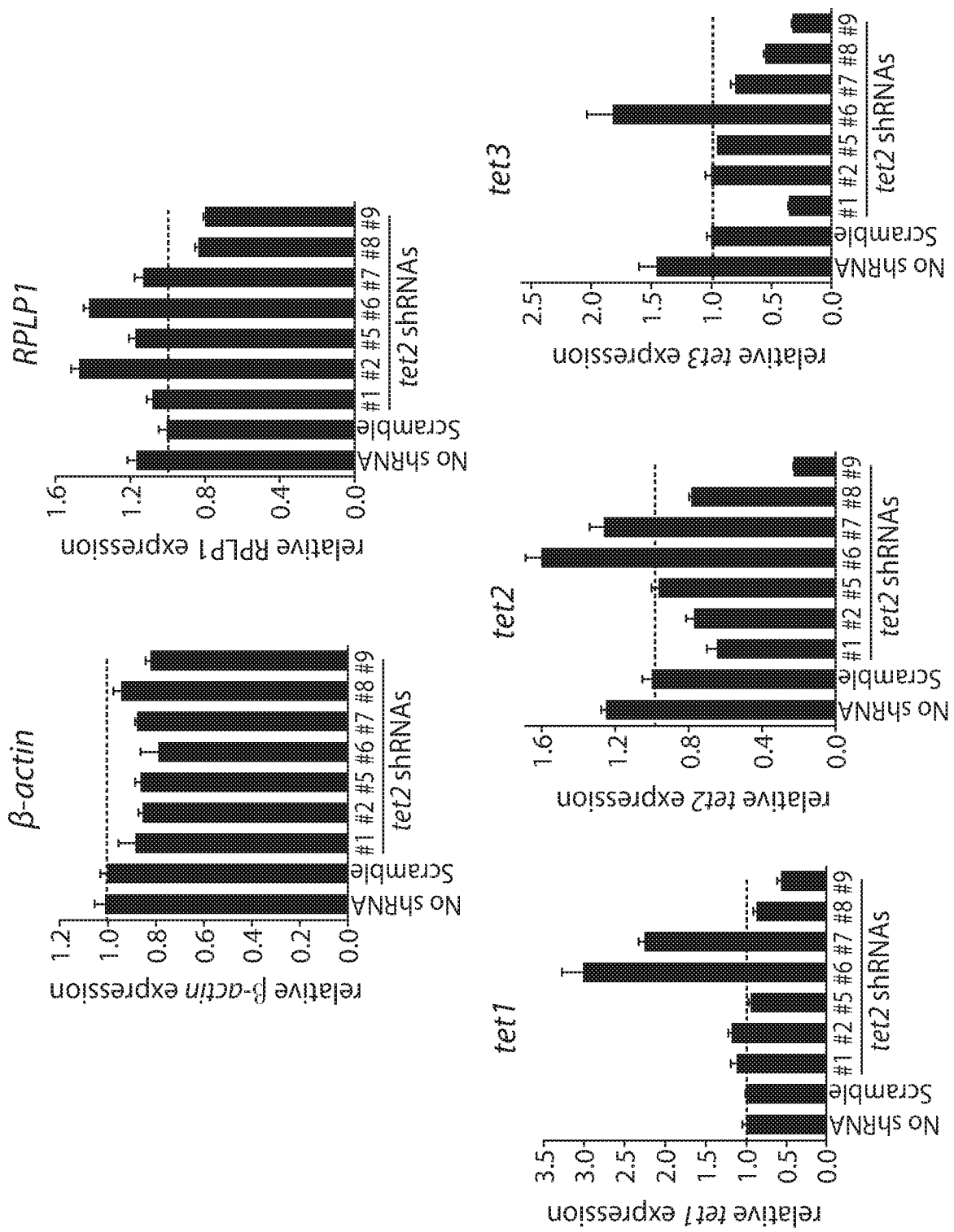

RPLP1
relative RPLP1 expression
1.6
1.2
0.8
0.4
0.0
No shRNA
Scramble
#1 #2 #5 #6 #7 #8 #9
tet2 shRNAs
β-actin
relative β-actin expression
1.2
1.0
0.8
0.6
0.4
0.2
0.0
tet3
relative tet3 expression
2.5
2.0
1.5
1.0
0.5
0.0
tet2
relative tet2 expression
tet1
relative tet1 expression
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

FIG. 29

No shRNA
Scramble
TET2 shRNAs
#1
#2
#5
#6
#7
#8
#9
270KD
40KD
TET2
β-actin

FIG. 30

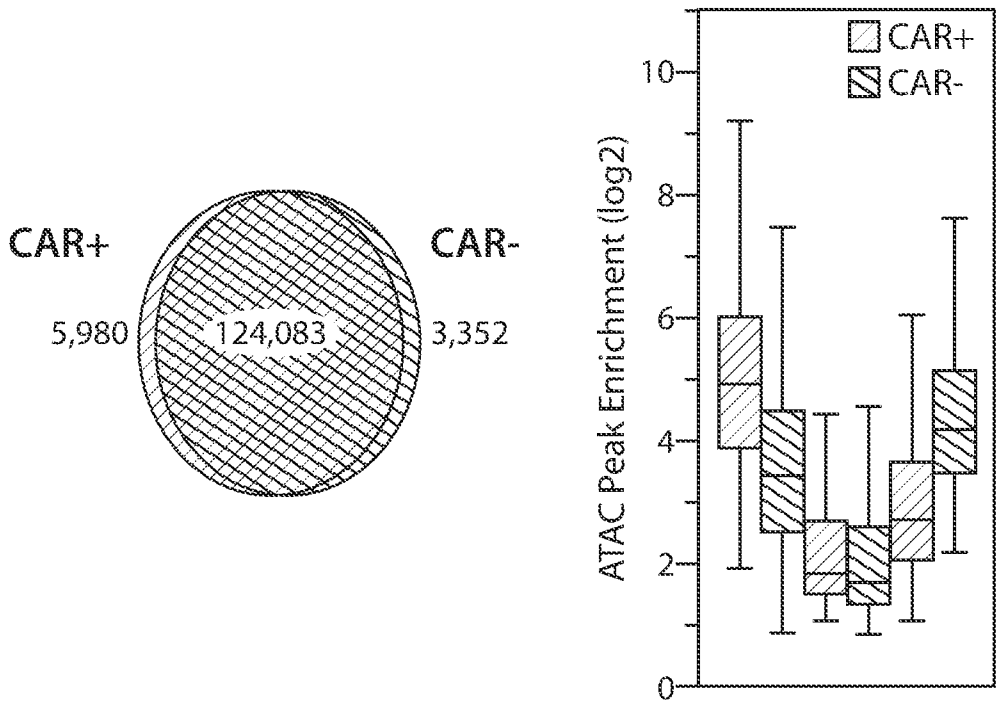

CAR+
CAR-
5,980
124,083
3,352
CAR+
CAR-
ATAC Peak Enrichment (log2)
0
2
4
6
8
10

FIG. 31A

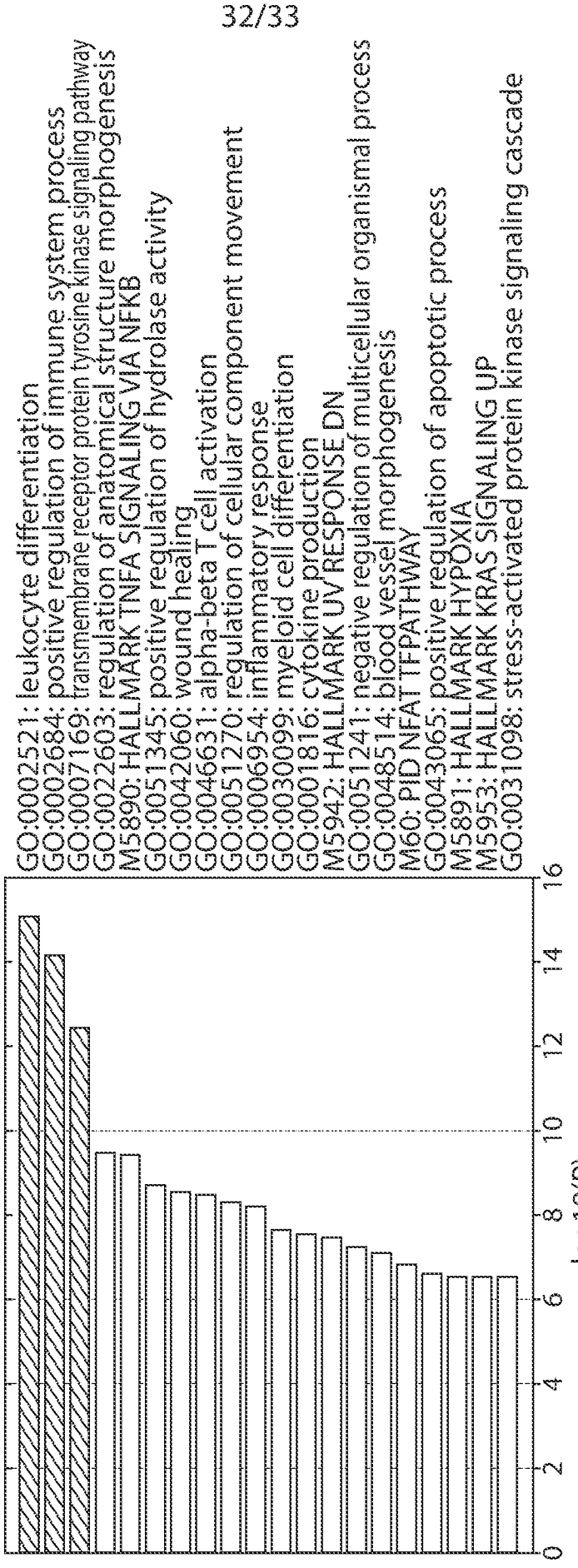

GO:0002521: leukocyte differentiation
GO:0002684: positive regulation of immune system process
GO:0007169: transmembrane receptor protein tyrosine kinase signaling pathway
GO:0022603: regulation of anatomical structure morphogenesis
M5890: HALLMARK TNFA SIGNALING VIA NFKB
GO:0051345: positive regulation of hydrolase activity
GO:0042060: wound healing
GO:0046631: alpha-beta T cell activation
GO:0051270: regulation of cellular component movement
GO:0006954: inflammatory response
GO:0030099: myeloid cell differentiation
GO:0001816: cytokine production
M5942: HALLMARK UV RESPONSE DN
GO:0051241: negative regulation of multicellular organismal process
GO:0048514: blood vessel morphogenesis
M60: PID NFAT TFPATHWAY
GO:0043065: positive regulation of apoptotic process
M5891: HALLMARK HYPOXIA
M5953: HALLMARK KRAS SIGNALING UP
GO:0031098: stress-activated protein kinase signaling cascade
0
2
4
6
8
10
12
14
16
-log10(P)

FIG. 31B

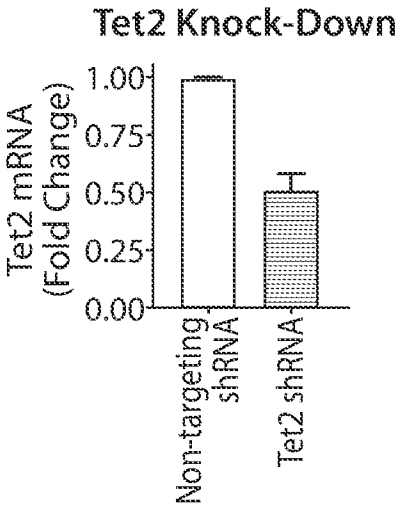


FIG. 32A

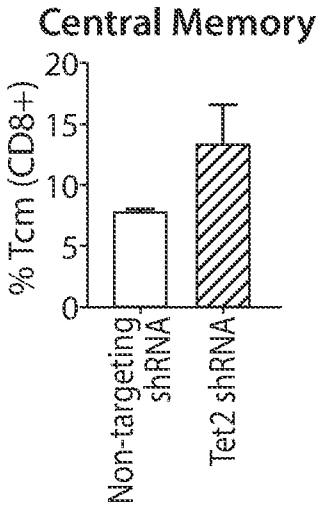


FIG. 32B

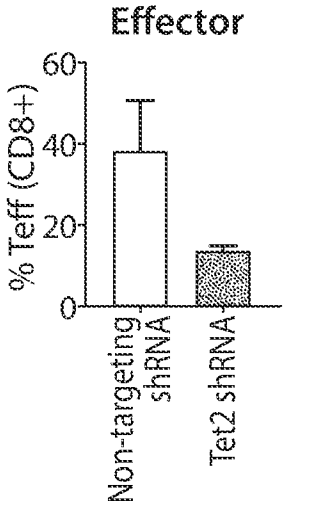


FIG. 32C

SEQUENCE LISTING

<110> NOVARTIS AG
THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA

<120> CAR T CELL THERAPIES WITH ENHANCED EFFICACY

<130> N2067-7098WO

<140>
<141>

<150> 62/220,196
<151> 2015-09-17

<160> 1363

<170> PatentIn version 3.5

<210> 1
<211> 1184
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1
cgtgaggctc cggtgcccgt cagtgggcag agcgcacatc gcccacagtc cccgagaagt 60

tgggggggagg ggtcggcaat tgaaccggtg cctagagaag gtggcgcggg gtaaactggg 120

aaagtgatgt cgtgtactgg ctccgccttt ttcccgaggg tgggggagaa ccgtatataa 180

gtgcagtagt cgccgtgaac gttcttttc gcaacgggtt tgccgccaga acacaggtaa 240

gtgccgtgtg tggttcccgc gggcctggcc tctttacggg ttatggccct tgcgtgcctt 300

gaattacttc cacctggctg cagtacgtga ttcttgatcc cgagcttcgg gttggaagtg 360

ggtgggagag ttcgaggcct tgcgcttaag gagccccttc gcctcgtgct tgagttgagg 420

cctggcctgg gcgctggggc cgccgcgtgc gaatctggtg gcaccttcgc gcctgtctcg 480

ctgctttcga taagtctcta gccatttaaa atttttgatg acctgctgcg acgcttttt 540

tctggcaaga tagtcttgta aatgcgggcc aagatctgca cactggtatt tcggtttttg 600

gggccgcggg cggcgacggg gcccgtgcgt cccagcgcac atgttcggcg aggcggggcc 660

tgcgagcgcg gccaccgaga atcggacggg ggtagtctca agctggccgg cctgctctgg 720

tgcctggcct cgcgccgccg tgtatcgccc cgccctgggc ggcaaggctg gcccggtcgg 780

caccagttgc gtgagcggaa agatggccgc ttcccggccc tgctgcaggg agctcaaaat 840

ggaggacgcg gcgctcggga gagcgggcgg gtgagtcacc cacacaaagg aaaagggcct 900

ttccgtcctc agccgtcgct tcatgtgact ccacggagta ccgggcgccg tccaggcacc 960

tcgattagtt ctcgagcttt tggagtacgt cgtctttagg ttgggggggag gggttttatg 1020

cgatggagtt tccccacact gagtgggtgg agactgaagt taggccagct tggcacttga 1080

tgtaattctc cttggaattt gccctttttg agtttggatc ttggttcatt ctcaagcctc 1140

agacagtggt tcaaagtttt tttcttccat ttcaggtgtc gtga 1184

<210> 2
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 2
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro
20

<210> 3
<211> 63
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 3
atggccctgc ctgtgacagc cctgctgctg cctctggctc tgctgctgca tgccgctaga 60

ccc 63

<210> 4
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 4
Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
1 5 10 15

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
20 25 30

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp

35 40 45

<210> 5
<211> 135
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 5
accacgacgc cagcgccgcg accaccaaca ccggcgccca ccatcgcgtc gcagcccctg 60

tccctgcgcc cagaggcgtg ccggccagcg gcgggggcg cagtgcacac gagggggctg 120

gacttcgcct gtgat 135

<210> 6
<211> 230
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 6
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1 5 10 15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
20 25 30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
35 40 45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
50 55 60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65 70 75 80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
85 90 95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
100 105 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
115 120 125

```
Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
145                 150                 155                 160

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
                165                 170                 175

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220

Leu Ser Leu Gly Lys Met
225                 230
```

<210> 7
<211> 690
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 7

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gagagcaagt acggccctcc ctgcccccct tgccctgccc ccgagttcct gggcggaccc       60

agcgtgttcc tgttcccccc caagcccaag gacaccctga tgatcagccg gacccccgag      120

gtgacctgtg tggtggtgga cgtgtcccag gaggaccccg aggtccagtt caactggtac      180

gtggacggcg tggaggtgca caacgccaag accaagcccc gggaggagca gttcaatagc      240

acctaccggg tggtgtccgt gctgaccgtg ctgcaccagg actggctgaa cggcaaggaa      300

tacaagtgta aggtgtccaa caagggcctg cccagcagca tcgagaaaac catcagcaag      360

gccaagggcc agcctcggga gccccaggtg tacaccctgc cccctagcca agaggagatg      420

accaagaacc aggtgtccct gacctgcctg gtgaagggct tctaccccag cgacatcgcc      480

gtggagtggg agagcaacgg ccagcccgag aacaactaca agaccacccc ccctgtgctg      540

gacagcgacg gcagcttctt cctgtacagc cggctgaccg tggacaagag ccggtggcag      600

gagggcaacg tctttagctg ctccgtgatg cacgaggccc tgcacaacca ctacacccag      660

aagagcctga gcctgtccct gggcaagatg                                       690
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<210> 8
<211> 282
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 8

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Arg Trp Pro Glu Ser Pro Lys Ala Gln Ala Ser Ser Val Pro Thr Ala
1               5                   10                  15

Gln Pro Gln Ala Glu Gly Ser Leu Ala Lys Ala Thr Thr Ala Pro Ala
            20                  25                  30

Thr Thr Arg Asn Thr Gly Arg Gly Gly Glu Glu Lys Lys Lys Glu Lys
        35                  40                  45

Glu Lys Glu Glu Gln Glu Glu Arg Glu Thr Lys Thr Pro Glu Cys Pro
    50                  55                  60

Ser His Thr Gln Pro Leu Gly Val Tyr Leu Leu Thr Pro Ala Val Gln
65                  70                  75                  80

Asp Leu Trp Leu Arg Asp Lys Ala Thr Phe Thr Cys Phe Val Val Gly
                85                  90                  95

Ser Asp Leu Lys Asp Ala His Leu Thr Trp Glu Val Ala Gly Lys Val
            100                 105                 110

Pro Thr Gly Gly Val Glu Glu Gly Leu Leu Glu Arg His Ser Asn Gly
        115                 120                 125

Ser Gln Ser Gln His Ser Arg Leu Thr Leu Pro Arg Ser Leu Trp Asn
    130                 135                 140

Ala Gly Thr Ser Val Thr Cys Thr Leu Asn His Pro Ser Leu Pro Pro
145                 150                 155                 160

Gln Arg Leu Met Ala Leu Arg Glu Pro Ala Ala Gln Ala Pro Val Lys
                165                 170                 175

Leu Ser Leu Asn Leu Leu Ala Ser Ser Asp Pro Pro Glu Ala Ala Ser
            180                 185                 190

Trp Leu Leu Cys Glu Val Ser Gly Phe Ser Pro Pro Asn Ile Leu Leu
        195                 200                 205
```

```
Met Trp Leu Glu Asp Gln Arg Glu Val Asn Thr Ser Gly Phe Ala Pro
    210                 215                 220

Ala Arg Pro Pro Pro Gln Pro Gly Ser Thr Thr Phe Trp Ala Trp Ser
225                 230                 235                 240

Val Leu Arg Val Pro Ala Pro Pro Ser Pro Gln Pro Ala Thr Tyr Thr
                245                 250                 255

Cys Val Val Ser His Glu Asp Ser Arg Thr Leu Leu Asn Ala Ser Arg
            260                 265                 270

Ser Leu Glu Val Ser Tyr Val Thr Asp His
        275                 280
```

<210> 9
<211> 847
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 9

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aggtggcccg aaagtcccaa ggcccaggca tctagtgttc ctactgcaca gccccaggca       60

gaaggcagcc tagccaaagc tactactgca cctgccacta cgcgcaatac tggccgtggc      120

ggggaggaga agaaaaagga gaaagagaaa gaagaacagg aagagaggga gaccaagacc      180

cctgaatgtc catcccatac ccagccgctg ggcgtctatc tcttgactcc cgcagtacag      240

gacttgtggc ttagagataa ggccaccttt acatgtttcg tcgtgggctc tgacctgaag      300

gatgcccatt tgacttggga ggttgccgga aaggtaccca cagggggggt tgaggaaggg      360

ttgctggagc gccattccaa tggctctcag agccagcact caagactcac ccttccgaga      420

tccctgtgga acgccgggac ctctgtcaca tgtactctaa atcatcctag cctgccccca      480

cagcgtctga tggcccttag agagccagcc gcccaggcac cagttaagct tagcctgaat      540

ctgctcgcca gtagtgatcc cccagaggcc gccagctggc tcttatgcga agtgtccggc      600

tttagcccgc ccaacatctt gctcatgtgg ctggaggacc agcgagaagt gaacaccagc      660

ggcttcgctc cagcccggcc cccaccccag ccgggttcta ccacattctg ggcctggagt      720

gtcttaaggg tcccagcacc acctagcccc cagccagcca catacacctg tgttgtgtcc      780

catgaagata gcaggaccct gctaaatgct tctaggagtc tggaggtttc ctacgtgact      840

gaccatt                                                                847
```

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

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 10
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10

<210> 11
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 11
ggtggcggag gttctggagg tggaggttcc 30

<210> 12
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 12
Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
1 5 10 15

Ser Leu Val Ile Thr Leu Tyr Cys
20

<210> 13
<211> 72
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 13
atctacatct gggcgccctt ggccgggact tgtggggtcc ttctcctgtc actggttatc 60

acccttttact gc 72

<210> 14
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 14
Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
1 5 10 15

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

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
35 40

<210> 15
<211> 126
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 15
aaacggggca gaaagaaact cctgtatata ttcaaacaac catttatgag accagtacaa 60

actactcaag aggaagatgg ctgtagctgc cgatttccag aagaagaaga aggaggatgt 120

gaactg 126

<210> 16
<211> 48
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 16
Gln Arg Arg Lys Tyr Arg Ser Asn Lys Gly Glu Ser Pro Val Glu Pro
1 5 10 15

Ala Glu Pro Cys Arg Tyr Ser Cys Pro Arg Glu Glu Glu Gly Ser Thr
20 25 30

Ile Pro Ile Gln Glu Asp Tyr Arg Lys Pro Glu Pro Ala Cys Ser Pro

35 40 45

<210> 17
<211> 123
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 17
aggagtaaga ggagcaggct cctgcacagt gactacatga acatgactcc ccgccgcccc 60

gggcccaccc gcaagcatta ccagccctat gccccaccac gcgacttcgc agcctatcgc 120

tcc 123

<210> 18
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 18
Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly
1 5 10 15

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
20 25 30

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
35 40 45

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
50 55 60

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
65 70 75 80

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
85 90 95

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
100 105 110

<210> 19
<211> 336
<212> DNA

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 19
agagtgaagt tcagcaggag cgcagacgcc cccgcgtaca agcagggcca gaaccagctc 60

tataacgagc tcaatctagg acgaagagag gagtacgatg ttttggacaa gagacgtggc 120

cgggaccctg agatgggggg aaagccgaga aggaagaacc ctcaggaagg cctgtacaat 180

gaactgcaga aagataagat ggcggaggcc tacagtgaga ttgggatgaa aggcgagcgc 240

cggaggggca aggggcacga tggcctttac cagggtctca gtacagccac caaggacacc 300

tacgacgccc ttcacatgca ggccctgccc cctcgc 336

<210> 20
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 20
Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly
1 5 10 15

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
20 25 30

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
35 40 45

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
50 55 60

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
65 70 75 80

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
85 90 95

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
100 105 110

<210> 21
<211> 336
<212> DNA

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 21
agagtgaagt tcagcaggag cgcagacgcc cccgcgtacc agcagggcca gaaccagctc 60

tataacgagc tcaatctagg acgaagagag gagtacgatg ttttggacaa gagacgtggc 120

cgggaccctg agatgggggg aaagccgaga aggaagaacc ctcaggaagg cctgtacaat 180

gaactgcaga aagataagat ggcggaggcc tacagtgaga ttgggatgaa aggcgagcgc 240

cggaggggca aggggcacga tggcctttac cagggtctca gtacagccac caaggacacc 300

tacgacgccc ttcacatgca ggccctgccc cctcgc 336

<210> 22
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 22
Gly Gly Gly Gly Ser
1 5

<210> 23
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 23
ggtggcggag gttctggagg tggaggttcc 30

<210> 24
<211> 150
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 24
Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp Asn Pro Pro Thr
1 5 10 15

```
Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp Asn Ala Thr Phe
            20                  25                  30

Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val Leu Asn Trp Tyr
        35                  40                  45

Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala Ala Phe Pro Glu
    50                  55                  60

Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg Val Thr Gln Leu
65                  70                  75                  80

Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg Ala Arg Arg Asn
                85                  90                  95

Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu Ala Pro Lys Ala
            100                 105                 110

Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val Thr Glu Arg Arg
        115                 120                 125

Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro Arg Pro Ala Gly
    130                 135                 140

Gln Phe Gln Thr Leu Val
145                 150
```

<210> 25
<211> 450
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 25

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cccggatggt ttctggactc tccggatcgc ccgtggaatc ccccaacctt ctcaccggca       60

ctcttggttg tgactgaggg cgataatgcg accttcacgt gctcgttctc caacacctcc      120

gaatcattcg tgctgaactg gtaccgcatg agcccgtcaa accagaccga caagctcgcc      180

gcgtttccgg aagatcggtc gcaaccggga caggattgtc ggttccgcgt gactcaactg      240

ccgaatggca gagacttcca catgagcgtg gtccgcgcta ggcgaaacga ctccgggacc      300

tacctgtgcg gagccatctc gctggcgcct aaggcccaaa tcaaagagag cttgagggcc      360

gaactgagag tgaccgagcg cagagctgag gtgccaactg cacatccatc cccatcgcct      420
```

cggcctgcgg ggcagtttca gaccctggtc 450

<210> 26
<211> 394
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 26

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Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro
            20                  25                  30

Trp Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly
        35                  40                  45

Asp Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe
    50                  55                  60

Val Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu
65                  70                  75                  80

Ala Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe
                85                  90                  95

Arg Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val
            100                 105                 110

Arg Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser
        115                 120                 125

Leu Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg
    130                 135                 140

Val Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser
145                 150                 155                 160

Pro Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Thr Thr Thr Pro Ala
                165                 170                 175

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
            180                 185                 190

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
```

195 200 205

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
210 215 220

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
225 230 235 240

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
245 250 255

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
260 265 270

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
275 280 285

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
290 295 300

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
305 310 315 320

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
325 330 335

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
340 345 350

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
355 360 365

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
370 375 380

Ala Leu His Met Gln Ala Leu Pro Pro Arg
385 390

<210> 27
<211> 1182
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 27
atggccctcc ctgtcactgc cctgcttctc cccctcgcac tcctgctcca cgccgctaga 60

ccacccggat ggtttctgga ctctccggat cgcccgtgga atcccccaac cttctcaccg 120

gcactcttgg ttgtgactga gggcgataat gcgaccttca cgtgctcgtt ctccaacacc 180

tccgaatcat tcgtgctgaa ctggtaccgc atgagcccgt caaaccagac cgacaagctc 240

gccgcgtttc cggaagatcg gtcgcaaccg ggacaggatt gtcggttccg cgtgactcaa 300

ctgccgaatg gcagagactt ccacatgagc gtggtccgcg ctaggcgaaa cgactccggg 360

acctacctgt gcggagccat ctcgctggcg cctaaggccc aaatcaaaga gagcttgagg 420

gccgaactga gagtgaccga gcgcagagct gaggtgccaa ctgcacatcc atccccatcg 480

cctcggcctg cggggcagtt tcagaccctg gtcacgacca ctccggcgcc gcgcccaccg 540

actccggccc caactatcgc gagccagccc ctgtcgctga ggccggaagc atgccgccct 600

gccgccggag gtgctgtgca tacccgggga ttggacttcg catgcgacat ctacatttgg 660

gctcctctcg ccggaacttg tggcgtgctc cttctgtccc tggtcatcac cctgtactgc 720

aagcggggtc ggaaaaagct tctgtacatt ttcaagcagc ccttcatgag gcccgtgcaa 780

accacccagg aggaggacgg ttgctcctgc cggttccccg aagaggaaga aggaggttgc 840

gagctgcgcg tgaagttctc ccggagcgcc gacgcccccg cctataagca gggccagaac 900

cagctgtaca acgaactgaa cctgggacgg cgggaagagt acgatgtgct ggacaagcgg 960

cgcggccggg accccgaaat gggcgggaag cctagaagaa agaaccctca ggaaggcctg 1020

tataacgagc tgcagaagga caagatggcc gaggcctact ccgaaattgg gatgaaggga 1080

gagcggcgga ggggaaaggg gcacgacggc ctgtaccaag gactgtccac cgccaccaag 1140

gacacatacg atgccctgca catgcaggcc cttccccctc gc 1182

<210> 28
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<220>
<221> MISC_FEATURE
<222> (1)..(40)
<223> /note="This sequence may encompass 1-10
"Gly-Gly-Gly-Ser" repeating units"

<400> 28
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser

20 25 30

Gly Gly Gly Ser Gly Gly Gly Ser
35 40

<210> 29
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 29
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser
20

<210> 30
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 30
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 31
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 31
Gly Gly Gly Ser
1

<210> 32
<211> 2000
<212> DNA
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<220>
<221> misc_feature
<222> (1)..(2000)
<223> /note="This sequence may encompass 50-2000 nucleotides"

<220>
<221> source
<223> /note="See specification as filed for detailed description of substitutions and preferred embodiments"

<400> 32
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 60

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 120

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 180

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 240

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 300

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 360

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 420

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 480

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 540

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 600

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 660

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 720

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 780

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 840

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 900

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 960

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1020

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1080

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1140

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1200

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1260

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1320

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1380

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1440

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1500

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1560

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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1680

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aaaaaaaaaa aaaaaaaaaa 2000

<210> 33
<211> 150
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 33
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 60

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 120

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 150

<210> 34
<211> 5000
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<220>
<221> misc_feature
<222> (1)..(5000)
<223> /note="This sequence may encompass 50-5000 nucleotides"

<220>
<221> source
<223> /note="See specification as filed for detailed description of substitutions and preferred embodiments"

<400> 34
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 180

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 240

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 300

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 360

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 420

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 480

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 540

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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 660

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 720

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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 900

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 960

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1020

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1080

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1140

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aaaaaaaaaa aaaaaaaaaa 5000

<210> 35
<211> 100
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 35
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ttttttttt ttttttttt ttttttttt ttttttttt 100

<210> 36
<211> 5000
<212> DNA
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<220>
<221> misc_feature
<222> (1)..(5000)
<223> /note="This sequence may encompass 50-5000 nucleotides"

<220>
<221> source
<223> /note="See specification as filed for detailed description of substitutions and preferred embodiments"

<400> 36
tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 60

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tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 180

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 240

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 300

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 360

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 420

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 480

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 540

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 600

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 660

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 720

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 780

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 840

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 900

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 960

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 1020

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 1080

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 1140

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 1200

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 1260

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tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 1440

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tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 1560

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tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 1860

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 1920

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 1980

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 2040

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tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 2160

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ttttttttct ttttttttct 5000

<210> 37
<211> 5000
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (1)..(5000)
<223> /note="This sequence may encompass 100-5000 nucleotides"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 37
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aaaaaaaaaa aaaaaaaaaa 5000

<210> 38
<211> 400

<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<220>
<221> misc_feature
<222> (1)..(400)
<223> /note="This sequence may encompass 100-400 nucleotides"

<220>
<221> source
<223> /note="See specification as filed for detailed description of substitutions and preferred embodiments"

<400> 38
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 60

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 120

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 180

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 240

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 300

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 360

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 400

<210> 39
<211> 373
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 39
Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp Asn Pro Pro Thr
1 5 10 15

Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp Asn Ala Thr Phe
20 25 30

Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val Leu Asn Trp Tyr
35 40 45

Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala Ala Phe Pro Glu
50 55 60

Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg Val Thr Gln Leu

```
65                  70                  75                  80

Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg Ala Arg Arg Asn
                85                  90                  95

Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu Ala Pro Lys Ala
            100                 105                 110

Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val Thr Glu Arg Arg
        115                 120                 125

Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro Arg Pro Ala Gly
    130                 135                 140

Gln Phe Gln Thr Leu Val Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr
145                 150                 155                 160

Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala
                165                 170                 175

Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe
            180                 185                 190

Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
        195                 200                 205

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys
    210                 215                 220

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
225                 230                 235                 240

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
                245                 250                 255

Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
            260                 265                 270

Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
        275                 280                 285

Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
    290                 295                 300

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
305                 310                 315                 320
```

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
325 330 335

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
340 345 350

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
355 360 365

Ala Leu Pro Pro Arg
370

<210> 40
<211> 42
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<220>
<221> modified_base
<222> (1)..(20)
<223> a, c, u, g, unknown or other

<400> 40
nnnnnnnnnn nnnnnnnnnn guuuuagagc uaugcuguuu ug 42

<210> 41
<211> 86
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<220>
<221> misc_feature
<222> (80)..(86)
<223> /note="This region may encompass 1-7 nucleotides"

<220>
<221> source
<223> /note="See specification as filed for detailed description of substitutions and preferred embodiments"

<400> 41
aacuuaccaa ggaacagcau agcaaguuaa aauaaggcua guccguuauc aacuugaaaa 60

aguggcaccg agucggugcu uuuuuu 86

<210> 42
<211> 74
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<220>
<221> misc_feature
<222> (68)..(74)
<223> /note="This region may encompass 1-7 nucleotides"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 42
aacagcauag caaguuaaaa uaaggcuagu ccguuaucaa cuugaaaaag uggcaccgag 60

ucggugcuuu uuuu 74

<210> 43
<211> 103
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> modified_base
<222> (1)..(20)
<223> a, c, u, g, unknown or other

<220>
<221> variation
<222> (97)..(103)
<223> /note="This region may encompass 1-7 nucleotides"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 43
nnnnnnnnnn nnnnnnnnnn guuuuagagc uagaaauagc aaguuaaaau aaggcuaguc 60

cguuaucaac uugaaaaagu ggcaccgagu cggugcuuuu uuu 103

<210> 44
<211> 20
<212> RNA

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 44
ccuuggacac cuucuccucc 20

<210> 45
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 45
ggaaccugug gaagaggagg 20

<210> 46
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 46
ggaacctgtg gaagaggagg 20

<210> 47
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 47
gaaggaagct gaggaacctg 20

<210> 48
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 48
atgacctcca aacaatacac 20

<210> 49
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 49
caagtgctgt ttcaacactg 20

<210> 50
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 50
gggagatgtg aactctggga 20

<210> 51
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 51
ggaggtgatg gtatcaggaa 20

<210> 52
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 52
ggttctgtct ggcaaatggg 20

<210> 53
<211> 20
<212> DNA

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 53
ggatgagctc tctcaggcag 20

<210> 54
<211> 132
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 54
Asp Val Pro Asp Tyr Ala Ser Leu Gly Gly Pro Ser Ser Pro Lys Lys
1 5 10 15

Lys Arg Lys Val Ser Arg Gly Val Gln Val Glu Thr Ile Ser Pro Gly
20 25 30

Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr
35 40 45

Thr Gly Met Leu Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg Asp Arg
50 55 60

Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly
65 70 75 80

Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala Lys Leu
85 90 95

Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile
100 105 110

Ile Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu Lys Leu
115 120 125

Glu Thr Ser Tyr
130

<210> 55
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 55
Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr Phe Pro Lys
1 5 10 15

Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu Glu Asp Gly
20 25 30

Lys Lys Phe Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe Lys Phe Met
35 40 45

Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly Val Ala Gln
50 55 60

Met Ser Val Gly Gln Arg Ala Lys Leu Thr Ile Ser Pro Asp Tyr Ala
65 70 75 80

Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His Ala Thr Leu
85 90 95

Val Phe Asp Val Glu Leu Leu Lys Leu Glu Thr Ser
100 105

<210> 56
<211> 93
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 56
Ile Leu Trp His Glu Met Trp His Glu Gly Leu Glu Glu Ala Ser Arg
1 5 10 15

Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu
20 25 30

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

Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp
50 55 60

Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Thr Gln Ala
65 70 75 80

Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys
85 90

<210> 57
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 57
Ile Leu Trp His Glu Met Trp His Glu Gly Leu Ile Glu Ala Ser Arg
1 5 10 15

Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu
20 25 30

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

Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp
50 55 60

Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Thr Gln Ala
65 70 75 80

Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys Thr Ser
85 90 95

<210> 58
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 58
Ile Leu Trp His Glu Met Trp His Glu Gly Leu Leu Glu Ala Ser Arg
1 5 10 15

Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu
20 25 30

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

Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp
    50   55   60

Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Thr Gln Ala
65   70   75   80

Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys Thr Ser
                85   90   95

<210> 59
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 59
Ile Leu Trp His Glu Met Trp His Glu Gly Leu Glu Glu Ala Ser Arg
1   5   10   15

Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu
            20   25   30

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

Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp
    50   55   60

Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Leu Gln Ala
65   70   75   80

Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys Thr Ser
                85   90   95

<210> 60
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<220>
<221> MOD_RES
<222> (12)..(12)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (78)..(78)
<223> Any amino acid

<400> 60
Ile Leu Trp His Glu Met Trp His Glu Gly Leu Xaa Glu Ala Ser Arg
1 5 10 15

Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu
20 25 30

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

Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp
50 55 60

Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Xaa Gln Ala
65 70 75 80

Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys Thr Ser
85 90 95

<210> 61
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 61
Ile Leu Trp His Glu Met Trp His Glu Gly Leu Ile Glu Ala Ser Arg
1 5 10 15

Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu
20 25 30

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

Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp
50 55 60

Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Leu Gln Ala
65 70 75 80

Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys Thr Ser

85 90 95

<210> 62
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 62
Ile Leu Trp His Glu Met Trp His Glu Gly Leu Leu Glu Ala Ser Arg
1 5 10 15

Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu
20 25 30

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

Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp
50 55 60

Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Leu Gln Ala
65 70 75 80

Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys Thr Ser
85 90 95

<210> 63
<211> 1132
<212> PRT
<213> Homo sapiens

<400> 63
Met Pro Arg Ala Pro Arg Cys Arg Ala Val Arg Ser Leu Leu Arg Ser
1 5 10 15

His Tyr Arg Glu Val Leu Pro Leu Ala Thr Phe Val Arg Arg Leu Gly
20 25 30

Pro Gln Gly Trp Arg Leu Val Gln Arg Gly Asp Pro Ala Ala Phe Arg
35 40 45

Ala Leu Val Ala Gln Cys Leu Val Cys Val Pro Trp Asp Ala Arg Pro
50 55 60

Pro Pro Ala Ala Pro Ser Phe Arg Gln Val Ser Cys Leu Lys Glu Leu
65 70 75 80

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Val Ala Arg Val Leu Gln Arg Leu Cys Glu Arg Gly Ala Lys Asn Val
                85                  90                  95

Leu Ala Phe Gly Phe Ala Leu Leu Asp Gly Ala Arg Gly Gly Pro Pro
            100                 105                 110

Glu Ala Phe Thr Thr Ser Val Arg Ser Tyr Leu Pro Asn Thr Val Thr
        115                 120                 125

Asp Ala Leu Arg Gly Ser Gly Ala Trp Gly Leu Leu Leu Arg Arg Val
    130                 135                 140

Gly Asp Asp Val Leu Val His Leu Leu Ala Arg Cys Ala Leu Phe Val
145                 150                 155                 160

Leu Val Ala Pro Ser Cys Ala Tyr Gln Val Cys Gly Pro Pro Leu Tyr
                165                 170                 175

Gln Leu Gly Ala Ala Thr Gln Ala Arg Pro Pro Pro His Ala Ser Gly
            180                 185                 190

Pro Arg Arg Arg Leu Gly Cys Glu Arg Ala Trp Asn His Ser Val Arg
        195                 200                 205

Glu Ala Gly Val Pro Leu Gly Leu Pro Ala Pro Gly Ala Arg Arg Arg
    210                 215                 220

Gly Gly Ser Ala Ser Arg Ser Leu Pro Leu Pro Lys Arg Pro Arg Arg
225                 230                 235                 240

Gly Ala Ala Pro Glu Pro Glu Arg Thr Pro Val Gly Gln Gly Ser Trp
                245                 250                 255

Ala His Pro Gly Arg Thr Arg Gly Pro Ser Asp Arg Gly Phe Cys Val
            260                 265                 270

Val Ser Pro Ala Arg Pro Ala Glu Glu Ala Thr Ser Leu Glu Gly Ala
        275                 280                 285

Leu Ser Gly Thr Arg His Ser His Pro Ser Val Gly Arg Gln His His
    290                 295                 300

Ala Gly Pro Pro Ser Thr Ser Arg Pro Pro Arg Pro Trp Asp Thr Pro
305                 310                 315                 320

Cys Pro Pro Val Tyr Ala Glu Thr Lys His Phe Leu Tyr Ser Ser Gly
                325                 330                 335
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Asp Lys Glu Gln Leu Arg Pro Ser Phe Leu Leu Ser Ser Leu Arg Pro
            340                 345                 350

Ser Leu Thr Gly Ala Arg Arg Leu Val Glu Thr Ile Phe Leu Gly Ser
        355                 360                 365

Arg Pro Trp Met Pro Gly Thr Pro Arg Arg Leu Pro Arg Leu Pro Gln
    370                 375                 380

Arg Tyr Trp Gln Met Arg Pro Leu Phe Leu Glu Leu Leu Gly Asn His
385                 390                 395                 400

Ala Gln Cys Pro Tyr Gly Val Leu Leu Lys Thr His Cys Pro Leu Arg
                405                 410                 415

Ala Ala Val Thr Pro Ala Ala Gly Val Cys Ala Arg Glu Lys Pro Gln
            420                 425                 430

Gly Ser Val Ala Ala Pro Glu Glu Glu Asp Thr Asp Pro Arg Arg Leu
        435                 440                 445

Val Gln Leu Leu Arg Gln His Ser Ser Pro Trp Gln Val Tyr Gly Phe
    450                 455                 460

Val Arg Ala Cys Leu Arg Arg Leu Val Pro Pro Gly Leu Trp Gly Ser
465                 470                 475                 480

Arg His Asn Glu Arg Arg Phe Leu Arg Asn Thr Lys Lys Phe Ile Ser
                485                 490                 495

Leu Gly Lys His Ala Lys Leu Ser Leu Gln Glu Leu Thr Trp Lys Met
            500                 505                 510

Ser Val Arg Gly Cys Ala Trp Leu Arg Arg Ser Pro Gly Val Gly Cys
        515                 520                 525

Val Pro Ala Ala Glu His Arg Leu Arg Glu Glu Ile Leu Ala Lys Phe
    530                 535                 540

Leu His Trp Leu Met Ser Val Tyr Val Val Glu Leu Leu Arg Ser Phe
545                 550                 555                 560

Phe Tyr Val Thr Glu Thr Thr Phe Gln Lys Asn Arg Leu Phe Phe Tyr
                565                 570                 575

Arg Lys Ser Val Trp Ser Lys Leu Gln Ser Ile Gly Ile Arg Gln His
```

```
            580                 585                 590

Leu Lys Arg Val Gln Leu Arg Glu Leu Ser Glu Ala Glu Val Arg Gln
        595                 600                 605

His Arg Glu Ala Arg Pro Ala Leu Leu Thr Ser Arg Leu Arg Phe Ile
    610                 615                 620

Pro Lys Pro Asp Gly Leu Arg Pro Ile Val Asn Met Asp Tyr Val Val
625                 630                 635                 640

Gly Ala Arg Thr Phe Arg Arg Glu Lys Arg Ala Glu Arg Leu Thr Ser
                645                 650                 655

Arg Val Lys Ala Leu Phe Ser Val Leu Asn Tyr Glu Arg Ala Arg Arg
            660                 665                 670

Pro Gly Leu Leu Gly Ala Ser Val Leu Gly Leu Asp Asp Ile His Arg
        675                 680                 685

Ala Trp Arg Thr Phe Val Leu Arg Val Arg Ala Gln Asp Pro Pro Pro
    690                 695                 700

Glu Leu Tyr Phe Val Lys Val Asp Val Thr Gly Ala Tyr Asp Thr Ile
705                 710                 715                 720

Pro Gln Asp Arg Leu Thr Glu Val Ile Ala Ser Ile Ile Lys Pro Gln
                725                 730                 735

Asn Thr Tyr Cys Val Arg Arg Tyr Ala Val Val Gln Lys Ala Ala His
            740                 745                 750

Gly His Val Arg Lys Ala Phe Lys Ser His Val Ser Thr Leu Thr Asp
        755                 760                 765

Leu Gln Pro Tyr Met Arg Gln Phe Val Ala His Leu Gln Glu Thr Ser
    770                 775                 780

Pro Leu Arg Asp Ala Val Val Ile Glu Gln Ser Ser Ser Leu Asn Glu
785                 790                 795                 800

Ala Ser Ser Gly Leu Phe Asp Val Phe Leu Arg Phe Met Cys His His
                805                 810                 815

Ala Val Arg Ile Arg Gly Lys Ser Tyr Val Gln Cys Gln Gly Ile Pro
            820                 825                 830
```

```
Gln Gly Ser Ile Leu Ser Thr Leu Leu Cys Ser Leu Cys Tyr Gly Asp
        835                 840                 845

Met Glu Asn Lys Leu Phe Ala Gly Ile Arg Arg Asp Gly Leu Leu Leu
    850                 855                 860

Arg Leu Val Asp Asp Phe Leu Leu Val Thr Pro His Leu Thr His Ala
865                 870                 875                 880

Lys Thr Phe Leu Arg Thr Leu Val Arg Gly Val Pro Glu Tyr Gly Cys
                885                 890                 895

Val Val Asn Leu Arg Lys Thr Val Val Asn Phe Pro Val Glu Asp Glu
            900                 905                 910

Ala Leu Gly Gly Thr Ala Phe Val Gln Met Pro Ala His Gly Leu Phe
        915                 920                 925

Pro Trp Cys Gly Leu Leu Leu Asp Thr Arg Thr Leu Glu Val Gln Ser
    930                 935                 940

Asp Tyr Ser Ser Tyr Ala Arg Thr Ser Ile Arg Ala Ser Leu Thr Phe
945                 950                 955                 960

Asn Arg Gly Phe Lys Ala Gly Arg Asn Met Arg Arg Lys Leu Phe Gly
                965                 970                 975

Val Leu Arg Leu Lys Cys His Ser Leu Phe Leu Asp Leu Gln Val Asn
            980                 985                 990

Ser Leu Gln Thr Val Cys Thr Asn  Ile Tyr Lys Ile Leu  Leu Leu Gln
        995                 1000                 1005

Ala Tyr  Arg Phe His Ala Cys  Val Leu Gln Leu Pro  Phe His Gln
    1010                1015                1020

Gln Val  Trp Lys Asn Pro Thr  Phe Phe Leu Arg Val  Ile Ser Asp
    1025                1030                1035

Thr Ala  Ser Leu Cys Tyr Ser  Ile Leu Lys Ala Lys  Asn Ala Gly
    1040                1045                1050

Met Ser  Leu Gly Ala Lys Gly  Ala Ala Gly Pro Leu  Pro Ser Glu
    1055                1060                1065

Ala Val  Gln Trp Leu Cys His  Gln Ala Phe Leu Leu  Lys Leu Thr
    1070                1075                1080
```

Arg His Arg Val Thr Tyr Val Pro Leu Leu Gly Ser Leu Arg Thr
1085 1090 1095

Ala Gln Thr Gln Leu Ser Arg Lys Leu Pro Gly Thr Thr Leu Thr
1100 1105 1110

Ala Leu Glu Ala Ala Ala Asn Pro Ala Leu Pro Ser Asp Phe Lys
1115 1120 1125

Thr Ile Leu Asp
1130

<210> 64
<211> 4027
<212> DNA
<213> Homo sapiens

<400> 64
caggcagcgt ggtcctgctg cgcacgtggg aagccctggc cccggccacc cccgcgatgc 60

cgcgcgctcc ccgctgccga gccgtgcgct ccctgctgcg cagccactac cgcgaggtgc 120

tgccgctggc cacgttcgtg cggcgcctgg ggccccaggg ctggcggctg gtgcagcgcg 180

gggacccggc ggctttccgc gcgctggtgg cccagtgcct ggtgtgcgtg ccctgggacg 240

cacggccgcc ccccgccgcc ccctccttcc gccaggtgtc ctgcctgaag gagctggtgg 300

cccgagtgct gcagaggctg tgcgagcgcg gcgcgaagaa cgtgctggcc ttcggcttcg 360

cgctgctgga cggggcccgc gggggccccc ccgaggcctt caccaccagc gtgcgcagct 420

acctgcccaa cacggtgacc gacgcactgc gggggagcgg ggcgtggggg ctgctgttgc 480

gccgcgtggg cgacgacgtg ctggttcacc tgctggcacg ctgcgcgctc tttgtgctgg 540

tggctcccag ctgcgcctac caggtgtgcg ggccgccgct gtaccagctc ggcgctgcca 600

ctcaggcccg gcccccgcca cacgctagtg gaccccgaag gcgtctggga tgcgaacggg 660

cctggaacca tagcgtcagg gaggccgggg tccccctggg cctgccagcc ccgggtgcga 720

ggaggcgcgg gggcagtgcc agccgaagtc tgccgttgcc caagaggccc aggcgtggcg 780

ctgcccctga gccggagcgg acgcccgttg ggcaggggtc ctgggcccac ccgggcagga 840

cgcgtggacc gagtgaccgt ggtttctgtg tggtgtcacc tgccagaccc gccgaagaag 900

ccacctcttt ggagggtgcg ctctctggca cgcgccactc ccacccatcc gtgggccgcc 960

agcaccacgc gggcccccca tccacatcgc ggccaccacg tccctgggac acgccttgtc 1020

ccccggtgta cgccgagacc aagcacttcc tctactcctc aggcgacaag gagcagctgc 1080

ggccctcctt cctactcagc tctctgaggc ccagcctgac tggcgctcgg aggctcgtgg 1140

agaccatctt tctgggttcc aggccctgga tgccagggac tccccgcagg ttgccccgcc 1200

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tgccccagcg ctactggcaa atgcggcccc tgtttctgga gctgcttggg aaccacgcgc     1260

agtgccccta cggggtgctc ctcaagacgc actgcccgct gcgagctgcg gtcaccccag     1320

cagccggtgt ctgtgcccgg gagaagcccc agggctctgt ggcggccccc gaggaggagg     1380

acacagaccc ccgtcgcctg gtgcagctgc tccgccagca cagcagcccc tggcaggtgt     1440

acggcttcgt gcgggcctgc ctgcgccggc tggtgccccc aggcctctgg ggctccaggc     1500

acaacgaacg ccgcttcctc aggaacacca agaagttcat ctccctgggg aagcatgcca     1560

agctctcgct gcaggagctg acgtggaaga tgagcgtgcg gggctgcgct tggctgcgca     1620

ggagcccagg ggttggctgt gttccggccg cagagcaccg tctgcgtgag gagatcctgg     1680

ccaagttcct gcactggctg atgagtgtgt acgtcgtcga gctgctcagg tctttctttt     1740

atgtcacgga gaccacgttt caaaagaaca ggctcttttt ctaccggaag agtgtctgga     1800

gcaagttgca aagcattgga atcagacagc acttgaagag ggtgcagctg cgggagctgt     1860

cggaagcaga ggtcaggcag catcgggaag ccaggcccgc cctgctgacg tccagactcc     1920

gcttcatccc caagcctgac gggctgcggc cgattgtgaa catggactac gtcgtgggag     1980

ccagaacgtt ccgcagagaa aagagggccg agcgtctcac ctcgagggtg aaggcactgt     2040

tcagcgtgct caactacgag cgggcgcggc gccccggcct cctgggcgcc tctgtgctgg     2100

gcctggacga tatccacagg gcctggcgca ccttcgtgct gcgtgtgcgg gcccaggacc     2160

cgccgcctga gctgtacttt gtcaaggtgg atgtgacggg cgcgtacgac accatccccc     2220

aggacaggct cacggaggtc atcgccagca tcatcaaacc ccagaacacg tactgcgtgc     2280

gtcggtatgc cgtggtccag aaggccgccc atgggcacgt ccgcaaggcc ttcaagagcc     2340

acgtctctac cttgacagac ctccagccgt acatgcgaca gttcgtggct cacctgcagg     2400

agaccagccc gctgagggat gccgtcgtca tcgagcagag ctcctccctg aatgaggcca     2460

gcagtggcct cttcgacgtc ttcctacgct tcatgtgcca ccacgccgtg cgcatcaggg     2520

gcaagtccta cgtccagtgc caggggatcc cgcagggctc catcctctcc acgctgctct     2580

gcagcctgtg ctacggcgac atggagaaca agctgtttgc ggggattcgg cgggacgggc     2640

tgctcctgcg tttggtggat gatttcttgt tggtgacacc tcacctcacc cacgcgaaaa     2700

ccttcctcag gaccctggtc cgaggtgtcc ctgagtatgg ctgcgtggtg aacttgcgga     2760

agacagtggt gaacttccct gtagaagacg aggccctggg tggcacggct tttgttcaga     2820

tgccggccca cggcctattc ccctggtgcg gcctgctgct ggatacccgg accctggagg     2880

tgcagagcga ctactccagc tatgcccgga cctccatcag agccagtctc accttcaacc     2940

gcggcttcaa ggctgggagg aacatgcgtc gcaaactctt tggggtcttg cggctgaagt     3000

gtcacagcct gtttctggat ttgcaggtga acagcctcca gacggtgtgc accaacatct     3060

acaagatcct cctgctgcag gcgtacaggt ttcacgcatg tgtgctgcag ctcccatttc     3120
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atcagcaagt ttggaagaac cccacatttt tcctgcgcgt catctctgac acggcctccc 3180

tctgctactc catcctgaaa gccaagaacg cagggatgtc gctgggggcc aagggcgccg 3240

ccggccctct gccctccgag gccgtgcagt ggctgtgcca ccaagcattc ctgctcaagc 3300

tgactcgaca ccgtgtcacc tacgtgccac tcctggggtc actcaggaca gcccagacgc 3360

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cactgccctc agacttcaag accatcctgg actgatggcc acccgcccac agccaggccg 3480

agagcagaca ccagcagccc tgtcacgccg ggctctacgt cccagggagg gaggggcggc 3540

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gccctgtaca caggcgagga ccctgcacct ggatgggggt ccctgtgggt caaattgggg 3960

ggaggtgctg tgggagtaaa atactgaata tatgagtttt tcagttttga aaaaaaaaaa 4020

aaaaaaa 4027

<210> 65
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 65
tgaaggagcc cagagagaga 20

<210> 66
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 66
gtaagccaag aaagaaatcc 20

<210> 67

<211> 6
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 67
Gly Gly Ser Gly Gly Ser
1 5

<210> 68
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
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<223> /replace=" "

<220>
<221> misc_feature
<222> (1)..(21)
<223> /note="Variant residues given in the sequence have no preference with respect to those in the annotations for variant positions"

<400> 68
Gly Ser Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp Val Glu
1 5 10 15

Glu Asn Pro Gly Pro
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<210> 69
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<213> Artificial Sequence

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<223> /note="Description of Artificial Sequence: Synthetic peptide"

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<223> /replace=" "

<220>
<221> misc_feature

<222> (1)..(22)
<223> /note="Variant residues given in the sequence have no
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for variant positions"

<400> 69
Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val
1 5 10 15

Glu Glu Asn Pro Gly Pro
20

<210> 70
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<220>
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<223> /replace=" "

<220>
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<222> (1)..(23)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<400> 70
Gly Ser Gly Gln Cys Thr Asn Tyr Ala Leu Leu Lys Leu Ala Gly Asp
1 5 10 15

Val Glu Ser Asn Pro Gly Pro
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<210> 71
<211> 25
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peptide"

<220>
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1 5 10 15

Gly Asp Val Glu Ser Asn Pro Gly Pro
20 25

<210> 72
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
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polypeptide"

<220>
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<222> (1)..(30)
<223> /note="This sequence may encompass 1-6
"Gly Gly Gly Gly Ser" repeating units"

<400> 72
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25 30

<210> 73
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
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<400> 73
ugucgggucu uuaaaaauac 20

<210> 74
<211> 20
<212> RNA
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic

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<400> 74
uacaggcccc uaaagcacua 20

<210> 75
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 75
acaggccccu aaagcacuaa 20

<210> 76
<211> 20
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 76
aagcacuaag ggcaugcccu 20

<210> 77
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<220>
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<400> 77
gggcaugccc ucggugaaac 20

<210> 78
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ggcaugcccu cggugaaaca 20

<210> 79

<211> 20
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<400> 80
ugagauuaaa gcgacagaaa 20

<210> 81
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<210> 82
<211> 20
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uaaagcgaca gaaaagggaa 20

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agaaaaggga aaggagagcg 20

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<220>
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<400> 85
ggaaaggaga gcgcgggcaa 20

<210> 86
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<400> 86
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<400> 87
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ucuaaaggga gauagagacg 20

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<400> 93
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gaggguaagg ugggcgcaag 20

<210> 97

<211> 20
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<210> 98
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gggcaugccc uuagugcuuu 20

<210> 100
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<220>
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<210> 102
<211> 20
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<210> 103
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<400> 103
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<210> 104
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<400> 116
ugcuuucgua gagaagcaga 20

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gcuggauugc ugcaaggcug 20

<210> 123
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<400> 124
aaggcugagg gacgagaacg 20

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gcugccacug ccgcuaccgc 20

<210> 126
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<210> 129
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<400> 145
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gtttcgccgt 130

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cgccgt 126

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oligonucleotide"

<400> 1281
ccaaggaagu uuaagcugcu 20

<210> 1282
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<213> Artificial Sequence

<220>
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<400> 1282
ccaagcagcu uaaacuuccu 20

<210> 1283
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uuggugccau aagaguggac 20

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<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<210> 1286
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<400> 1286
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<400> 1287
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<210> 1292
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<210> 1294
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<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

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<210> 1295
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<400> 1295
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<210> 1296
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ucgguguuuu uuu 73

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<211> 13
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Thr Phe

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<211> 46
<212> DNA
<213> Artificial Sequence

<220>
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<400> 1301
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<212> DNA
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<223> /note="Description of Artificial Sequence: Synthetic
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ctgataccat cacctccc 78

<210> 1305
<211> 77
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oligonucleotide"

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tgataccatc acctccc 77

<210> 1306
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<212> DNA
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<210> 1307
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<212> DNA
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gctccagaat ggaagcccac 80

<210> 1308
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agctccagaa tggaagccc 79

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<211> 79

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agctccagaa tggaagccc 79

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agaatggaag cccac 75

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ctaagtccat tcctgatac 79

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aagtccattc ctgatacca 79

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agtccattcc tgatacca 78

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<213> Homo sapiens

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Lys Leu Gln Asn Gly Ser Pro Leu Pro Glu Arg Ala His Pro Glu Val
        35                  40                  45

Asn Gly Asp Thr Lys Trp His Ser Phe Lys Ser Tyr Tyr Gly Ile Pro
    50                  55                  60

Cys Met Lys Gly Ser Gln Asn Ser Arg Val Ser Pro Asp Phe Thr Gln
65                  70                  75                  80

Glu Ser Arg Gly Tyr Ser Lys Cys Leu Gln Asn Gly Gly Ile Lys Arg
                85                  90                  95

Thr Val Ser Glu Pro Ser Leu Ser Gly Leu Leu Gln Ile Lys Lys Leu
            100                 105                 110

Lys Gln Asp Gln Lys Ala Asn Gly Glu Arg Arg Asn Phe Gly Val Ser
        115                 120                 125

Gln Glu Arg Asn Pro Gly Glu Ser Ser Gln Pro Asn Val Ser Asp Leu
    130                 135                 140

Ser Asp Lys Lys Glu Ser Val Ser Ser Val Ala Gln Glu Asn Ala Val
145                 150                 155                 160

Lys Asp Phe Thr Ser Phe Ser Thr His Asn Cys Ser Gly Pro Glu Asn
                165                 170                 175

Pro Glu Leu Gln Ile Leu Asn Glu Gln Glu Gly Lys Ser Ala Asn Tyr
            180                 185                 190

His Asp Lys Asn Ile Val Leu Leu Lys Asn Lys Ala Val Leu Met Pro
        195                 200                 205

Asn Gly Ala Thr Val Ser Ala Ser Ser Val Glu His Thr His Gly Glu
    210                 215                 220

Leu Leu Glu Lys Thr Leu Ser Gln Tyr Tyr Pro Asp Cys Val Ser Ile
225                 230                 235                 240
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Ala Val Gln Lys Thr Thr Ser His Ile Asn Ala Ile Asn Ser Gln Ala
                245                 250                 255

Thr Asn Glu Leu Ser Cys Glu Ile Thr His Pro Ser His Thr Ser Gly
            260                 265                 270

Gln Ile Asn Ser Ala Gln Thr Ser Asn Ser Glu Leu Pro Pro Lys Pro
        275                 280                 285

Ala Ala Val Val Ser Glu Ala Cys Asp Ala Asp Asp Ala Asp Asn Ala
    290                 295                 300

Ser Lys Leu Ala Ala Met Leu Asn Thr Cys Ser Phe Gln Lys Pro Glu
305                 310                 315                 320

Gln Leu Gln Gln Gln Lys Ser Val Phe Glu Ile Cys Pro Ser Pro Ala
                325                 330                 335

Glu Asn Asn Ile Gln Gly Thr Thr Lys Leu Ala Ser Gly Glu Glu Phe
            340                 345                 350

Cys Ser Gly Ser Ser Ser Asn Leu Gln Ala Pro Gly Gly Ser Ser Glu
        355                 360                 365

Arg Tyr Leu Lys Gln Asn Glu Met Asn Gly Ala Tyr Phe Lys Gln Ser
    370                 375                 380

Ser Val Phe Thr Lys Asp Ser Phe Ser Ala Thr Thr Thr Pro Pro Pro
385                 390                 395                 400

Pro Ser Gln Leu Leu Leu Ser Pro Pro Pro Pro Leu Pro Gln Val Pro
                405                 410                 415

Gln Leu Pro Ser Glu Gly Lys Ser Thr Leu Asn Gly Gly Val Leu Glu
            420                 425                 430

Glu His His His Tyr Pro Asn Gln Ser Asn Thr Thr Leu Leu Arg Glu
        435                 440                 445

Val Lys Ile Glu Gly Lys Pro Glu Ala Pro Pro Ser Gln Ser Pro Asn
    450                 455                 460

Pro Ser Thr His Val Cys Ser Pro Ser Pro Met Leu Ser Glu Arg Pro
465                 470                 475                 480

Gln Asn Asn Cys Val Asn Arg Asn Asp Ile Gln Thr Ala Gly Thr Met
                485                 490                 495
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Thr Val Pro Leu Cys Ser Glu Lys Thr Arg Pro Met Ser Glu His Leu
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Lys His Asn Pro Pro Ile Phe Gly Ser Ser Gly Glu Leu Gln Asp Asn
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Cys Gln Gln Leu Met Arg Asn Lys Glu Gln Glu Ile Leu Lys Gly Arg
    530                 535                 540

Asp Lys Glu Gln Thr Arg Asp Leu Val Pro Pro Thr Gln His Tyr Leu
545                 550                 555                 560

Lys Pro Gly Trp Ile Glu Leu Lys Ala Pro Arg Phe His Gln Ala Glu
                565                 570                 575

Ser His Leu Lys Arg Asn Glu Ala Ser Leu Pro Ser Ile Leu Gln Tyr
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Gln Pro Asn Leu Ser Asn Gln Met Thr Ser Lys Gln Tyr Thr Gly Asn
        595                 600                 605

Ser Asn Met Pro Gly Gly Leu Pro Arg Gln Ala Tyr Thr Gln Lys Thr
    610                 615                 620

Thr Gln Leu Glu His Lys Ser Gln Met Tyr Gln Val Glu Met Asn Gln
625                 630                 635                 640

Gly Gln Ser Gln Gly Thr Val Asp Gln His Leu Gln Phe Gln Lys Pro
                645                 650                 655

Ser His Gln Val His Phe Ser Lys Thr Asp His Leu Pro Lys Ala His
            660                 665                 670

Val Gln Ser Leu Cys Gly Thr Arg Phe His Phe Gln Gln Arg Ala Asp
        675                 680                 685

Ser Gln Thr Glu Lys Leu Met Ser Pro Val Leu Lys Gln His Leu Asn
    690                 695                 700

Gln Gln Ala Ser Glu Thr Glu Pro Phe Ser Asn Ser His Leu Leu Gln
705                 710                 715                 720

His Lys Pro His Lys Gln Ala Ala Gln Thr Gln Pro Ser Gln Ser Ser
                725                 730                 735

His Leu Pro Gln Asn Gln Gln Gln Gln Gln Lys Leu Gln Ile Lys Asn
```

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            740                 745                 750

Lys Glu Glu Ile Leu Gln Thr Phe Pro His Pro Gln Ser Asn Asn Asp
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Gln Gln Arg Glu Gly Ser Phe Phe Gly Gln Thr Lys Val Glu Glu Cys
    770                 775                 780

Phe His Gly Glu Asn Gln Tyr Ser Lys Ser Ser Glu Phe Glu Thr His
785                 790                 795                 800

Asn Val Gln Met Gly Leu Glu Glu Val Gln Asn Ile Asn Arg Arg Asn
                805                 810                 815

Ser Pro Tyr Ser Gln Thr Met Lys Ser Ser Ala Cys Lys Ile Gln Val
            820                 825                 830

Ser Cys Ser Asn Asn Thr His Leu Val Ser Glu Asn Lys Glu Gln Thr
        835                 840                 845

Thr His Pro Glu Leu Phe Ala Gly Asn Lys Thr Gln Asn Leu His His
    850                 855                 860

Met Gln Tyr Phe Pro Asn Asn Val Ile Pro Lys Gln Asp Leu Leu His
865                 870                 875                 880

Arg Cys Phe Gln Glu Gln Glu Gln Lys Ser Gln Gln Ala Ser Val Leu
                885                 890                 895

Gln Gly Tyr Lys Asn Arg Asn Gln Asp Met Ser Gly Gln Gln Ala Ala
            900                 905                 910

Gln Leu Ala Gln Gln Arg Tyr Leu Ile His Asn His Ala Asn Val Phe
        915                 920                 925

Pro Val Pro Asp Gln Gly Gly Ser His Thr Gln Thr Pro Pro Gln Lys
    930                 935                 940

Asp Thr Gln Lys His Ala Ala Leu Arg Trp His Leu Leu Gln Lys Gln
945                 950                 955                 960

Glu Gln Gln Gln Thr Gln Gln Pro Gln Thr Glu Ser Cys His Ser Gln
                965                 970                 975

Met His Arg Pro Ile Lys Val Glu Pro Gly Cys Lys Pro His Ala Cys
            980                 985                 990
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Met His Thr Ala Pro Pro Glu Asn  Lys Thr Trp Lys Lys  Val Thr Lys
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Gln Glu  Asn Pro Pro Ala Ser  Cys Asp Asn Val Gln  Gln Lys Ser
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Ile Ile  Glu Thr Met Glu Gln  His Leu Lys Gln Phe  His Ala Lys
    1025                1030                1035

Ser Leu  Phe Asp His Lys Ala  Leu Thr Leu Lys Ser  Gln Lys Gln
    1040                1045                1050

Val Lys  Val Glu Met Ser Gly  Pro Val Thr Val Leu  Thr Arg Gln
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Thr Thr  Ala Ala Glu Leu Asp  Ser His Thr Pro Ala  Leu Glu Gln
    1070                1075                1080

Gln Thr  Thr Ser Ser Glu Lys  Thr Pro Thr Lys Arg  Thr Ala Ala
    1085                1090                1095

Ser Val  Leu Asn Asn Phe Ile  Glu Ser Pro Ser Lys  Leu Leu Asp
    1100                1105                1110

Thr Pro  Ile Lys Asn Leu Leu  Asp Thr Pro Val Lys  Thr Gln Tyr
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Asp Phe  Pro Ser Cys Arg Cys  Val Glu Gln Ile Ile  Glu Lys Asp
    1130                1135                1140

Glu Gly  Pro Phe Tyr Thr His  Leu Gly Ala Gly Pro  Asn Val Ala
    1145                1150                1155

Ala Ile  Arg Glu Ile Met Glu  Glu Arg Phe Gly Gln  Lys Gly Lys
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Ala Ile  Arg Ile Glu Arg Val  Ile Tyr Thr Gly Lys  Glu Gly Lys
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Ser Ser  Gln Gly Cys Pro Ile  Ala Lys Trp Val Val  Arg Arg Ser
    1190                1195                1200

Ser Ser  Glu Glu Lys Leu Leu  Cys Leu Val Arg Glu  Arg Ala Gly
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His Thr  Cys Glu Ala Ala Val  Ile Val Ile Leu Ile  Leu Val Trp
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Thr Glu  Thr Leu Arg Lys Tyr  Gly Thr Leu Thr Asn  Arg Arg Cys
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Ala Leu  Asn Glu Glu Arg Thr  Cys Ala Cys Gln Gly  Leu Asp Pro
    1265                 1270                 1275

Glu Thr  Cys Gly Ala Ser Phe  Ser Phe Gly Cys Ser  Trp Ser Met
    1280                 1285                 1290

Tyr Tyr  Asn Gly Cys Lys Phe  Ala Arg Ser Lys Ile  Pro Arg Lys
    1295                 1300                 1305

Phe Lys  Leu Leu Gly Asp Asp  Pro Lys Glu Glu Glu  Lys Leu Glu
    1310                 1315                 1320

Ser His  Leu Gln Asn Leu Ser  Thr Leu Met Ala Pro  Thr Tyr Lys
    1325                 1330                 1335

Lys Leu  Ala Pro Asp Ala Tyr  Asn Asn Gln Ile Glu  Tyr Glu His
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Arg Ala  Pro Glu Cys Arg Leu  Gly Leu Lys Glu Gly  Arg Pro Phe
    1355                 1360                 1365

Ser Gly  Val Thr Ala Cys Leu  Asp Phe Cys Ala His  Ala His Arg
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Asp Leu  His Asn Met Gln Asn  Gly Ser Thr Leu Val  Cys Thr Leu
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Thr Arg  Glu Asp Asn Arg Glu  Phe Gly Gly Lys Pro  Glu Asp Glu
    1400                 1405                 1410

Gln Leu  His Val Leu Pro Leu  Tyr Lys Val Ser Asp  Val Asp Glu
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Phe Gly  Ser Val Glu Ala Gln  Glu Glu Lys Lys Arg  Ser Gly Ala
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Ile Gln  Val Leu Ser Ser Phe  Arg Arg Lys Val Arg  Met Leu Ala
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Glu Pro  Val Lys Thr Cys Arg  Gln Arg Lys Leu Glu  Ala Lys Lys
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Asn Ala  Ser Gln Ala Lys Gln  Leu Ala Glu Leu Leu  Arg Leu Ser
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Gly Pro  Val Met Gln Gln Ser  Gln Gln Pro Gln Pro  Leu Gln Lys
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Gln Pro  Pro Gln Pro Gln Gln  Gln Gln Arg Pro Gln  Gln Gln Gln
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Pro His  His Pro Gln Thr Glu  Ser Val Asn Ser Tyr  Ser Ala Ser
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Gly Ser  Thr Asn Pro Tyr Met  Arg Arg Pro Asn Pro  Val Ser Pro
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Tyr Pro  Asn Ser Ser His Thr  Ser Asp Ile Tyr Gly  Ser Thr Ser
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Pro Met  Asn Phe Tyr Ser Thr  Ser Ser Gln Ala Ala  Gly Ser Tyr
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Leu Asn  Ser Ser Asn Pro Met  Asn Pro Tyr Pro Gly  Leu Leu Asn
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Gln Asn  Thr Gln Tyr Pro Ser  Tyr Gln Cys Asn Gly  Asn Leu Ser
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Val Asp  Asn Cys Ser Pro Tyr  Leu Gly Ser Tyr Ser  Pro Gln Ser
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Gln Pro  Met Asp Leu Tyr Arg  Tyr Pro Ser Gln Asp  Pro Leu Ser
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Lys Leu  Ser Leu Pro Pro Ile  His Thr Leu Tyr Gln  Pro Arg Phe
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Gly Asn  Ser Gln Ser Phe Thr  Ser Lys Tyr Leu Gly  Tyr Gly Asn
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Gln Asn  Met Gln Gly Asp Gly  Phe Ser Ser Cys Thr  Ile Arg Pro
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Leu Ser Asn Pro Asn Met Asp Tyr Lys Asn Gly Glu His His Ser
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Pro Ser His Ile Ile His Asn Tyr Ser Ala Ala Pro Gly Met Phe
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Asn Ser Ser Leu His Ala Leu His Leu Gln Asn Lys Glu Asn Asp
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Met Leu Ser His Thr Ala Asn Gly Leu Ser Lys Met Leu Pro Ala
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ggtcatagaa taaagttatg ctcaaatgtt caaa 4594