TREATMENT OF CANCER USING A CHIMERIC ANTIGEN RECEPTOR IN COMBINATION WITH AN INHIBITOR OF A PRO-M2 MACROPHAGE MOLECULE

RELATED APPLICATIONS

[001] This application claims priority to U.S. Serial No. 62/369589 filed August 1, 2016, the contents of which are incorporated herein by reference in its entirety.

SEQUENCE LISTING

[002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in their entirety. Said ASCII copy, created on July 31, 2017, is named N2067-7113WO_SL.txt and is 1,549,304 bytes in size.

FIELD OF THE INVENTION

[003] The present invention relates generally to the use of T cells engineered to express a Chimeric Antigen Receptor (CAR), e.g., in combination with another agent such as, e.g., an inhibitor of a pro-M2 macrophage molecule, e.g., an inhibitor of IL-13, IL-13Rα1, IL-4, IL-4Rα, IL-10 or CSF-1, to treat a disease associated with expression of a cancer antigen, e.g., a solid tumor antigen or antigen on a cancer cell associated with tumor associated macrophages.

BACKGROUND OF THE INVENTION

[004] Many patients with malignancies are incurable with standard therapy. In addition, traditional treatment options often have serious side effects. Attempts have been made in cancer immunotherapy, however, several obstacles render this a very difficult goal to achieve clinical effectiveness. Although hundreds of so-called tumor antigens have been identified, these are generally derived from self and thus are poorly immunogenic. Furthermore, tumors use several mechanisms to render themselves hostile to the initiation and propagation of immune attack. Some of these mechanisms involve non-tumor cells that can be associated with the tumor cells, for example tumor-associated macrophages (TAMs), that can have a phenotype that is inhibitory to the immune response, e.g., an M2 phenotype.

[005] Recent developments using chimeric antigen receptor (CAR) modified autologous T cell (CART) therapy, which relies on redirecting T cells to a suitable cell-surface molecule on cancer cells such as B cell malignancies, show promising results in harnessing the power of the immune system to treat B cell malignancies and other cancers (see, e.g., Sadelain et al., Cancer Discovery 3:388-398 (2013)). The clinical results of the murine derived CART19 (i.e., "CTL019") have shown promise in establishing complete remissions in patients suffering with CLL as well as in childhood ALL (see, e.g., Kalos et al., Sci Transl Med 3:95ra73 (2011), Porter et al., NEJM 365:725-733 (2011), Grupp et al., NEJM 368:1509-1518 (2013)). Besides the ability for the chimeric antigen receptor on the genetically modified T cells to recognize and destroy the targeted cells, a successful therapeutic T cell therapy needs to have the ability to proliferate and persist over time, remain effective in an environment that inhibits their function, and to further monitor for malignant cell escapees. The variable quality of T cells, as well as *in vivo* anergy, suppression or exhaustion will have effects on CAR-transformed T cells' performance, over which skilled practitioners have limited control at this time. While certain CAR-transformed T cell products have proven effective, there is a need for CAR-transfromed T cell therapies with enhanced efficacy, e.g., enhanced efficacy against solid tumors and their associated immunoinhibitory tumor microenvironment (TME).

SUMMARY OF THE INVENTION

[006] The disclosure features, at least in part, compositions and methods of treating disorders such as cancer (e.g., solid tumors or tumors associated with tumor-associated macrophages) using immune effector cells (e.g., T cells or NK cells) that express a chimeric antigen receptor (CAR) molecule, e.g., a CAR that binds to a tumor antigen, e.g., an antigen expressed on the surface of a solid tumor or tumor associated with tumor-associated macrophages. The compositions include, and the methods include administering, immune effector cells (e.g., T cells or NK cells) expressing a tumor targeting CAR, in combination with an inhibitor of a pro-M2 macrophage molecule (e.g., an inhibitor of colony stimulating factor-1 (CSF-1), interleukin 10 (IL-10), interleukin 13 (IL-13), interleukin 4 (IL-4) or a receptor present on the surface of macrophage cells for IL-13 or IL-4, e.g., IL-13Rα1 or IL-4Rα). In some embodiments, the combination maintains or has better clinical effectiveness, e.g., against a solid tumor or tumor associated with tumor-associated macrophages, as compared to either

therapy alone. Without being bound by theory, it is shown herein that use of an inhibitor of a pro-M2 macrophage molecule (e.g., as described herein) inhibits polarization of macrophages, e.g., tumor-associated macrophages (TAMs) to the M2 phenotype, or reverses the phenotype of M2 macrophages, e.g., tumor-associated macrophages (TAMs), thereby removing a source of inhibition of a function of CAR-expressing cells, e.g., CAR-expressing T cells, e.g., an anti-tumor or proliferative activity of the CAR-expressing cells. The invention further pertains to the use of engineered cells, e.g., immune effector cells (e.g., T cells or NK cells), that express a CAR molecule that binds to a tumor antigen, e.g., a solid tumor antigen or antigen on a tumor cell associated with tumor-associated macrophages, in combination with an inhibitor of a pro-M2 macrophage molecule (e.g., an inhibitor of a pro-M2 macrophage molecule described herein) to treat a disorder associated with expression of a tumor antigen, e.g., a solid tumor antigen or antigen on a tumor associated with tumor-associated macrophages (e.g., a cancer).

[007] In a first aspect, the invention provides a method of treating a subject having a disease associated with expression of a tumor antigen (e.g., a subject having a cancer (e.g., a solid tumor or a tumor associated with tumor-associated macrophages)), including administering to the subject: (i) a CAR therapy including a cell, e.g., a population of immune effector cells, including, e.g., expressing, a chimeric antigen receptor (CAR) (e.g., as described herein). The CAR includes a tumor antigen binding domain (e.g., the tumor antigen binding domain of the CAR binds to CD19 or CD123), a transmembrane domain, and an intracellular signaling domain; and (ii) an inhibitor of a pro-M2 macrophage molecule (e.g., as described herein).

[008] In another aspect, the invention provides a CAR therapy including a cell, e.g., a population of immune effector cells, including (e.g., expressing) a chimeric antigen receptor (CAR) for use in combination with an inhibitor of a pro-M2 macrophage molecule in treating a subject having a disease associated with expression of a tumor antigen (e.g., a subject having a cancer (e.g., a solid tumor or a tumor associated with tumor-associated macrophages)). The CAR includes a tumor antigen binding domain (e.g., the tumor antigen binding domain of the CAR binds to CD19 or CD123), a transmembrane domain, and an intracellular signaling domain.

[009] In embodiments, the CAR therapy and the inhibitor of a pro-M2 macrophage molecule are administered sequentially.

[0010] In embodiments, including in any of the aforementioned aspects and embodiments, the inhibitor of a pro-M2 macrophage molecule is administered prior to the CAR therapy. In embodiments, including in any of the aforementioned aspects and embodiments, the inhibitor of a pro-M2 macrophage molecule and the CAR therapy are administered simultaneously or concurrently.

[0011] In embodiments, including in any of the aforementioned aspects and embodiments, the CAR therapy is administered as (a) single infusion or (b) multiple infusions (e.g., a single dose split into multiple infusions), and the inhibitor of a pro-M2 macrophage molecule is administered as (a) a single dose, or (b) multiple doses (e.g., a first and second, and optionally one or more subsequent doses).

[0012] In embodiments, including in any of the aforementioned aspects and embodiments, a dose of the CAR therapy is administered after (e.g., at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, or more, after) administration of a first dose of the inhibitor of a pro-M2 macrophage molecule, e.g., and before administration of the second dose of the inhibitor.

[0013] In embodiments, including in any of the aforementioned aspects and embodiments, a dose of the CAR therapy is administered concurrently with (e.g., within 2 days (e.g., within 2 days, 1 day, 24 hours, 12 hours, 6 hours, 4 hours, 2 hours, or less) of), the administration of a first dose of the inhibitor of a pro-M2 macrophage molecule.

[0014] In embodiments, including in any of the aforementioned aspects and embodiments, one or more subsequent doses of the inhibitor of a pro-M2 macrophage molecule are administered after a second dose of the inhibitor of a pro-M2 macrophage molecule.

[0015] In embodiments, including in any of the aforementioned aspects and embodiments, the inhibitor of a pro-M2 macrophage moleculeis administered in more than one dose, and the doses are administered twice a day (BID), once a day, once a week, once every 14 days, or once every month.

[0016] In embodiments, including in any of the aforementioned aspects and embodiments, the administering of the inhibitor of a pro-M2 macrophage molecule includes multiple doses including a duration of at least 7 days, e.g., at least 7 days, 8 days, 9 days, 10 days, 1 week, 2

weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, or more.

[0017] In embodiments, including in any of the aforementioned aspects and embodiments, the CAR therapy is administered at a dose comprising at least about 5 x 10^6, 1 x 10^7, 1.5 x 10^7, 2 x 10^7, 2.5 x 10^7, 3 x 10^7, 3.5 x 10^7, 4 x 10^7, 5 x 10^7, 1 x 10^8, 1.5 x 10^8, 2 x 10^8, 2.5 x 10^8, 3 x 10^8, 3.5 x 10^8, 4 x 10^8, 5 x 10^8, 1 x 10^9, 2 x 10^9, or 5 x 10^9 cells, e.g., CAR positive cells.

[0018] In another aspect, the invention provides a pharmaceutical composition including (i) a cell, e.g., a population of immune effector cells, including, e.g., expressing, a chimeric antigen receptor (CAR) (e.g., as described herein), wherein the CAR includes a tumor antigen binding domain, a transmembrane domain, and an intracellular signaling domain; and (ii) an inhibitor of a pro-M2 macrophage molecule (e.g., as described herein).

[0019] In another aspect, the invention provides a pharmaceutical composition including (i) a cell, e.g., a population of immune effector cells, including, e.g., expressing, a chimeric antigen receptor (CAR) (e.g., described herein), wherein the CAR includes a tumor antigen binding domain, a transmembrane domain, and an intracellular signaling domain; and (ii) an inhibitor of a pro-M2 macrophage molecule, (e.g., as described herein), for use in treating a disease or disorder described herein.

[0020] In another aspect, the invention provides a method for stimulating a T cell-mediated immune response to a solid tumor cell in a mammal, the method including administering to a mammal an effective amount of a composition of the previous aspects.

[0021] In another aspect, the invention provides a method of providing an anti-tumor, e.g., an anti-solid tumor, immunity in a mammal, including administering to the mammal an effective amount of the composition

[0022] In another aspect, the invention provides a method of treating a mammal having a disease associated with expression of a tumor antigen, e.g., a solid tumor antigen, said method including administering an effective amount of the composition of the previous aspects.

[0023] In embodiments, including in any of the method embodiments above, the cell, e.g., the population of immune effector cells, and the inhibitor of a pro-M2 macrophage molecule are provided for separate administration (e.g., in two separate compositions). In other

embodiments, including in any of the method embodiments above, the cell, e.g., the population of immune effector cells, and the inhibitor of a pro-M2 macrophage molecule are provided for simultaneous administration (e.g., in one composition).

[0024] The following aspects of the inhibitor of the pro-M2 macrophage molecule may be utilized with any of the aforementioned aspects and embodiments.

[0025] In embodiments, the inhibitor of a pro-M2 macrophage molecule is an IL-13 inhibitor, an IL-4 inhibitor, an IL-13Rα1 inhibitor, an IL-4Rα inhibitor, an IL-10 inhibitor, a CSF-1 inhibitor, a TGF beta inhibitor, or combinations thereof, e.g., as described herein. In embodiments, the inhibitor of a pro-M2 macrophage molecule is an IL-13 inhibitor, an IL-4 inhibitor, an IL-13Rα1 inhibitor, an IL-4Rα inhibitor or combinations thereof, e.g., as described herein. In some embodiments, the inhibitor of a pro-M2 macrophage molecule is a small molecule, an antibody or antigen-binding fragment thereof, a protein (e.g., a fusion protein), a nucleic acid (e.g., an shRNA or siRNA), or a gene editing system. In some embodiment, the inhibitor of a pro-M2 macrophage molecule is an antibody or antigen-biding fragment thereof.

[0026] In some embodiments, the inhibitor of a pro-M2 macrophage molecule is an IL-13 inhibitor, an IL-4 inhibitor, an IL-13Rα1 inhibitor, an IL-4Rα inhibitor, an IL-10 inhibitor, a CSF-1 inhibitor, a TGF beta inhibitor, a JAK2 inhibitor, a cell surface molecule, an iron oxide, a small molecule inhibitor, a PI3K inhibitor, an HDAC inhibitor, an inhibitor of the glycolytic pathway, a mitochondria-targeted antioxidant, or a combination thereof, e.g., as described herein.

[0027] In one embodiment, the inhibitor of a pro-M2 macrophage molecule is an IL-13 inhibitor (e.g., fenretinide (4-HPR)).

[0028] In another embodiment, the inhibitor of a pro-M2 macrophage molecule is an IL-4 inhibitor (e.g., 4-HPR).

[0029] In another embodiment, the inhibitor of a pro-M2 macrophage molecule is an an IL-13Rα1 inhibitor.

[0030] In another embodiment, the inhibitor of a pro-M2 macrophage molecule is an IL-4Rα inhibitor.

[0031] In another embodiment, the inhibitor of a pro-M2 macrophage molecule is a CSF-1 inhibitor (e.g., nintedanib).

[0032] In another embodiment, the inhibitor of a pro-M2 macrophage molecule is a TGF beta inhibitor.

[0033] In another embodiment, the inhibitor of a pro-M2 macrophage molecule is a JAK2 inhibitor (e.g., ruxolitinib).

[0034] In another embodiment, the inhibitor of a pro-M2 macrophage molecule is a cell surface molecule (e.g., Dipeptidyl peptidase 4 (DPP4) or CD26).

[0035] In another embodiment, the inhibitor of a pro-M2 macrophage molecule is an iron oxide (e.g., ferumoxytol).

[0036] In another embodiment, the inhibitor of a pro-M2 macrophage molecule is a small molecule inhibitor (e.g., pterostilbene).

[0037] In another embodiment, the inhibitor of a pro-M2 macrophage molecule is a phosphoinositide 3-kinase (PI3K) inhibitor (e.g., tenalisib (RP6530)).

[0038] In another embodiment, the inhibitor of a pro-M2 macrophage molecule is an HDAC inhibitor (e.g., SAHA).

[0039] In another embodiment, the inhibitor of a pro-M2 macrophage molecule is an inhibitor of the glycolytic pathway (e.g., 2-deoxy-d-glucose (2-DG)).

[0040] In another embodiment, the inhibitor of a pro-M2 macrophage molecule is a mitochondria-targeted antioxidant (e.g., MitoQ).

[0041] In another aspect, the invention provides a method of treating a subject having a disease associated with expression of a tumor antigen (e.g., a subject having a cancer (e.g., a solid tumor or a tumor associated with tumor-associated macrophages)). The method includes administering to the subject (i) a CAR therapy including a cell, e.g., a population of immune effector cells, including (e.g., expressing) a chimeric antigen receptor (CAR), wherein the CAR includes a tumor antigen binding domain that binds to CD123, a transmembrane domain, and an intracellular signaling domain; and (ii) a tumor targeting therapy. In some embodiments, the CD123 CAR is administered in an amount and/or time sufficient to result in inhibition of an

M2 macrophage activity. In embodiments, the inhibition of the M2 macrophage activity comprises inhibition of polarization of a macrophage to an M2 phenotype, and/or reversal of a phenotype of an M2 macrophage.

[0042] In another aspect, the invention provides a CAR therapy including a cell, e.g., a population of immune effector cells, comprising (e.g., expressing) a chimeric antigen receptor (CAR) for use in combination with a tumor targeting therapy in treating a subject having a disease associated with expression of a tumor antigen (e.g., a subject having cancer (e.g., a solid tumor or a tumor associated with tumor-associated macrophages)). The CAR includes a tumor antigen binding domain that binds CD123, a transmembrane domain, and an intracellular signaling domain. In some embodiments, the CD123 CAR is administered in an amount and/or time sufficient to result in inhibition of an M2 macrophage activity. In embodiments, the inhibition of the M2 macrophage activity comprises inhibition of polarization of a macrophage to an M2 phenotype, and/or reversal of a phenotype of an M2 macrophage.

[0043] In some embodiments of the methods and the CAR therapies for use disclosed herein, the tumor targeting therapy is a second CAR therapy that includes a cell, e.g., a population of immune effector cells, including (e.g., expressing) a CAR including a tumor antigen binding domain that binds to a tumor antigen other than CD123 (e.g., a CAR that binds to a solid tumor antigen or a hematologic tumor antigen other than CD123). In one embodiment, the tumor antigen binding domain binds to CD19, mesothelin, or EGFRviii.

[0044] In some embodiments of the methods and the CAR therapies for use disclosed herein, the tumor targeting therapy is or includes a CD19-inhibiting or depleting therapy, e.g., a therapy that includes a CD19 inhibitor. In some embodiments, the tumor targeting therapy includes a CD19 CAR-expressing cell, e.g., a CD19 CART cell, or an anti-CD19 antibody (e.g., an anti-CD19 mono- or bispecific antibody) or a fragment or conjugate thereof. In one embodiment, the CD19 inhibitor is a CD19 antibody, e.g., a CD19 bispecific antibody (e.g., a bispecific T cell engager that targets CD19, e.g., blinatumomab).

[0045] In other embodiments, including in any of the aforementioned aspects and embodiments, the CAR therapy and the tumor targeting therapy are administered sequentially.

[0046] In other embodiments, including in any of the aforementioned aspects and embodiments, the tumor targeting therapy is administered prior to the CAR therapy.

[0047] In other embodiments, including in any of the aforementioned aspects and embodiments, the CD123 CAR therapy is administered prior to the tumor targeting therapy. In some embodiments, the CD123 CAR therapy is administered at least 5 days, at least 7 days, at least 10 days, at least 15 days, at least 20 days, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months or at least 10 months, prior to administration of the tumor targeting therapy.

[0048] In other embodiments, including in any of the aforementioned aspects and embodiments, the tumor targeting therapy and the CAR therapy are administered simultaneously or concurrently.

[0049] In other embodiments, including in any of the aforementioned aspects and embodiments, the CAR therapy is administered as (a) single infusion or (b) multiple infusions (e.g., a single dose split into multiple infusions), and the tumor targeting therapy is administered as (a) a single dose, or (b) multiple doses (e.g., a first and second, and optionally one or more subsequent doses).

[0050] In other embodiments, including in any of the aforementioned aspects and embodiments, a dose of the CAR therapy is administered after (e.g., at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, or more, after) administration of a first dose of the tumor targeting therapy, e.g., but before administration of the second dose of the tumor targeting therapy.

[0051] In other embodiments, a dose of the CAR therapy is administered concurrently with (e.g., within 2 days (e.g., within 2 days, 1 day, 24 hours, 12 hours, 6 hours, 4 hours, 2 hours, or less) of), the administration of a first dose of the tumor targeting therapy.

[0052] In other embodiments, one or more subsequent doses of the tumor targeting therapy are administered after a second dose of the tumor targeting therapy.

[0053] In other embodiments, the tumor targeting therapy is administered in more than one dose, and the doses are administered twice a day (BID), once a day, once a week, once every 14 days, or once every month.

[0054] In other embodiments, the administering of the tumor targeting therapy includes multiple doses comprising a duration of at least 7 days, e.g., at least 7 days, 8 days, 9 days, 10 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, or more.

[0055] In other embodiments, the CAR therapy or the tumor targeting therapy is administered at a dose comprising at least about 5×10^6, 1×10^7, 1.5×10^7, 2×10^7, 2.5×10^7, 3×10^7, 3.5×10^7, 4×10^7, 5×10^7, 1×10^8, 1.5×10^8, 2×10^8, 2.5×10^8, 3×10^8, 3.5×10^8, 4×10^8, 5×10^8, 1×10^9, 2×10^9, or 5×10^9 cells, e.g., CAR positive cells.

[0056] In some embodiments, the CAR therapy and the tumor targeting therapy are formulated in a pharmaceutical composition (e.g., comprising a pharmaceutical excipient).

[0057] The following aspects of the CAR and CAR-expressing cell, e.g., population of immune effector cells, may be utilized with any of the aforementioned aspects and embodiments.

[0058] In an aspect, the tumor antigen binding domain of the CAR binds CD123.

[0059] In embodiments, the tumor antigen binding domain of the CAR includes a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of any CD123 heavy chain binding domain amino acid sequence listed in Table 16, Table 18, Table 20, Table 22, Table 24, Table 25, Table 26, Table 27 or Table 28; and a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of any CD123 light chain binding domain amino acid sequence listed in Table 17, Table 19, Table 21, Table 23, Table 24, Table 25, Table 26, Table 27 or Table 28. In embodiments, the CD123 binding domain includes a CD123 binding domain (e.g., scFv) amino acid sequence listed in Table 26, Table 27 or Table 28. In embodiments, the CAR includes (e.g., consists of) a CAR amino acid sequence listed in Table 26 or Table 27.

[0060] In another aspect, the tumor antigen binding domain of the CAR binds mesothelin. In embodiments, the tumor antigen binding domain of the CAR includes a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of

any mesothelin heavy chain binding domain amino acid sequence listed in Table 2, Table 3 or Table 11; and a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of any mesothelin light chain binding domain amino acid sequence listed in Table 2, Table 4 or Table 11. In embodiments, the mesothelin binding domain includes a mesothelin binding domain (e.g., scFv) amino acid sequence listed in Table 2 or Table 11. In embodiments, the CAR includes (e.g., consists of) a CAR amino acid sequence listed in Table 11.

[0061] In another aspect, the tumor antigen binding domain of the CAR binds EGFRvIII. In embodiments, the tumor antigen binding domain of the CAR includes a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of any EGFRvIII heavy chain binding domain amino acid sequence listed in Table 5; and a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of any EGFRvIII light chain binding domain amino acid sequence listed in Table 5. In embodiments, the EGFRvIII binding domain includes a EGFRvIII binding domain (e.g., scFv) amino acid sequence listed in Table 5. In embodiments, the CAR includes (e.g., consists of) a CAR amino acid sequence listed in Table 30.

[0062] In another aspect, the tumor antigen binding domain of the CAR binds CD19. In some embodiments, the tumor antigen binding domain of the CAR includes a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of any CD19 heavy chain binding domain amino acid sequence listed in Table 6, Table 7, or Table 9; and a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of any CD19 light chain binding domain amino acid sequence listed in Table 6, Table 8, or Table 9. In particular embodiments, the CD19 binding domain includes a CD19 binding domain (e.g., scFv) amino acid sequence listed in Table 6 or Table 9. In certain embodiments, the CD19 binding domain includes an amino acid sequence selected from the group consisting of SEQ ID NO: 83; SEQ ID NO: 84, SEQ ID NO: 85; SEQ

ID NO: 86; SEQ ID NO: 87; SEQ ID NO: 88; SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, and SEQ ID NO: 112.

[0063] In another aspect, the tumor antigen binding domain of the CAR binds a solid tumor antigen. In another aspect, the tumor antigen binding domain of the CAR binds an antigen expressed on a tumor associated with tumor-associated macrophages (TAMs) and/or myeloid derived suppressor cells (MDSCs). In embodiments, the solid tumor antigen or the antigen expressed on a tumor associated with tumor-associated macrophages (TAMs) and/or myeloid derived suppressor cells (MDSCs) is CD123, EGFRvIII, mesothelin, GD2, Tn antigen, sTn antigen, Tn-O-Glycopeptides, sTn-O-Glycopeptides, PSMA, CD97, TAG72, CD44v6, CEA, EPCAM, KIT, IL-13Ra2, leguman, GD3, CD171, IL-11Ra, PSCA, MAD-CT-1, MAD-CT-2, VEGFR2, LewisY, CD24, PDGFR-beta, SSEA-4, folate receptor alpha, ERBBs (e.g., ERBB2), Her2/neu, MUC1, EGFR, NCAM, Ephrin B2, CAIX, LMP2, sLe, HMWMAA, o-acetyl-GD2, folate receptor beta, TEM1/CD248, TEM7R, FAP, Legumain, HPV E6 or E7, ML-IAP, CLDN6, TSHR, GPRC5D, ALK, Polysialic acid, Fos-related antigen, neutrophil elastase, TRP-2, CYP1B1, sperm protein 17, beta human chorionic gonadotropin, AFP, thyroglobulin, PLAC1, globoH, RAGE1, MN-CA IX, human telomerase reverse transcriptase, intestinal carboxyl esterase, mut hsp 70-2, NA-17, NY-BR-1, UPK2, HAVCR1, ADRB3, PANX3, NY-ESO-1, GPR20, Ly6k, OR51E2, TARP, GFRα4, or a peptide of any of these antigens presented on MHC.

[0064] In another aspect, the tumor antigen binding domain of the CAR binds to a hematological cancer, e.g., as described herein. In some embodiments, the tumor antigen binding domain of the CAR binds to CD19. Any of the aforesaid CARs binding to CD19 can be used to treat a disease associated with expression of CD19, e.g., a CD19-expressing B cell malignancy as described herein.

[0065] In embodiments, including in any of the aforementioned aspects and embodiments, the intracellular signaling domain includes a primary signaling domain including a CD3-zeta stimulatory domain.

[0066] In embodiments, including in any of the aforementioned aspects and embodiments, the intracellular signaling domain includes a costimulatory domain which is an intracellular domain of a costimulatory protein selected from the group consisting of 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. In embodiments, including in any of the aforementioned aspects and embodiments, the costimulatory domain includes an intracellular domain of 4-1BB. In embodiments, including in any of the aforementioned aspects and embodiments, the costimulatory domain includes an intracellular domain of CD28. In embodiments, including in any of the aforementioned aspects and embodiments, the intracellular signaling domain includes two costimulatory domains, e.g., a 4-1BB costimulatory domain and a CD28 costimulatory domain.

[0067] In embodiments, including in any of the aforementioned aspects and embodiments, the disease associated with expression of a tumor antigen is cancer. In embodiments, including in any of the aforementioned aspects and embodiments, the cancer is Hodgkin lymphoma. In embodiments where the cancer is Hodgkin lymphoma, the antigen binding domain of the CAR binds CD19 or CD123, e.g., binds CD123.

[0068] In embodiments, including in any of the aforementioned aspects and embodiments, the cancer is a solid cancer.

[0069] In embodiments, including in any of the aforementioned aspects and embodiments, the cell including a CAR includes a nucleic acid encoding the CAR. In embodiments, the nucleic acid encoding the CAR is a lentiviral vector. In embodiments, the nucleic acid encoding the CAR is introduced into the cells by lentiviral transduction.

[0070] In embodiments, including in any of the aforementioned aspects and embodiments, the nucleic acid encoding the CAR is an RNA, e.g., an in vitro transcribed RNA. In embodiments, the nucleic acid encoding the CAR is introduced into the cells by electroporation.

[0071] In embodiments, including in any of the aforementioned aspects and embodiments, the cell is a T cell or an NK cell. In embodiments, the T cell is an autologous or allogeneic T cell.

[0072] In embodiments, including in any of the aforementioned aspects and embodiments, the subject is a mammal, e.g., a human.

[0073] Headings, sub-headings or numbered or lettered elements, e.g., (a), (b), (i) etc, are presented merely for ease of reading. The use of headings or numbered or lettered elements in this document does not require the steps or elements be performed in alphabetical order or that the steps or elements are necessarily discrete from one another.

[0074] All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

[0075] The disclosure includes all combinations of any one or more of the foregoing aspects and/or embodiments, as well as combinations with any one or more of the embodiments set forth in the detailed description and examples.

[0076] Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0077] The following detailed description of preferred embodiments of the invention will be better understood when read in conjunction with the appended drawings. For the purpose of illustrating the invention, there are shown in the drawings embodiments which are presently preferred. It should be understood, however, that the invention is not limited to the precise arrangements and instrumentalities of the embodiments shown in the drawings.

[0078] FIG. 1A shows Primary samples of Hodgkin lymphoma stained by immunohistochemistry for CD30 and CD123. Expression of CD123 was found of the HL Reed-sternberg cells but also in the tumor microenvironment, as opposed to CD30 that was only positive on HRS. FIG. 1B shows RNA expression of CD123 in 4 standard HL cell lines (MOLM-14 and A357 used as positive and negative controls). FIG. 1C shows CD123 was found to be also expressed on the surface of the HL cell lines (CD30 used as standard marker of HL).

[0079] FIG. 2A shows human normal donor macrophages differentiated from peripheral blood monocytes were co-cultured with HDLM-2 cells or IL-4 (M2 positive control) or a control acute lymphoblastic leukemia cell line (NALM-6). HL lymphoma cells (HDLM-2) can polarize macrophages to an M2 phenotype (CD163+CD206+) after a 24-hour culture. FIG. 2B

shows M2-polarized macrophages (IL-4) are CD123+ by flow cytometry. FIG. 2C shows M2-polarized macrophages (IL-4) can inhibit anti-CD19 chimeric antigen receptor proliferation, as shown by CFSE dilution assay. FIG. 2D shows HL-polarized macrophages strongly inhibit CART19 proliferation, as shown by CFSE dilution assay and absolute T cell numbers at day 5 (FIG. 2E). FIG. 2F shows Luminex analysis of cytokines present in the supernatant of co-cultures of HL cells (HDLM-2) with macrophages reveales high levels of IL-13 as compared to controls. FIG. 2G shows blocking IL-13 with an anti-IL13 antibody reverted the HL-drived M2 polarization as shown by reduced PD-L1 expression.

[0080] FIG. 3A shows HL cells (HDLM-2) were co-cultured with CART123 for 4-6 hours. CAR+ but not CAR- T cells expressed high levels of the degranulation marker CD107A and produced intra-cellular cytokines like IFNγ, IL-2 and TNFα. FIG. 3B shows CART123 exert potent cytotoxicity against HL cells in a dose-dependent manner. FIG. 3C shows HL cells (HDLM-2) were co-cultured at long term with CART123 or control UTD. At day 20, CART123 but not UTD killed HL cells and proliferated. FIG. 3D shows CART123 or UTD were co-cultured with HL cell lines (or positive and negative controls) for 5 days. CART123 but not UTD controls showed significant proliferation as absolute number and CFSE dilution (FIG. 3E). FIG. 3F shows HL cells stimulated CART123 but not UTD cells to release multiple cytokines including GM-CSF, IFNγ, MIP1β and TNFα. In these Figures, E:T = effector:target cell ratio.

[0081] FIG. 4A shows the experimental schema for mouse experiments testing CD123 CART against HL. 2 x106 Luciferase-positive HDLM-2 cells were injected i.v. in NSG mice and tumor engraftment was monitored by bioluminescence imaging. At day 42 mice were randomized to receive no treatment, 2 x106 control untransduced T cells (UTD) or 2 x106 CART123. FIG. 4B shows mice receiving CART123, but not controls, experienced complete response with long term remission of disease (>250 days). FIG. 4C shows CART123-treated mice have a significantly longer overall survival as compared to controls. FIG. 4D shows CAR123 T cells engraft, expand and disappear from the peripheral blood after clearing the tumor. T cells in the PB of CART123-treated mice were both CD8 and CD4 with high expression of the CAR.

[0082] FIG. 5A shows the experiment schema for establishment of long-term immunological memory in mice with HL: mice previously treated with CART123 and

experiencing a long-term remission were rechallenged at day 250 with HL cells (HDLM-2). As a control a tumor-naïve group of mice were also injected with tumor. FIG. 5B shows HL cells only engrafted and grew in tumor-naïve mice while long-term surviving mice were able to control disease growth. FIG. 5C shows a re-expansion of CART123 cells observed in mice previously treated with CART123. FIG. 5D shows an improved overall survival was observed in mice with previous exposure to CART123.

[0083] FIG. 6A shows that in a 5-day CFSE proliferation CART123 are completely resistant to HL-polarized macrophages. FIG. 6B shows CART123 cells rapidly (day 1) recognize M2-macrophages, clustering around them and clearing them by day 5, as shown by phase contrast microscopy (20X) and flow cytometry, respectively. FIG. 6C shows CART123 were also able to secrete cytokines in the presence of HL-polarized M2 macrophages as opposed to control CART19 cells.

DETAILED DESCRIPTION

Definitions

[0084] 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.

[0085] The term "pro-M2 macrophage molecule" refers to a molecule that, alone or in combination with other molecules, contributes to the polarization of macrophages to an M2 phenotype. Non-limiting examples of pro-M2 macrophage molecules include the cytokines IL-13 (OMIM Acc. No. 147683; Entrez No. 3596; Swiss Prot. Acc. No. P35225), IL-4 (OMIM Acc. No. 147780; Entrez No. 3565; Swiss Prot. Acc. No. P05112), CSF-1 (Entrez No. 1435; Swiss Prot. Acc. No. P09603) and/or IL-10 (OMIM Acc. No. 124092; Entrez No. 3586; Swiss Prot. Acc. No. P22301).

[0086] The term "inhibitor of a pro-M2 macrophage molecule" refers to a molecule that inhibits the expression or function, e.g., receptor binding function, of a pro-M2 macrophage molecule. Inhibitors of pro-M2 macrophage molecules include a small molecule, an antibody molecule, a polypeptide, e.g., a fusion protein, an inhibitory nucleic acid, e.g., a siRNA or

shRNA, or a gene editing system, e.g., a CRISPR/Cas9 system. An example of an inhibitor of pro-M2 macrophage molecule includes an inhibitor of IL-13. Another example of an inhibitor of pro-M2 macrophage molecule includes an inhibitor of IL-4. Another example of an inhibitor of pro-M2 macrophage molecule includes an inhibitor of IL-13Rα1 (Entrez No. 3597; Swiss Prot. Acc. No. P78552). Another example of an inhibitor of pro-M2 macrophage molecule includes an inhibitor of IL-10. Another example of an inhibitor of pro-M2 macrophage molecule includes an inhibitor of CSF-1. Additional detail regarding an inhibitor of pro-M2 macrophage molecule is provided below. In embodiments, the inhibitor of a pro-M2 macrophage inhibits a function, e.g., an inhibitory function, of a myeloid derived suppressor cell (MDSC).

[0087] The term "tumor associated macrophage" or "TAM" refers to cells of macrophage lineage, typically derived from monocytes or resident tissue macrophages, which are found in close proximity or within tumor masses, e.g., within the tumor stroma.

[0088] The term "myeloid derived supresssor cells" or "MDSCs" refer to myeloid derived cells which are found in close proximity or within tumor masses, e.g., within the tumor stroma.

[0089] 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.

[0090] 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.

[0091] 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 each other, e.g., are in the same

polypeptide chain (e.g., comprise a chimeric fusion protein). In some embodiments, the set of polypeptides are not contiguous with each other, e.g., are in different polypeptide chains. 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.

[0092] 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.

[0093] As used herein, the terms "alpha subunit of the IL-3 receptor," "IL3Rα," "CD123," "IL3Rα chain" and "IL3Rα subunit" refer interchangeably to an antigenic determinant known to be detectable on leukemia precursor cells. The human and murine amino acid and nucleic acid sequences can be found in a public database, such as GenBank, UniProt and Swiss-Prot. For example, the amino acid sequence of human IL3Rα can be found at Accession No. NP 002174 and the nucleotide sequence encoding of the human IL3Rα can be found at Accession No. NM 005191. In one aspect the antigen-binding portion of the CAR recognizes and binds an epitope within the extracellular domain of the CD123 protein. In one aspect, the CD123 protein is expressed on a cancer cell. As used herein, "CD123" includes proteins comprising mutations, e.g., point mutations, fragments, insertions, deletions and splice variants of full length wild-type CD123.

[0094] As used herein, the term "CD19" refers to the Cluster of Differentiation 19 protein, which is an antigenic de terminant detectable on leukemia precursor cells. The human and murine amino acid and nucleic acid sequences can be found in a public database, such as GenBank, UniProt and Swiss-Prot. For example, the amino acid sequence of human CD19 can be found as UniProt/Swiss-Prot Accession No. P15391 and the nucleotide sequence encoding of the human CD19 can be found at Accession No. NM_001178098. As used herein, "CD19" includes proteins comprising mutations, e.g., point mutations, fragments, insertions, deletions and splice variants of full length wild-type CD19. CD19 is expressed on most B lineage cancers, including, e.g., acute lymphoblastic leukaemia, chronic lymphocyte leukaemia and non-Hodgkin lymphoma. Other cells with express CD19 are provided below in the definition of "disease associated with expression of CD19." It is also an early marker of B cell progenitors. See, e.g., Nicholson et al. Mol. Immun. 34 (16-17): 1157-1165 (1997). In one aspect the antigen-binding portion of the CART recognizes and binds an antigen within the extracellular domain of the CD19 protein. In one aspect, the CD19 protein is expressed on a cancer cell.

[0095] As used herein, the term "CD20" refers to an antigenic determinant known to be detectable on B cells. Human CD20 is also called membrane-spanning 4-domains, subfamily A, member 1 (MS4A1). The human and murine amino acid and nucleic acid sequences can be

found in a public database, such as GenBank, UniProt and Swiss-Prot. For example, the amino acid sequence of human CD20 can be found at Accession Nos. NP_690605.1 and NP_068769.2, and the nucleotide sequence encoding transcript variants 1 and 3 of the human CD20 can be found at Accession No. NM_152866.2 and NM_021950.3, respectively. In one aspect the antigen-binding portion of the CAR recognizes and binds an antigen within the extracellular domain of the CD20 protein. In one aspect, the CD20 protein is expressed on a cancer cell.

[0096] As used herein, the term "CD22," refers to an antigenic determinant known to be detectable on leukemia precursor cells. The human and murine amino acid and nucleic acid sequences can be found in a public database, such as GenBank, UniProt and Swiss-Prot. For example, the amino acid sequences of isoforms 1-5 human CD22 can be found at Accession Nos. NP 001762.2, NP 001172028.1, NP 001172029.1, NP 001172030.1, and NP 001265346.1, respectively, and the nucleotide sequence encoding variants 1-5 of the human CD22 can be found at Accession No. NM 001771.3, NM 001185099.1, NM 001185100.1, NM 001185101.1, and NM 001278417.1, respectively. In one aspect the antigen-binding portion of the CAR recognizes and binds an antigen within the extracellular domain of the CD22 protein. In one aspect, the CD22 protein is expressed on a cancer cell.

[0097] As used herein, the term "ROR1" refers to an antigenic determinant known to be detectable on leukemia precursor cells. The human and murine amino acid and nucleic acid sequences can be found in a public database, such as GenBank, UniProt and Swiss-Prot. For example, the amino acid sequences of isoforms 1 and 2 precursors of human ROR1 can be found at Accession Nos. NP_005003.2 and NP_001077061.1, respectively, and the mRNA sequences encoding them can be found at Accession Nos. NM_005012.3 and NM_001083592.1, respectively. In one aspect the antigen-binding portion of the CAR recognizes and binds an antigen within the extracellular domain of the ROR1 protein. In one aspect, the ROR1 protein is expressed on a cancer cell.

[0098] As used herein, the term "CD33" refers to the Cluster of Differentiation 33 protein, which is an antigenic determinant detectable on leukemia cells as well on normal precursor cells of the myeloid lineage. The human and murine amino acid and nucleic acid sequences can be found in a public database, such as GenBank, UniProt and Swiss-Prot. For example, the amino acid sequence of human CD33 can be found as UniProt/Swiss-Prot Accession No.

P20138 and the nucleotide sequence encoding of the human CD33 can be found at Accession No. NM_001772.3. In one aspect the antigen-binding portion of the CAR recognizes and binds an epitope within the extracellular domain of the CD33 protein or fragments thereof. In one aspect, the CD33 protein is expressed on a cancer cell. As used herein, "CD33" includes proteins comprising mutations, e.g., point mutations, fragments, insertions, deletions and splice variants of full length wild-type CD33.

[0099] As used herein, the term "BCMA" refers to B-cell maturation antigen. BCMA (also known as TNFRSF17, BCM or CD269) is a member of the tumor necrosis receptor (TNFR) family and is predominantly expressed on terminally differentiated B cells, e.g., memory B cells, and plasma cells. Its ligand is called B-cell activator of the TNF family (BAFF) and a proliferation inducing ligand (APRIL). BCMA is involved in mediating the survival of plasma cells for mataining long-term humoral immunity. The gene for BCMA is encoded on chromosome 16 producing a primary mRNA transcript of 994 nucleotides in length (NCBI accession NM_001192.2) that encodes a protein of 184 amino acids (NP_001183.2). A second antisense transcript derived from the BCMA locus has been described, which may play a role in regulating BCMA expression. (Laabi Y. et al., Nucleic Acids Res., 1994, 22:1147-1154). Additional transcript variants have been described with unknown significance (Smirnova AS et al. Mol Immunol., 2008, 45(4):1179-1183. A second isoform, also known as TV4, has been identified (Uniprot identifier Q02223-2). As used herein, "BCMA" includes proteins comprising mutations, e.g., point mutations, fragments, insertions, deletions and splice variants of full length wild-type BCMA.

[00100] As used herein, the term "CLL-1" refers to C-type lectin-like molecule-1, which is an antigenic determinant detectable on leukemia precursor cells and on normal immune cells. C-type lectin-like-1 (CLL-1) is also known as MICL, CLEC12A, CLEC-1, Dendritic Cell-Associated Lectin 1, and DCAL-2. The human and murine amino acid and nucleic acid sequences can be found in a public database, such as GenBank, UniProt and Swiss-Prot. For example, the amino acid sequence of human CLL-1 can be found as UniProt/Swiss-Prot Accession No. Q5QGZ9 and the nucleotide sequence encoding of the human CLL-1 can be found at Accession Nos. NM 001207010.1, NM 138337.5, NM 201623.3, and NM 201625.1. In one embodiment, the antigen-binding portion of the CAR recognizes and binds an epitope

within the extracellular domain of the CLL-1 protein or a fragment thereof. In one embodiment, the CLL-1 protein is expressed on a cancer cell.

[00101] The term "EGFR" refers to any mammalian mature full-length epidermal growth factor receptor, including human and non-human forms. The 1186 amino acid human EGFR is described in Ullrich *et al.*, Nature 309:418-425 (1984)) and GenBank Accession No. AF125253 and SwissProt Acc No P00533-2.

[00102] The term "EGFRvIII" refers to Epidermal growth factor receptor variant III. EGFRvIII is the most common variant of EGFR observed in human tumors but is rarely observed in normal tissue. This protein results from the in-frame deletion of exons 2-7 and the generation of a novel glycine residue at the junction of exons 1 and 8 within the extra-cellular domain of the EGFR, thereby creating a tumor specific epitope. EGFRvIII is expressed in 24% to 67% of GBM, but not in normal tissues. EGFRvIII is also known as type III mutant, delta-EGFR, EGFRde2-7, and ΔEGFR and is described in U.S. Pat. Nos. 6,455,498, 6,127,126, 5,981,725, 5,814,317, 5,710,010, 5,401,828, and 5,212,290. Expression of EGFRvIII may result from a chromosomal deletion, and may also result from aberrant alternative splicing. See Sugawa *et al.*, 1990, Proc. Natl. Acad. Sci. 87:8602-8606.

[00103] As used herein, the term "mesothelin" refers to the 40-kDa protein, mesothelin, which is anchored at the cell membrane by a glycosylphosphatidyl inositol (GPI) linkage and an amino-terminal 31-kDa shed fragment, called megkaryocyte potentiating factor (MPF). Both fragments contain N-glycosylation sites. The term also refers to a soluble splice variant of the 40-kDa carboxyl-terminal fragment also called "soluble mesothelin/MPF-related". Preferably, the term refers to a human mesothelin of GenBank accession number AAH03512.1, and naturally cleaved portions thereof, e.g., as expressed on a cell membrane, e.g., a cancer cell membrane.

[00104] 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.

[00105] 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).

[00106] 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.

[00107] 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.

[00108] 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.

[00109] 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.

[00110] 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.

[00111] 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.

[00112] 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.

[00113] 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.

[00114] The term "autologous" refers to any material derived from the same individual to whom it is later to be re-introduced into the individual.

[00115] 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

[00116] The term "xenogeneic" refers to a graft derived from an animal of a different species.

[00117] 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.

[00118] The phrase "disease associated with expression of CD19" includes, but is not limited to, a disease associated with expression of CD19 or condition associated with cells

which express, or at any time expressed, CD19 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 CD19. For the avoidance of doubt, a disease associated with expression of CD19 may include a condition associated with cells which do not presently express CD19, e.g., because CD19 expression has been downregulated, e.g., due to treatment with a molecule targeting CD19, e.g., a CD19 CAR, but which at one time expressed CD19. In one aspect, a cancer associated with expression of CD19 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 CD19 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 Lymphoid Leukemia (BALL), T-cell acute Lymphoid Leukemia (TALL), acute lymphoid 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 CD19 comprise, 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 (MCL), Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin lymphoma, 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 diseases associated with expression of CD19 expression include, but not limited to, e.g., atypical and/or non-classical cancers, malignancies, precancerous conditions or proliferative diseases associated with expression of CD19. Non-cancer related indications associated with expression of CD19 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.

[00119] The phrase "disease associated with expression of a B-cell antigen" includes, but is not limited to, a disease associated with expression of one or more of CD19, CD20, CD22 or ROR1, or a condition associated with cells which express, or at any time expressed, one or more of CD19, CD20, CD22 or ROR1, 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 one or more of CD19, CD20, CD22 or ROR1. For the avoidance of doubt, a disease associated with expression of the B-cell antigen may include a condition associated with cells which do not presently express the B-cell antigen, e.g., because the antigen expression has been downregulated, e.g., due to treatment with a molecule targeting the B-cell antigen, e.g., a B-cell targeting CAR, but which at one time expressed the antigen. The phrase "disease associated with expression of a B-cell antigen" includes a disease associated with expression of CD19, as described herein.

The phrase "disease associated with expression of CD123" as used herein includes but is not limited to, a disease associated with expression of CD123 or condition associated with a cell which expresses CD123 (e.g., wild-type or mutant CD123) including, e.g., a proliferative disease such as a cancer or malignancy; a precancerous condition such as a myelodysplasia, a myelodysplastic syndrome or a preleukemia; or a non-cancer related indication associated with a cell which expresses CD123 (e.g., wild-type or mutant CD123). In one aspect, a cancer associated with expression of CD123 (e.g., wild-type or mutant CD123) is a hematological cancer. In one aspect, the disease includes AML, ALL, hairy cell leukemia, Prolymphocytic leukemia, Chronic myeloid leukemia (CML), Hodgkin lymphoma, Blastic plasmacytoid dendritic cell neoplasm, lymphoblastic B-cell leukemia (B-cell acute lymphoid leukemia, BALL), acute lymphoblastic T-cell leukemia (T-cell acute lymphoid leukemia (TALL); myelodysplastic syndrome; a myeloproliferative neoplasm; a histiocytic disorder (e.g., a mast cell disorder or a blastic plasmacytoid dendritic cell neoplasm); a mast cell disorder, e.g., systemic mastocytosis or mast cell leukemia, and the like. Further disease associated with expression of CD123 expression include, but are not limited to, e.g., atypical and/or non-classical cancers, malignancies, precancerous conditions or proliferative diseases associated with expression of CD123. Non-cancer related indications associated with expression of CD123 may also be included.

The phrase "disease associated with expression of CD33" as used herein includes but is not limited to, a disease associated with a cell which expresses CD33 (e.g., wild-type or mutant CD33) or condition associated with a cell which expresses CD33 (e.g., wild-type or mutant CD33) including, e.g., a proliferative disease 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 a cell which expresses CD33 (e.g., wild-type or mutant CD33). For the avoidance of doubt, a disease associated with expression of CD33 may include a condition associated with a cell which do not presently express CD33, e.g., because CD33 expression has been downregulated, e.g., due to treatment with a molecule targeting CD33, e.g., a CD33 inhibitor described herein, but which at one time expressed CD33. In one aspect, a cancer associated with expression of CD33 (e.g., wild-type or mutant CD33) is a hematological cancer. In one aspect, a hematological cancer includes but is not limited to acute myeloid leukemia (AML), myelodysplasia and myelodysplastic syndrome, myelofibrosis and myeloproliferative neoplasms, acute lymphoid leukemia (ALL), hairy cell leukemia, Prolymphocytic leukemia, chronic myeloid leukemia (CML), Blastic plasmacytoid dendritic cell neoplasm, and the like. Further disease associated with expression of CD33 (e.g., wild-type or mutant CD33) expression include, but are not limited to, e.g., atypical and/or non-classical cancers, malignancies, precancerous conditions or proliferative diseases associated with expression of CD33 (e.g., wild-type or mutant CD33). Non-cancer related indications associated with expression of CD33 (e.g., wild-type or mutant CD33) may also be included. In embodiments, a non-cancer related indication associated with expression of CD33 includes but is not limited to, e.g., autoimmune disease, (e.g., lupus), inflammatory disorders (allergy and asthma) and transplantation. In some embodiments, the tumor antigen-expressing cell expresses, or at any time expressed, mRNA encoding the tumor antigen. In an embodiment, the tumor antigen-expressing cell produces 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 cell produced detectable levels of a tumor antigen protein at one point, and subsequently produced substantially no detectable tumor antigen protein.

The phrase "disease associated with expression of BCMA" includes, but is not limited to, a disease associated with a cell which expresses BCMA (e.g., wild-type or mutant BCMA)

or condition associated with a cell which expresses BCMA (e.g., wild-type or mutant BCMA) 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 a cell which expresses BCMA (e.g., wild-type or mutant BCMA). For the avoidance of doubt, a disease associated with expression of BCMA may include a condition associated with a cell which does not presently express BCMA, e.g., because BCMA expression has been downregulated, e.g., due to treatment with a molecule targeting BCMA, e.g., a BCMA inhibitor described herein, but which at one time expressed BCMA. In one aspect, a cancer associated with expression of BCMA (e.g., wild-type or mutant BCMA) is a hematological cancer. In one aspect, the hematogical cancer is a leukemia or a lymphoma. In one aspect, a cancer associated with expression of BCMA (e.g., wild-type or mutant BCMA) is a malignancy of differentiated plasma B cells. In one aspect, a cancer associated with expression of BCMA(e.g., wild-type or mutant BCMA) 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 Lymphoid Leukemia ("BALL"), T-cell acute Lymphoid Leukemia ("TALL"), acute lymphoid 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 BMCA (e.g., wild-type or mutant BCMA) comprise, 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's 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. In some embodiments, the cancer is multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, or glioblastoma. In embodiments, a disease associated with expression of BCMA includes a plasma cell proliferative disorder, e.g., asymptomatic myeloma (smoldering multiple myeloma or indolent myeloma), monoclonal gammapathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia, plasmacytomas (e.g.,

plasma cell dyscrasia, solitary myeloma, solitary plasmacytoma, extramedullary plasmacytoma, and multiple plasmacytoma), systemic amyloid light chain amyloidosis, and POEMS syndrome (also known as Crow-Fukase syndrome, Takatsuki disease, and PEP syndrome). Further diseases associated with expression of BCMA (e.g., wild-type or mutant BCMA) expression include, but not limited to, e.g., atypical and/or non-classical cancers, malignancies, precancerous conditions or proliferative diseases associated with expression of BCMA (e.g., wild-type or mutant BCMA), e.g., a cancer described herein, e.g., a prostate cancer (e.g., castrate-resistant or therapy-resistant prostate cancer, or metastatic prostate cancer), pancreatic cancer, or lung cancer.

Non-cancer related conditions that are associated with BCMA (e.g., wild-type or mutant BCMA) include viral infections; e.g., HIV, fungal invections, e.g., *C. neoformans*; autoimmune disease; e.g. rheumatoid arthritis, system lupus erythematosus (SLE or lupus), pemphigus vulgaris, and Sjogren's syndrome; inflammatory bowel disease, ulcerative colitis; transplant-related allospecific immunity disorders related to mucosal immunity; and unwanted immune responses towards biologics (e.g., Factor VIII) where humoral immunity is important. In embodiments, a non-cancer related indication associated with expression of BCMA includes but is not limited to, e.g., autoimmune disease, (e.g., lupus), inflammatory disorders (allergy and asthma) and transplantation. In some embodiments, the tumor antigen-expressing cell expresses, or at any time expressed, mRNA encoding the tumor antigen. In an embodiment, the tumor antigen -expressing cell produces 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 cell produced detectable levels of a tumor antigen protein at one point, and subsequently produced substantially no detectable tumor antigen protein.

The phrase "disease associated with expression of CLL-1" includes, but is not limited to, a disease associated with a cell which expresses CLL-1 or condition associated with a cell which expresses CLL-1 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 a cell which expresses CLL-1 (e.g., wild-type or mutant CLL-1). For the avoidance of doubt, a disease associated with expression of CLL-1 may include a condition associated with a cell which do not presently

express CLL-1, e.g., because CLL-1 expression has been downregulated, e.g., due to treatment with a molecule targeting CLL-1, e.g., a CLL-1 inhibitor described herein, but which at one time expressed CLL-1. In one aspect, a cancer associated with expression of CLL-1 is a hematological cancer. In one aspect, a hematological cancer includes but is not limited to leukemia (such as acute myelogenous leukemia, chronic myelogenous leukemia, acute lymphoid leukemia, chronic lymphoid leukemia and myelodysplastic syndrome) and malignant lymphoproliferative conditions, including lymphoma (such as multiple myeloma, non-Hodgkin's lymphoma, Burkitt's lymphoma, and small cell- and large cell-follicular lymphoma). Further diseases associated with expression of CLL-1 expression include, but not limited to, e.g., atypical and/or non-classical cancers, malignancies, precancerous conditions or proliferative diseases associated with expression of CLL-1. Non-cancer related indications associated with expression of CLL-1 may also be included. In some embodiments, the tumor antigen-expressing cell expresses, or at any time expressed, mRNA encoding the tumor antigen. In an embodiment, the tumor antigen-expressing cell produces 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 cell produced detectable levels of a tumor antigen protein at one point, and subsequently produced substantially no detectable tumor antigen protein.

The term "disease associated with expression of EGFRvIII" as used herein includes, but is not limited to, a disease associated with expression of EGFRvIII or condition associated with cells which express EGFRvIII including, tumor cells of various cancers such as, e.g., glioblastoma (including glioblastoma stem cells); breast, ovarian, and non-small cell lung carcinomas; head and neck squamous cell carcinoma; medulloblastoma, colorectal cancer, prostate cancer, and bladder carcinoma. Without being bound to a particular theory or mechanism, it is believed that by eliciting an antigen-specific response against EGFRvIII, the CARs disclosed herein provide for one or more of the following: targeting and destroying EGFRvIII-expressing tumor cells, reducing or eliminating tumors, facilitating infiltration of immune cells to the tumor site, and enhancing/extending anti-tumor responses. Because EGFRvIII is not expressed at detectable levels in normal (i.e., non-cancerous) tissue, it is contemplated that the inventive CARs advantageously substantially avoid targeting/destroying normal tissues and cells.

[00120] The phrase "disease associated with expression of mesothelin" as used herein includes, but is not limited to, a disease associated with expression of mesothelin or condition associated with cells which express mesothelin including, e.g., proliferative diseases such as a cancer or malignancy or a precancerous condition such as a mesothelial hyperplasia; or a noncancer related indication associated with cells which express mesothelin. Examples of various cancers that express mesothelin include but are not limited to, mesothelioma, ovarian cancer, pancreatic cancer, and the like.

[00121] 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.

[00122] 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.

[00123] The term "stimulatory molecule," refers to a molecule expressed by 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: 17, 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: 43, or the equivalent residues from a non-human species, e.g., mouse, rodent, monkey, ape and the like.

[00124] 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.

[00125] 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.

[00126] 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.

[00127] 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.

[00128] 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:17. In one aspect, the "zeta stimulatory domain" or a "CD3-zeta stimulatory domain" is the sequence provided as SEQ ID NO:43.

[00129] The term "costimulatory molecule" refers to the 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.

[00130] 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.

[00131] 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.

[00132] 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 accno. 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:16

or the equivalent residues from a non-human species, e.g., mouse, rodent, monkey, ape and the like.

[00133] "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 cells, e.g., T cells or NK cells, may be derived directly from a subject, or may be differentiated from cells derived from a subject (e.g., may be differentiated from stem cells, e.g., embryonic stem cells or induced pluripotent stem cells (iPSCs)).

[00134] "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.

[00135] 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.

[00136] 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).

[00137] 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. In one non-limiting embodiment, the term "a therapeutically effective amount" refers to the amount of the compound described herein that, when administered to a subject, is effective to (1) at least partially alleviate, inhibit, preventand/or ameliorate a condition, or a disorder or a disease (i) mediated by BTK, or (ii) associated with BTK activity, or (iii) characterized by activity (normal or abnormal) of BTK; or (2) reducing or inhibiting the activity of BTK; or (3) reducing or inhibiting the expression of BTK. In another non-limiting embodiment, the term "a therapeutically effective amount" refers to the amount of the compound described herein, that when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective to at least partially reducing or inhibiting the activity of BTK; or reducing or inhibiting the expression of BTK partially or completely.

[00138] The term "endogenous" refers to any material from or produced inside an organism, cell, tissue or system.

[00139] The term "exogenous" refers to any material introduced from or produced outside an organism, cell, tissue or system.

[00140] The term "expression" refers to the transcription and/or translation of a particular nucleotide sequence driven by a promoter.

[00141] 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.

[00142] 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.

[00143] 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.

[00144] 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.

[00145] 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.

[00146] "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.

[00147] "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.

[00148] 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.

[00149] 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.

[00150] 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.

[00151] 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.

[00152] 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)).

[00153] 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.

[00154] 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.

[00155] 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.

[00156] 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.

[00157] 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.

[00158] 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.

[00159] 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 $(Gly\text{-}Gly\text{-}Gly\text{-}Ser)_n$, where n is a positive integer equal to or greater than 1 (SEQ ID NO: 31). 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, $(Gly_4 Ser)_4$ (SEQ ID NO: 29) or $(Gly_4 Ser)_3$ (SEQ ID NO: 30). In another embodiment, the linkers include multiple repeats of (Gly_2Ser), (GlySer) or (Gly_3Ser) (SEQ ID NO: 31). Also included within the scope of the invention are linkers described in WO2012/138475, incorporated herein by reference).

[00160] 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.

[00161] 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.

[00162] 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: 2589), 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.

[00163] 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.

[00164] 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.

[00165] 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.

[00166] The term "subject" is intended to include living organisms in which an immune response can be elicited (e.g., mammals, human).

[00167] 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.

[00168] The term "therapeutic" as used herein means a treatment. A therapeutic effect is obtained by reduction, suppression, remission, or eradication of a disease state.

[00169] The term “prophylaxis” as used herein means the prevention of or protective treatment for a disease or disease state.

[00170] 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.

[00171] 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.

[00172] The term “specifically binds,” refers to an antibody, or a ligand, which recognizes and binds with a binding partner (e.g., a stimulatory tumor antigen) protein present in a sample, but which antibody or ligand does not substantially recognize or bind other molecules in the sample.

[00173] “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.

[00174] "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.

[00175] "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.

[00176] "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.

[00177] "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 refractory during a treatment.

[00178] A "complete responder" as used herein refers to a subject having a disease, e.g., a cancer, who exhibits a complete response, e.g., a complete remission, to a treatment. A complete response may be identified, e.g., using the Cheson criteria as described herein.

[00179] A "partial responder" as used herein refers to a subject having a disease, e.g., a cancer, who exhibits a partial response, e.g., a partial remission, to a treatment. A partial response may be identified, e.g., using the Cheson criteria.

[00180] A "non-responder" as used herein refers to a subject having a disease, e.g., a cancer, who does not exhibit a response to a treatment, e.g., the patient has stable disease or progressive disease. A non-responder may be identified, e.g., using the Cheson criteria as described herein.

[00181] The term "relapse" as used herein refers to reappearance of a disease (e.g., cancer) after an initial period of responsiveness (e.g., complete response or partial response). The initial period of responsiveness may involve the level of cancer cells falling below a certain threshold, e.g., below 20%, 1%, 10%, 5%, 4%, 3%, 2%, or 1%. The reappearance may involve the level of cancer cells rising above a certain threshold, e.g., above 20%, 1%, 10%, 5%, 4%, 3%, 2%, or 1%. Relapse may be identified, e.g., using the Cheson criteria as described herein.

[00182] 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.

Description

[00183] Provided herein are compositions of matter and methods of use for the treatment of a disease such as cancer (e.g., a solid tumor or tumor associated with tumor associated macrophages) using immune effector cells (e.g., T cells or NK cells) that express a chimeric antigen receptor (CAR) (e.g., a CAR that targets an antigen on a solid tumor or antigen on a tumor associated with tumor associated macrophages). The methods include, inter alia, administering immune effector cells (e.g., T cells or NK cells) expressing a CAR described herein in combination with another agent such as an inhibitor of a pro-M2 macrophage molecule, e.g., an inhibitor of a pro-M2 macrophage molecule described herein, e.g., an anti-IL-13 antibody, an anti-IL-4 antibody or an anti-IL-13Rα1 antibody.

[00184] The present invention provides, at least in part, experiments supporting the high efficacy of a combination of a CAR therapy (e.g., a CAR that targets an antigen on a solid tumor or antigen on a tumor associated with tumor associated macrophages) and an inhibitor of a pro-M2 macrophage molecule. The combination of an inhibitor of a pro-M2 macrophage molecule, with a CAR therapy can increase efficacy of the combination therapy relative to a monotherapy of the inhibitor of a pro-M2 macrophage molecule, or a dose of CAR-expressing cells, or both. These beneficial effects can, for example, allow for a lower dose of the inhibitor of a pro-M2 macrophage molecule or the CAR-expressing cells, or both, while maintaining efficacy. The results herein are applicable to a wide range of cancers, e.g., solid tumors or tumors associated with tumor assoiciated macrophages. For example, lymphomas, such as Hodgkin lymphoma are known to be associated with MDSCs or TAMs, which may inhibit the function of the CAR-expressing immune effector cell against said lymphoma, e.g., a CD123 CAR. An immune effector cell (e.g., T cell or NK cell) that expresses a CD123 CAR, e.g., as described herein, targets cancers with CD123 surface expression (such as Hodgkin lymphoma). Alternatively or in combination with CD123 CAR, any other lymphoma-targeting CAR can be used in the combination therapies described herein. Therefore, the combination of a CAR therapy (e.g., one or more of a CD123 CAR, or other CAR targeting a lymphoma antigen) with an inhibitor of a pro-M2 macrophage molecule (e.g., as described herein) is suitable for treating a wide range of lymphomas (e.g., Hodgkin lymphoma). Similarly, an immune effector cell (e.g., T cell or NK cell) that expresses a CAR which targets an antigen on a solid tumor, e.g., as described herein, e.g., mesothelin or EGFRvIII, targets cancers with surface expression of the

antigen. Therefore, the combination of a CAR therapy (e.g., one or more of a solid tumor-targeting CAR, e.g., a CAR targeting mesothelin or EGFRvIII, e.g., as described herein) with an inhibitor of a pro-M2 macrophage molecule (e.g., as described herein) is suitable for treating a wide range of solid tumors, e.g., a disease associated with expression on mesothelin or a disease associated with expression of EGFRvIII.

[00185] According to the present invention, an inhibitor of a pro-M2 macrophage molecule can reduce inhibition, e.g., macrophage-mediated inhibition, of immune effector cells, e.g., CAR-expressing tumor effector cells, e.g., as described herein, against a cancer, e.g., a solid tumor or tumor associated with MDSCs or TAMs. Without wishing to be bound by theory, certain lymphomas, such as Hodgkin lymphoma, and solid tumors are characterized by masses of cancerous cells associated with MDSCs or TAMs. CAR-expressing immune effector cells sometimes have difficulty penetrating these densely packed masses and their anti-cancer function may be impaired by the inhibitory tumor microenvironment, e.g., inhibited by MDSCs or TAMs. Thus, an inhibitor of a pro-M2 macrophage molecule may be administered in combination with a CAR-expressing cell therapy, making the cancer cells more vulnerable to the CAR-expressing cells.

[00186] In one aspect, the invention provides a number of chimeric antigen receptors (CAR) comprising an antibody or antibody fragment engineered for specific binding to an antigen expressed on a solid tumor or tumor associated with MDSCs or TAMs (e.g., in the case of Hodgkin lymphoma, the antigen being, e.g., CD123). In one aspect, the invention provides a cell (e.g., T cell) engineered to express a CAR, wherein the CAR T cell ("CART") 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) 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) 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.

[00187] In one aspect, the antigen binding portion of the CAR 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 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 some aspects, the antibodies of the invention are incorporated into a chimeric antigen receptor (CAR).

[00188] In one aspect, the CAR or binding domain, e.g., a humanized scFv, portion of a CAR of the invention is encoded by a transgene 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 transgene 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.

[00189] 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.

[00190] Furthermore, the present invention provides CAR compositions 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 the target antigen recognized by the CAR.

[00191] In one aspect, the CAR of the invention can be used to eradicate target antigen-expressing normal cells, thereby applicable for use as a cellular conditioning therapy prior to cell transplantation. In one aspect, the target antigen-expressing normal cell is a CD19-expressing normal stem cell and the cell transplantation is a stem cell transplantation.

[00192] In one aspect, the invention provides a cell (e.g., T cell) engineered to express a chimeric antigen receptor (CAR), wherein the CAR-expressing cell, e.g., CAR T cell ("CART"), exhibits an anticancer property. With respect to anticancer peroperties against, e.g., Hodgkin lymphoma, a preferred antigen is CD123. In one aspect, the antigen binding domain of the CAR comprises a plurality of antigen-binding fragments. In one aspect, the antigen binding domain of the CAR comprises a plurality of antibody fragments comprising a scFv.

[00193] In one aspect, the CAR comprises at least one intracellular domain selected from the group of a CD137 (4-1BB) signaling domain, a CD28 signaling domain, a CD3zeta signaling domain, and any combination thereof. In one aspect, the CAR comprises at least one intracellular signaling domain is from one or more co-stimulatory molecule(s) other than a CD137 (4-1BB) or CD28.

Chimeric Antigen Receptor (CAR)

[00194] The present invention encompasses a recombinant DNA construct comprising sequences encoding a CAR, wherein the CAR comprises an antibody or antibody fragment that binds specifically to an antigen (e.g., an antigen expressed on a solid tumor or tumor associated with MDSCs or TAMs), wherein the sequence of the antibody fragment 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 one embodiment, the antigen binding domain is a murine antibody or antibody fragment described herein. In one embodiment, the antigen binding domain is a humanized antibody or antibody fragment.

[00195] In one aspect an exemplary CAR construct, e.g., as described herein, comprises an optional leader sequence, an extracellular antigen binding domain, a hinge, a transmembrane domain, and an intracellular stimulatory domain. In one aspect an exemplary CAR construct comprises an optional leader sequence, an extracellular antigen binding domain, a hinge, a transmembrane domain, an intracellular costimulatory domain and an intracellular stimulatory

domain. Specific CAR constructs containing murine, fully human and/or humanized scFv domains of the invention are provided below.

[00196] 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.

[00197] 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 transgene encoding a CAR, wherein the nucleic acid molecule comprises a nucleic acid sequence encoding an antigen binding domain, described herein. 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, 4-1BB, and the like. In some instances, the CAR can comprise any combination of CD3-zeta, CD28, 4-1BB, and the like.

[00198] 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 nucleic acid of interest can be produced synthetically, rather than cloned.

[00199] The present invention includes retroviral and lentiviral vector constructs expressing a CAR that can be directly transduced into a cell.

[00200] 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"), 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) (e.g., SEQ ID NO:32-34 or SEQ ID NO:37-38). 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 T cell by electroporation.

[00201] Sequences of non-limiting examples of various components that can be part of a CAR molecule described herein, are listed in Table 1, where "aa" stands for amino acids, and "na" stands for nucleic acids that encode the corresponding peptide.

[00202] **Table 1.** Sequences of various components of CAR (aa – amino acids, na – nucleic acids that encodes the corresponding protein)

SEQ ID NO	Description	Sequence
1	EF-1 promoter (na)	CGTGAGGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCC CACAGTCCCCGAGAAGTTGGGGGGAGGGGTCGGCAATTGAACC GGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAAAGTGATG TCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCG TATATAAGTGCAGTAGTCGCCGTGAACGTTCTTTTTCGCAACGG GTTTGCCGCCAGAACACAGGTAAGTGCCGTGTGTGGTTCCCGCG GGCCTGGCCTCTTTACGGGTTATGGCCCTTGCGTGCCTTGAATT ACTTCCACCTGGCTGCAGTACGTGATTCTTGATCCCGAGCTTCG GGTTGGAAGTGGGTGGGAGAGTTCGAGGCCTTGCGCTTAAGGA GCCCCTTCGCCTCGTGCTTGAGTTGAGGCCTGGCCTGGGCGCTG GGGCCGCCGCGTGCGAATCTGGTGGCACCTTCGCGCCTGTCTCG CTGCTTTCGATAAGTCTCTAGCCATTTAAAATTTTTGATGACCTG CTGCGACGCTTTTTTTCTGGCAAGATAGTCTTGTAAATGCGGGC CAAGATCTGCACACTGGTATTTCGGTTTTTGGGGCCGCGGGCGG CGACGGGGCCCGTGCGTCCCAGCGCACATGTTCGGCGAGGCGG GGCCTGCGAGCGCGGCCACCGAGAATCGGACGGGGGTAGTCTC AAGCTGGCCGGCCTGCTCTGGTGCCTGGCCTCGCGCCGCCGTGT ATCGCCCCGCCCTGGGCGGCAAGGCTGGCCCGGTCGGCACCAG TTGCGTGAGCGGAAAGATGGCCGCTTCCCGGCCCTGCTGCAGG GAGCTCAAAATGGAGGACGCGGCGCTCGGGAGAGCGGGCGGG TGAGTCACCCACACAAAGGAAAAGGGCCTTTCCGTCCTCAGCC GTCGCTTCATGTGACTCCACGGAGTACCGGGCGCCGTCCAGGCA CCTCGATTAGTTCTCGAGCTTTTGGAGTACGTCGTCTTTAGGTTG GGGGGAGGGGTTTTATGCGATGGAGTTTCCCCACACTGAGTGG GTGGAGACTGAAGTTAGGCCAGCTTGGCACTTGATGTAATTCTC CTTGGAATTTGCCCTTTTTGAGTTTGGATCTTGGTTCATTCTCAA GCCTCAGACAGTGGTTCAAAGTTTTTTTCTTCCATTTCAGGTGTC GTGA
2	Leader (aa)	MALPVTALLLPLALLLHAARP

3	Leader (na)	ATGGCCCTGCCTGTGACAGCCCTGCTGCTGCCTCTGGCTCTGCT GCTGCATGCCGCTAGACCC
	Leader codon optimized (na)	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTG CTCCACGCCGCTCGGCCC
4	CD 8 hinge (aa)	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD
5	CD8 hinge (na)	ACCACGACGCCAGCGCCGCGACCACCAACACCGGCGCCCACCA TCGCGTCGCAGCCCCTGTCCCTGCGCCCAGAGGCGTGCCGGCCA GCGGCGGGGGGCGCAGTGCACACGAGGGGGCTGGACTTCGCCT GTGAT
6	Ig4 hinge (aa)	ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSL GKM
7	Ig4 hinge (na)	GAGAGCAAGTACGGCCCTCCCTGCCCCCCTTGCCCTGCCCCCGA GTTCCTGGGCGGACCCAGCGTGTTCCTGTTCCCCCCCAAGCCCA AGGACACCCTGATGATCAGCCGGACCCCCGAGGTGACCTGTGT GGTGGTGGACGTGTCCCAGGAGGACCCCGAGGTCCAGTTCAAC TGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAAGC CCCGGGAGGAGCAGTTCAATAGCACCTACCGGGTGGTGTCCGT GCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAATAC AAGTGTAAGGTGTCCAACAAGGGCCTGCCCAGCAGCATCGAGA AAACCATCAGCAAGGCCAAGGGCCAGCCTCGGGAGCCCCAGGT GTACACCCTGCCCCCTAGCCAAGAGGAGATGACCAAGAACCAG GTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACAT CGCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAACAACTAC AAGACCACCCCCCCTGTGCTGGACAGCGACGGCAGCTTCTTCCT GTACAGCCGGCTGACCGTGGACAAGAGCCGGTGGCAGGAGGGC AACGTCTTTAGCTGCTCCGTGATGCACGAGGCCCTGCACAACCA CTACACCCAGAAGAGCCTGAGCCTGTCCCTGGGCAAGATG
8	IgD hinge (aa)	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGRGGEEKK KEKEKEEQEERETKTPECPSHTQPLGVYLLTPAVQDLWLRDKATF TCFVVGSDLKDAHLTWEVAGKVPTGGVEEGLLERHSNGSQSQHS RLTLPRSLWNAGTSVTCTLNHPSLPPQRLMALREPAAQAPVKLSL NLLASSDPPEAASWLLCEVSGFSPPNILLMWLEDQREVNTSGFAPA RPPPQPGSTTFWAWSVLRVPAPPSPQPATYTCVVSHEDSRTLLNAS RSLEVSYVTDH
9	IgD hinge (na)	AGGTGGCCCGAAAGTCCCAAGGCCCAGGCATCTAGTGTTCCTA CTGCACAGCCCCAGGCAGAAGGCAGCCTAGCCAAAGCTACTAC TGCACCTGCCACTACGCGCAATACTGGCCGTGGCGGGGAGGAG AAGAAAAAGGAGAAAGAGAAAGAAGAACAGGAAGAGAGGGA GACCAAGACCCCTGAATGTCCATCCCATACCCAGCCGCTGGGC GTCTATCTCTTGACTCCCGCAGTACAGGACTTGTGGCTTAGAGA TAAGGCCACCTTTACATGTTTCGTCGTGGGCTCTGACCTGAAGG ATGCCCATTTGACTTGGGAGGTTGCCGGAAAGGTACCCACAGG GGGGGTTGAGGAAGGGTTGCTGGAGCGCCATTCCAATGGCTCT CAGAGCCAGCACTCAAGACTCACCCTTCCGAGATCCCTGTGGA ACGCCGGGACCTCTGTCACATGTACTCTAAATCATCCTAGCCTG CCCCCACAGCGTCTGATGGCCCTTAGAGAGCCAGCCGCCCAGG

		CACCAGTTAAGCTTAGCCTGAATCTGCTCGCCAGTAGTGATCCC CCAGAGGCCGCCAGCTGGCTCTTATGCGAAGTGTCCGGCTTTAG CCCGCCCAACATCTTGCTCATGTGGCTGGAGGACCAGCGAGAA GTGAACACCAGCGGCTTCGCTCCAGCCCGGCCCCCACCCCAGCC GGGTTCTACCACATTCTGGGCCTGGAGTGTCTTAAGGGTCCCAG CACCACCTAGCCCCCAGCCAGCCACATACACCTGTGTTGTGTCC CATGAAGATAGCAGGACCCTGCTAAATGCTTCTAGGAGTCTGG AGGTTTCCTACGTGACTGACCATT
10	GS hinge/linker (aa)	GGGGSGGGGS
11	GS hinge/linker (na)	GGTGGCGGAGGTTCTGGAGGTGGAGGTTCC
12	CD8TM (aa)	IYIWAPLAGTCGVLLLSLVITLYC
13	CD8 TM (na)	ATCTACATCTGGGCGCCCTTGGCCGGGACTTGTGGGGTCCTTCT CCTGTCACTGGTTATCACCCTTTACTGC
	CD8 TM, codon optimized (na)	ATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCT GCTTTCACTCGTGATCACTCTTTACTGT
14	4-1BB intracellular domain (aa)	KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL
15	4-1BB intracellular domain (na)	AAACGGGGCAGAAAGAAACTCCTGTATATATTCAAACAACCAT TTATGAGACCAGTACAAACTACTCAAGAGGAAGATGGCTGTAG CTGCCGATTTCCAGAAGAAGAAGAAGGAGGATGTGAACTG
	4-1BB intracellular domain, codon optimized (na)	AAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTT CATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCA TGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTG
16	CD27 intracellular domain (aa)	QRRKYRSNKGESPVEPAEPCRYSCPREEEGSTIPIQEDYRKPEPACS P
17	CD27 intracellular domain (na)	AGGAGTAAGAGGAGCAGGCTCCTGCACAGTGACTACATGAACA TGACTCCCCGCCGCCCCGGGCCCACCCGCAAGCATTACCAGCCC TATGCCCCACCACGCGACTTCGCAGCCTATCGCTCC
18	CD3-zeta (aa)	RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPE MGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHD GLYQGLSTATKDTYDALHMQALPPR
19	CD3-zeta (na)	AGAGTGAAGTTCAGCAGGAGCGCAGACGCCCCCGCGTACAAGC AGGGCCAGAACCAGCTCTATAACGAGCTCAATCTAGGACGAAG AGAGGAGTACGATGTTTTGGACAAGAGACGTGGCCGGGACCCT GAGATGGGGGGAAAGCCGAGAAGGAAGAACCCTCAGGAAGGC CTGTACAATGAACTGCAGAAAGATAAGATGGCGGAGGCCTACA GTGAGATTGGGATGAAAGGCGAGCGCCGGAGGGGCAAGGGGC ACGATGGCCTTTACCAGGGTCTCAGTACAGCCACCAAGGACAC CTACGACGCCCTTCACATGCAGGCCCTGCCCCCTCGC
20	CD3-zeta (aa)	RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPE MGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHD GLYQGLSTATKDTYDALHMQALPPR
21	CD3-zeta (na)	AGAGTGAAGTTCAGCAGGAGCGCAGACGCCCCCGCGTACCAGC

		AGGGCCAGAACCAGCTCTATAACGAGCTCAATCTAGGACGAAG AGAGGAGTACGATGTTTTGGACAAGAGACGTGGCCGGGACCCT GAGATGGGGGGAAAGCCGAGAAGGAAGAACCCTCAGGAAGGC CTGTACAATGAACTGCAGAAAGATAAGATGGCGGAGGCCTACA GTGAGATTGGGATGAAAGGCGAGCGCCGGAGGGGCAAGGGGC ACGATGGCCTTTACCAGGGTCTCAGTACAGCCACCAAGGACAC CTACGACGCCCTTCACATGCAGGCCCTGCCCCCTCGC
	CD3-zeta, codon optimized (na)	CGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGC AGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAG AGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCC AGAAATGGGCGGGAAGCCGCGCAGAAAGAATCCCCAAGAGGG CCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCCTAT AGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGC CACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACA CCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
22	linker	GGGGS
23	linker	GGTGGCGGAGGTTCTGGAGGTGGAGGTTCC
24	PD-1 extracellular domain (aa)	Pgwfldspdrpwnpptfspallvvtegdnatftcsfsntsesfvlnwyrmspsnqtdklaafpedrsqp gqdcrfrvtqlpngrdfhmsvvrarrndsgtylcgaislapkaqikeslraelrvterraevptahpspsp rpagqfqtlv
25	PD-1 extracellular domain (na)	Cccggatggtttctggactctccggatcgcccgtggaatcccccaaccttctcaccggcactcttggttgtg actgagggcgataatgcgaccttcacgtgctcgttctccaacacctccgaatcattcgtgctgaactggtac cgcatgagcccgtcaaaccagaccgacaagctcgccgcgtttccggaagatcggtcgcaaccgggaca ggattgtcggttccgcgtgactcaactgccgaatggcagagacttccacatgagcgtggtccgcgctagg cgaaacgactccgggacctacctgtgcggagccatctcgctggcgcctaaggcccaaatcaaagagag cttgagggccgaactgagagtgaccgagcgcagagctgaggtgccaactgcacatccatccccatcgcc tcggcctgcggggcagtttcagaccctggtc
26	PD-1 CAR (aa) with signal	Malpvtalllplalllhaarppgwfldspdrpwnpptfspallvvtegdnatftcsfsntsesfvlnwyr mspsnqtdklaafpedrsqpgqdcrfrvtqlpngrdfhmsvvrarrndsgtylcgaislapkaqikesl raelrvterraevptahpspsprpagqfqtlvtttpaprpptpaptiasqplslrpeacrpaaggavhtrgl dfacdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeeggcelr vkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkprrknpqeglynelqkdkm aeayseigmkgerrrgkghdglyqglstatkdtydalhmqalppr
27	PD-1 CAR (na)	Atggccctccctgtcactgccctgcttctccccctcgcactcctgctccacgccgctagaccacccggatg gtttctggactctccggatcgcccgtggaatcccccaaccttctcaccggcactcttggttgtgactgaggg cgataatgcgaccttcacgtgctcgttctccaacacctccgaatcattcgtgctgaactggtaccgcatgag cccgtcaaaccagaccgacaagctcgccgcgtttccggaagatcggtcgcaaccgggacaggattgtcg gttccgcgtgactcaactgccgaatggcagagacttccacatgagcgtggtccgcgctaggcgaaacga ctccgggacctacctgtgcggagccatctcgctggcgcctaaggcccaaatcaaagagagcttgagggc cgaactgagagtgaccgagcgcagagctgaggtgccaactgcacatccatccccatcgcctcggcctgc ggggcagtttcagaccctggtcacgaccactccggcgccgcgcccaccgactccggccccaactatcg cgagccagcccctgtcgctgaggccggaagcatgccgccctgccgccggaggtgctgtgcatacccgg ggattggacttcgcatgcgacatctacatttgggctcctctcgccggaacttgtggcgtgctccttctgtcct ggtcatcaccctgtactgcaagcggggtcggaaaaagcttctgtacattttcaagcagcccttcatgaggc ccgtgcaaaccacccaggaggaggacggttgctcctgccggttccccgaagaggaagaaggaggttgc gagctgcgcgtgaagttctcccggagcgccgacgcccccgcctataagcagggccagaaccagctgta caacgaactgaacctgggacggcgggaagagtacgatgtgctggacaagcggcgcggccgggaccc cgaaatgggcgggaagcctagaagaaagaaccctcaggaaggcctgtataacgagctgcagaaggac aagatggccgaggcctactccgaaattgggatgaagggagagcggcggaggggaaaggggcacgac ggcctgtaccaaggactgtccaccgccaccaaggacacatacgatgccctgcacatgcaggcccttccc cctcgc

28	linker	(Gly-Gly-Gly-Ser)$_n$, where n = 1-10
29	linker	$(Gly_4\ Ser)_4$
30	linker	$(Gly_4\ Ser)3$
31	linker	(Gly_3Ser)
32	polyA (2000 A's)	$[a]_{2000}$
33	polyA (150 A's)	$[a]_{150}$
34	polyA (5000 A's)	$[a]_{5000}$
35	polyA (100 T's)	$[t]_{100}$
36	polyA (500 T's)	$[t]_{500}$
37	polyA (64 A's)	$[a]_{64}$
38	polyA (400 A's)	$[a]_{400}$
39	PD1 CAR (aa)	Pgwfldspdrpwnpptfspallvvtegdnatftcsfsntsesfvlnwyrmspsnqtdklaafpedrsqpgqdcrfrvtqlpngrdfhmsvvrarrndsgtylcgaislapkaqikeslraelrvterraevptahpspsprpagqfqtlvtttpaprpptpaptiasqplslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeeggcelrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdglyqglstatkdtydalhmqalppr
40	ICOS intracellular domain (aa)	T K N K Y S S S V H D P N G E Y M F M R A V N T A K K S R L T D V T L
41	ICOS intracellular domain (na)	ACAAAAAAGAAGTATTCATCCAGTGTGCACGACCCTAACGGTGAATACATGTTCATGAGAGCAGTGAACACAGCCAAAAAATCCAGACTCACAGATGTGACCCTA
42	ICOS TM domain (aa)	T T T P A P R P P T P A P T I A S Q P L S L R P E A C R P A A G G A V H T R G L D F A C D F W L P I G C A A F V V V C I L G C I L I C W L
43	ICOS TM domain (na)	ACCACGACGCCAGCGCCGCGACCACCAACACCGGCGCCCACCATCGCGTCGCAGCCCCTGTCCCTGCGCCCAGAGGCGTGCCGGCCAGCGGCGGGGGGCGCAGTGCACACGAGGGGGCTGGACTTCGCCTGTGATTTCTGGTTACCCATAGGATGTGCAGCCTTTGTTGTAGTCTGCATTTTGGGATGCATACTTATTTGTTGGCTT
44	CD28 intracellular domain (aa)	RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS
45	CD28 intracellular domain (na)	AGGAGTAAGAGGAGCAGGCTCCTGCACAGTGACTACATGAACATGACTCCCCGCCGCCCCGGGCCCACCCGCAAGCATTACCAGCCCTATGCCCCACCACGCGACTTCGCAGCCTATCGCTCC

Antigen binding domains and CARs

[00203] 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.

[00204] 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.

[00205] In one aspect, the CAR comprises an antigen binding domain which targets a solid tumor antigen. In one aspect the CAR comprises an antigen binding domain which targets a tumor antigen expressed on a tumor associated with MDSCs or TAMs, e.g., Hodgkin lymphoma.

[00206] 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 murine 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, and the like.

[00207] In an embodiment, the antigen binding domain of a CAR binds to human mesothelin. In an embodiment, the antigen binding domain is a murine scFv domain that binds to human mesothelin, e.g., SS1 or SEQ ID NO: 46. In an embodiment, the antigen binding domain is a humanized antibody or antibody fragment, e.g., scFv domain, derived from the murine SS1 scFv. In an embodiment, the antigen binding domain is a human antibody or antibody fragment that binds to human mesothelin. Exemplary human scFv domains (and their sequences) and the murine SS1 scFv that bind to mesothelin are provided in Table 2. CDR sequences are underlined. The scFv domain sequences provided in Table 2 include a light chain variable region (VL) and a heavy chain variable region (VH). The VL and VH are attached by a linker comprising the sequence GGGGSGGGGSGGGGS (SEQ ID NO: 30) (e.g., as shown in SS1 scFv domains) or GGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 29) (e.g.,

as shown in M1, M2, M3, M4, M5, M6, M7, M8, M9, M10, M11, M12, M13, M14, M15, M16, M17, M18, M19, M20, M21, M22, M23, or M24 scFv domains). The scFv domains listed in Table 2 are in the following orientation: VL-linker-VH.

Table 2. Examples of antigen binding domains that bind to mesothelin

Tumor antigen	Name	Amino acid sequence	SEQ ID NO:
mesothelin	M5 (human)	QVQLVQSGAEVEKPGASVKVSCKASGYTFTDYYMHWVRQAPGQGLEWMGW INPNSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCASGW DFDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIVMTQSPSSLSASV GDRVTITCRASQSIRYYLSWYQQKPGKAPKLLIYTASILQNGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCLQTYTTPDFGPGTKVEIK	51
mesothelin	M11 (human)	QVQLQQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGW INPNSGGTNYAQNFQGRVTMTRDTSISTAYMELRRLRSDDTAVYYCASGW DFDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIRMTQSPSSLSASV GDRVTITCRASQSIRYYLSWYQQKPGKAPKLLIYTASILQNGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCLQTYTTPDFGPGTKVEIK	57
mesothelin	ss1 (murine)	Q V Q L Q Q S G P E L E K P G A S V K I S C K A S G Y S F T G Y T M N W V K Q S H G K S L E W I G L I T P Y N G A S S Y N Q K F R G K A T L T V D K S S S T A Y M D L L S L T S E D S A V Y F C A R G G Y D G R G F D Y W G Q G T T V T V S S G G G G S G G G G G S D I E L T Q S P A I M S A S P G E K V T M T C S A S S S V S Y M H W Y Q Q K S G T S P K R W I Y D T S K L A S G V P G R F S G S G S G N S Y S L T I S S V E A E D D A T Y Y C Q Q W S G Y P L T F G A G T K L E I	46
mesothelin	M1 (human)	QVQLQQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGR INPNSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSEDTAVYYCARGR YYGMDVWGQGTMVTVSSGGGGSGGGGSGGGGSGGGGSEIVLTQSPATLSL SPGERATISCRASQSVSSNFAWYQQRPGQAPRLLIYDASNRATGIPPRFS GSGSGTDFTLTISSLEPEDFAAYYCHQRSNWLYTFGQGTKVDIK	47
mesothelin	M2 (human)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGW INPNSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCARDL RRTVVTPRAYYGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDIQL TQSPSTLSASVGDRVTITCQASQDISNSLNWYQQKAGKAPKLLIYDASTL ETGVPSRFSGSGSGTDFSFTISSLQPEDIATYYCQQHDNLPLTFGQGTKV EIK	48
mesothelin	M3 (human)	QVQLVQSGAEVKKPGAPVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGW INPNSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCARGE WDGSYYYDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIVLTQTPSS LSASVGDRVTITCRASQSINTYLNWYQHKPGKAPKLLIYAASSLQSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQSFSPLTFGGGTKLEIK	49
mesothelin	M4 (human)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMHWVRQVPGKGLVWVSR INTDGSTTTYADSVEGRFTISRDNAKNTLYLQMNSLRDDDTAVYYCVGGH WAVWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSTLSASVG DRVTITCRASQSISDRLAWYQQKPGKAPKLLIYKASSLESGVPSRFSGSG SGTEFTLTISSLQPDDFAVYYCQQYGHLPMYTFGQGTKVEIK	50
mesothelin	M6 (human)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGI INPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYR	52

		LIAVAGDYYYYGMDVWGQGTMVTVSSGGGGSGGGGSGGGGSGGGGSDIQM TQSPSSVASVGDRVTITCRASQGVGRWLAWYQQKPGTAPKLLIYAASTLQ SGVPSRFSGSGSGTDFTLTINNLQPEDFATYYCQQANSFPLTFGGGTRLE IK	
mesothelin	M7 (human)	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAV ISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARWK VSSSSPAFDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSEIVLTQSPA TLSLSPGERAILSCRASQSVYTKYLGWYQQKPGQAPRLLIYDASTRATGI PDRFSGSGSGTDFTLTINRLEPEDFAVYYCQHYGGSPLITFGQGTRLEIK	53
mesothelin	M8 (human)	QVQLQQSGAEVKKPGASVKVSCKTSGYPFTGYSLHWVRQAPGQGLEWMGW INPNSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCARDH YGGNSLFYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIQLTQSPSSI SASVGDTVSITCRASQDSGTWLAWYQQKPGKAPNLLMYDASTLEDGVPSR FSGSASGTEFTLTVNRLQPEDSATYYCQQYNSYPLTFGGGTKVDIK	54
mesothelin	M9 (human)	QVQLVQSGAEVKKPGASVEVSCKASGYTFTSYYMHWVRQAPGQGLEWMGI INPSGGSTGYAQKFQGRVTMTRDTSTSTVHMELSSLRSEDTAVYYCARGG YSSSSDAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQSPP SLSASVGDRVTITCRASQDISSALAWYQQKPGTPPKLLIYDASSLESGVP SRFSGSGSGTDFTLTISSLQPEDFATYYCQQFSSYPLTFGGGTRLEIK	55
mesothelin	M10 (human)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMGW ISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARVA GGIYYYYGMDVWGQGTTITVSSGGGGSGGGGSGGGGSGGGGSDIVMTQTP DSLAVSLGERATISCKSSHSVLYNRNNKNYLAWYQQKPGQPPKLLFYWAS TRKSGVPDRFSGSGSGTDFTLTISSLQPEDFATYFCQQTQTFPLTFGQGT RLEIN	56
mesothelin	M12 (human)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGR INPNSGGTNYAQKFQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARTT TSYAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSGGGGSDIQLTQSPSTLS ASVGDRVTITCRASQSISTWLAWYQQKPGKAPNLLIYKASTLESGVPSRF SGSGSGTEFTLTISSLQPDDFATYYCQQYNTYSPYTFGQGTKLEIK	58
mesothelin	M13 (human)	QVQLVQSGGGLVKPGGSLRLSCEASGFIFSDYYMGWIRQAPGKGLEWVSY IGRSGSSMYYADSVKGRFTFSRDNAKNSLYLQMNSLRAEDTAVYYCAASP VVAATEDFQHWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIVMTQTPA TLSLSPGERATLSCRASQSVTSNYLAWYQQKPGQAPRLLLFGASTRATGI PDRFSGSGSGTDFTLTINRLEPEDFAMYYCQQYGSAPVTFGQGTKLEIK	59
mesothelin	M14 (human)	QVQLVQSGAEVRAPGASVKISCKASGFTFRGYYIHWVRQAPGQGLEWMGI INPSGGSRAYAQKFQGRVTMTRDTSTSTVYMELSSLRSDDTAMYYCARTA SCGGDCYYLDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQSP PTLSASVGDRVTITCRASENVNIWLAWYQQKPGKAPKLLIYKSSSLASGV PSRFSGSGSGAEFTLTISSLQPDDFATYYCQQYQSYPLTFGGGTKVDIK	60
mesothelin	M15 (human)	QVQLVQSGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSG ISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKDG SSSWSWGYFDYWGQGTLVTVSSGGGGSGGGGSGGGGSSSELTQDPAVSVA LGQTVRITCQGDALRSYYASWYQQKPGQAPMLVIYGKNNRPSGIPDRFSG SDSGDTASLTITGAQAEDEADYYCNSRDSSGYPVFGTGTKVTVL	61
mesothelin	M16 (human)	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSG ISWNSGSTGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDS SSWYGGGSAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSSSELTQEPAVSV ALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIFGRSRRPSGIPDRFS GSSSGNTASLIITGAQAEDEADYYCNSRDNTANHYVFGTGTKLTVL	62
mesothelin	M17 (human)	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSG ISWNSGSTGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDS SSWYGGGSAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSSSELTQDPAVSV ALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRGSSGNHYVFGTGTKVTVL	63
mesothelin	M18	QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYWMHWVRQAPGKGLVWVSR INSDGSSTSYADSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCVRTG	64

	(human)	WVGSYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGGGSEIVLTQSP GTLSLSPGERATLSCRASQSVSSNYLAWYQQKPGQPPRLLIYDVSTRATG IPARFSGGGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPWTFGQGTKVEI K	
mesothelin	M19 (human)	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAV ISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGY SRYYYYGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSEIVMTQSPA TLSLSPGERAILSCRASQSVYTKYLGWYQQKPGQAPRLLIYDASTRATGI PDRFSGSGSGTDFTLTINRLEPEDFAVYYCQHYGGSPLITFGQGTKVDIK	65
mesothelin	M20 (human)	QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKRE AAAGHDWYFDLWGRGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIRVTQSP SSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV PSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSIPLTFGQGTKVEIK	66
mesothelin	M21 (human)	QVQLVQSWAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGI INPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSNLRSEDTAVYYCARSP RVTTGYFDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIQLTQSPST LSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLESGVPS RFSGSGSGTEFTLTISSLQPDDFATYYCQQYSSYPLTFGGGTRLEIK	67
mesothelin	M22 (human)	QVQLVQSGAEVRRPGASVKISCRASGDTSTRHYIHWLRQAPGQGPEWMGV INPTTGPATGSPAYAQMLQGRVTMTRDTSTRTVYMELRSLRFEDTAVYYC ARSVVGRSAPYYFDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIQM TQSPSSLSASVGDRVTITCRASQGISDYSAWYQQKPGKAPKLLIYAASTL QSGVPSRFSGSGSGTDFTLTISYLQSEDFATYYCQQYYSYPLTFGGGTKV DIK	68
mesothelin	M23 (human)	QVQLQQSGAEVKKPGASVKVSCKASGYTFTNYYMHWVRQAPGQGLEWMGI INPSGGYTTYAQKFQGRLTMTRDTSTSTVYMELSSLRSEDTAVYYCARIR SCGGDCYYFDNWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIQLTQSP STLSASVGDRVTITCRASENVNIWLAWYQQKPGKAPKLLIYKSSSLASGV PSRFSGSGSGAEFTLTISSLQPDDFATYYCQQYQSYPLTFGGGTKVDIK	69
mesothelin	M24 (human)	QITLKESGPALVKPTQTLTLTCTFSGFSLSTAGVHVGWIRQPPGKALEWL ALISWADDKRYRPSLRSRLDITRVTSKDQVVLSMTNMQPEDTATYYCALQ GFDGYEANWGPGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIVMTQSPSSL SASAGDRVTITCRASRGISSALAWYQQKPGKPPKLLIYDASSLESGVPSR FSGSGSGTDFTLTIDSLEPEDFATYYCQQSYSTPWTFGQGTKVDIK	70

[00208] The sequences of the CDR sequences of the scFv domains of the mesothelin antigen binding domains provided in Table 2 are shown in Table 3 for the heavy chain variable domains and in Table 4 for the light chain variable domains.

Table 3. Amino acid sequences for the heavy chain (HC) CDR1, CDR2, and CDR3 regions of human anti-mesothelin scFvs

Descrip.	HC-CDR1	SEQ ID NO:	HC-CDR2	SEQ ID NO:	HC-CDR3	SEQ ID NO:
M5	GYTFTDYYMH	115	WINPNSGGTNYAQKFQG	134	GWDFDY	159
M11	GYTFTGYYMH	121	WINPNSGGTNYAQNFQG	141	GWDFDY	165
Ss1	GYSFTGYTMN	132	LITPYNGASSYNQKFRG	154	GGYDGRGFDY	179
M1	GYTFTGYYMH	113	RINPNSGGTNYAQKFQG	133	GRYYGMDV	155
M2	GYTFTGYYMH	113	WINPNSGGTNYAQKFQG	134	DLRRTVVTPRAYYG MDV	156
M3	GYTFTGYYMH	113	WINPNSGGTNYAQKFQG	134	GEWDGSYYYDY	157

M4	GFTFSSYWMH	114	RINTDGSTTTYADSVEG	135	GHWAV	158
M6	GYTFTSYYMH	116	IINPSGGSTSYAQKFQ	136	YRLIAVAGDYYYYGMDV	160
M7	GFTFSSYAMH	117	VISYDGSNKYYADSVKG	137	WKVSSSSPAFDY	161
M8	GYPFTGYSLH	118	WINPNSGGTNYAQKFQG	138	DHYGGNSLFY	162
M9	GYTFTSYYMH	119	IINPSGGSTGYAQKFQG	139	GGYSSSSDAFDI	163
M10	GYTFTSYGIS	120	WISAYNGNTNYAQKLQ	140	VAGGIYYYYGMDV	164
M12	GYTFTGYYMH	121	RINPNSGGTNYAQKFQG	142	TTTSYAFDI	166
M13	GFIFSDYYMG	122	YIGRSGSSMYYADSVKG	143	SPVVAATEDFQH	167
M14	GFTFRGYYIH	123	IINPSGGSRAYAQKFQG	144	TASCGGDCYYLDY	168
M15	GFTFDDYAMH	124	GISWNSGSIGYADSVK	145	DGSSSWSWGYFDY	169
M16	GFTFDDYAMH	124	GISWNSGSTGYADSVKG	146	DSSSWYGGGSAFDI	170
M17	GFTFDDYAMH	124	GISWNSGSTGYADSVKG	146	DSSSWYGGGSAFDI	171
M18	GFTFSSYWMH	125	RINSDGSSTSYADSVKG	147	TGWVGSYYYYMDV	172
M19	GFTFSSYGMH	126	VISYDGSNKYYADSVKG	148	GYSRYYYYGMDV	173
M20	GFTFSSYAMS	127	AISGSGGSTYYADSVKG	149	REAAAGHDWYFDL	174
M21	GYTFTSYYMH	128	IINPSGGSTSYAQKFQG	150	SPRVTTGYFDY	175
M22	GDTSTRHYIH	129	VINPTTGPATGSPAYAQMLQG	151	SVVGRSAPYYFDY	176
M23	GYTFTNYYMH	130	IINPSGGYTTYAQKFQG	152	IRSCGGDCYYFDN	177
M24	GFSLSTAGVHVG	131	LISWADDKRYRPSLRS	153	QGFDGYEAN	178

Table 4. Amino acid sequences for the light chain (LC) CDR1, CDR2, and CDR3 regions of human anti-mesothelin scFvs

Description	LC-CDR1	SEQ ID NO:	LC-CDR2	SEQ ID NO:	LC-CDR3	SEQ ID NO:
M5	RASQSIRYYLS	184	TASILQN	209	LQTYTTPD	234
M11	RASQSIRYYLS	190	TASILQN	215	LQTYTTPD	240
Ss1	SASSSVSYMH	204	DTSKLAS	229	QQWSGYPLT	254
M1	RASQSVSSNFA	180	DASNRAT	205	HQRSNWLYT	230
M2	QASQDISNSLN	181	DASTLET	206	QQHDNLPLT	231
M3	RASQSINTYLN	182	AASSLQS	207	QQSFSPLT	232
M4	RASQSISDRLA	183	KASSLES	208	QQYGHLPMYT	233
M6	RASQGVGRWLA	185	AASTLQS	210	QQANSFPLT	235
M7	RASQSVYTKYLG	186	DASTRAT	211	QHYGGSPLIT	236
M8	RASQDSGTWLA	187	DASTLED	212	QQYNSYPLT	237
M9	RASQDISSALA	188	DASSLES	213	QQFSSYPLT	238
M10	KSSHSVLYNRNNKNYLA	189	WASTRKS	214	QQTQTFPLT	239
M12	RASQSISTWLA	191	KASTLES	216	QQYNTYSPYT	241
M13	RASQSVTSNYLA	192	GASTRAT	217	QQYGSAPVT	242
M14	RASENVNIWLA	193	KSSSLAS	218	QQYQSYPLT	243
M15	QGDALRSYYAS	194	GKNNRPS	219	NSRDSSGYPV	244

M16	QGDSLRSYYAS	195	GRSRRPS	220	NSRDNTANHYV	245
M17	QGDSLRSYYAS	196	GKNNRPS	221	NSRGSSGNHYV	246
M18	RASQSVSSNYLA	197	DVSTRAT	222	QQRSNWPPWT	247
M19	RASQSVYTKYLG	198	DASTRAT	223	QHYGGSPLIT	248
M20	RASQSISSYLN	199	AASSLQS	224	QQSYSIPLT	249
M21	RASQSISSWLA	200	KASSLES	225	QQYSSYPLT	250
M22	RASQGISDYS	201	AASTLQS	226	QQYYSYPLT	251
M23	RASENVNIWLA	202	KSSSLAS	227	QQYQSYPLT	252
M24	RASRGISSALA	203	DASSLES	228	QQSYSTPWT	253

[00209] Any known anti-mesothelin binding domain, from, for example, a known antibody, bispecific molecule or CAR, may be suitable for use in the CAR of the present invention. For example, the antigen binding domain against mesothelin is or may be derived from an antigen binding, e.g., CDRs or VH and VL, of an antibody, antigen-binding fragment or CAR described in, e.g., PCT publication WO2015/090230. In embodiments, the antigen binding domain against mesothelin is or is derived from 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 WO1997/025068, WO1999/028471, WO2005/014652, WO2006/099141, WO2009/045957, WO2009/068204, WO2013/142034, WO2013/040557, or WO2013/063419.

[00210] In one embodiment, the mesothelin binding domain comprises one or more (e.g., all three) light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and light chain complementary determining region 3 (LC CDR3) of a mesothelin binding domain described herein, e.g., provided in Table 2 or 4, and/or one or more (e.g., all three) heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of a mesothelin binding domain described herein, e.g., provided in Table 2 or 3. In one embodiment, the mesothelin binding domain comprises one, two, or all of LC CDR1, LC CDR2, and LC CDR3 of any amino acid sequences as provided in Table 4; and one, two or three of all of HC CDR1, HC CDR2 and HC CDR3, of any amino acid acid sequences as provided in Table 3.

[00211] In one embodiment, the mesothelin antigen binding domain comprises:

(i) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 184, a LC CDR2 amino acid sequence of SEQ ID NO: 209, and a LC CDR3 amino acid sequence of SEQ ID NO: 234; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 115, a HC CDR2 amino acid sequence of SEQ ID NO: 134, and a HC CDR3 amino acid sequence of SEQ ID NO: 159;

(ii) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 190, a LC CDR2 amino acid sequence of SEQ ID NO: 215, and a LC CDR3 amino acid sequence of SEQ ID NO: 240; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 121, a HC CDR2 amino acid sequence of SEQ ID NO: 141, and a HC CDR3 amino acid sequence of SEQ ID NO: 165;

(iii) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 204, a LC CDR2 amino acid sequence of SEQ ID NO: 229, and a LC CDR3 amino acid sequence of SEQ ID NO: 254; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 132, a HC CDR2 amino acid sequence of SEQ ID NO: 154, and a HC CDR3 amino acid sequence of SEQ ID NO: 179;

(iv) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 180, a LC CDR2 amino acid sequence of SEQ ID NO: 205, and a LC CDR3 amino acid sequence of SEQ ID NO: 230; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 113, a HC CDR2 amino acid sequence of SEQ ID NO: 133, and a HC CDR3 amino acid sequence of SEQ ID NO: 155;

(v) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 181, a LC CDR2 amino acid sequence of SEQ ID NO: 206, and a LC CDR3 amino acid sequence of SEQ ID NO: 231; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 113, a HC CDR2 amino acid sequence of SEQ ID NO: 134, and a HC CDR3 amino acid sequence of SEQ ID NO: 156;

(vi) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 182, a LC CDR2 amino acid sequence of SEQ ID NO: 207, and a LC CDR3 amino acid sequence of SEQ ID NO: 232; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 113, a HC CDR2 amino acid sequence of SEQ ID NO: 134, and a HC CDR3 amino acid sequence of SEQ ID NO: 157;

(vii) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 183, a LC CDR2 amino acid sequence of SEQ ID NO: 208, and a LC CDR3 amino acid sequence of SEQ ID NO: 233; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 114, a HC CDR2 amino acid sequence of SEQ ID NO: 135, and a HC CDR3 amino acid sequence of SEQ ID NO: 158;

(viii) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 186, a LC CDR2 amino acid sequence of SEQ ID NO: 210, and a LC CDR3 amino acid sequence of SEQ ID NO: 235; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 116, a HC CDR2 amino acid sequence of SEQ ID NO: 136, and a HC CDR3 amino acid sequence of SEQ ID NO: 160;

(ix) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 186, a LC CDR2 amino acid sequence of SEQ ID NO: 211, and a LC CDR3 amino acid sequence of SEQ ID NO: 236; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 117, a HC CDR2 amino acid sequence of SEQ ID NO: 137, and a HC CDR3 amino acid sequence of SEQ ID NO: 161;

(x) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 187, a LC CDR2 amino acid sequence of SEQ ID NO: 212, and a LC CDR3 amino acid sequence of SEQ ID NO: 237; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 118, a HC CDR2 amino acid sequence of SEQ ID NO: 138, and a HC CDR3 amino acid sequence of SEQ ID NO: 162;

(xi) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 188, a LC CDR2 amino acid sequence of SEQ ID NO: 213, and a LC CDR3 amino acid sequence of SEQ ID NO: 238; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 119, a HC CDR2 amino acid sequence of SEQ ID NO: 139, and a HC CDR3 amino acid sequence of SEQ ID NO: 163;

(xii) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 189, a LC CDR2 amino acid sequence of SEQ ID NO: 214, and a LC CDR3 amino acid sequence of SEQ ID NO: 239; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 120, a HC CDR2 amino acid sequence of SEQ ID NO: 140, and a HC CDR3 amino acid sequence of SEQ ID NO: 164;

(xiii) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 191, a LC CDR2 amino acid sequence of SEQ ID NO: 216, and a LC CDR3 amino acid sequence of SEQ ID NO: 241; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 121, a HC CDR2 amino acid sequence of SEQ ID NO: 142, and a HC CDR3 amino acid sequence of SEQ ID NO: 166;

(xiv) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 192, a LC CDR2 amino acid sequence of SEQ ID NO: 217, and a LC CDR3 amino acid sequence of SEQ ID NO: 242; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 122, a HC CDR2 amino acid sequence of SEQ ID NO: 143, and a HC CDR3 amino acid sequence of SEQ ID NO: 167;

(xv) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 193, a LC CDR2 amino acid sequence of SEQ ID NO: 218, and a LC CDR3 amino acid sequence of SEQ ID NO: 243; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 123, a HC CDR2 amino acid sequence of SEQ ID NO: 144, and a HC CDR3 amino acid sequence of SEQ ID NO: 168;

(xvi) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 194, a LC CDR2 amino acid sequence of SEQ ID NO: 219, and a LC CDR3 amino acid sequence of SEQ ID NO: 244; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 124, a HC CDR2 amino acid sequence of SEQ ID NO: 145, and a HC CDR3 amino acid sequence of SEQ ID NO: 169;

(xvii) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 195, a LC CDR2 amino acid sequence of SEQ ID NO: 220, and a LC CDR3 amino acid sequence of SEQ ID NO: 245; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 124, a HC CDR2 amino acid sequence of SEQ ID NO: 146, and a HC CDR3 amino acid sequence of SEQ ID NO: 170;

(xviii) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 196, a LC CDR2 amino acid sequence of SEQ ID NO: 221, and a LC CDR3 amino acid sequence of SEQ ID NO: 246; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 124, a HC CDR2 amino acid sequence of SEQ ID NO: 146, and a HC CDR3 amino acid sequence of SEQ ID NO: 171;

(xix) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 197, a LC CDR2 amino acid sequence of SEQ ID NO: 222, and a LC CDR3 amino acid sequence of SEQ ID NO: 247; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 125, a HC CDR2 amino acid sequence of SEQ ID NO: 147, and a HC CDR3 amino acid sequence of SEQ ID NO: 172;

(xx) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 198, a LC CDR2 amino acid sequence of SEQ ID NO: 223, and a LC CDR3 amino acid sequence of SEQ ID NO: 248; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 126, a HC CDR2 amino acid sequence of SEQ ID NO: 148, and a HC CDR3 amino acid sequence of SEQ ID NO: 173;

(xxi) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 199, a LC CDR2 amino acid sequence of SEQ ID NO: 224, and a LC CDR3 amino acid sequence of SEQ ID NO: 249; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 127, a HC CDR2 amino acid sequence of SEQ ID NO: 149, and a HC CDR3 amino acid sequence of SEQ ID NO: 174;

(xxii) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 200, a LC CDR2 amino acid sequence of SEQ ID NO: 225, and a LC CDR3 amino acid sequence of SEQ ID NO: 250; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 128, a HC CDR2 amino acid sequence of SEQ ID NO: 150, and a HC CDR3 amino acid sequence of SEQ ID NO: 175;

(xxiii) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 201, a LC CDR2 amino acid sequence of SEQ ID NO: 226, and a LC CDR3 amino acid sequence of SEQ ID NO: 251; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 129, a HC CDR2 amino acid sequence of SEQ ID NO: 151, and a HC CDR3 amino acid sequence of SEQ ID NO: 176;

(xxiv) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 202, a LC CDR2 amino acid sequence of SEQ ID NO: 227, and a LC CDR3 amino acid sequence of SEQ ID NO: 252; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 130, a HC CDR2 amino acid sequence of SEQ ID NO: 152, and a HC CDR3 amino acid sequence of SEQ ID NO: 177; or

(xxv) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 203, a LC CDR2 amino acid sequence of SEQ ID NO: 228, and a LC CDR3 amino acid sequence of SEQ ID NO: 253; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 131, a HC CDR2 amino acid sequence of SEQ ID NO: 153, and a HC CDR3 amino acid sequence of SEQ ID NO: 178.

[00212] In one embodiment, the mesothelin binding domain comprises a light chain variable region described herein (e.g., in Table 2) and/or a heavy chain variable region described herein (e.g., in Table 2). In one embodiment, the mesothelin binding domain is a scFv comprising a light chain and a heavy chain of an amino acid sequence listed in Table 2. In an embodiment,

the mesothelin binding domain (e.g., an scFv) comprises: a light chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a light chain variable region provided in Table 2, or a sequence with 95-99% identity with an amino acid sequence provided in Table 2; and/or a heavy chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a heavy chain variable region provided in Table 2, or a sequence with 95-99% identity to an amino acid sequence provided in Table 2.

[00213] In one embodiment, the mesothelin binding domain comprises an amino acid sequence selected from a group consisting of SEQ ID NO: 46; SEQ ID NO: 47; SEQ ID NO: 48; SEQ ID NO: 49; SEQ ID NO: 50; SEQ ID NO: 51; SEQ ID NO: 52; SEQ ID NO: 53; SEQ ID NO: 54; SEQ ID NO: 55; SEQ ID NO: 56; SEQ ID NO: 57; SEQ ID NO: 58; SEQ ID NO: 59; SEQ ID NO: 60; SEQ ID NO: 61; SEQ ID NO: 62; SEQ ID NO: 63; SEQ ID NO: 64; SEQ ID NO: 65; SEQ ID NO: 66; SEQ ID NO: 67, SEQ ID NO: 68; SEQ ID NO: 69; and SEQ ID NO: 70; or an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) to any of the aforesaid sequences; or a sequence with 95-99% identity to any of the aforesaid sequences. In one embodiment, the mesothelin binding domain is a scFv, and a light chain variable region comprising an amino acid sequence described herein, e.g., in Table 2, is attached to a heavy chain variable region comprising an amino acid sequence described herein, e.g., in Table 2, via a linker, e.g., a linker described herein. In one embodiment, the mesothelin binding domain includes a (Gly4-Ser)n linker, wherein n is 1, 2, 3, 4, 5, or 6, preferably 4 (SEQ ID NO: 80). The light chain variable region and heavy chain variable region of a scFv can be, e.g., in any of the following orientations: light chain variable region-linker-heavy chain variable region or heavy chain variable region-linker-light chain variable region.

[00214] Such antigen binding domains which bind mesothelin, e.g., as described herein, are useful, for example, in embodiments of the invention in which a disease associated with the expression of mesothelin, e.g., as described herein, is treated.

[00215] In an embodiment, the antigen binding domain of a CAR, e.g., a CAR expressed by a cell of the invention, binds to human EGFRvIII. In an embodiment, the antigen binding domain is a murine scFv domain that binds to human EGFRvIII such as, e.g., mu310C. In an embodiment, the antigen binding domain is a humanized antibody or antibody fragment, e.g., scFv domain, derived from the murine mu310C scFv. Exemplary humanized scFv domains (and their sequences) that bind to EGFRvIII are provided in Table 5.

[00216] In an embodiment, the antigen binding domain of a CAR, e.g., a CAR expressed by a cell of the inveniton, binds to human claudin 6 (CLDN6). In an embodiment, the antigen binding domain is a murine scFv domain that binds to human CLDN6. In an embodiment, the antigen binding domain is a humanized antibody or antibody fragment. Exemplary scFv domains (and their sequences) that bind to CLDN6 are provided in Table 5. The scFv domain sequences provided in Table 5 include a light chain variable region (VL) and a heavy chain variable region (VH). The VL and VH are attached by a linker comprising the sequence GGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 29), e.g., in the following orientation: VL-linker-VH.

Table 5. Examples of antigen binding domains that bind to the tumor antigen EGFRvIII or CLDN6 (as indicated)

Tumor antigen	Name	Amino acid sequence	SEQ ID NO:
EGFR vIII	huscFv1	Eiqlvqsgaevkkpgatvkisckgsgfniedyyihwvqqapgkglewmgridpendetkygpif qgrvtitadtstntvymelsslrsedtavyycafrggvywgqgttvtvssggggsggggsggggsgg ggsdvvmtqspdslavslgeratinckssqslldsdgktylnwlqqkpgqppkrlislvskldsgvp drfsgsgsgtdftltisslqaedvavyycwqgthfpgtfgggtkveik	71
EGFR vIII	huscFv2	Dvvmtqspdslavslgeratinckssqslldsdgktylnwlqqkpgqppkrlislvskldsgvpdrfs gsgsgtdftltisslqaedvavyycwqgthfpgtfgggtkveikggggsggggsggggsggggsei qlvqsgaevkkpgatvkisckgsgfniedyyihwvqqapgkglewmgridpendetkygpifqg rvtitadtstntvymelsslrsedtavyycafrggvywgqgttvtvss	72
EGFR vIII	huscFv3	Eiqlvqsgaevkkpgeslrisckgsgfniedyyihwvrqmpgkglewmgridpendetkygpif qghvtisadtsintvylqwsslkasdtamyycafrggvywgqgttvtvssggggsggggsggggs ggggsdvvmtqsplslpvtlgqpasisckssqslldsdgktylnwlqqrpgqsprrlislvskldsgv pdrfsgsgsgtdftlkisrveaedvgvyycwqgthfpgtfgggtkveik	73
EGFR vIII	huscFv4	Dvvmtqsplslpvtlgqpasisckssqslldsdgktylnwlqqrpgqsprrlislvskldsgvpdrfsg sgsgtdftlkisrveaedvgvyycwqgthfpgtfgggtkveikggggsggggsggggsggggseiq lvqsgaevkkpgeslrisckgsgfniedyyihwvrqmpgkglewmgridpendetkygpifqgh vtisadtsintvylqwsslkasdtamyycafrggvywgqgttvtvss	74

EGFR vIII	huscFv5	Eiqlvqsgaevkkpgatvkisckgsgfniedyyihwvqqapgkglewmgridpendetkygpif qgrvtitadtstntvymelsslrsedtavyycafrggvywgqgttvtvssggggsggggsggggsgg ggsdvvmtqsplslpvtlgqpasisckssqslldsdgktylnwlqqrpgqsprrlislvskldsgvpdr fsgsgsgtdftlkisrveaedvgvyycwqgthfpgtfgggtkveik	75
EGFR vIII	huscFv6	Eiqlvqsgaevkkpgeslriscksgfniedyyihwvrqmpgkglewmgridpendetkygpif qghvtisadtsintvylqwsslkasdtamyycafrggvywgqgttvtvssggggsggggsggggs ggggsdvvmtqspdslavslgeratinckssqslldsdgktylnwlqqkpgqppkrlislvskldsg vpdrfsgsgsgtdftltisslqaedvavyycwqgthfpgtfgggtkveik	76
EGFR vIII	huscFv7	Dvvmtqspdslavslgeratinckssqslldsdgktylnwlqqkpgqppkrlislvskldsgvpdrfs gsgsgtdftltisslqaedvavyycwqgthfpgtfgggtkveikggggsggggsggggsggggseiq lvqsgaevkkpgeslrisckgsgfniedyyihwvrqmpgkglewmgridpendetkygpifqgg hvtisadtsintvylqwsslkasdtamyycafrggvywgqgttvtvss	77
EGFR vIII	huscFv8	Dvvmtqsplslpvtlgqpasisckssqslldsdgktylnwlqqrpgqsprrlislvskldsgvpdrfsg sgsgtdftlkisrveaedvgvyycwqgthfpgtfgggtkveikggggsggggsggggsggggseiq lvqsgaevkkpgatvkisckgsgfniedyyihwvqqapgkglewmgridpendetkygpifqgr vtitadtstntvymelsslrsedtavyycafrggvywgqgttvtvss	78
EGFR vIII	Mu310C	eiqlqqsgaelvkpgasvklsctgsgfniedyyihwvkqrteqglewigridpendetkygpifqgr atitadtssntvylqlssltsedtavyycafrggvywgpgttltvssggggsggggsggggshmdvv mtqspltlsvaigqsasisckssqslldsdgktylnwllqrpgqspkrlislvskldsgvpdrftgsgsgt dftlrisrveaedlgiyycwqgthfpgtfgggtkleik	79
Claudin6	muMAB 64A	EVQLQQSGPELVKPGASMKISCKASGYSFTGYTMNWVKQSHGK NLEWIGLINPYNGGTIYNQKFKGKATLTVDKSSSTAYMELLSLTS EDSAVYYCARDYGFVLDYWGQGTTLTVSSGGGGSGGGGSGGGG SGGGGSQIVLTQSPSIMSVSPGEKVTITCSASSSVSYMHWFQQKPG TSPKLCIYSTSNLASGVPARFSGRGSGTSYSLTISRVAAEDAATYY CQQRSNYPPWTFGGGTKLEIK	98
Claudin6	mAb206-LCC	EVQLQQSGPELVKPGASMKISCKASGYSFTGYTMNWVKQSHGK NLEWIGLINPYNGGTIYNQKFKGKATLTVDKSSSTAYMELLSLTS EDSAVYYCARDYGFVLDYWGQGTTLTVSSGGGGSGGGGSGGGG SGGGGSQIVLTQSPAIMSASPGEKVTITCSASSSVSYLHWFQQKPG TSPKLWVYSTSNLPSGVPARFGGSGSGTSYSLTISRMEAEDAATY YCQQRSIYPPWTFGGGTKLEIK	99
Claudin6	mAb206-SUBG	EVQLQQSGPELVKPGASMKISCKASGYSFTGYTMNWVKQSHGK NLEWIGLINPYNGGTIYNQKFKGKATLTVDKSSSTAYMELLSLTS EDSAVYYCARDYGFVLDYWGQGTTLTVSSGGGGSGGGGSGGGG SGGGGSQIVLTQSPSIMSVSPGEKVTITCSASSSVSYMHWFQQKPG TSPKLGIYSTSNLASGVPARFSGRGSGTSYSLTISRVAAEDAATYY CQQRSNYPPWTFGGGTKLEIK	100

[00217] In one embodiment, the EGFRvIII binding domain comprises one or more (e.g., all three) light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and light chain complementary determining region 3 (LC CDR3) of an EGFRvIII binding domain described herein, e.g., provided in Table 5, and/or one or more (e.g., all three) heavy chain complementary determining region 1 (HC CDR1), heavy

chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of an EGFRvIII binding domain described herein, e.g., provided in Table 5.

[00218] In one embodiment, the EGFRvIII binding domain comprises a light chain variable region described herein (e.g., in Table 5) and/or a heavy chain variable region described herein (e.g., in Table 5). In one embodiment, the EGFRvIII binding domain is a scFv comprising a light chain and a heavy chain of an amino acid sequence listed in Table 5. In an embodiment, the EGFRvIII binding domain (e.g., an scFv) comprises: a light chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a light chain variable region provided in Table 5, or a sequence with 95-99% identity with an amino acid sequence provided in Table 5; and/or a heavy chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a heavy chain variable region provided in Table 5, or a sequence with 95-99% identity to an amino acid sequence provided in Table 5.

[00219] In one embodiment, the EGFRvIII binding domain comprises an amino acid sequence selected from a group consisting of SEQ ID NO: 71; SEQ ID NO: 72; SEQ ID NO: 73; SEQ ID NO: 74; SEQ ID NO: 75; SEQ ID NO: 76; SEQ ID NO: 77; SEQ ID NO: 78; and SEQ ID NO: 79; or an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) to any of the aforesaid sequences; or a sequence with 95-99% identity to any of the aforesaid sequences. In one embodiment, the EGFRvIII binding domain is a scFv, and a light chain variable region comprising an amino acid sequence described herein, e.g., in Table 5, is attached to a heavy chain variable region comprising an amino acid sequence described herein, e.g., in Table 5, via a linker, e.g., a linker described herein. In one embodiment, the EGFRvIII binding domain includes a (Gly4-Ser)n linker, wherein n is 1, 2, 3, 4, 5, or 6, preferably 4 (SEQ ID NO: 80). The light chain variable region and heavy chain variable region of a scFv can be, e.g., in any of

the following orientations: light chain variable region-linker-heavy chain variable region or heavy chain variable region-linker-light chain variable region.

[00220] In one embodiment, the claudin-6 binding domain comprises one or more (e.g., all three) light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and light chain complementary determining region 3 (LC CDR3) of an EGFRvIII binding domain described herein, e.g., provided in Table 5, and/or one or more (e.g., all three) heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of an claudin-6 binding domain described herein, e.g., provided in Table 5.

[00221] In one embodiment, the claudin-6 binding domain comprises a light chain variable region described herein (e.g., in Table 5) and/or a heavy chain variable region described herein (e.g., in Table 5). In one embodiment, the claudin-6 binding domain is a scFv comprising a light chain and a heavy chain of an amino acid sequence listed in Table 5. In an embodiment, the claudin-6 binding domain (e.g., an scFv) comprises: a light chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a light chain variable region provided in Table 5, or a sequence with 95-99% identity with an amino acid sequence provided in Table 5; and/or a heavy chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a heavy chain variable region provided in Table 5, or a sequence with 95-99% identity to an amino acid sequence provided in Table 5.

[00222] Such antigen binding domains which bind EGFRvIII, e.g., as described herein, are useful, for example, in embodiments of the invention in which a disease associated with the expression of EGFRvIII, e.g., as described herein, is treated.

[00223] In one embodiment, the claudin-6 binding domain comprises an amino acid sequence selected from a group consisting of SEQ ID NO: 98; SEQ ID NO: 99; and SEQ ID

NO: 100; or an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) to any of the aforesaid sequences; or a sequence with 95-99% identity to any of the aforesaid sequences. In one embodiment, the claudin-6 binding domain is a scFv, and a light chain variable region comprising an amino acid sequence described herein, e.g., in Table 5, is attached to a heavy chain variable region comprising an amino acid sequence described herein, e.g., in Table 5, via a linker, e.g., a linker described herein. In one embodiment, the claudin-6 binding domain includes a (Gly4-Ser)n linker, wherein n is 1, 2, 3, 4, 5, or 6, preferably 4 (SEQ ID NO: 80). The light chain variable region and heavy chain variable region of a scFv can be, e.g., in any of the following orientations: light chain variable region-linker-heavy chain variable region or heavy chain variable region-linker-light chain variable region.

[00224] 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.

[00225] In one embodiment, an antigen binding domain against the Tn antigen, the sTn antigen, a Tn-O-glycopeptide antigen, or a sTn-O-glycopeptide antigen is an antigen binding portion, e.g., CDRs, of an antibody described in, e.g., US 2014/0178365, US8,440,798, EP 2083868 A2, Brooks et al., PNAS 107(22):10056-10061 (2010), and Stone et al., OncoImmunology 1(6):863-873(2012).

[00226] 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).

[00227] 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.

[00228] 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.

[00229] 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).

[00230] 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).

[00231] 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).

[00232] 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.

[00233] 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.

[00234] 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).

[00235] 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.

[00236] 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.

[00237] 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.

[00238] 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.

[00239] In one embodiment, an antigen binding domain against MUC1 is an antigen binding portion, e.g., CDRs, of the antibody SAR566658.

[00240] 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.

[00241] 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)

[00242] 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).

[00243] 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).

[00244] 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.

[00245] In one embodiment, an antigen binding domain against PDGFR-beta is an antigen binding portion, e.g., CDRs, of an antibody Abcam ab32570.

[00246] 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).

[00247] In one embodiment, an antigen binding domain against plysialic 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).

[00248] 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.

[00249] 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).

[00250] 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).

[00251] 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).

[00252] 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).

[00253] 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).

[00254] In one embodiment, an antigen binding domain against RAGE-1 is an antigen binding portion, e.g., CDRs, of the antibody MAB5328 (EMD Millipore).

[00255] 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)

[00256] 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).

[00257] 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).

[00258] 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.

[00259] 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.

[00260] In one embodiment, the antigen-binding domain of a CAR, e.g., the CAR expressed by a cell of the invention, can be chosen such that a myeloid tumor population is targeted. Alternatively, when targeting of more than one type of myeloid tumor is desired, an antigen binding domain that targets a myeloid tumor antigen that is expressed by more than one, e.g., all, of the myeloid tumors to be targeted can be selected.

[00261] In one aspect, the antigen-binding domain of a CAR, e.g., the CAR expressed by a cell of the invention, binds to CD123, e.g., human CD123. Any known CD123 binding domain may be used in the invention. In one embodiment, an antigen binding domain against CD123 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 WO2014/130635. In one embodiment, an antigen binding domain against CD123 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 WO2016/028896. In one embodiment, an antigen binding domain against CD123 is an antigen binding portion, e.g., CDRs, 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. In embodiments, the antigen binding domain is or is derived from a murine anti-human CD123 binding domain. In embodiments, the antigen binding domain is a humanized antibody or antibody fragment, e.g., scFv domain. In an embodiment, the antigen binding domain is a human antibody or antibody fragment that binds to human CD123. In embodiments, the antigen binding domain is an scFv domain which includes a light chain variable region (VL) and a heavy chain variable region (VH). The VL and VH may attached by a linker described herein, e.g., comprising the sequence GGGGSGGGGSGGGGS (SEQ ID NO: 30), and may be in any orientation, e.g., VL-linker-VH, or VH-linker-VL.

[00262] In one embodiment, the human CD123 binding domain comprises one or more (e.g., all three) light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and light chain complementary determining region 3 (LC CDR3) of a human CD123 binding domain described herein, and/or one or more (e.g., all three) heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of a human CD123 binding domain described herein, e.g., a human CD123 binding domain comprising one or more, e.g., all three, LC CDRs and one or more, e.g., all three, HC CDRs. In one embodiment, the human CD123 binding domain comprises one or more (e.g., all three) heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of a human CD123 binding domain described herein, e.g., the human CD123 binding domain has two variable heavy chain regions, each comprising a HC CDR1, a HC CDR2 and a HC CDR3 described herein. In one embodiment, the human CD123 binding domain comprises a human light chain variable region described herein (e.g., in Table 26 or 28) and/or a human heavy chain variable region described herein (e.g., in Table 26 or 28). In one embodiment, the human CD123 binding domain comprises a human heavy chain variable region described herein (e.g., in Table 26 or 28), e.g., at least two human heavy chain variable regions described herein (e.g., in Table 26 or 28). In one embodiment, the CD123 binding domain is a scFv comprising a light chain and a heavy chain of an amino acid sequence of Table 26 or 28. In an embodiment, the CD123 binding

domain (e.g., an scFv) comprises: a light chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions) of an amino acid sequence of a light chain variable region provided in Table 26 or 28, or a sequence with at least 95% identity, e.g., 95-99% identity, with an amino acid sequence of Table 26; and/or a heavy chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions) of an amino acid sequence of a heavy chain variable region provided in Table 26 or 28, or a sequence with at least 95% identity, e.g., 95-99% identity, to an amino acid sequence of Table 26 or 28. In one embodiment, the human CD123 binding domain comprises a sequence selected from a group consisting of SEQ ID NO:2157-2160, 2478, 2480, 2483, and 2485, or a sequence with at least 95% identity, e.g., 95-99% identity, thereof. In one embodiment, the human CD123 binding domain is a scFv, and a light chain variable region comprising an amino acid sequence described herein, e.g., in Table 26 or 28, is attached to a heavy chain variable region comprising an amino acid sequence described herein, e.g., in Table 26, via a linker, e.g., a linker described herein. In one embodiment, the human CD123 binding domain includes a $(Gly_4\text{-}Ser)n$ linker, wherein n is 1, 2, 3, 4, 5, or 6, preferably 3 or 4 (SEQ ID NO: 80). The light chain variable region and heavy chain variable region of a scFv can be, e.g., in any of the following orientations: light chain variable region-linker-heavy chain variable region or heavy chain variable region-linker-light chain variable region.

[00263] 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. Thus, in one aspect, the antigen binding domain comprises a humanized antibody or an antibody fragment. In one embodiment, the humanized CD123 binding domain comprises one or more (e.g., all three) light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and light chain complementary determining region 3 (LC CDR3) of a humanized CD123 binding domain described herein, and/or one or more (e.g., all three) heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of a humanized CD123 binding domain described herein, e.g., a humanized CD123 binding domain comprising one or more,

e.g., all three, LC CDRs and one or more, e.g., all three, HC CDRs. In one embodiment, the humanized CD123 binding domain comprises one or more (e.g., all three) heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of a humanized CD123 binding domain described herein, e.g., the humanized CD123 binding domain has two variable heavy chain regions, each comprising a HC CDR1, a HC CDR2 and a HC CDR3 described herein. In one embodiment, the humanized CD123 binding domain comprises a humanized light chain variable region described herein (e.g., in Table 27) and/or a humanized heavy chain variable region described herein (e.g., in Table 27). In one embodiment, the humanized CD123 binding domain comprises a humanized heavy chain variable region described herein (e.g., in Table 27), e.g., at least two humanized heavy chain variable regions described herein (e.g., in Table 27). In one embodiment, the CD123 binding domain is a scFv comprising a light chain and a heavy chain of an amino acid sequence of Table 27. In an embodiment, the CD123 binding domain (e.g., an scFv) comprises: a light chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions) of an amino acid sequence of a light chain variable region provided in Table 27, or a sequence with at least 95% identity, e.g., 95-99% identity, with an amino acid sequence of Table 27; and/or a heavy chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions) of an amino acid sequence of a heavy chain variable region provided in Table 27, or a sequence with at least 95% identity, e.g., 95-99% identity, to an amino acid sequence of Table 27. In one embodiment, the humanized CD123 binding domain comprises a sequence selected from a group consisting of SEQ ID NO:2184-2215 and 2302-2333, or a sequence with at least 95% identity, e.g., 95-99% identity, thereof. In one embodiment, the humanized CD123 binding domain is a scFv, and a light chain variable region comprising an amino acid sequence described herein, e.g., in Table 27, is attached to a heavy chain variable region comprising an amino acid sequence described herein, e.g., in Table 27, via a linker, e.g., a linker described herein. In one embodiment, the humanized CD123 binding domain includes a (Gly4-Ser)n linker, wherein n is 1, 2, 3, 4, 5, or 6, preferably 3 or 4 (SEQ ID NO: 80). The light chain variable region and heavy chain variable region of a scFv can be, e.g.,

in any of the following orientations: light chain variable region-linker-heavy chain variable region or heavy chain variable region-linker-light chain variable region.

[00264] Exemplary CD123 CAR constructs disclose herein comprise an scFv (e.g., a human scFv as disclosed in Tables 26, 27 and 28 herein, optionally preceded with an optional leader sequence (e.g., SEQ ID NO:2 and SEQ ID NO:3 for exemplary leader amino acid and nucleotide sequences, respectively). The sequences of the human scFv fragments (amino acid sequences of SEQ ID NOs:2157-2160) are provided herein in Table 26. The sequences of human scFv fragments, without the leader sequence, are provided herein in Table 28 (SEQ ID NOs: 2479, 2481, 2482, and 2484 for the nucleotide sequences, and SEQ ID NOs: 2478, 2480, 2483, and 2485 for the amino acid sequences). The CD123 CAR construct can further include an optional hinge domain, e.g., a CD8 hinge domain (e.g., including the amino acid sequence of SEQ ID NO: 4 or encoded by a nucleic acid sequence of SEQ ID NO:5); a transmembrane domain, e.g., a CD8 transmembrane domain (e.g., including the amino acid sequence of SEQ ID NO: 12 or encoded by the nucleotide sequence of SEQ ID NO: 13); an intracellular domain, e.g., a 4-1BB intracellular domain (e.g., including the amino acid sequence of SEQ ID NO: 14 or encoded by the nucleotide sequence of SEQ ID NO: 15; and a functional signaling domain, e.g., a CD3 zeta domain (e.g., including amino acid sequence of SEQ ID NO: 18 or 20, or encoded by the nucleotide sequence of SEQ ID NO: 19 or 21). In certain embodiments, the domains are contiguous with and in the same reading frame to form a single fusion protein. In other embodiments, the domain are in separate polypeptides, e.g., as in an RCAR molecule as described herein.

[00265] In certain embodiments, the full length CD123 CAR molecule includes the amino acid sequence of, or is encoded by the nucleotide sequence of, CD123-1, CD123-2, CD123-3, CD123-4, hzCD123-1, hzCD123-2, hzCD123-3, hzCD123-4, hzCD123-5, hzCD123-6, hzCD123-7, hzCD123-8, hzCD123-9, hzCD123-10, hzCD123-11, hzCD123-12, hzCD123-13, hzCD123-14, hzCD123-15, hzCD123-16, hzCD123-17, hzCD123-18, hzCD123-19, hzCD123-20, hzCD123-21, hzCD123-22, hzCD123-23, hzCD123-24, hzCD123-25, hzCD123-26, hzCD123-27, hzCD123-28, hzCD123-29, hzCD123-30, hzCD123-31, or hzCD123-32, provided in Table 26, 27, or 28, or a sequence substantially identical (e.g., with at least 95% identity, e.g., 95-99% identity) thereto.

[00266] In certain embodiments, the CD123 CAR molecule, or the CD123 antigen binding domain, includes the scFv amino acid sequence of CD123-1, CD123-2, CD123-3, CD123-4, hzCD123-1, hzCD123-2, hzCD123-3, hzCD123-4, hzCD123-5, hzCD123-6, hzCD123-7, hzCD123-8, hzCD123-9, hzCD123-10, hzCD123-11, hzCD123-12, hzCD123-13, hzCD123-14, hzCD123-15, hzCD123-16, hzCD123-17, hzCD123-18, hzCD123-19, hzCD123-20, hzCD123-21, hzCD123-22, hzCD123-23, hzCD123-24, hzCD123-25, hzCD123-26, hzCD123-27, hzCD123-28, hzCD123-29, hzCD123-30, hzCD123-31, or hzCD123-32, provided in Table 26, 27, or 28; or includes the scFv amino acid sequence of, or is encoded by the nucleotide sequence of, CD123-1, CD123-2, CD123-3, CD123-4, hzCD123-1, hzCD123-2, hzCD123-3, hzCD123-4, hzCD123-5, hzCD123-6, hzCD123-7, hzCD123-8, hzCD123-9, hzCD123-10, hzCD123-11, hzCD123-12, hzCD123-13, hzCD123-14, hzCD123-15, hzCD123-16, hzCD123-17, hzCD123-18, hzCD123-19, hzCD123-20, hzCD123-21, hzCD123-22, hzCD123-23, hzCD123-24, hzCD123-25, hzCD123-26, hzCD123-27, hzCD123-28, hzCD123-29, hzCD123-30, hzCD123-31, or hzCD123-32, or a sequence substantially identical (e.g., with at least 95% identity, e.g., 95-99% identity, or up to 20, 15, 10, 8, 6, 5, 4, 3, 2, or 1 amino acid changes) to any of the aforesaid sequences.

[00267] In certain embodiments, the CD123 CAR molecule, or the CD123 antigen binding domain, includes the heavy chain variable region and/or the light chain variable region of CD123-1, CD123-2, CD123-3, CD123-4, hzCD123-1, hzCD123-2, hzCD123-3, hzCD123-4, hzCD123-5, hzCD123-6, hzCD123-7, hzCD123-8, hzCD123-9, hzCD123-10, hzCD123-11, hzCD123-12, hzCD123-13, hzCD123-14, hzCD123-15, hzCD123-16, hzCD123-17, hzCD123-18, hzCD123-19, hzCD123-20, hzCD123-21, hzCD123-22, hzCD123-23, hzCD123-24, hzCD123-25, hzCD123-26, hzCD123-27, hzCD123-28, hzCD123-29, hzCD123-30, hzCD123-31, or hzCD123-32, provided in Table 26 or 27, or a sequence substantially identical (e.g., with at least 95% identity, e.g., 95-99% identity, or up to 20, 15, 10, 8, 6, 5, 4, 3, 2, or 1 amino acid changes) to any of the aforesaid sequences.

[00268] In certain embodiments, the CD123 CAR molecule, or the CD123 antigen binding domain, includes one, two or three CDRs from the heavy chain variable region (e.g., HCDR1, HCDR2 and/or HCDR3), provided in Table 16 or 18; and/or one, two or three CDRs from the light chain variable region (e.g., LCDR1, LCDR2 and/or LCDR3) of CD123-1, CD123-2, CD123-3, CD123-4, hzCD123-1, hzCD123-2, hzCD123-3, hzCD123-4, hzCD123-5,

hzCD123-6, hzCD123-7, hzCD123-8, hzCD123-9, hzCD123-10, hzCD123-11, hzCD123-12, hzCD123-13, hzCD123-14, hzCD123-15, hzCD123-16, hzCD123-17, hzCD123-18, hzCD123-19, hzCD123-20, hzCD123-21, hzCD123-22, hzCD123-23, hzCD123-24, hzCD123-25, hzCD123-26, hzCD123-27, hzCD123-28, hzCD123-29, hzCD123-30, hzCD123-31, or hzCD123-32, provided in Table 17 or 19; or a sequence substantially identical (e.g., at least 95% identical, e.g., 95-99% identical, or up to 5, 4, 3, 2, or 1 amino acid changes) to any of the aforesaid sequences.

[00269] In certain embodiments, the CD123 CAR molecule, or the CD123 antigen binding domain, includes one, two or three CDRs from the heavy chain variable region (e.g., HCDR1, HCDR2 and/or HCDR3), provided in Table 20; and/or one, two or three CDRs from the light chain variable region (e.g., LCDR1, LCDR2 and/or LCDR3) of CD123-1, CD123-2, CD123-3, CD123-4, hzCD123-1, hzCD123-2, hzCD123-3, hzCD123-4, hzCD123-5, hzCD123-6, hzCD123-7, hzCD123-8, hzCD123-9, hzCD123-10, hzCD123-11, hzCD123-12, hzCD123-13, hzCD123-14, hzCD123-15, hzCD123-16, hzCD123-17, hzCD123-18, hzCD123-19, hzCD123-20, hzCD123-21, hzCD123-22, hzCD123-23, hzCD123-24, hzCD123-25, hzCD123-26, hzCD123-27, hzCD123-28, hzCD123-29, hzCD123-30, hzCD123-31, or hzCD123-32, provided in Table 21; or a sequence substantially identical (e.g., at least 95% identical, e.g., 95-99% identical, or up to 5, 4, 3, 2, or 1 amino acid changes) to any of the aforesaid sequences.

[00270] In certain embodiments, the CD123 molecule, or the CD123 antigen binding domain, includes one, two or three CDRs from the heavy chain variable region (e.g., HCDR1, HCDR2 and/or HCDR3), provided in Table 22; and/or one, two or three CDRs from the light chain variable region (e.g., LCDR1, LCDR2 and/or LCDR3) of CD123-1, CD123-2, CD123-3, CD123-4, hzCD123-1, hzCD123-2, hzCD123-3, hzCD123-4, hzCD123-5, hzCD123-6, hzCD123-7, hzCD123-8, hzCD123-9, hzCD123-10, hzCD123-11, hzCD123-12, hzCD123-13, hzCD123-14, hzCD123-15, hzCD123-16, hzCD123-17, hzCD123-18, hzCD123-19, hzCD123-20, hzCD123-21, hzCD123-22, hzCD123-23, hzCD123-24, hzCD123-25, hzCD123-26, hzCD123-27, hzCD123-28, hzCD123-29, hzCD123-30, hzCD123-31, or hzCD123-32, provided in Table 23; or a sequence substantially identical (e.g., at least 95% identical, e.g., 95-99% identical, or up to 5, 4, 3, 2, or 1 amino acid changes) to any of the aforesaid sequences.

[00271] The sequences of CDR sequences of the scFv domains are shown in Tables 16, 18, 20, and 22 for the heavy chain variable domains and in Tables 17, 19, 21, and 23 for the light chain variable domains. "ID" stands for the respective SEQ ID NO for each CDR.

[00272] The CDRs provided in Tables 16, 17, 18, and 19 are according to a combination of the Kabat and Chothia numbering scheme.

Table 16. Heavy Chain Variable Domain CDRs

Candidate	HCDR1	SEQ ID NO:	HCDR2	SEQ ID NO:	HCDR3	SEQ ID NO:
CAR123-2	GYTFTGYYMH	2335	WINPNSGGTNYAQKFQG	2363	DMNILATVPFDI	2391
CAR123-3	GYIFTGYYIH	2337	WINPNSGGTNYAQKFQG	2364	DMNILATVPFDI	2392
CAR123-4	GYTFTGYYMH	2336	WINPNSGGTNYAQKFQG	2365	DMNILATVPFDI	2393
CAR123-1	GYTFTDYYMH	2334	WINPNSGDTNYAQKFQG	2362	DMNILATVPFDI	2390

Table 17. Light Chain Variable Domain CDRs

Candidate	LCDR1	SEQ ID NO:	LCDR2	SEQ ID NO:	LCDR3	SEQ ID NO:
CAR123-2	RASQSISSYLN	2419	AAFSLQS	2447	QQGDSVPLT	2475
CAR123-3	RASQSISSYLN	2420	AASSLQS	2448	QQGDSVPLT	2476
CAR123-4	RASQSISSYLN	2421	AASSLQS	2449	QQGDSVPLT	2477
CAR123-1	RASQSISTYLN	2418	AASSLQS	2446	QQGDSVPLT	2474

Table 18. Heavy Chain Variable Domain CDR

	HCDR1	SEQ ID NO:	HCDR2	SEQ ID NO:	HCDR3	SEQ ID NO:
hzCAR123	GYTFTSYWMN	2361	RIDPYDSETHYNQKFKD	2389	GNWDDY	2417

Table 19. Light Chain Variable Domain CDR

	LCDR1	SEQ ID NO:	LCDR2	SEQ ID NO:	LCDR3	SEQ ID NO:
hzCAR123	RASKSISKDLA	2445	SGSTLQS	2473	QQHNKYPYT	2515

Table 20. Heavy Chain Variable Domain CDRs according to the Kabat numbering scheme (Kabat et al. (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD)

Candidate	**HCDR1**	SEQ ID NO:	**HCDR2**	SEQ ID NO:	**HCDR3**	SEQ ID NO:
CAR123-2	GYYMH	2487	WINPNSGGTNYAQKFQG	2492	DMNILATVPFDI	2497
CAR123-3	GYYIH	2488	WINPNSGGTNYAQKFQG	2493	DMNILATVPFDI	2498
CAR123-4	DYYMH	2489	WINPNSGDTNYAQKFQG	2494	DMNILATVPFDI	2499
CAR123-1	GYYMH	2486	WINPNSGGTNYAQKFQG	2491	DMNILATVPFDI	2496
hzCAR123-1	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-2	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-3	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-4	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-5	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-6	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-7	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-8	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-9	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-10	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-11	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-12	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-13	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-14	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-15	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-16	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-17	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-18	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-19	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-20	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-21	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500

hzCAR123-22	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-23	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-24	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-25	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-26	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-27	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-28	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-29	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-30	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-31	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500
hzCAR123-32	SYWMN	2490	RIDPYDSETHYNQKFKD	2495	GNWDDY	2500

Table 21. Light Chain Variable Domain CDRs according to the Kabat numbering scheme (Kabat et al. (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD)

Candidate	**LCDR1**	SEQ ID NO:	**LCDR2**	SEQ ID NO:	**LCDR3**	SEQ ID NO:
CAR123-2	RASQSISSYLN	2502	AASSLQS	2507	QQGDSVPLT	2512
CAR123-3	RASQSISSYLN	2503	AASSLQS	2508	QQGDSVPLT	2513
CAR123-4	RASQSISSYLN	2504	AASSLQS	2509	QQGDSVPLT	2514
CAR123-1	RASQSISTYLN	1501	AAFSLQS	2506	QQGDSVPLT	2511
hzCAR123-1	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-2	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-3	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-4	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-5	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-6	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-7	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-8	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-10	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-10	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-11	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-12	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-13	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-14	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515

hzCAR123-15	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-16	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-17	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-18	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-19	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-20	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-21	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-22	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-23	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-24	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-25	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-26	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-27	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-28	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-29	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-30	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-31	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515
hzCAR123-32	RASKSISKDLA	2505	SGSTLQS	2510	QQHNKYPYT	2515

Table 22. Heavy Chain Variable Domain CDRs according to the Chothia numbering scheme (Al-Lazikani et al., (1997) JMB 273,927-948)

Candidate	**HCDR1**	SEQ ID NO:	**HCDR2**	SEQ ID NO:	**HCDR3**	SEQ ID NO:
CAR123-2	GYTFTGY	2517	NPNSGG	2522	DMNILATVPFDI	2527
CAR123-3	GYIFTGY	2518	NPNSGG	2523	DMNILATVPFDI	2528
CAR123-4	GYTFTDY	2519	NPNSGD	2524	DMNILATVPFDI	2529
CAR123-1	GYTFTGY	2516	NPNSGG	2521	DMNILATVPFDI	2526
hzCAR123-1	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-2	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-3	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-4	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-5	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-6	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-7	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-8	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-9	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530

hzCAR123-10	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-11	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-12	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-13	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-14	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-15	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-16	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-17	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-18	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-19	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-20	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-21	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-22	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-23	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-24	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-25	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-26	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-27	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-28	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-29	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-30	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-31	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530
hzCAR123-32	GYTFTSY	2520	DPYDSE	2525	GNWDDY	2530

Table 23. Light Chain Variable Domain CDRs according to the Chothia numbering scheme (Al-Lazikani et al., (1997) JMB 273,927-948)

Candidate	LCDR1	SEQ ID NO:	LCDR2	SEQ ID NO:	LCDR3	SEQ ID NO:
CAR123-2	SQSISSY	2532	AAS	2537	GDSVPL	2542
CAR123-3	SQSISSY	2533	AAS	2538	GDSVPL	2543
CAR123-4	SQSISSY	2534	AAS	2539	GDSVPL	2544
CAR123-1	SQSISTY	2531	AAF	2536	GDSVPL	2541
hzCAR123-1	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-2	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-3	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-4	SKSISKD	2535	SGS	2540	HNKYPY	2555

hzCAR123-5	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-6	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-7	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-8	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-10	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-10	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-11	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-12	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-13	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-14	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-15	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-16	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-17	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-18	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-19	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-20	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-21	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-22	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-23	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-24	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-25	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-26	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-27	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-28	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-29	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-30	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-31	SKSISKD	2535	SGS	2540	HNKYPY	2555
hzCAR123-32	SKSISKD	2535	SGS	2540	HNKYPY	2555

[00273] In embodiments, CD123 single chain variable fragments are generated and cloned into lentiviral CAR expression vectors with the intracellular CD3zeta domain and the intracellular co-stimulatory domain of 4-1BB. Names of exemplary fully human CD123 scFvs are depicted in Table 24. Names of exemplary humanized CD123 scFvs are depicted in Table 25.

Table 24: CAR-CD123 constructs

Construct ID	CAR Nickname
EBB-C1357-F11	CAR123-1
EBB-C1358-B10	CAR123-2
EBB-C1358-D5	CAR123-3
EBB-C1357-C4	CAR123-4

Table 25: CAR-CD123 constructs

Construct ID	CAR Nickname
VH1_1-46_X_VK1_L8	hzCAR-1
VH1_1-46_X_VK3_L6	hzCAR-2
VH1_1-46_X_VK6_A14	hzCAR-3
VH1_1-46_X_VK4_B3	hzCAR-4
VK1_L8_X_VH1_1-46	hzCAR-5
VK3_L6_X_VH1_1-46	hzCAR-6
VK6_A14_X_VH1_1-46	hzCAR-7
VK4_B3_X_VH1_1-46	hzCAR-8
VH7_7-4.1_X_VK1_L8	hzCAR-9
VH7_7-4.1_X_VK3_L6	hzCAR-10
VH7_7-4.1_X_VK6_A14	hzCAR-11
VH7_7-4.1_X_VK4_B3	hzCAR-12
VK1_L8_X_VH7_7-4.1	hzCAR-13
VK3_L6_X_VH7_7-4.1	hzCAR-14
VK6_A14_X_VH7_7-4.1	hzCAR-15
VK4_B3_X_VH7_7-4.1	hzCAR-16
VH5_5-A_X_VK1_L8	hzCAR-17
VH5_5-A_X_VK3_L6	hzCAR-18
VH5_5-A_X_VK6_A14	hzCAR-19
VH5_5-A_X_VK4_B3	hzCAR-20
VK1_L8_X_VH5_5-A	hzCAR-21
VK3_L6_X_VH5_5-A	hzCAR-22
VK6_A14_X_VH5_5-A	hzCAR-23
VK4_B3_X_VH5_5-A	hzCAR-24
VH3_3-74_X_VK1_L8	hzCAR-25
VH3_3-74_X_VK3_L6	hzCAR-26
VH3_3-74_X_VK6_A14	hzCAR-27
VH3_3-74_X_VK4_B3	hzCAR-28
VK1_L8_X_VH3_3-74	hzCAR-29
VK3_L6_X_VH3_3-74	hzCAR-30
VK6_A14_X_VH3_3-74	hzCAR-31
VK4_B3_X_VH3_3-74	hzCAR-32

[00274] In embodiments, the order in which the VL and VH domains appear in the scFv is varied (i.e., VL-VH, or VH-VL orientation), and where either three (SEQ ID NO: 30) or four (SEQ ID NO: 29) copies of the "G4S" (SEQ ID NO: 22) subunit, in which each subunit comprises the sequence GGGGS (SEQ ID NO: 22) (e.g., $(G4S)_3$ (SEQ ID NO:30) or $(G4S)_4$ (SEQ ID NO:29)), connect the variable domains to create the entirety of the scFv domain, as shown in Table 26, Table 27, and Table 28.

[00275] The amino acid and nucleic acid sequences of the CD123 scFv domains and CD123 CAR molecules are provided in Table 26, Table 27, and Table 28. The amino acid sequences for the variable heavy chain and variable light chain for each scFv is also provided in Table 26 and Table 27. It is noted that the scFv fragments (SEQ ID NOs: 2157-2160, and 2184-2215) with a leader sequence (e.g., the amino acid sequence of SEQ ID NO: 2 or the nucleotide sequence of SEQ ID NO: 3) and without a leader sequence (SEQ ID NOs: 2478, 2480, 2483, 2485, and 2556-2587) are also encompassed by the present invention.

[00276] In embodiments, these clones in Table 26 and 27 all contained a Q/K residue change in the signal domain of the co-stimulatory domain derived from CD3zeta chain.

Table 26. Exemplary CD123 CAR sequences

Name	SEQ ID NO:	Sequence
CAR123-2 NT	2040	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccac gccgctcggccccaagtgcaactcgtccaaagcggagcggaagtcaagaaa cccggagcgagcgtgaaagtgtcctgcaaagcctccggctacacctttacg ggctactacatgcactgggtgcgccaggcaccaggacagggtcttgaatgg atgggatggatcaaccctaattcgggcggaactaactacgcacagaagttc caggggagagtgactctgactcgggatacctccatctcaactgtctacatg gaactctcccgcttgcggtcagatgatacggcagtgtactactgcgcccgc gacatgaatatcctggctaccgtgccgttcgacatctggggacaggggact atggttactgtctcatcgggcggtggaggttcaggaggaggcggctcggga ggcggaggttcggacattcagatgacccagtccccatcctctctgtcggcc agcgtcggagatagggtgaccattacctgtcgggcctcgcaaagcatctcc tcgtacctcaactggtatcagcaaaagccgggaaaggcgcctaagctgctg atctacgccgcttcgagcttgcaaagcggggtgccatccagattctcggga tcaggctcaggaaccgacttcaccctgaccgtgaacagcctccagccggag gactttgccacttactactgccagcagggagactccgtgccgcttactttc ggggggggtacccgcctggagatcaagaccactaccccagcaccgaggcca cccaccccggctcctaccatcgcctcccagcctctgtccctgcgtccggag gcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc

		gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctg ctgctttcactcgtgatcactctttactgtaagcgcggtcggaagaagctg ctgtacatctttaagcaacccttcatgaggcctgtgcagactactcaagag gaggacggctgttcatgccggttcccagaggaggaggaaggcggctgcgaa ctgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcagggg cagaaccagctctacaacgaactcaatcttggtcggagagaggagtacgac gtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgc agaaagaatccccaagagggcctgtacaacgagctccaaaaggataagatg gcagaagcctatagcgagattggtatgaaaggggaacgcagaagaggcaaa ggccacgacggactgtaccagggactcagcaccgccaccaaggacacctat gacgctcttcacatgcaggccctgccgcctcgg
CAR123-2 AA	2099	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFT GYYMHWVRQAPGQGLEWMGWINPNSGGTNYAQKFQGRVTLTRDTSISTVYM ELSRLRSDDTAVYYCARDMNILATVPFDIWGQGTMVTVSSGGGGSGGGGSG GGGSDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLL IYAASSLQSGVPSRFSGSGSGTDFTLTVNSLQPEDFATYYCQQGDSVPLTF GGGTRLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDF ACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQE EDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYD VLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGK GHDGLYQGLSTATKDTYDALHMQALPPR
CAR123-2 scFv	2158	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFT GYYMHWVRQAPGQGLEWMGWINPNSGGTNYAQKFQGRVTLTRDTSISTVYM ELSRLRSDDTAVYYCARDMNILATVPFDIWGQGTMVTVSSGGGGSGGGGSG GGGSDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLL IYAASSLQSGVPSRFSGSGSGTDFTLTVNSLQPEDFATYYCQQGDSVPLTF GGGTRLEIK
CAR123-2 VH	2217	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWI NPNSGGTNYAQKFQGRVTLTRDTSISTVYMELSRLRSDDTAVYYCARDMNI LATVPFDIWGQGTMVTVSS
CAR123-2 VL	2276	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAA SSLQSGVPSRFSGSGSGTDFTLTVNSLQPEDFATYYCQQGDSVPLTFGGGT RLEIK
CAR123-3 NT	2041	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccac gccgctcggccccaagtccaactcgttcaatccggcgcagaagtcaagaag ccaggagcatcagtgaaagtgtcctgcaaagcctcaggctacatcttcacg ggatactacatccactgggtgcgccaggctccgggccagggccttgagtgg atgggctggatcaaccctaactctgggggaaccaactacgctcagaagttc caggggagggtcactatgactcgcgatacctccatctccactgcgtacatg gaactctcgggactgagatccgacgatcctgccgtgtactactgcgcccgg gacatgaacatcttggcgaccgtgccgtttgacatttggggacagggcacc ctcgtcactgtgtcgagcggtggaggaggctcgggggtggcggatcagga gggggaggaagcgacatccagctgactcagagcccatcgtcgttgtccgcg tcggtgggggatagagtgaccattacttgccgcgccagccagagcatctca tcatatctgaattggtaccagcagaagcccggaaaggccccaaaactgctg

		atctacgctgcaagcagcctccaatcgggagtgccgtcacggttctccggg tccggttcgggaactgactttaccctgaccgtgaattcgctgcaaccggag gatttcgccacgtactactgtcagcaaggagactccgtgccgctgaccttc ggtggaggcaccaaggtcgaaatcaagaccactaccccagcaccgaggcca cccaccccggctcctaccatcgcctcccagcctctgtccctgcgtccggag gcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctg ctgctttcactcgtgatcactctttactgtaagcgcggtcggaagaagctg ctgtacatctttaagcaacccttcatgaggcctgtgcagactactcaagag gaggacggctgttcatgccggttcccagaggaggaggaaggcggctgcgaa ctgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcagggg cagaaccagctctacaacgaactcaatcttggtcggagagaggagtacgac gtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgc agaaagaatccccaagagggcctgtacaacgagctccaaaaggataagatg gcagaagcctatagcgagattggtatgaaaggggaacgcagaagaggcaaa ggccacgacggactgtaccagggactcagcaccgccaccaaggacacctat gacgctcttcacatgcaggccctgccgcctcgg
CAR123-3 AA	2100	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYIFT GYYIHWVRQAPGQGLEWMGWINPNSGGTNYAQKFQGRVTMTRDTSISTAYM ELSGLRSDDPAVYYCARDMNILATVPFDIWGQGTLVTVSSGGGGSGGGGSG GGGSDIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLL IYAASSLQSGVPSRFSGSGSGTDFTLTVNSLQPEDFATYYCQQGDSVPLTF GGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDF ACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQE EDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYD VLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGK GHDGLYQGLSTATKDTYDALHMQALPPR
CAR123-3 scFv	2159	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYIFT GYYIHWVRQAPGQGLEWMGWINPNSGGTNYAQKFQGRVTMTRDTSISTAYM ELSGLRSDDPAVYYCARDMNILATVPFDIWGQGTLVTVSSGGGGSGGGGSG GGGSDIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLL IYAASSLQSGVPSRFSGSGSGTDFTLTVNSLQPEDFATYYCQQGDSVPLTF GGGTKVEIK
CAR123-3 VH	2218	QVQLVQSGAEVKKPGASVKVSCKASGYIFTGYYIHWVRQAPGQGLEWMGWI NPNSGGTNYAQKFQGRVTMTRDTSISTAYMELSGLRSDDPAVYYCARDMNI LATVPFDIWGQGTLVTVSS
CAR123-3 VL	2277	DIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAA SSLQSGVPSRFSGSGSGTDFTLTVNSLQPEDFATYYCQQGDSVPLTFGGGT KVEIK
CAR123-4 NT	2042	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccac gccgctcggccccaagtccaactccaacagtcaggcgcagaagtgaaaaag agcggtgcatcggtgaaagtgtcatgcaaagcctcgggctacaccttcact gactactatatgcactggctgcggcaggcaccgggacagggacttgagtgg atgggatggatcaacccgaattcaggggacactaactacgcgcagaagttc caggggagagtgaccctgacgagggacacctcaatttcgaccgtctacatg

		gaattgtcgcgcctgagatcggacgatactgctgtgtactactgtgcccgc gacatgaacatcctcgcgactgtgccttttgatatctggggacaggggact atggtcaccgtttcctccgcttccggtggcggaggctcgggaggccgggcc tccggtggaggaggcagcgacatccagatgactcagagcccttcctcgctg agcgcctcagtgggagatcgcgtgaccatcacttgccgggccagccagtcc atttcgtcctacctcaattggtaccagcagaagccgggaaaggcgcccaag ctcttgatctacgctgcgagctccctgcaaagcggggtgccgagccgattc tcgggttccggctcgggaaccgacttcactctgaccatctcatccctgcaa ccagaggactttgccacctactactgccaacaaggagattctgtcccactg acgttcggcggaggaaccaaggtcgaaatcaagaccactaccccagcaccg aggccacccaccccggctcctaccatcgcctcccagcctctgtccctgcgt ccggaggcatgtagacccgcagctggtggggccgtgcatacccggggtctt gacttcgcctgcgatatctacatttgggcccctctggctggtacttgcggg gtcctgctgctttcactcgtgatcactctttactgtaagcgcggtcggaag aagctgctgtacatctttaagcaacccttcatgaggcctgtgcagactact caagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggc tgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaag caggggcagaaccagctctacaacgaactcaatcttggtcggagagaggag tacgacgtgctggacaagcggagaggacgggacccagaaatgggcgggaag ccgcgcagaaagaatccccaagagggcctgtacaacgagctccaaaaggat aagatggcagaagcctatagcgagattggtatgaaaggggaacgcagaaga ggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggac acctatgacgctcttcacatgcaggccctgccgcctcgg
CAR123-4 AA	2101	MALPVTALLLPLALLLHAARPQVQLQQSGAEVKKSGASVKVSCKASGYTFT DYYMHWLRQAPGQGLEWMGWINPNSGDTNYAQKFQGRVTLTRDTSISTVYM ELSRLRSDDTAVYYCARDMNILATVPFDIWGQGTMVTVSSASGGGGSGGRA SGGGGSDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPK LLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGDSVPL TFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGL DFACDIYIWAPLAGTCGVLLLSLVITLYCK
CAR123-4 scFv	2160	MALPVTALLLPLALLLHAARPQVQLQQSGAEVKKSGASVKVSCKASGYTFT DYYMHWLRQAPGQGLEWMGWINPNSGDTNYAQKFQGRVTLTRDTSISTVYM ELSRLRSDDTAVYYCARDMNILATVPFDIWGQGTMVTVSSASGGGGSGGRA SGGGGSDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPK LLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGDSVPL TFGGGTKVEIK
CAR123-4 VH	2219	QVQLQQSGAEVKKSGASVKVSCKASGYTFTDYYMHWLRQAPGQGLEWMGWI NPNSGDTNYAQKFQGRVTLTRDTSISTVYMELSRLRSDDTAVYYCARDMNI LATVPFD**I**WGQGTMVTVSS
CAR123-4 VL	2278	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAA SSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGDSVPLTFGGGT KVEIK
CAR123-1 NT	2039	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccac gccgctcggccccaagtccaactcgtccagtcaggagcggaagtcaagaag cccggagcgtcagtcaaagtgtcatgcaaagcctcgggctacactttcact

		gggtactacatgcactgggtgcgccaggctccaggacagggactggaatgg atgggatggatcaacccgaactccggtggcaccaattacgcccagaagttc caggggagggtgaccatgactcgcgacacgtcgatcagcaccgcatacatg gagctgtcaagactccggtccgacgatactgccgtgtactactgcgcacgg gacatgaacattctggccaccgtgccttttgacatctggggtcagggaact atggttaccgtgtcctctggtggaggcggctccggcgggggggggaagcgga ggcggtggaagcgacattcagatgacccagtcgccttcatccctttcggcg agcgtgggagatcgcgtcactatcacttgtcgggcctcgcagtccatctcc acctacctcaattggtaccagcagaagccaggaaaagcaccgaatctgctg atctacgccgcgttttccttgcaatcgggagtgccaagcagattcagcgga tcgggatcaggcactgatttcaccctcaccatcaactcgctgcaaccggag gatttcgctacgtactattgccaacaaggagacagcgtgccgctcaccttc ggcggagggactaagctggaaatcaagaccactaccccagcaccgaggcca cccaccccggctcctaccatcgcctcccagcctctgtccctgcgtccggag gcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctg ctgctttcactcgtgatcactctttactgtaagcgcggtcggaagaagctg ctgtacatctttaagcaacccttcatgaggcctgtgcagactactcaagag gaggacggctgttcatgccggttcccagaggaggaggaaggcggctgcgaa ctgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcagggg cagaaccagctctacaacgaactcaatcttggtcggagagaggagtacgac gtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgc agaaagaatccccaagagggcctgtacaacgagctccaaaaggataagatg gcagaagcctatagcgagattggtatgaaaggggaacgcagaagaggcaaa ggccacgacggactgtaccagggactcagcaccgccaccaaggacacctat gacgctcttcacatgcaggccctgccgcctcgg
CAR123-1 AA	2098	malpvtalllplalllhaarpqvqlvqsgaevkkpgasvkvsckasgytft gyymhwvrqapgqglewmgwinpnsggtnyaqkfqgrvtmtrdtsistaym elsrlrsddtavyycardmnilatvpfdiwgqgtmvtvssggggsggggsg gggsdiqmtqspsslsasvgdrvtitcrasqsistylnwyqqkpgkapnll iyaafslqsgvpsrfsgsgsgtdftltinslqpedfatyycqqgdsvpltf gggtkleikpaprppptpaptiasqplslrpeacrpaaggavhtrgldf acdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqe edgcscrfpeeeeggcelrvkfsrsadapaykqgqnqlynelnlgrreeyd vldkrrgrdpemggkprrknpqeglynelqkdkmaeayseigmkgerrrgk ghdglyqglstatkdtydalhmqalppr
CAR123-1 scFv	2157	malpvtalllplalllhaarpqvqlvqsgaevkkpgasvkvsckasgytft gyymhwvrqapgqglewmgwinpnsggtnyaqkfqgrvtmtrdtsistaym elsrlrsddtavyycardmnilatvpfdiwgqgtmvtvssggggsggggsg gggsdiqmtqspsslsasvgdrvtitcrasqsistylnwyqqkpgkapnll iyaafslqsgvpsrfsgsgsgtdftltinslqpedfatyycqqgdsvpltf gggtkleik
CAR123-1 VH	2216	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWI NPNSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCARDMNI LATVPFDIWGQGTMVTVSS

CAR123-1 VL	2275	DIQMTQSPSSLSASVGDRVTITCRASQSISTYLNWYQQKPGKAPNLLIYAA FSLQSGVPSRFSGSGSGTDFTLTINSLQPEDFATYYCQQGDSVPLTFGGGT KLEIK

Table 27: Humanized CD123 CAR Sequences

Name	SEQ ID NO:	Sequence
hzCAR123-1 NT	2066	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCCAAGTGCAGCTGGTCCAGTCGGGAGCCGAAGTCAAGAAGCCCGGCGCTAGCGTGAAAGT GTCCTGCAAAGCCTCCGGGTACACATTCACCTCCTACTGGATGAATTGGGTCAGACAGGCG CCCGGCCAGGGACTCGAGTGGATGGGAAGGATTGATCCTTACGACTCCGAAACCCATTACA ACCAGAAGTTCAAGGACCGCGTGACCATGACTGTGGATAAGTCCACTTCCACCGCTTACAT GGAGCTGTCCAGCCTGCGCTCCGAGGATACCGCAGTGTACTACTGCGCCCGGGGAAACTGG GACGACTATTGGGGACAGGGAACTACCGTGACCGTGTCAAGCGGGGGTGGCGGTAGCGGAG GAGGGGGCTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGACGTGCAGCTCACCCAGTC GCCCTCATTTCTGTCGGCCTCAGTGGGAGACAGAGTGACCATTACTTGTCGGGCCTCCAAG AGCATCTCCAAGGACCTGGCCTGGTATCAGCAGAAGCCAGGAAAGGCGCCTAAGTTGCTCA TCTACTCGGGGTCGACCCTGCAATCTGGCGTGCCGTCCCGGTTCTCCGGTTCGGGAAGCGG TACCGAATTCACCCTTACTATCTCCTCCCTGCAACCGGAGGACTTCGCCACCTACTACTGC CAACAGCACAACAAGTACCCGTACACTTTCGGGGGTGGCACGAAGGTCGAAATCAAGACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR123-1 AA	2125	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQA PGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARGNW DDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVQLTQSPSFLSASVGDRVTITCRASK SISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYC QQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDF ACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPE EEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKN PQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
hzCAR123-1 scFv	2184	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQA PGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARGNW DDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVQLTQSPSFLSASVGDRVTITCRASK SISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYC QQHNKYPYTFGGGTKVEIK
hzCAR123	2243	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYN QKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARGNWDDYWGQGTTVTVSS

3-1 VH		
hzCAR12 3-1 VL	2302	DVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSR FSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-2 NT	2067	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCCAAGTGCAGCTGGTCCAGTCGGGAGCCGAAGTCAAGAAGCCCGGCGCTAGCGTGAAAGT GTCCTGCAAAGCCTCCGGGTACACATTCACCTCCTACTGGATGAATTGGGTCAGACAGGCG CCCGGCCAGGGACTCGAGTGGATGGGAAGGATTGATCCTTACGACTCCGAAACCCATTACA ACCAGAAGTTCAAGGACCGCGTGACCATGACTGTGGATAAGTCCACTTCCACCGCTTACAT GGAGCTGTCCAGCCTGCGCTCCGAGGATACCGCAGTGTACTACTGCGCCCGGGGAAACTGG GACGACTATTGGGGACAGGGAACTACCGTGACCGTGTCAAGCGGGGGTGGCGGTAGCGGAG GAGGGGGCTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGAAGTGGTGCTGACCCAGTC GCCCGCAACCCTCTCTCTGTCGCCGGGAGAACGCGCCACTCTTTCCTGTCGGGCGTCCAAG AGCATCTCAAAGGACCTCGCCTGGTACCAGCAGAAGCCTGGTCAAGCCCCGCGGCTGCTGA TCTACTCCGGCTCCACGCTGCAATCAGGAATCCCAGCCAGATTTTCCGGTTCGGGGTCGGG GACTGACTTCACCTTGACCATTAGCTCGCTGGAACCTGAGGACTTCGCCGTGTATTACTGC CAGCAGCACAACAAGTACCCGTACACCTTCGGAGGCGGTACTAAGGTCGAGATCAAGACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-2 AA	2126	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSEVVLTQSPATLSLSPGERATLSCR ASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFA VYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-2 scFv	2185	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSEVVLTQSPATLSLSPGERATLSCR ASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFA VYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-2 VH	2244	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYN QKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-2 VL	2303	EVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR12	2068	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC

3-3 NT		CCCAAGTGCAGCTGGTCCAGTCGGGAGCCGAAGTCAAGAAGCCCGGCGCTAGCGTGAAAGT GTCCTGCAAAGCCTCCGGGTACACATTCACCTCCTACTGGATGAATTGGGTCAGACAGGCG CCCGGCCAGGGACTCGAGTGGATGGGAAGGATTGATCCTTACGACTCCGAAACCCATTACA ACCAGAAGTTCAAGGACCGCGTGACCATGACTGTGGATAAGTCCACTTCCACCGCTTACAT GGAGCTGTCCAGCCTGCGCTCCGAGGATACCGCAGTGTACTACTGCGCCCGGGGAAACTGG GACGACTATTGGGGACAGGGAACTACCGTGACCGTGTCAAGCGGGGGTGGCGGTAGCGGAG GAGGGGGCTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGACGTCGTGATGACCCAGTC ACCGGCATTCCTGTCCGTGACTCCCGGAGAAAAGGTCACGATTACTTGCCGGGCGTCCAAG AGCATCTCCAAGGACCTCGCCTGGTACCAACAGAAGCCGGACCAGGCCCCTAAGCTGTTGA TCTACTCGGGGTCCACCCTTCAATCGGGAGTGCCATCGCGGTTTAGCGGTTCGGGTTCTGG GACCGACTTCACTTTCACCATCTCCTCACTGGAAGCCGAGGATGCCGCCACTTACTACTGT CAGCAGCACAACAAGTATCCGTACACCTTCGGAGGCGGTACCAAAGTGGAGATCAAGACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-3 AA	2127	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPAFLSVTPGEKVTITCR ASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAA TYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-3 scFv	2186	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPAFLSVTPGEKVTITCR ASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAA TYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-3 VH	2245	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYN QKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-3 VL	2304	DVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSR FSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-4 NT	2069	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCCAAGTGCAGCTGGTCCAGTCGGGAGCCGAAGTCAAGAAGCCCGGCGCTAGCGTGAAAGT GTCCTGCAAAGCCTCCGGGTACACATTCACCTCCTACTGGATGAATTGGGTCAGACAGGCG CCCGGCCAGGGACTCGAGTGGATGGGAAGGATTGATCCTTACGACTCCGAAACCCATTACA ACCAGAAGTTCAAGGACCGCGTGACCATGACTGTGGATAAGTCCACTTCCACCGCTTACAT GGAGCTGTCCAGCCTGCGCTCCGAGGATACCGCAGTGTACTACTGCGCCCGGGGAAACTGG GACGACTATTGGGGACAGGGAACTACCGTGACCGTGTCAAGCGGGGGTGGCGGTAGCGGAG

		GAGGGGGCTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGACGTGGTCATGACTCAGTC CCCGGACTCACTCGCGGTGTCGCTTGGAGAGAGAGCGACCATCAACTGTCGGGCCTCAAAG AGCATCAGCAAGGACCTGGCCTGGTACCAGCAGAAGCCGGGACAGCCGCCAAAGCTGCTGA TCTACTCCGGGTCCACCTTGCAATCTGGTGTCCCTGACCGGTTCTCCGGTTCCGGGTCGGG TACCGACTTCACGCTCACTATTTCGTCGCTGCAAGCCGAAGATGTGGCCGTGTACTATTGC CAACAGCACAACAAGTACCCCTACACTTTTGGCGGAGGCACCAAGGTGGAAATCAAGACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-4 AA	2128	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPDSLAVSLGERATINCR ASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVA VYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-4 scFv	2187	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPDSLAVSLGERATINCR ASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVA VYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-4 VH	2246	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYN QKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-4 VL	2305	DVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDR FSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-5 NT	2070	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCGACGTGCAGCTCACCCAGTCGCCCTCATTTCTGTCGGCCTCAGTGGGAGACAGAGTGAC CATTACTTGTCGGGCCTCCAAGAGCATCTCCAAGGACCTGGCCTGGTATCAGCAGAAGCCA GGAAAGGCGCCTAAGTTGCTCATCTACTCGGGGTCGACCCTGCAATCTGGCGTGCCGTCCC GGTTCTCCGGTTCGGGAAGCGGTACCGAATTCACCCTTACTATCTCCTCCCTGCAACCGGA GGACTTCGCCACCTACTACTGCCAACAGCACAACAAGTACCCGTACACTTTCGGGGGTGGC ACGAAGGTCGAAATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCT CAGGGGGCGGAGGAAGCCAAGTGCAGCTGGTCCAGTCGGGAGCCGAAGTCAAGAAGCCCGG CGCTAGCGTGAAAGTGTCCTGCAAAGCCTCCGGGTACACATTCACCTCCTACTGGATGAAT TGGGTCAGACAGGCGCCCGGCCAGGGACTCGAGTGGATGGGAAGGATTGATCCTTACGACT CCGAAACCCATTACAACCAGAAGTTCAAGGACCGCGTGACCATGACTGTGGATAAGTCCAC TTCCACCGCTTACATGGAGCTGTCCAGCCTGCGCTCCGAGGATACCGCAGTGTACTACTGC GCCCGGGGAAACTGGGACGACTATTGGGGACAGGGAACTACCGTGACCGTGTCAAGCACCA

		CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-5 AA	2129	MALPVTALLLPLALLLHAARPDVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQK PGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTA VYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-5 scFv	2188	MALPVTALLLPLALLLHAARPDVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQK PGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-5 VH	2247	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYN QKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-5 VL	2306	DVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSR FSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-6 NT	2071	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCGAAGTGGTGCTGACCCAGTCGCCCGCAACCCTCTCTCTGTCGCCGGGAGAACGCGCCAC TCTTTCCTGTCGGGCGTCCAAGAGCATCTCAAAGGACCTCGCCTGGTACCAGCAGAAGCCT GGTCAAGCCCCGCGGCTGCTGATCTACTCCGGCTCCACGCTGCAATCAGGAATCCCAGCCA GATTTTCCGGTTCGGGGTCGGGGACTGACTTCACCTTGACCATTAGCTCGCTGGAACCTGA GGACTTCGCCGTGTATTACTGCCAGCAGCACAACAAGTACCCGTACACCTTCGGAGGCGGT ACTAAGGTCGAGATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCT CAGGGGGCGGAGGAAGCCAAGTGCAGCTGGTCCAGTCGGGAGCCGAAGTCAAGAAGCCCGG CGCTAGCGTGAAAGTGTCCTGCAAAGCCTCCGGGTACACATTCACCTCCTACTGGATGAAT TGGGTCAGACAGGCGCCCGGCCAGGGACTCGAGTGGATGGGAAGGATTGATCCTTACGACT CCGAAACCCATTACAACCAGAAGTTCAAGGACCGCGTGACCATGACTGTGGATAAGTCCAC TTCCACCGCTTACATGGAGCTGTCCAGCCTGCGCTCCGAGGATACCGCAGTGTACTACTGC GCCCGGGGAAACTGGGACGACTATTGGGGACAGGGAACTACCGTGACCGTGTCAAGCACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct

		acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-6 AA	2130	MALPVTALLLPLALLLHAARPEVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQK PGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTA VYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-6 scFv	2189	MALPVTALLLPLALLLHAARPEVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQK PGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-6 VH	2248	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYN QKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-6 VL	2307	EVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-7 NT	2072	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCGACGTCGTGATGACCCAGTCACCGGCATTCCTGTCCGTGACTCCCGGAGAAAAGGTCAC GATTACTTGCCGGGCGTCCAAGAGCATCTCCAAGGACCTCGCCTGGTACCAACAGAAGCCG GACCAGGCCCCTAAGCTGTTGATCTACTCGGGGTCCACCCTTCAATCGGGAGTGCCATCGC GGTTTAGCGGTTCGGGTTCTGGGACCGACTTCACTTTCACCATCTCCTCACTGGAAGCCGA GGATGCCGCCACTTACTACTGTCAGCAGCACAACAAGTATCCGTACACCTTCGGAGGCGGT ACCAAAGTGGAGATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCT CAGGGGGCGGAGGAAGCCAAGTGCAGCTGGTCCAGTCGGGAGCCGAAGTCAAGAAGCCCGG CGCTAGCGTGAAAGTGTCCTGCAAAGCCTCCGGGTACACATTCACCTCCTACTGGATGAAT TGGGTCAGACAGGCGCCCGGCCAGGGACTCGAGTGGATGGGAAGGATTGATCCTTACGACT CCGAAACCCATTACAACCAGAAGTTCAAGGACCGCGTGACCATGACTGTGGATAAGTCCAC TTCCACCGCTTACATGGAGCTGTCCAGCCTGCGCTCCGAGGATACCGCAGTGTACTACTGC GCCCGGGGAAACTGGGACGACTATTGGGGACAGGGAACTACCGTGACCGTGTCAAGCACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg

hzCAR12 3-7 AA	2131	MALPVTALLLPLALLLHAARPDVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQK PDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTA VYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-7 scFv	2190	MALPVTALLLPLALLLHAARPDVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQK PDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-7 VH	2249	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYN QKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-7 VL	2308	DVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSR FSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-8 NT	2073	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCGACGTGGTCATGACTCAGTCCCCGGACTCACTCGCGGTGTCGCTTGGAGAGAGAGCGAC CATCAACTGTCGGGCCTCAAAGAGCATCAGCAAGGACCTGGCCTGGTACCAGCAGAAGCCG GGACAGCCGCCAAAGCTGCTGATCTACTCCGGGTCCACCTTGCAATCTGGTGTCCCTGACC GGTTCTCCGGTTCCGGGTCGGGTACCGACTTCACGCTCACTATTTCGTCGCTGCAAGCCGA AGATGTGGCCGTGTACTATTGCCAACAGCACAACAAGTACCCCTACACTTTTGGCGGAGGC ACCAAGGTGGAAATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCT CAGGGGGCGGAGGAAGCCAAGTGCAGCTGGTCCAGTCGGGAGCCGAAGTCAAGAAGCCCGG CGCTAGCGTGAAAGTGTCCTGCAAAGCCTCCGGGTACACATTCACCTCCTACTGGATGAAT TGGGTCAGACAGGCGCCCGGCCAGGGACTCGAGTGGATGGGAAGGATTGATCCTTACGACT CCGAAACCCATTACAACCAGAAGTTCAAGGACCGCGTGACCATGACTGTGGATAAGTCCAC TTCCACCGCTTACATGGAGCTGTCCAGCCTGCGCTCCGAGGATACCGCAGTGTACTACTGC GCCCGGGGAAACTGGGACGACTATTGGGGACAGGGAACTACCGTGACCGTGTCAAGCACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-8 AA	2132	MALPVTALLLPLALLLHAARPDVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQK PGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTA VYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC

		SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-8 scFv	2191	MALPVTALLLPLALLLHAARPDVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQK PGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-8 VH	2250	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYN QKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-8 VL	2309	DVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDR FSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-9 NT	2074	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCCAAGTGCAGCTGGTGCAGTCAGGCAGCGAACTGAAGAAGCCCGGAGCCTCCGTCAAAGT GTCCTGCAAAGCCTCGGGATACACCTTCACCTCCTACTGGATGAACTGGGTCCGCCAGGCA CCTGGACAGGGGCTGGAGTGGATGGGAAGGATCGATCCCTACGATTCCGAAACCCATTACA ATCAGAAGTTCAAGGACCGGTTTGTGTTCTCCGTGGACAAGTCCGTGTCCACCGCCTACCT CCAAATTAGCAGCCTGAAGGCGGAGGATACAGCTGTCTACTACTGCGCTCGCGGAAACTGG GATGACTATTGGGGCCAGGGAACTACCGTGACTGTGTCCTCCGGGGGTGGCGGTAGCGGAG GAGGGGGCTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGACGTGCAGCTCACCCAGTC GCCCTCATTTCTGTCGGCCTCAGTGGGAGACAGAGTGACCATTACTTGTCGGGCCTCCAAG AGCATCTCCAAGGACCTGGCCTGGTATCAGCAGAAGCCAGGAAAGGCGCCTAAGTTGCTCA TCTACTCGGGGTCGACCCTGCAATCTGGCGTGCCGTCCCGGTTCTCCGGTTCGGGAAGCGG TACCGAATTCACCCTTACTATCTCCTCCCTGCAACCGGAGGACTTCGCCACCTACTACTGC CAACAGCACAACAAGTACCCGTACACTTTCGGGGGTGGCACGAAGGTCGAAATCAAGACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-9 AA	2133	MALPVTALLLPLALLLHAARPQVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVQLTQSPSFLSASVGDRVTITCR ASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFA TYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-9	2192	MALPVTALLLPLALLLHAARPQVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVQLTQSPSFLSASVGDRVTITCR

scFv		ASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFA TYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-9 VH	2251	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYN QKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-10 VL	2310	DVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSR FSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-10 NT	2075	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCCAAGTGCAGCTGGTGCAGTCAGGCAGCGAACTGAAGAAGCCCGGAGCCTCCGTCAAAGT GTCCTGCAAAGCCTCGGGATACACCTTCACCTCCTACTGGATGAACTGGGTCCGCCAGGCA CCTGGACAGGGGCTGGAGTGGATGGGAAGGATCGATCCCTACGATTCCGAAACCCATTACA ATCAGAAGTTCAAGGACCGGTTTGTGTTCTCCGTGGACAAGTCCGTGTCCACCGCCTACCT CCAAATTAGCAGCCTGAAGGCGGAGGATACAGCTGTCTACTACTGCGCTCGCGGAAACTGG GATGACTATTGGGGCCAGGGAACTACCGTGACTGTGTCCTCCGGGGGTGGCGGTAGCGGAG GAGGGGGCTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGAAGTGGTGCTGACCCAGTC GCCCGCAACCCTCTCTCTGTCGCCGGGAGAACGCGCCACTCTTTCCTGTCGGGCGTCCAAG AGCATCTCAAAGGACCTCGCCTGGTACCAGCAGAAGCCTGGTCAAGCCCCGCGGCTGCTGA TCTACTCCGGCTCCACGCTGCAATCAGGAATCCCAGCCAGATTTTCCGGTTCGGGGTCGGG GACTGACTTCACCTTGACCATTAGCTCGCTGGAACCTGAGGACTTCGCCGTGTATTACTGC CAGCAGCACAACAAGTACCCGTACACCTTCGGAGGCGGTACTAAGGTCGAGATCAAGACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-10 AA	2134	MALPVTALLLPLALLLHAARPQVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSEVVLTQSPATLSLSPGERATLSCR ASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFA VYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-10 scFv	2193	MALPVTALLLPLALLLHAARPQVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSEVVLTQSPATLSLSPGERATLSCR ASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFA VYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-10 VH	2252	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYN QKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARGNWDDYWGQGTTVTVSS

hzCAR12 3-10 VL	2311	EVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-11 NT	2076	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCCAAGTGCAGCTGGTGCAGTCAGGCAGCGAACTGAAGAAGCCCGGAGCCTCCGTCAAAGT GTCCTGCAAAGCCTCGGGATACACCTTCACCTCCTACTGGATGAACTGGGTCCGCCAGGCA CCTGGACAGGGGCTGGAGTGGATGGGAAGGATCGATCCCTACGATTCCGAAACCCATTACA ATCAGAAGTTCAAGGACCGGTTTGTGTTCTCCGTGGACAAGTCCGTGTCCACCGCCTACCT CCAAATTAGCAGCCTGAAGGCGGAGGATACAGCTGTCTACTACTGCGCTCGCGGAAACTGG GATGACTATTGGGGCCAGGGAACTACCGTGACTGTGTCCTCCGGGGGTGGCGGTAGCGGAG GAGGGGGCTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGACGTCGTGATGACCCAGTC ACCGGCATTCCTGTCCGTGACTCCCGGAGAAAAGGTCACGATTACTTGCCGGGCGTCCAAG AGCATCTCCAAGGACCTCGCCTGGTACCAACAGAAGCCGGACCAGGCCCCTAAGCTGTTGA TCTACTCGGGGTCCACCCTTCAATCGGGAGTGCCATCGCGGTTTAGCGGTTCGGGTTCTGG GACCGACTTCACTTTCACCATCTCCTCACTGGAAGCCGAGGATGCCGCCACTTACTACTGT CAGCAGCACAACAAGTATCCGTACACCTTCGGAGGCGGTACCAAAGTGGAGATCAAGACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-11 AA	2135	MALPVTALLLPLALLLHAARPQVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPAFLSVTPGEKVTITCR ASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAA TYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-11 scFv	2194	MALPVTALLLPLALLLHAARPQVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPAFLSVTPGEKVTITCR ASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAA TYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-11 VH	2253	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYN QKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-11 VL	2312	DVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSR FSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-12 NT	2077	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCCAAGTGCAGCTGGTGCAGTCAGGCAGCGAACTGAAGAAGCCCGGAGCCTCCGTCAAAGT GTCCTGCAAAGCCTCGGGATACACCTTCACCTCCTACTGGATGAACTGGGTCCGCCAGGCA

		CCTGGACAGGGGCTGGAGTGGATGGGAAGGATCGATCCCTACGATTCCGAAACCCATTACA ATCAGAAGTTCAAGGACCGGTTTGTGTTCTCCGTGGACAAGTCCGTGTCCACCGCCTACCT CCAAATTAGCAGCCTGAAGGCGGAGGATACAGCTGTCTACTACTGCGCTCGCGGAAACTGG GATGACTATTGGGGCCAGGGAACTACCGTGACTGTGTCCTCCGGGGGTGGCGGTAGCGGAG GAGGGGGCTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGACGTGGTCATGACTCAGTC CCCGGACTCACTCGCGGTGTCGCTTGGAGAGAGAGCGACCATCAACTGTCGGGCCTCAAAG AGCATCAGCAAGGACCTGGCCTGGTACCAGCAGAAGCCGGGACAGCCGCCAAAGCTGCTGA TCTACTCCGGGTCCACCTTGCAATCTGGTGTCCCTGACCGGTTCTCCGGTTCCGGGTCGGG TACCGACTTCACGCTCACTATTTCGTCGCTGCAAGCCGAAGATGTGGCCGTGTACTATTGC CAACAGCACAACAAGTACCCCTACACTTTTGGCGGAGGCACCAAGGTGGAAATCAAGACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-12 AA	2136	MALPVTALLLPLALLLHAARPQVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPDSLAVSLGERATINCR ASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVA VYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-12 scFv	2195	MALPVTALLLPLALLLHAARPQVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPDSLAVSLGERATINCR ASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVA VYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-12 VH	2254	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYN QKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-12 VL	2313	DVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDR FSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-13 NT	2078	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCGACGTGCAGCTCACCCAGTCGCCCTCATTTCTGTCGGCCTCAGTGGGAGACAGAGTGAC CATTACTTGTCGGGCCTCCAAGAGCATCTCCAAGGACCTGGCCTGGTATCAGCAGAAGCCA GGAAAGGCGCCTAAGTTGCTCATCTACTCGGGGTCGACCCTGCAATCTGGCGTGCCGTCCC GGTTCTCCGGTTCGGGAAGCGGTACCGAATTCACCCTTACTATCTCCTCCCTGCAACCGGA GGACTTCGCCACCTACTACTGCCAACAGCACAACAAGTACCCGTACACTTTCGGGGGTGGC ACGAAGGTCGAAATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCT CAGGGGGCGGAGGAAGCCAAGTGCAGCTGGTGCAGTCAGGCAGCGAACTGAAGAAGCCCGG AGCCTCCGTCAAAGTGTCCTGCAAAGCCTCGGGATACACCTTCACCTCCTACTGGATGAAC

		TGGGTCCGCCAGGCACCTGGACAGGGGCTGGAGTGGATGGGAAGGATCGATCCCTACGATT CCGAAACCCATTACAATCAGAAGTTCAAGGACCGGTTTGTGTTCTCCGTGGACAAGTCCGT GTCCACCGCCTACCTCCAAATTAGCAGCCTGAAGGCGGAGGATACAGCTGTCTACTACTGC GCTCGCGGAAACTGGGATGACTATTGGGGCCAGGGAACTACCGTGACTGTGTCCTCCACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-13 AA	2137	MALPVTALLLPLALLLHAARPDVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQK PGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGSELKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTA VYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-13 scFv	2196	MALPVTALLLPLALLLHAARPDVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQK PGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGSELKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-13 VH	2255	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYN QKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-13 VL	2314	DVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSR FSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-14 NT	2079	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCGAAGTGGTGCTGACCCAGTCGCCCGCAACCCTCTCTCTGTCGCCGGGAGAACGCGCCAC TCTTTCCTGTCGGGCGTCCAAGAGCATCTCAAAGGACCTCGCCTGGTACCAGCAGAAGCCT GGTCAAGCCCCGCGGCTGCTGATCTACTCCGGCTCCACGCTGCAATCAGGAATCCCAGCCA GATTTTCCGGTTCGGGGTCGGGGACTGACTTCACCTTGACCATTAGCTCGCTGGAACCTGA GGACTTCGCCGTGTATTACTGCCAGCAGCACAACAAGTACCCGTACACCTTCGGAGGCGGT ACTAAGGTCGAGATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCT CAGGGGGCGGAGGAAGCCAAGTGCAGCTGGTGCAGTCAGGCAGCGAACTGAAGAAGCCCGG AGCCTCCGTCAAAGTGTCCTGCAAAGCCTCGGGATACACCTTCACCTCCTACTGGATGAAC TGGGTCCGCCAGGCACCTGGACAGGGGCTGGAGTGGATGGGAAGGATCGATCCCTACGATT CCGAAACCCATTACAATCAGAAGTTCAAGGACCGGTTTGTGTTCTCCGTGGACAAGTCCGT GTCCACCGCCTACCTCCAAATTAGCAGCCTGAAGGCGGAGGATACAGCTGTCTACTACTGC GCTCGCGGAAACTGGGATGACTATTGGGGCCAGGGAACTACCGTGACTGTGTCCTCCACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc

		gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-14 AA	2138	MALPVTALLLPLALLLHAARPEVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQK PGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGSELKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTA VYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-14 scFv	2197	MALPVTALLLPLALLLHAARPEVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQK PGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGSELKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-14 VH	2256	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYN QKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-14 VL	2315	EVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-15 NT	2080	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCGACGTCGTGATGACCCAGTCACCGGCATTCCTGTCCGTGACTCCCGGAGAAAAGGTCAC GATTACTTGCCGGGCGTCCAAGAGCATCTCCAAGGACCTCGCCTGGTACCAACAGAAGCCG GACCAGGCCCCTAAGCTGTTGATCTACTCGGGGTCCACCCTTCAATCGGGAGTGCCATCGC GGTTTAGCGGTTCGGGTTCTGGGACCGACTTCACTTTCACCATCTCCTCACTGGAAGCCGA GGATGCCGCCACTTACTACTGTCAGCAGCACAACAAGTATCCGTACACCTTCGGAGGCGGT ACCAAAGTGGAGATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCT CAGGGGGCGGAGGAAGCCAAGTGCAGCTGGTGCAGTCAGGCAGCGAACTGAAGAAGCCCGG AGCCTCCGTCAAAGTGTCCTGCAAAGCCTCGGGATACACCTTCACCTCCTACTGGATGAAC TGGGTCCGCCAGGCACCTGGACAGGGGCTGGAGTGGATGGGAAGGATCGATCCCTACGATT CCGAAACCCATTACAATCAGAAGTTCAAGGACCGGTTTGTGTTCTCCGTGGACAAGTCCGT GTCCACCGCCTACCTCCAAATTAGCAGCCTGAAGGCGGAGGATACAGCTGTCTACTACTGC GCTCGCGGAAACTGGGATGACTATTGGGGCCAGGGAACTACCGTGACTGTGTCCTCCACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat

		ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-15 AA	2139	MALPVTALLLPLALLLHAARPDVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQK PDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGSELKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTA VYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-15 scFv	2198	MALPVTALLLPLALLLHAARPDVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQK PDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGSELKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-15 VH	2257	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYN QKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-15 VL	2316	DVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSR FSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-16 NT	2081	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCGACGTGGTCATGACTCAGTCCCCGGACTCACTCGCGGTGTCGCTTGGAGAGAGAGCGAC CATCAACTGTCGGGCCTCAAAGAGCATCAGCAAGGACCTGGCCTGGTACCAGCAGAAGCCG GGACAGCCGCCAAAGCTGCTGATCTACTCCGGGTCCACCTTGCAATCTGGTGTCCCTGACC GGTTCTCCGGTTCCGGGTCGGGTACCGACTTCACGCTCACTATTTCGTCGCTGCAAGCCGA AGATGTGGCCGTGTACTATTGCCAACAGCACAACAAGTACCCCTACACTTTTGGCGGAGGC ACCAAGGTGGAAATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCT CAGGGGGCGGAGGAAGCCAAGTGCAGCTGGTGCAGTCAGGCAGCGAACTGAAGAAGCCCGG AGCCTCCGTCAAAGTGTCCTGCAAAGCCTCGGGATACACCTTCACCTCCTACTGGATGAAC TGGGTCCGCCAGGCACCTGGACAGGGGCTGGAGTGGATGGGAAGGATCGATCCCTACGATT CCGAAACCCATTACAATCAGAAGTTCAAGGACCGGTTTGTGTTCTCCGTGGACAAGTCCGT GTCCACCGCCTACCTCCAAATTAGCAGCCTGAAGGCGGAGGATACAGCTGTCTACTACTGC GCTCGCGGAAACTGGGATGACTATTGGGGCCAGGGAACTACCGTGACTGTGTCCTCCACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-16 AA	2140	MALPVTALLLPLALLLHAARPDVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQK PGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGSELKKPGASVKVSCKASGYTFTSY

		WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTA VYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-16 scFv	2199	MALPVTALLLPLALLLHAARPDVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQK PGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGSELKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-16 VH	2258	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYN QKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-16 VL	2317	DVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDR FSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-17 NT	2082	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCGAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTCAAGAAGCCTGGAGAATCCCTGAGGAT CAGCTGCAAAGGCAGCGGGTATACCTTCACCTCCTACTGGATGAATTGGGTCCGCCAGATG CCCGGAAAAGGCCTGGAGTGGATGGGACGGATTGACCCCTACGACTCGGAAACCCATTACA ACCAGAAGTTCAAGGATCACGTGACCATCTCCGTGGACAAGTCCATTTCCACTGCGTACCT CCAGTGGTCAAGCCTGAAGGCCTCCGACACTGCTATGTACTACTGCGCACGCGGAAACTGG GATGATTACTGGGGACAGGGAACAACCGTGACTGTGTCCTCCGGGGGTGGCGGTAGCGGAG GAGGGGGCTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGACGTGCAGCTCACCCAGTC GCCCTCATTTCTGTCGGCCTCAGTGGGAGACAGAGTGACCATTACTTGTCGGGCCTCCAAG AGCATCTCCAAGGACCTGGCCTGGTATCAGCAGAAGCCAGGAAAGGCGCCTAAGTTGCTCA TCTACTCGGGGTCGACCCTGCAATCTGGCGTGCCGTCCCGGTTCTCCGGTTCGGGAAGCGG TACCGAATTCACCCTTACTATCTCCTCCCTGCAACCGGAGGACTTCGCCACCTACTACTGC CAACAGCACAACAAGTACCCGTACACTTTCGGGGGTGGCACGAAGGTCGAAATCAAGACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-17 AA	2141	MALPVTALLLPLALLLHAARPEVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQ MPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVQLTQSPSFLSASVGDRVTITCR ASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFA TYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR

hzCAR12 3-17 scFv	2200	MALPVTALLLPLALLLHAARPEVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQ MPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVQLTQSPSFLSASVGDRVTITCR ASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFA TYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-17 VH	2259	EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQMPGKGLEWMGRIDPYDSETHYN QKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-17 VL	2318	DVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSR FSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-18 NT	2083	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCGAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTCAAGAAGCCTGGAGAATCCCTGAGGAT CAGCTGCAAAGGCAGCGGGTATACCTTCACCTCCTACTGGATGAATTGGGTCCGCCAGATG CCCGGAAAAGGCCTGGAGTGGATGGGACGGATTGACCCCTACGACTCGGAAACCCATTACA ACCAGAAGTTCAAGGATCACGTGACCATCTCCGTGGACAAGTCCATTTCCACTGCGTACCT CCAGTGGTCAAGCCTGAAGGCCTCCGACACTGCTATGTACTACTGCGCACGCGGAAACTGG GATGATTACTGGGGACAGGGAACAACCGTGACTGTGTCCTCCGGGGGTGGCGGTAGCGGAG GAGGGGGCTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGAAGTGGTGCTGACCCAGTC GCCCGCAACCCTCTCTCTGTCGCCGGGAGAACGCGCCACTCTTTCCTGTCGGGCGTCCAAG AGCATCTCAAAGGACCTCGCCTGGTACCAGCAGAAGCCTGGTCAAGCCCCGCGGCTGCTGA TCTACTCCGGCTCCACGCTGCAATCAGGAATCCCAGCCAGATTTTCCGGTTCGGGGTCGGG GACTGACTTCACCTTGACCATTAGCTCGCTGGAACCTGAGGACTTCGCCGTGTATTACTGC CAGCAGCACAACAAGTACCCGTACACCTTCGGAGGCGGTACTAAGGTCGAGATCAAGACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-18 AA	2142	MALPVTALLLPLALLLHAARPEVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQ MPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSEVVLTQSPATLSLSPGERATLSCR ASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFA VYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-18 scFv	2201	MALPVTALLLPLALLLHAARPEVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQ MPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSEVVLTQSPATLSLSPGERATLSCR ASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFA VYYCQQHNKYPYTFGGGTKVEIK

hzCAR12 3-18 VH	2260	EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQMPGKGLEWMGRIDPYDSETHYN QKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-18 VL	2319	EVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-19 NT	2084	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCGAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTCAAGAAGCCTGGAGAATCCCTGAGGAT CAGCTGCAAAGGCAGCGGGTATACCTTCACCTCCTACTGGATGAATTGGGTCCGCCAGATG CCCGGAAAAGGCCTGGAGTGGATGGGACGGATTGACCCCTACGACTCGGAAACCCATTACA ACCAGAAGTTCAAGGATCACGTGACCATCTCCGTGGACAAGTCCATTTCCACTGCGTACCT CCAGTGGTCAAGCCTGAAGGCCTCCGACACTGCTATGTACTACTGCGCACGCGGAAACTGG GATGATTACTGGGGACAGGGAACAACCGTGACTGTGTCCTCCGGGGGTGGCGGTAGCGGAG GAGGGGGCTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGACGTCGTGATGACCCAGTC ACCGGCATTCCTGTCCGTGACTCCCGGAGAAAAGGTCACGATTACTTGCCGGGCGTCCAAG AGCATCTCCAAGGACCTCGCCTGGTACCAACAGAAGCCGGACCAGGCCCCTAAGCTGTTGA TCTACTCGGGGTCCACCCTTCAATCGGGAGTGCCATCGCGGTTTAGCGGTTCGGGTTCTGG GACCGACTTCACTTTCACCATCTCCTCACTGGAAGCCGAGGATGCCGCCACTTACTACTGT CAGCAGCACAACAAGTATCCGTACACCTTCGGAGGCGGTACCAAAGTGGAGATCAAGACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-19 AA	2143	MALPVTALLLPLALLLHAARPEVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQ MPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPAFLSVTPGEKVTITCR ASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAA TYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-19 scFv	2202	MALPVTALLLPLALLLHAARPEVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQ MPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPAFLSVTPGEKVTITCR ASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAA TYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-19 VH	2261	EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQMPGKGLEWMGRIDPYDSETHYN QKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-19 VL	2320	DVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSR FSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFGGGTKVEIK

hzCAR12 3-20 NT	2085	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCGAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTCAAGAAGCCTGGAGAATCCCTGAGGAT CAGCTGCAAAGGCAGCGGGTATACCTTCACCTCCTACTGGATGAATTGGGTCCGCCAGATG CCCGGAAAAGGCCTGGAGTGGATGGGACGGATTGACCCCTACGACTCGGAAACCCATTACA ACCAGAAGTTCAAGGATCACGTGACCATCTCCGTGGACAAGTCCATTTCCACTGCGTACCT CCAGTGGTCAAGCCTGAAGGCCTCCGACACTGCTATGTACTACTGCGCACGCGGAAACTGG GATGATTACTGGGGACAGGGAACAACCGTGACTGTGTCCTCCGGGGGTGGCGGTAGCGGAG GAGGGGGCTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGACGTGGTCATGACTCAGTC CCCGGACTCACTCGCGGTGTCGCTTGGAGAGAGAGCGACCATCAACTGTCGGGCCTCAAAG AGCATCAGCAAGGACCTGGCCTGGTACCAGCAGAAGCCGGGACAGCCGCCAAAGCTGCTGA TCTACTCCGGGTCCACCTTGCAATCTGGTGTCCCTGACCGGTTCTCCGGTTCCGGGTCGGG TACCGACTTCACGCTCACTATTTCGTCGCTGCAAGCCGAAGATGTGGCCGTGTACTATTGC CAACAGCACAACAAGTACCCCTACACTTTTGGCGGAGGCACCAAGGTGGAAATCAAGACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-20 AA	2144	MALPVTALLLPLALLLHAARPEVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQ MPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPDSLAVSLGERATINCR ASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVA VYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-20 scFv	2203	MALPVTALLLPLALLLHAARPEVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQ MPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPDSLAVSLGERATINCR ASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVA VYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-20 VH	2262	EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQMPGKGLEWMGRIDPYDSETHYN QKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-20 VL	2321	DVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDR FSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-21 NT	2086	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCGACGTGCAGCTCACCCAGTCGCCCTCATTTCTGTCGGCCTCAGTGGGAGACAGAGTGAC CATTACTTGTCGGGCCTCCAAGAGCATCTCCAAGGACCTGGCCTGGTATCAGCAGAAGCCA GGAAAGGCGCCTAAGTTGCTCATCTACTCGGGGTCGACCCTGCAATCTGGCGTGCCGTCCC GGTTCTCCGGTTCGGGAAGCGGTACCGAATTCACCCTTACTATCTCCTCCCTGCAACCGGA GGACTTCGCCACCTACTACTGCCAACAGCACAACAAGTACCCGTACACTTTCGGGGGTGGC

		ACGAAGGTCGAAATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCT CAGGGGGCGGAGGAAGCGAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTCAAGAAGCCTGG AGAATCCCTGAGGATCAGCTGCAAAGGCAGCGGGTATACCTTCACCTCCTACTGGATGAAT TGGGTCCGCCAGATGCCCGGAAAAGGCCTGGAGTGGATGGGACGGATTGACCCCTACGACT CGGAAACCCATTACAACCAGAAGTTCAAGGATCACGTGACCATCTCCGTGGACAAGTCCAT TTCCACTGCGTACCTCCAGTGGTCAAGCCTGAAGGCCTCCGACACTGCTATGTACTACTGC GCACGCGGAAACTGGGATGATTACTGGGGACAGGGAACAACCGTGACTGTGTCCTCCACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-21 AA	2145	MALPVTALLLPLALLLHAARPDVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQK PGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVQSGAEVKKPGESLRISCKGSGYTFTSY WMNWVRQMPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTA MYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-21 scFv	2204	MALPVTALLLPLALLLHAARPDVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQK PGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVQSGAEVKKPGESLRISCKGSGYTFTSY WMNWVRQMPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTA MYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-21 VH	2263	EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQMPGKGLEWMGRIDPYDSETHYN QKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-21 VL	2322	DVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSR FSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-22 NT	2087	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCGAAGTGGTGCTGACCCAGTCGCCCGCAACCCTCTCTCTGTCGCCGGGAGAACGCGCCAC TCTTTCCTGTCGGGCGTCCAAGAGCATCTCAAAGGACCTCGCCTGGTACCAGCAGAAGCCT GGTCAAGCCCCGCGGCTGCTGATCTACTCCGGCTCCACGCTGCAATCAGGAATCCCAGCCA GATTTTCCGGTTCGGGGTCGGGGACTGACTTCACCTTGACCATTAGCTCGCTGGAACCTGA GGACTTCGCCGTGTATTACTGCCAGCAGCACAACAAGTACCCGTACACCTTCGGAGGCGGT ACTAAGGTCGAGATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCT CAGGGGGCGGAGGAAGCGAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTCAAGAAGCCTGG AGAATCCCTGAGGATCAGCTGCAAAGGCAGCGGGTATACCTTCACCTCCTACTGGATGAAT TGGGTCCGCCAGATGCCCGGAAAAGGCCTGGAGTGGATGGGACGGATTGACCCCTACGACT CGGAAACCCATTACAACCAGAAGTTCAAGGATCACGTGACCATCTCCGTGGACAAGTCCAT TTCCACTGCGTACCTCCAGTGGTCAAGCCTGAAGGCCTCCGACACTGCTATGTACTACTGC

		GCACGCGGAAACTGGGATGATTACTGGGGACAGGGAACAACCGTGACTGTGTCCTCCACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-22 AA	2146	MALPVTALLLPLALLLHAARPEVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQK PGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVQSGAEVKKPGESLRISCKGSGYTFTSY WMNWVRQMPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTA MYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-22 scFv	2205	MALPVTALLLPLALLLHAARPEVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQK PGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVQSGAEVKKPGESLRISCKGSGYTFTSY WMNWVRQMPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTA MYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-22 VH	2264	EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQMPGKGLEWMGRIDPYDSETHYN QKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-22 VL	2323	EVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-23 NT	2088	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCGACGTCGTGATGACCCAGTCACCGGCATTCCTGTCCGTGACTCCCGGAGAAAAGGTCAC GATTACTTGCCGGGCGTCCAAGAGCATCTCCAAGGACCTCGCCTGGTACCAACAGAAGCCG GACCAGGCCCCTAAGCTGTTGATCTACTCGGGGTCCACCCTTCAATCGGGAGTGCCATCGC GGTTTAGCGGTTCGGGTTCTGGGACCGACTTCACTTTCACCATCTCCTCACTGGAAGCCGA GGATGCCGCCACTTACTACTGTCAGCAGCACAACAAGTATCCGTACACCTTCGGAGGCGGT ACCAAAGTGGAGATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCT CAGGGGGCGGAGGAAGCGAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTCAAGAAGCCTGG AGAATCCCTGAGGATCAGCTGCAAAGGCAGCGGGTATACCTTCACCTCCTACTGGATGAAT TGGGTCCGCCAGATGCCCGGAAAAGGCCTGGAGTGGATGGGACGGATTGACCCCTACGACT CGGAAACCCATTACAACCAGAAGTTCAAGGATCACGTGACCATCTCCGTGGACAAGTCCAT TTCCACTGCGTACCTCCAGTGGTCAAGCCTGAAGGCCTCCGACACTGCTATGTACTACTGC GCACGCGGAAACTGGGATGATTACTGGGGACAGGGAACAACCGTGACTGTGTCCTCCACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag

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hzCAR12 3-23 AA	2147	MALPVTALLLPLALLLHAARPDVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQK PDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVQSGAEVKKPGESLRISCKGSGYTFTSY WMNWVRQMPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTA MYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-23 scFv	2206	MALPVTALLLPLALLLHAARPDVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQK PDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVQSGAEVKKPGESLRISCKGSGYTFTSY WMNWVRQMPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTA MYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-23 VH	2265	EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQMPGKGLEWMGRIDPYDSETHYN QKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-23 VL	2324	DVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSR FSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-24 NT	2089	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCGACGTGGTCATGACTCAGTCCCCGGACTCACTCGCGGTGTCGCTTGGAGAGAGAGCGAC CATCAACTGTCGGGCCTCAAAGAGCATCAGCAAGGACCTGGCCTGGTACCAGCAGAAGCCG GGACAGCCGCCAAAGCTGCTGATCTACTCCGGGTCCACCTTGCAATCTGGTGTCCCTGACC GGTTCTCCGGTTCCGGGTCGGGTACCGACTTCACGCTCACTATTTCGTCGCTGCAAGCCGA AGATGTGGCCGTGTACTATTGCCAACAGCACAACAAGTACCCCTACACTTTTGGCGGAGGC ACCAAGGTGGAAATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCT CAGGGGGCGGAGGAAGCGAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTCAAGAAGCCTGG AGAATCCCTGAGGATCAGCTGCAAAGGCAGCGGGTATACCTTCACCTCCTACTGGATGAAT TGGGTCCGCCAGATGCCCGGAAAAGGCCTGGAGTGGATGGGACGGATTGACCCCTACGACT CGGAAACCCATTACAACCAGAAGTTCAAGGATCACGTGACCATCTCCGTGGACAAGTCCAT TTCCACTGCGTACCTCCAGTGGTCAAGCCTGAAGGCCTCCGACACTGCTATGTACTACTGC GCACGCGGAAACTGGGATGATTACTGGGGACAGGGAACAACCGTGACTGTGTCCTCCACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg

hzCAR12 3-24 AA	2148	MALPVTALLLPLALLLHAARPDVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQK PGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVQSGAEVKKPGESLRISCKGSGYTFTSY WMNWVRQMPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTA MYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-24 scFv	2207	MALPVTALLLPLALLLHAARPDVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQK PGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVQSGAEVKKPGESLRISCKGSGYTFTSY WMNWVRQMPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTA MYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-24 VH	2266	EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQMPGKGLEWMGRIDPYDSETHYN QKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-24 VL	2325	DVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDR FSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-25 NT	2090	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCGAAGTGCAGCTCGTCGAGAGCGGAGGGGGACTGGTGCAGCCCGGAGGAAGCCTGAGGCT GTCCTGCGCTGCCTCCGGCTACACCTTCACCTCCTACTGGATGAACTGGGTCAGACAGGCA CCTGGAAAGGGACTGGTCTGGGTGTCGCGCATTGACCCCTACGACTCCGAAACCCATTACA ATCAGAAATTCAAGGACCGCTTCACCATCTCCGTGGACAAAGCCAAGAGCACCGCGTACCT CCAAATGAACTCCCTGCGCGCTGAGGATACAGCAGTGTACTATTGCGCCCGGGGAAACTGG GATGATTACTGGGGCCAGGGAACTACTGTGACTGTGTCATCCGGGGGTGGCGGTAGCGGAG GAGGGGGCTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGACGTGCAGCTCACCCAGTC GCCCTCATTTCTGTCGGCCTCAGTGGGAGACAGAGTGACCATTACTTGTCGGGCCTCCAAG AGCATCTCCAAGGACCTGGCCTGGTATCAGCAGAAGCCAGGAAAGGCGCCTAAGTTGCTCA TCTACTCGGGGTCGACCCTGCAATCTGGCGTGCCGTCCCGGTTCTCCGGTTCGGGAAGCGG TACCGAATTCACCCTTACTATCTCCTCCCTGCAACCGGAGGACTTCGCCACCTACTACTGC CAACAGCACAACAAGTACCCGTACACTTTCGGGGGTGGCACGAAGGTCGAAATCAAGACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-25 AA	2149	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQ APGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVQLTQSPSFLSASVGDRVTITCR ASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFA TYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC

		SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-25 scFv	2208	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQ APGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVQLTQSPSFLSASVGDRVTITCR ASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFA TYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-25 VH	2267	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQAPGKGLVWVSRIDPYDSETHYN QKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-25 VL	2326	DVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSR FSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-26 NT	2091	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCGAAGTGCAGCTCGTCGAGAGCGGAGGGGGACTGGTGCAGCCCGGAGGAAGCCTGAGGCT GTCCTGCGCTGCCTCCGGCTACACCTTCACCTCCTACTGGATGAACTGGGTCAGACAGGCA CCTGGAAAGGGACTGGTCTGGGTGTCGCGCATTGACCCCTACGACTCCGAAACCCATTACA ATCAGAAATTCAAGGACCGCTTCACCATCTCCGTGGACAAAGCCAAGAGCACCGCGTACCT CCAAATGAACTCCCTGCGCGCTGAGGATACAGCAGTGTACTATTGCGCCCGGGGAAACTGG GATGATTACTGGGGCCAGGGAACTACTGTGACTGTGTCATCCGGGGGTGGCGGTAGCGGAG GAGGGGGCTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGAAGTGGTGCTGACCCAGTC GCCCGCAACCCTCTCTCTGTCGCCGGGAGAACGCGCCACTCTTTCCTGTCGGGCGTCCAAG AGCATCTCAAAGGACCTCGCCTGGTACCAGCAGAAGCCTGGTCAAGCCCCGCGGCTGCTGA TCTACTCCGGCTCCACGCTGCAATCAGGAATCCCAGCCAGATTTTCCGGTTCGGGGTCGGG GACTGACTTCACCTTGACCATTAGCTCGCTGGAACCTGAGGACTTCGCCGTGTATTACTGC CAGCAGCACAACAAGTACCCGTACACCTTCGGAGGCGGTACTAAGGTCGAGATCAAGACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-26 AA	2150	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQ APGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSEVVLTQSPATLSLSPGERATLSCR ASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFA VYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-26	2209	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQ APGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSEVVLTQSPATLSLSPGERATLSCR

scFv		ASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFA VYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-26 VH	2268	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQAPGKGLVWVSRIDPYDSETHYN QKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-26 VL	2327	EVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-27 NT	2092	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCGAAGTGCAGCTCGTCGAGAGCGGAGGGGGACTGGTGCAGCCCGGAGGAAGCCTGAGGCT GTCCTGCGCTGCCTCCGGCTACACCTTCACCTCCTACTGGATGAACTGGGTCAGACAGGCA CCTGGAAAGGGACTGGTCTGGGTGTCGCGCATTGACCCCTACGACTCCGAAACCCATTACA ATCAGAAATTCAAGGACCGCTTCACCATCTCCGTGGACAAAGCCAAGAGCACCGCGTACCT CCAAATGAACTCCCTGCGCGCTGAGGATACAGCAGTGTACTATTGCGCCCGGGGAAACTGG GATGATTACTGGGGCCAGGGAACTACTGTGACTGTGTCATCCGGGGGTGGCGGTAGCGGAG GAGGGGGCTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGACGTCGTGATGACCCAGTC ACCGGCATTCCTGTCCGTGACTCCCGGAGAAAAGGTCACGATTACTTGCCGGGCGTCCAAG AGCATCTCCAAGGACCTCGCCTGGTACCAACAGAAGCCGGACCAGGCCCCTAAGCTGTTGA TCTACTCGGGGTCCACCCTTCAATCGGGAGTGCCATCGCGGTTTAGCGGTTCGGGTTCTGG GACCGACTTCACTTTCACCATCTCCTCACTGGAAGCCGAGGATGCCGCCACTTACTACTGT CAGCAGCACAACAAGTATCCGTACACCTTCGGAGGCGGTACCAAAGTGGAGATCAAGACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-27 AA	2151	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQ APGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPAFLSVTPGEKVTITCR ASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAA TYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-27 scFv	2210	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQ APGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPAFLSVTPGEKVTITCR ASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAA TYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-27 VH	2269	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQAPGKGLVWVSRIDPYDSETHYN QKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARGNWDDYWGQGTTVTVSS

hzCAR12 3-27 VL	2328	DVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSR FSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-28 NT	2093	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCGAAGTGCAGCTCGTCGAGAGCGGAGGGGGACTGGTGCAGCCCGGAGGAAGCCTGAGGCT GTCCTGCGCTGCCTCCGGCTACACCTTCACCTCCTACTGGATGAACTGGGTCAGACAGGCA CCTGGAAAGGGACTGGTCTGGGTGTCGCGCATTGACCCCTACGACTCCGAAACCCATTACA ATCAGAAATTCAAGGACCGCTTCACCATCTCCGTGGACAAAGCCAAGAGCACCGCGTACCT CCAAATGAACTCCCTGCGCGCTGAGGATACAGCAGTGTACTATTGCGCCCGGGGAAACTGG GATGATTACTGGGGCCAGGGAACTACTGTGACTGTGTCATCCGGGGGTGGCGGTAGCGGAG GAGGGGGCTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGACGTGGTCATGACTCAGTC CCCGGACTCACTCGCGGTGTCGCTTGGAGAGAGAGCGACCATCAACTGTCGGGCCTCAAAG AGCATCAGCAAGGACCTGGCCTGGTACCAGCAGAAGCCGGGACAGCCGCCAAAGCTGCTGA TCTACTCCGGGTCCACCTTGCAATCTGGTGTCCCTGACCGGTTCTCCGGTTCCGGGTCGGG TACCGACTTCACGCTCACTATTTCGTCGCTGCAAGCCGAAGATGTGGCCGTGTACTATTGC CAACAGCACAACAAGTACCCCTACACTTTTGGCGGAGGCACCAAGGTGGAAATCAAGACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-28 AA	2152	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQ APGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPDSLAVSLGERATINCR ASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVA VYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-28 scFv	2211	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQ APGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPDSLAVSLGERATINCR ASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVA VYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-28 VH	2270	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQAPGKGLVWVSRIDPYDSETHYN QKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-28 VL	2329	DVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDR FSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-29 NT	2094	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCGACGTGCAGCTCACCCAGTCGCCCTCATTTCTGTCGGCCTCAGTGGGAGACAGAGTGAC CATTACTTGTCGGGCCTCCAAGAGCATCTCCAAGGACCTGGCCTGGTATCAGCAGAAGCCA

		GGAAAGGCGCCTAAGTTGCTCATCTACTCGGGGTCGACCCTGCAATCTGGCGTGCCGTCCC GGTTCTCCGGTTCGGGAAGCGGTACCGAATTCACCCTTACTATCTCCTCCCTGCAACCGGA GGACTTCGCCACCTACTACTGCCAACAGCACAACAAGTACCCGTACACTTTCGGGGGTGGC ACGAAGGTCGAAATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCT CAGGGGGCGGAGGAAGCGAAGTGCAGCTCGTCGAGAGCGGAGGGGGACTGGTGCAGCCCGG AGGAAGCCTGAGGCTGTCCTGCGCTGCCTCCGGCTACACCTTCACCTCCTACTGGATGAAC TGGGTCAGACAGGCACCTGGAAAGGGACTGGTCTGGGTGTCGCGCATTGACCCCTACGACT CCGAAACCCATTACAATCAGAAATTCAAGGACCGCTTCACCATCTCCGTGGACAAAGCCAA GAGCACCGCGTACCTCCAAATGAACTCCCTGCGCGCTGAGGATACAGCAGTGTACTATTGC GCCCGGGGAAACTGGGATGATTACTGGGGCCAGGGAACTACTGTGACTGTGTCATCCACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-29 AA	2153	MALPVTALLLPLALLLHAARPDVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQK PGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGYTFTSY WMNWVRQAPGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTA VYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-29 scFv	2212	MALPVTALLLPLALLLHAARPDVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQK PGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGYTFTSY WMNWVRQAPGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-29 VH	2271	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQAPGKGLVWVSRIDPYDSETHYN QKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-29 VL	2330	DVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSR FSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-30 NT	2095	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCGAAGTGGTGCTGACCCAGTCGCCCGCAACCCTCTCTCTGTCGCCGGGAGAACGCGCCAC TCTTTCCTGTCGGGCGTCCAAGAGCATCTCAAAGGACCTCGCCTGGTACCAGCAGAAGCCT GGTCAAGCCCCGCGGCTGCTGATCTACTCCGGCTCCACGCTGCAATCAGGAATCCCAGCCA GATTTTCCGGTTCGGGGTCGGGGACTGACTTCACCTTGACCATTAGCTCGCTGGAACCTGA GGACTTCGCCGTGTATTACTGCCAGCAGCACAACAAGTACCCGTACACCTTCGGAGGCGGT ACTAAGGTCGAGATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCT CAGGGGGCGGAGGAAGCGAAGTGCAGCTCGTCGAGAGCGGAGGGGGACTGGTGCAGCCCGG AGGAAGCCTGAGGCTGTCCTGCGCTGCCTCCGGCTACACCTTCACCTCCTACTGGATGAAC

		TGGGTCAGACAGGCACCTGGAAAGGGACTGGTCTGGGTGTCGCGCATTGACCCCTACGACT CCGAAACCCATTACAATCAGAAATTCAAGGACCGCTTCACCATCTCCGTGGACAAAGCCAA GAGCACCGCGTACCTCCAAATGAACTCCCTGCGCGCTGAGGATACAGCAGTGTACTATTGC GCCCGGGGAAACTGGGATGATTACTGGGGCCAGGGAACTACTGTGACTGTGTCATCCACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaaccc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-30 AA	2154	MALPVTALLLPLALLLHAARPEVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQK PGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGYTFTSY WMNWVRQAPGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTA VYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-30 scFv	2213	MALPVTALLLPLALLLHAARPEVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQK PGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGYTFTSY WMNWVRQAPGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-30 VH	2272	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQAPGKGLVWVSRIDPYDSETHYN QKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-30 VL	2331	EVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPAR FSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-31 NT	2096	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCGACGTCGTGATGACCCAGTCACCGGCATTCCTGTCCGTGACTCCCGGAGAAAAGGTCAC GATTACTTGCCGGGCGTCCAAGAGCATCTCCAAGGACCTCGCCTGGTACCAACAGAAGCCG GACCAGGCCCCTAAGCTGTTGATCTACTCGGGGTCCACCCTTCAATCGGGAGTGCCATCGC GGTTTAGCGGTTCGGGTTCTGGGACCGACTTCACTTTCACCATCTCCTCACTGGAAGCCGA GGATGCCGCCACTTACTACTGTCAGCAGCACAACAAGTATCCGTACACCTTCGGAGGCGGT ACCAAAGTGGAGATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCT CAGGGGGCGGAGGAAGCGAAGTGCAGCTCGTCGAGAGCGGAGGGGGACTGGTGCAGCCCGG AGGAAGCCTGAGGCTGTCCTGCGCTGCCTCCGGCTACACCTTCACCTCCTACTGGATGAAC TGGGTCAGACAGGCACCTGGAAAGGGACTGGTCTGGGTGTCGCGCATTGACCCCTACGACT CCGAAACCCATTACAATCAGAAATTCAAGGACCGCTTCACCATCTCCGTGGACAAAGCCAA GAGCACCGCGTACCTCCAAATGAACTCCCTGCGCGCTGAGGATACAGCAGTGTACTATTGC GCCCGGGGAAACTGGGATGATTACTGGGGCCAGGGAACTACTGTGACTGTGTCATCCACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc

		gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-31 AA	2155	MALPVTALLLPLALLLHAARPDVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQK PDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGYTFTSY WMNWVRQAPGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTA VYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-31 scFv	2214	MALPVTALLLPLALLLHAARPDVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQK PDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGYTFTSY WMNWVRQAPGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-31 VH	2273	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQAPGKGLVWVSRIDPYDSETHYN QKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-31 VL	2332	DVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSR FSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFGGGTKVEIK
hzCAR12 3-32 NT	2097	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGC CCGACGTGGTCATGACTCAGTCCCCGGACTCACTCGCGGTGTCGCTTGGAGAGAGAGCGAC CATCAACTGTCGGGCCTCAAAGAGCATCAGCAAGGACCTGGCCTGGTACCAGCAGAAGCCG GGACAGCCGCCAAAGCTGCTGATCTACTCCGGGTCCACCTTGCAATCTGGTGTCCCTGACC GGTTCTCCGGTTCCGGGTCGGGTACCGACTTCACGCTCACTATTTCGTCGCTGCAAGCCGA AGATGTGGCCGTGTACTATTGCCAACAGCACAACAAGTACCCCTACACTTTTGGCGGAGGC ACCAAGGTGGAAATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCT CAGGGGGCGGAGGAAGCGAAGTGCAGCTCGTCGAGAGCGGAGGGGGACTGGTGCAGCCCGG AGGAAGCCTGAGGCTGTCCTGCGCTGCCTCCGGCTACACCTTCACCTCCTACTGGATGAACC TGGGTCAGACAGGCACCTGGAAAGGGACTGGTCTGGGTGTCGCGCATTGACCCCTACGACT CCGAAACCCATTACAATCAGAAATTCAAGGACCGCTTCACCATCTCCGTGGACAAAGCCAA GAGCACCGCGTACCTCCAAATGAACTCCCTGCGCGCTGAGGATACAGCAGTGTACTATTGC GCCCGGGGAAACTGGGATGATTACTGGGGCCAGGGAACTACTGTGACTGTGTCATCCACCA CTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCT GCGTCCGGAggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttc gcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacga cgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaat

		ccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgaga ttggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcag caccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
hzCAR12 3-32 AA	2156	MALPVTALLLPLALLLHAARPDVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQK PGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGYTFTSY WMNWVRQAPGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTA VYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR12 3-32 scFv	2215	MALPVTALLLPLALLLHAARPDVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQK PGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGYTFTSY WMNWVRQAPGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-32 VH	2274	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQAPGKGLVWVSRIDPYDSETHYN QKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR12 3-32 VL	2333	DVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDR FSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFGGGTKVEIK

In embodiments, a CAR molecule described herein comprises a scFv that specifically binds to CD123, and does not contain a leader sequence, e.g., the amino acid sequence SEQ ID NO: 2. Table 28 below provides amino acid and nucleotide sequences for CD123 scFv sequences that do not contain a leader sequence SEQ ID NO: 2.

Table 28. CD123 CAR scFv sequences

Name	SEQ ID NO:	Sequence
CAR123-2 scFv - NT	2479	CAAGTGCAACTCGTCCAAAGCGGAGCGGAAGTCAAGAAACCCGGAGCGAGCGTGAAAGTG TCCTGCAAAGCCTCCGGCTACACCTTTACGGGCTACTACATGCACTGGGTGCGCCAGGCA CCAGGACAGGGTCTTGAATGGATGGGATGGATCAACCCTAATTCGGGCGGAACTAACTAC GCACAGAAGTTCCAGGGGAGAGTGACTCTGACTCGGGATACCTCCATCTCAACTGTCTAC ATGGAACTCTCCCGCTTGCGGTCAGATGATACGGCAGTGTACTACTGCGCCCGCGACATG AATATCCTGGCTACCGTGCCGTTCGACATCTGGGGACAGGGGACTATGGTTACTGTCTCA TCGGGCGGTGGAGGTTCAGGAGGAGGCGGCTCGGGAGGCGGAGGTTCGGACATTCAGATG ACCCAGTCCCCATCCTCTCTGTCGGCCAGCGTCGGAGATAGGGTGACCATTACCTGTCGG GCCTCGCAAAGCATCTCCTCGTACCTCAACTGGTATCAGCAAAAGCCGGGAAAGGCGCCT AAGCTGCTGATCTACGCCGCTTCGAGCTTGCAAAGCGGGGTGCCATCCAGATTCTCGGGA TCAGGCTCAGGAACCGACTTCACCCTGACCGTGAACAGCCTCCAGCCGGAGGACTTTGCC ACTTACTACTGCCAGCAGGGAGACTCCGTGCCGCTTACTTTCGGGGGGGGTACCCGCCTG GAGATCAAG

CAR123-2 scFv - AA	2480	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPNSGGTNY AQKFQGRVTLTRDTSISTVYMELSRLRSDDTAVYYCARDMNILATVPFDIWGQGTMVTVS SGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAP KLLIYAASSLQSGVPSRFSGSGSGTDFTLTVNSLQPEDFATYYCQQGDSVPLTFGGGTRL EIK
CAR123-2 ORF-free NT	2481	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggccccaagtgcaactcgtccaaagcg gagcggaagtcaagaaacccggagcgagcgtgaaagtgtcctgcaaagcctccggctacacctttacgggctactacatgcact gggtgcgccaggcaccaggacagggtcttgaatggatgggatggatcaaccctaattcgggcggaactaactacgcacagaag ttccaggggagagtgactctgactcgggatacctccatctcaactgtctacatggaactctcccgcttgcggtcagatgatacggc agtgtactactgcgcccgcgacatgaatatcctggctaccgtgccgttcgacatctggggacaggggactatggttactgtctcat cgggcggtggaggttcaggaggaggcggctcgggaggcggaggttcggacattcagatgacccagtccccatcctctctgtcg gccagcgtcggagatagggtgaccattacctgtcgggcctcgcaaagcatctcctcgtacctcaactggtatcagcaaaagccg ggaaaggcgcctaagctgctgatctacgccgcttcgagcttgcaaagcggggtgccatccagattctcgggatcaggctcagga accgacttcaccctgaccgtgaacagcctccagccggaggactttgccacttactactgccagcagggagactccgtgccgctta ctttcgggggggtacccgcctggagatcaagaccactaccccagcaccgaggccacccaccccggctcctaccatcgcctcc cagcctctgtccctgcgtccggaggcatgtagacccgcagctggtggggccgtgcataccggggtcttgacttcgcctgcgat atctacatttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactctttactgtaagcgcggtcggaaga agctgctgtacatctttaagcaacccttcatgaggcctgtgcagactactcaagaggaggacggctgttcttgccggttcccagag gaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagacgctccagcctacaagcaggggcagaaccca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagaggacgggacccagaaatgggc gggaagccgcgcagaaagaatccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgag attggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacc tatgacgctcttcacatgcaggccctgccgcctcggtaagtcgacagctcgctttcttgctgtccaatttctattaaaggttcctttgttc cctaagtccaactactaaactgggggatattatgaagggccttgagcatctggattctgcctaataaaaaacatttattttcattgctgc gtcgagagctcgctttcttgctgtccaatttctattaaaggttcctttgttccctaagtccaactactaaactgggggatattatgaagg gccttgagcatctggattctgcctaataaaaaacatttattttcattgctgcctcgacgaattc
CAR123-3 scFv - NT	2482	CAAGTCCAACTCGTTCAATCCGGCGCAGAAGTCAAGAAGCCAGGAGCATCAGTGAAAGTG TCCTGCAAAGCCTCAGGCTACATCTTCACGGGATACTACATCCACTGGGTGCGCCAGGCT CCGGGCCAGGGCCTTGAGTGGATGGGCTGGATCAACCCTAACTCTGGGGGAACCAACTAC GCTCAGAAGTTCCAGGGGAGGGTCACTATGACTCGCGATACCTCCATCTCCACTGCGTAC ATGGAACTCTCGGGACTGAGATCCGACGATCCTGCCGTGTACTACTGCGCCCGGGACATG AACATCTTGGCGACCGTGCCGTTTGACATTTGGGGACAGGGCACCCTCGTCACTGTGTCG AGCGGTGGAGGAGGCTCGGGGGGTGGCGGATCAGGAGGGGGAGGAAGCGACATCCAGCTG ACTCAGAGCCCATCGTCGTTGTCCGCGTCGGTGGGGGATAGAGTGACCATTACTTGCCGC GCCAGCCAGAGCATCTCATCATATCTGAATTGGTACCAGCAGAAGCCCGGAAAGGCCCCA AAACTGCTGATCTACGCTGCAAGCAGCCTCCAATCGGGAGTGCCGTCACGGTTCTCCGGG TCCGGTTCGGGAACTGACTTTACCCTGACCGTGAATTCGCTGCAACCGGAGGATTTCGCC ACGTACTACTGTCAGCAAGGAGACTCCGTGCCGCTGACCTTCGGTGGAGGCACCAAGGTC GAAATCAAG
CAR123-3 scFv - AA	2483	QVQLVQSGAEVKKPGASVKVSCKASGYIFTGYYIHWVRQAPGQGLEWMGWINPNSGGTNY AQKFQGRVTMTRDTSISTAYMELSGLRSDDPAVYYCARDMNILATVPFDIWGQGTLVTVS SGGGGSGGGGSGGGGSDIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAP KLLIYAASSLQSGVPSRFSGSGSGTDFTLTVNSLQPEDFATYYCQQGDSVPLTFGGGTKV EIK
CAR123-4 scFv - NT	2484	CAAGTCCAACTCCAACAGTCAGGCGCAGAAGTGAAAAAGAGCGGTGCATCGGTGAAAGTG TCATGCAAAGCCTCGGGCTACACCTTCACTGACTACTATATGCACTGGCTGCGGCAGGCA CCGGGACAGGGACTTGAGTGGATGGGATGGATCAACCCGAATTCAGGGGACACTAACTAC GCGCAGAAGTTCCAGGGGAGAGTGACCCTGACGAGGGACACCTCAATTTCGACCGTCTAC ATGGAATTGTCGCGCCTGAGATCGGACGATACTGCTGTGTACTACTGTGCCCGCGACATG

		AACATCCTCGCGACTGTGCCTTTTGATATCTGGGGACAGGGGACTATGGTCACCGTTTCC TCCGCTTCCGGTGGCGGAGGCTCGGGAGGCCGGGCCTCCGGTGGAGGAGGCAGCGACATC CAGATGACTCAGAGCCCTTCCTCGCTGAGCGCCTCAGTGGGAGATCGCGTGACCATCACT TGCCGGGCCAGCCAGTCCATTTCGTCCTACCTCAATTGGTACCAGCAGAAGCCGGGAAAG GCGCCCAAGCTCTTGATCTACGCTGCGAGCTCCCTGCAAAGCGGGGTGCCGAGCCGATTC TCGGGTTCCGGCTCGGGAACCGACTTCACTCTGACCATCTCATCCCTGCAACCAGAGGAC TTTGCCACCTACTACTGCCAACAAGGAGATTCTGTCCCACTGACGTTCGGCGGAGGAACC AAGGTCGAAATCAAG
CAR123-4 scFv - AA	2485	QVQLQQSGAEVKKSGASVKVSCKASGYTFTDYYMHWLRQAPGQGLEWMGWINPNSGDTNY AQKFQGRVTLTRDTSISTVYMELSRLRSDDTAVYYCARDMNILATVPFDIWGQGTMVTVS SASGGGGSGGRASGGGGSDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGK APKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGDSVPLTFGGGT KVEIK
CAR123-1 scFv - AA	2478	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPNSGGTNY AQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCARDMNILATVPFDIWGQGTMVTVS SGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQSISTYLNWYQQKPGKAP NLLIYAAFSLQSGVPSRFSGSGSGTDFTLTINSLQPEDFATYYCQQGDSVPLTFGGGTKL EIK
hzCAR123-1 scFv	2556	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHY NQKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARGNWDDYWGQGTTVTVSSGGGGS GGGGSGGGGSGGGGSDVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQKPGKAPK LLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFGGGTKVE IK
hzCAR123-2 scFv	2557	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSEVVLTQSPATLSLSPGERATLSCR ASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFA VYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-3 scFv	2558	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPAFLSVTPGEKVTITCR ASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAA TYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-4 scFv	2559	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPDSLAVSLGERATINCR ASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVA VYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-5 scFv	2560	DVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQK PGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR123-6 scFv	2561	EVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQK PGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR123-	2562	DVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQK

7 scFv		PDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR123-8 scFv	2563	DVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQK PGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR123-9 scFv	2564	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVQLTQSPSFLSASVGDRVTITCR ASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFA TYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-10 scFv	2565	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSEVVLTQSPATLSLSPGERATLSCR ASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFA VYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-11 scFv	2566	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPAFLSVTPGEKVTITCR ASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAA TYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-12 scFv	2567	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPDSLAVSLGERATINCR ASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVA VYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-13 scFv	2568	DVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQK PGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGSELKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR123-14 scFv	2569	EVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQK PGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGSELKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR123-15 scFv	2570	DVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQK PDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGSELKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR123-16 scFv	2571	DVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQK PGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGSELKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTA VYYCARGNWDDYWGQGTTVTVSS

hzCAR123-17 scFv	2572	EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQ MPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVQLTQSPSFLSASVGDRVTITCR ASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFA TYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-18 scFv	2573	EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQ MPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSEVVLTQSPATLSLSPGERATLSCR ASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFA VYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-19 scFv	2574	EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQ MPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPAFLSVTPGEKVTITCR ASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAA TYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-20 scFv	2575	EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQ MPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPDSLAVSLGERATINCR ASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVA VYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-21 scFv	2576	DVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQK PGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVQSGAEVKKPGESLRISCKGSGYTFTSY WMNWVRQMPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTA MYYCARGNWDDYWGQGTTVTVSS
hzCAR123-22 scFv	2577	EVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQK PGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVQSGAEVKKPGESLRISCKGSGYTFTSY WMNWVRQMPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTA MYYCARGNWDDYWGQGTTVTVSS
hzCAR123-23 scFv	2578	DVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQK PDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVQSGAEVKKPGESLRISCKGSGYTFTSY WMNWVRQMPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTA MYYCARGNWDDYWGQGTTVTVSS
hzCAR123-24 scFv	2579	DVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQK PGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVQSGAEVKKPGESLRISCKGSGYTFTSY WMNWVRQMPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTA MYYCARGNWDDYWGQGTTVTVSS
hzCAR123-25 scFv	2580	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQ APGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVQLTQSPSFLSASVGDRVTITCR ASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFA TYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-26 scFv	2581	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQ APGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSEVVLTQSPATLSLSPGERATLSCR ASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFA

		VYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-27 scFv	2582	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQ APGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPAFLSVTPGEKVTITCR ASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAA TYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-28 scFv	2583	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQ APGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPDSLAVSLGERATINCR ASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVA VYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-29 scFv	2584	DVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQK PGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGYTFTSY WMNWVRQAPGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR123-30 scFv	2585	EVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQK PGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGYTFTSY WMNWVRQAPGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR123-31 scFv	2586	DVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQK PDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGYTFTSY WMNWVRQAPGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR123-32 scFv	2587	DVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQK PGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGYTFTSY WMNWVRQAPGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTA VYYCARGNWDDYWGQGTTVTVSS

[00277] In one aspect, the antigen-binding domain of a CAR, e.g., the CAR expressed by a cell of the invention, binds to CD33, e.g., human CD33. Any known CD33 binding domain may be used in the invention. In one embodiment, an antigen binding domain against CD33 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 WO2016/014576, the contents of which are incorporated herein in their entirety. In one embodiment, an antigen binding domain against CD33 is an antigen binding portion of or derived from Gemtuzumab ozogamicin (e.g., comprising an antigen binding domain comprising one or more, e.g., one, two, or three, CDRs of the heavy chain variable domain and/or one or more, e.g., one, two, or three, CDRs of the light chain variable domain, or the VH or VL, or the scFv sequence, of the scFv sequence of Gemtuzumab ozogamicin) (previously marketed as Mylotarg), e.g., Bross et al., Clin Cancer

Res 7(6):1490-1496 (2001) (Gemtuzumab Ozogamicin, hP67.6). In one embodiment, an antigen binding domain against CD33 is an antigen binding portion of or derived from (e.g., comprising an antigen binding domain comprising one or more, e.g., one, two, or three, CDRs of the heavy chain variable domain and/or one or more, e.g., one, two, or three, CDRs of the light chain variable domain, or the VH or VL, or the scFv sequence) of the scFv sequence encoded by GenBank reference no. AM402974.1 (See, Wang et al., *Mol. Ther.*, vol. 23:1, pp. 184-191 (2015), hereby incorporated by reference. In one embodiment, an antigen binding domain against CD33 is an antigen binding portion, e.g., CDRs, of an antibody described in,, e.g., 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). In embodiments, the antigen binding domain is or is derived from a murine anti-human CD33 binding domain. In embodiments, the antigen binding domain is a humanized antibody or antibody fragment, e.g., scFv domain. In an embodiment, the antigen binding domain is a human antibody or antibody fragment that binds to human CD33. In embodiments, the antigen binding domain is an scFv domain which includes a light chain variable region (VL) and a heavy chain variable region (VH). The VL and VH may attached by a linker described herein, e.g., comprising the sequence GGGGSGGGGSGGGGS (SEQ ID NO: 30), and may be in any orientation, e.g., VL-linker-VH, or VH-linker-VL.

[00278] In one aspect, the antigen-binding domain of a CAR, e.g., the CAR expressed by a cell of the invention, binds to CLL-1, e.g., human CLL-1. Any known CLL-1 binding domain may be used in the invention. 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 embodiments, the antigen binding domain is or is derived from a murine anti-human CLL-1 binding domain. In embodiments, the antigen binding domain is a humanized antibody or antibody fragment, e.g., scFv domain. In an embodiment,

the antigen binding domain is a human antibody or antibody fragment that binds to human CLL-1. In embodiments, the antigen binding domain is an scFv domain which includes a light chain variable region (VL) and a heavy chain variable region (VH). The VL and VH may attached by a linker described herein, e.g., comprising the sequence GGGGSGGGGSGGGGS (SEQ ID NO: 30), and may be in any orientation, e.g., VL-linker-VH, or VH-linker-VL.

[00279] In one aspect, the antigen-binding domain of a CAR, e.g., the CAR expressed by a cell of the invention, binds to a B-cell antigen, e.g., a human B-cell antigen. Any known B-cell antigen binding domain may be used in the invention.

[00280] In an embodiment, the B cell antigen is an antigen that is preferentially or specifically expressed on the surface of the B cell. The antigen can be expressed on the surface of any one of the following types of B cells: progenitor B cells (e.g., pre-B cells or pro-B cells), early pro-B cells, late pro-B cells, large pre-B cells, small pre-B cells, immature B cells, e.g., naïve B cells, mature B cells, plama B cells, plasmablasts, memory B cells, B-1 cells, B-2 cells, marginal-zone B cells, follicular B cells, germinal center B cells, or regulatory B cells (Bregs).

[00281] The present disclosure provides CARs that can target the following B cell antigens: CD10, CD19, CD20, CD21, CD22, CD23, CD24, CD25, CD37, CD38, CD53, CD72, CD73, CD74, CD75, CD77, CD79a, CD79b, CD80, CD81, CD82, CD83, CD84, CD85, ROR1, BCMA, CD86, and CD179b. Other B cell antigens that can be targeted by a CAR described herein include: CD1a, CD1b, CD1c, CD1d, CD2, CD5, CD6, CD9, CD11a, CD11b, CD11c, CD17, CD18, CD26, CD27, CD29, CD30, CD31, CD32a, CD32b, CD35, CD38, CD39, CD40, CD44, CD45, CD45RA, CD45RB, CD45RC, CD45RO, CD46, CD47, CD48, CD49b, CD49c, CD49d, CD50, CD52, CD54, CD55, CD58, CD60a, CD62L, CD63, CD63, CD68 CD69, CD70, CD85E, CD85I, CD85J, CD92, CD95, CD97, CD98, CD99, CD100, CD102, CD108, CD119, CD120a, CD120b, CD121b, CD122, CD124, CD125, CD126, CD130, CD132, CD137, CD138, CD139, CD147, CD148, CD150, CD152, CD162, CD164, CD166, CD167a, CD170, CD175, CD175s, CD180, CD184, CD185, CD192, CD196, CD197, CD200, CD205, CD210a, CDw210b, CD212, CD213a1, CD213a2, CD215, CD217, CD218a, CD218b, CD220, CD221, CD224, CD225, CD226, CD227, CD229, CD230, CD232, CD252, CD253, CD257, CD258, CD261, CD262, CD263, CD264, CD267, CD268, CD269, CD270, CD272, CD274, CD275, CD277, CD279, CD283, CD289, CD290, CD295, CD298, CD300a, CD300c, CD305, CD306, CD307a, CD307b, CD307c, CD307d, CD307e, CD314, CD315, CD316, CD317,

CD319, CD321, CD327, CD328, CD329, CD338, CD351, CD352, CD353, CD354, CD355, CD357, CD358, CD360, CD361, CD362, and CD363.

[00282] In another embodiment, the B cell antigen targeted by the CAR is chosen from CD19, BCMA, CD20, CD22, FcRn5, FcRn2, CS-1 and CD138. In an embodiment, the B-Cell antigen targeted by the CAR is CD19. In an embodiment, the B-Cell antigen targeted by the CAR is CD20. In an embodiment, the B-Cell antigen targeted by the CAR is CD22. In an embodiment, the B-Cell antigen targeted by the CAR is BCMA. In an embodiment, the B-Cell antigen targeted by the CAR is FcRn5. In an embodiment, the B-Cell antigen targeted by the CAR is FcRn2. In an embodiment, the B-Cell antigen targeted by the CAR is CS-1. In an embodiment, the B-Cell antigen targeted by the CAR is CD138.

[00283] In one embodiment, the antigen-binding domain of a CAR, e.g., the CAR expressed by a cell of the invention, can be chosen such that a preferred B cell population is targeted. For example, in an embodiment where targeting of B regulatory cells is desired, an antigen binding domain is selected that targets a B cell antigen that is expressed on regulatory B cells and not on other B cell populations, e.g., plasma B cells and memory B cells. Cell surface markers expressed on regulatory B cells include: CD19, CD24, CD25, CD38, or CD86, or markers described in He et al., 2014, *J Immunology Research*, Article ID 215471. When targeting of more than one type of B cells is desired, an antigen binding domain that targets a B cell antigen that is expressed by all of the B cells to be targeted can be selected.

[00284] In an embodiment, the antigen-binding domain of a CAR, e.g., the CAR expressed by a cell of the invention, binds to CD19. CD19 is found on B cells throughout differentiation of the lineage from the pro/pre-B cell stage through the terminally differentiated plasma cell stage. In an embodiment, the antigen binding domain is a murine scFv domain that binds to human CD19, e.g., CTL019 (e.g., SEQ ID NO: 95). In an embodiment, the antigen binding domain is a humanized antibody or antibody fragment, e.g., scFv domain, derived from the murine CTL019 scFv. In an embodiment, the antigen binding domain is a human antibody or antibody fragment that binds to human CD19. Exemplary scFv domains (and their sequences, e.g., CDRs, VL and VH sequences) that bind to CD19 are provided in Table 6. The scFv domain sequences provided in Table 6 include a light chain variable region (VL) and a heavy chain variable region (VH). The VL and VH are attached by a linker comprising the sequence GGGGSGGGGSGGGGS (SEQ ID NO: 30), e.g., in the following orientation: VL-linker-VH.

Table 6. Antigen Binding domains that bind B cell antigen CD19

B cell antigen	Name	Amino Acid Sequence	SEQ ID NO:
CD19	muCTL019	DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDGTVKLLIY HTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPYTF GGGTKLEITGGGGSGGGGSGGGGSEVKLQESGPGLVAPSQSLSVTCTVS GVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTIIKDNS KSQVFLKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSS	95
CD19	huscFv1	EIVMTQSPATLSLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIY HTSRLHSGIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTF GQGTKLEIKGGGGSGGGGSGGGGSQVQLQESGPGLVKPSETLSLTCTVS GVSLPDYGVSWIRQPPGKGLEWIGVIWGSETTYYSSSLKSRVTISKDNS KNQVSLKLSSVTAADTAVYYCAKHYYYGGSYAMDYWGQGTLVTVSS	83
CD19	huscFv2	EIVMTQSPATLSLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIY HTSRLHSGIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTF GQGTKLEIKGGGGSGGGGSGGGGSQVQLQESGPGLVKPSETLSLTCTVS GVSLPDYGVSWIRQPPGKGLEWIGVIWGSETTYYQSSLKSRVTISKDNS KNQVSLKLSSVTAADTAVYYCAKHYYYGGSYAMDYWGQGTLVTVSS	84
CD19	huscFv3	QVQLQESGPGLVKPSETLSLTCTVSGVSLPDYGVSWIRQPPGKGLEWIG VIWGSETTYYSSSLKSRVTISKDNSKNQVSLKLSSVTAADTAVYYCAKH YYYGGSYAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSEIVMTQSPATLS LSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIYHTSRLHSGIPAR FSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTFGQGTKLEIK	85
CD19	huscFv4	QVQLQESGPGLVKPSETLSLTCTVSGVSLPDYGVSWIRQPPGKGLEWIG VIWGSETTYYQSSLKSRVTISKDNSKNQVSLKLSSVTAADTAVYYCAKH YYYGGSYAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSEIVMTQSPATLS LSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIYHTSRLHSGIPAR FSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTFGQGTKLEIK	86
CD19	huscFv5	EIVMTQSPATLSLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIY HTSRLHSGIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTF GQGTKLEIKGGGGSGGGGSGGGGSGGGGSQVQLQESGPGLVKPSETLSL TCTVSGVSLPDYGVSWIRQPPGKGLEWIGVIWGSETTYYSSSLKSRVTI SKDNSKNQVSLKLSSVTAADTAVYYCAKHYYYGGSYAMDYWGQGTLVTV SS	87
CD19	huscFv6	EIVMTQSPATLSLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIY HTSRLHSGIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTF GQGTKLEIKGGGGSGGGGSGGGGSGGGGSQVQLQESGPGLVKPSETLSL TCTVSGVSLPDYGVSWIRQPPGKGLEWIGVIWGSETTYYQSSLKSRVTI SKDNSKNQVSLKLSSVTAADTAVYYCAKHYYYGGSYAMDYWGQGTLVTV SS	88
CD19	huscFv7	QVQLQESGPGLVKPSETLSLTCTVSGVSLPDYGVSWIRQPPGKGLEWIG VIWGSETTYYSSSLKSRVTISKDNSKNQVSLKLSSVTAADTAVYYCAKH YYYGGSYAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSEIVMTQS PATLSLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIYHTSRLHS GIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTFGQGTKLE IK	89
CD19	huscFv8	QVQLQESGPGLVKPSETLSLTCTVSGVSLPDYGVSWIRQPPGKGLEWIG VIWGSETTYYQSSLKSRVTISKDNSKNQVSLKLSSVTAADTAVYYCAKH YYYGGSYAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSEIVMTQS PATLSLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIYHTSRLHS	90

		GIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTFGQGTKLE IK	
CD19	huscFv9	EIVMTQSPATLSLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIY HTSRLHSGIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTF GQGTKLEIKGGGGSGGGGSGGGGSGGGGSQVQLQESGPGLVKPSETLSL TCTVSGVSLPDYGVSWIRQPPGKGLEWIGVIWGSETTYYNSSLKSRVTI SKDNSKNQVSLKLSSVTAADTAVYYCAKHYYYGGSYAMDYWGQGTLVTV SS	91
CD19	Hu scFv10	QVQLQESGPGLVKPSETLSLTCTVSGVSLPDYGVSWIRQPPGKGLEWIG VIWGSETTYYNSSLKSRVTISKDNSKNQVSLKLSSVTAADTAVYYCAKH YYYGGSYAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSEIVMTQS PATLSLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIYHTSRLHS GIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTFGQGTKLE IK	92
CD19	Hu scFv11	EIVMTQSPATLSLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIY HTSRLHSGIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTF GQGTKLEIKGGGGSGGGGSGGGGSQVQLQESGPGLVKPSETLSLTCTVS GVSLPDYGVSWIRQPPGKGLEWIGVIWGSETTYYNSSLKSRVTISKDNS KNQVSLKLSSVTAADTAVYYCAKHYYYGGSYAMDYWGQGTLVTVSS	93
CD19	Hu scFv12	QVQLQESGPGLVKPSETLSLTCTVSGVSLPDYGVSWIRQPPGKGLEWIG VIWGSETTYYNSSLKSRVTISKDNSKNQVSLKLSSVTAADTAVYYCAKH YYYGGSYAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSEIVMTQSPATLS LSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIYHTSRLHSGIPAR FSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTFGQGTKLEIK	94

[00285] The sequences of the CDR sequences of the scFv domains of the CD19 antigen binding domains provided in Table 6 are shown in Table 7 for the heavy chain variable domains and in Table 8 for the light chain variable domains. “ID” stands for the respective SEQ ID NO for each CDR.

Table 7. Heavy Chain Variable Domain CDRs

Description	FW	HCDR1	SEQ ID NO:	HCDR2	SEQ ID NO:	HCDR3	SEQ ID NO:
murine_CART19		GVSLPDYGVS	255	VIWGSETTYYNSALKS	256	HYYYGGSYAMDY	260
humanized_CART19 a	VH4	GVSLPDYGVS	255	VIWGSETTYY***S***S***S***LKS	257	HYYYGGSYAMDY	260
humanized_CART19 b	VH4	GVSLPDYGVS	255	VIWGSETTYY***Q***S***S***LKS	258	HYYYGGSYAMDY	260
humanized_CART19 c	VH4	GVSLPDYGVS	255	VIWGSETTYYNS***S***LKS	259	HYYYGGSYAMDY	260

Table 8. Light Chain Variable Domain CDRs

Description	FW	LCDR1	SEQ ID	LCDR2	SEQ ID	LCDR3	SEQ ID

			NO:		NO:		NO:
murine_CART19		RASQDISKYLN	261	HTSRLHS	262	QQGNTLPYT	263
humanized_CART19 a	VK3	RASQDISKYLN	261	HTSRLHS	262	QQGNTLPYT	263
humanized_CART19 b	VK3	RASQDISKYLN	261	HTSRLHS	262	QQGNTLPYT	263
humanized_CART19 c	VK3	RASQDISKYLN	261	HTSRLHS	262	QQGNTLPYT	263

[00286] In an embodiment, the antigen binding domain comprises an anti-CD19 antibody, or fragment thereof, e.g., an scFv. For example, the antigen binding domain comprises a variable heavy chain and a variable light chain listed in Table 9. The linker sequence joining the variable heavy and variable light chains can be any of the linker sequences described herein, or alternatively, can be GSTSGSGKPGSGEGSTKG (SEQ ID NO: 81). The light chain variable region and heavy chain variable region of a scFv can be, e.g., in any of the following orientations: light chain variable region-linker-heavy chain variable region or heavy chain variable region-linker-light chain variable region.

Table 9. Additional Anti-CD19 antibody binding domains

Ab Name	VH Sequence	VL Sequence
SJ25-C1	QVQLLESGAELVRPGSSVKISCKASG YAFSSYWMNWVKQRPGQGLEWIGQIY PGDGDTNYNGKFKGQATLTADKSSST AYMQLSGLTSEDSAVYSCARKTISSV VDFYFDYWGQGTTVT (SEQ ID NO: 96)	ELVLTQSPKFMSTSVGDRVSVTCKASQNV GTNVAWYQQKPGQSPKPLIYSATYRNSGV PDRFTGSGSGTDFTLTITNVQSKDLADYF YFCQYNRYPYTSGGGTKLEIKRRS (SEQ ID NO: 97)
	ScFv Sequence	
SJ25-C1 scFv	QVQLLESGAELVRPGSSVKISCKASGYAFSSYWMNWVKQRPGQGLEWIGQIYPGDGD TNYNGKFKGQATLTADKSSSTAYMQLSGLTSEDSAVYSCARKTISSVVDFYFDYWGQ GTTVTGSTSGSGKPGSGEGSTKGELVLTQSPKFMSTSVGDRVSVTCKASQNVGTNVA WYQQKPGQSPKPLIYSATYRNSGVPDRFTGSGSGTDFTLTITNVQSKDLADYFYFCQ YNRYPYTSGGGTKLEIKRRS (SEQ ID NO: 112)	

[00287] In one embodiment, the CD19 binding domain comprises one or more (e.g., all three) light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and light chain complementary determining region 3 (LC CDR3) of a CD19 binding domain described herein, e.g., provided in Table 6 or 7, and/or one or more (e.g., all three) heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary

determining region 3 (HC CDR3) of a CD19 binding domain described herein, e.g., provided in Table 6 or 8. In one embodiment, the CD19 binding domain comprises one, two, or all of LC CDR1, LC CDR2, and LC CDR3 of any amino acid sequences as provided in Table 8, incorporated herein by reference; and one, two or all of HC CDR1, HC CDR2, and HC CDR3 of any amino acid sequences as provided in Table 7.

[00288] In one embodiment, the CD19 antigen binding domain comprises:

(i) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 261, a LC CDR2 amino acid sequence of SEQ ID NO: 262, and a LC CDR3 amino acid sequence of SEQ ID NO: 263; and
(b) a HC CDR1 amino acid sequence of SEQ ID NO: 255, a HC CDR2 amino acid sequence of SEQ ID NO: 256, and a HC CDR3 amino acid sequence of SEQ ID NO: 260

(ii) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 261, a LC CDR2 amino acid sequence of SEQ ID NO: 262, and a LC CDR3 amino acid sequence of SEQ ID NO: 263; and
(b) a HC CDR1 amino acid sequence of SEQ ID NO: 255, a HC CDR2 amino acid sequence of SEQ ID NO: 257, and a HC CDR3 amino acid sequence of SEQ ID NO: 260;

(iii) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 261, a LC CDR2 amino acid sequence of SEQ ID NO: 262, and a LC CDR3 amino acid sequence of SEQ ID NO: 263; and
(b) a HC CDR1 amino acid sequence of SEQ ID NO: 255, a HC CDR2 amino acid sequence of SEQ ID NO: 258, and a HC CDR3 amino acid sequence of SEQ ID NO: 260; or

(iv) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 261, a LC CDR2 amino acid sequence of SEQ ID NO: 262, and a LC CDR3 amino acid sequence of SEQ ID NO: 263; and
(b) a HC CDR1 amino acid sequence of SEQ ID NO: 255, a HC CDR2 amino acid sequence of SEQ ID NO: 259, and a HC CDR3 amino acid sequence of SEQ ID NO: 260.

[00289] In one embodiment, the CD19 binding domain comprises a light chain variable region described herein (e.g., in Table 6 or 9) and/or a heavy chain variable region described herein (e.g., in Table 6 or 9). In one embodiment, the CD19 binding domain is a scFv comprising a light chain and a heavy chain of an amino acid sequence listed in Table 6 or 9. In an embodiment, the CD19 binding domain (e.g., an scFv) comprises: a light chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a light chain variable region provided in Table 6 or 9, or a sequence with 95-99% identity with an amino acid sequence provided in Table 6 or 9; and/or a heavy chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a heavy chain variable region provided in Table 6 or 9, or a sequence with 95-99% identity to an amino acid sequence provided in Table 6 or 9.

[00290] In one embodiment, the CD19 binding domain comprises an amino acid sequence selected from a group consisting of SEQ ID NO: 83; SEQ ID NO: 84, SEQ ID NO: 85; SEQ ID NO: 86; SEQ ID NO: 87; SEQ ID NO: 88; SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, and SEQ ID NO: 112; or an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) to any of the aforesaid sequences; or a sequence with 95-99% identity to any of the aforesaid sequences. In one embodiment, the CD19 binding domain is a scFv, and a light chain variable region comprising an amino acid sequence described herein, e.g., in Table 6 or 9, is attached to a heavy chain variable region comprising an amino acid sequence described herein, e.g., in Table 6 or 9, via a linker, e.g., a linker described herein. In one embodiment, the CD19 binding domain includes a (Gly4-Ser)n linker, wherein n is 1, 2, 3, 4, 5, or 6, preferably 4 (SEQ ID NO: 80). The light chain variable region and heavy chain variable region of a scFv can be, e.g., in any of the following orientations: light chain variable region-linker-heavy chain variable region or heavy chain variable region-linker-light chain variable region.

[00291] Any known CD19 CAR, e.g., the CD19 antigen binding domain of any known CD19 CAR, in the art can be used in accordance with the instant invention to construct a CAR. For example, CD19 CAR is described in the 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); and 16th Annu Meet Am Soc Gen Cell Ther (ASGCT) (May 15-18, Salt Lake City) 2013, Abst 10, each of which is incorporated herein by referene 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 WO2012/079000; 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 incorporated herein by referene in its entirety.

[00292] In an embodiment, the antigen-binding domain of a CAR, e.g., the CAR expressed by a cell of the invention, binds to BCMA. BCMA is found preferentially expressed in mature B lymphocytes. In an embodiment, the antigen binding domain is a murine scFv domain that binds to human BCMA. In an embodiment, the antigen binding domain is a humanized antibody or antibody fragment, e.g., scFv domain, that binds human BCMA. In an embodiment, the antigen binding domain is a human antibody or antibody fragment that binds to human BCMA. Exemplary scFv domains (and their sequences, e.g., CDRs, VL and VH sequences) that bind to BCMA are provided in Table 12, Table 13, Table 14 and Table 15. The scFv domain sequences provided in Table 12 and Table 13 include a light chain variable region (VL) and a heavy chain variable region (VH). The VL and VH are attached by a linker, e.g., in the following orientation: VH-linker-VL.

Table 12. Antigen Binding domains that bind the B-Cell antigen BCMA

The amino acid sequences variable heavy chain and variable light chain sequences for each scFv is also provided.

Name/ Description	**SEQ ID NO:**	**Sequence**
139109		

139109- aa ScFv domain	349	EVQLVESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSG IVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGG ESDVWGQGTTVTVSSASGGGGSGGRASGGGGSDIQLTQSPSSLSASVGDR VTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQSYSTPYTFGQGTKVEIK
139109- nt ScFv domain	364	GAAGTGCAATTGGTGGAATCAGGGGGAGGACTTGTGCAGCCTGGAGGATC GCTGAGACTGTCATGTGCCGTGTCCGGCTTTGCCCTGTCCAACCACGGGA TGTCCTGGGTCCGCCGCGCGCCTGGAAAGGGCCTCGAATGGGTGTCGGGT ATTGTGTACAGCGGTAGCACCTACTATGCCGCATCCGTGAAGGGGAGATT CACCATCAGCCGGGACAACTCCAGGAACACTCTGTACCTCCAAATGAATT CGCTGAGGCCAGAGGACACTGCCATCTACTACTGCTCCGCGCATGGCGGA GAGTCCGACGTCTGGGGACAGGGGACCACCGTGACCGTGTCTAGCGCGTC CGGCGGAGGCGGCAGCGGGGGTCGGGCATCAGGGGGCGGCGGATCGGACA TCCAGCTCACCCAGTCCCCGAGCTCGCTGTCCGCCTCCGTGGGAGATCGG GTCACCATCACGTGCCGCGCCAGCCAGTCGATTTCCTCCTACCTGAACTG GTACCAACAGAAGCCCGGAAAAGCCCCGAAGCTTCTCATCTACGCCGCCT CGAGCCTGCAGTCAGGAGTGCCCTCACGGTTCTCCGGCTCCGGTTCCGGT ACTGATTTCACCCTGACCATTTCCTCCCTGCAACCGGAGGACTTCGCTAC TTACTACTGCCAGCAGTCGTACTCCACCCCCTACACTTTCGGACAAGGCA CCAAGGTCGAAATCAAG
139109- aa VH	379	EVQLVESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSG IVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGG ESDVWGQGTTVTVSS
139109- aa VL	394	DIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYA ASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPYTFGQ GTKVEIK
139103		
139103- aa ScFv domain	339	QVQLVESGGGLVQPGRSLRLSCAASGFTFSNYAMSWVRQAPGKGLGWVSG ISRSGENTYYADSVKGRFTISRDNSKNTLYLQMNSLRDEDTAVYYCARSP AHYYGGMDVWGQGTTVTVSSASGGGGSGGRASGGGGSDIVLTQSPGTLSL SPGERATLSCRASQSISSSFLAWYQQKPGQAPRLLIYGASRRATGIPDRF SGSGSGTDFTLTISRLEPEDSAVYYCQQYHSSPSWTFGQGTKLEIK
139103- nt ScFv domain	354	CAAGTGCAACTCGTGGAATCTGGTGGAGGACTCGTGCAACCCGGAAGATC GCTTAGACTGTCGTGTGCCGCCAGCGGGTTCACTTTCTCGAACTACGCGA TGTCCTGGGTCCGCCAGGCACCCGGAAAGGGACTCGGTTGGGTGTCCGGC ATTTCCCGGTCCGGCGAAAATACCTACTACGCCGACTCCGTGAAGGGCCG CTTCACCATCTCAAGGGACAACAGCAAAAACACCCTGTACTTGCAAATGA ACTCCCTGCGGGATGAAGATACAGCCGTGTACTATTGCGCCCGGTCGCCT GCCCATTACTACGGCGGAATGGACGTCTGGGGACAGGGAACCACTGTGAC TGTCAGCAGCGCGTCGGGTGGCGGCGGCTCAGGGGGTCGGGCCTCCGGGG GGGGAGGGTCCGACATCGTGCTGACCCAGTCCCCGGGAACCCTGAGCCTG AGCCCGGGAGAGCGCGCGACCCTGTCATGCCGGGCATCCCAGAGCATTAG CTCCTCCTTTCTCGCCTGGTATCAGCAGAAGCCCGGACAGGCCCCGAGGC TGCTGATCTACGGCGCTAGCAGAAGGGCTACCGGAATCCCAGACCGGTTC TCCGGCTCCGGTTCCGGGACCGATTTCACCCTTACTATCTCGCGCCTGGA ACCTGAGGACTCCGCCGTCTACTACTGCCAGCAGTACCACTCATCCCCGT CGTGGACGTTCGGACAGGGCACCAAGCTGGAGATTAAG
139103- aa VH	369	QVQLVESGGGLVQPGRSLRLSCAASGFTFSNYAMSWVRQAPGKGLGWVSG ISRSGENTYYADSVKGRFTISRDNSKNTLYLQMNSLRDEDTAVYYCARSP AHYYGGMDVWGQGTTVTVSS
139103- aa	384	DIVLTQSPGTLSLSPGERATLSCRASQSISSSFLAWYQQKPGQAPRLLIY

VL		GASRRATGIPDRFSGSGSGTDFTLTISRLEPEDSAVYYCQQYHSSPSWTF GQGTKLEIK
139105		
139105- aa ScFv domain	340	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSG ISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCSVHS FLAYWGQGTLVTVSSASGGGGSGGRASGGGGSDIVMTQTPLSLPVTPGEP ASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFS GSGSGTDFTLKISRVEAEDVGVYYCMQALQTPYTFGQGTKVEIK
139105- nt ScFv domain	355	CAAGTGCAACTCGTCGAATCCGGTGGAGGTCTGGTCCAACCTGGTAGAAG CCTGAGACTGTCGTGTGCGGCCAGCGGATTCACCTTTGATGACTATGCTA TGCACTGGGTGCGGCAGGCCCCAGGAAAGGGCCTGGAATGGGTGTCGGGA ATTAGCTGGAACTCCGGGTCCATTGGCTACGCCGACTCCGTGAAGGGCCG CTTCACCATCTCCCGCGACAACGCAAAGAACTCCCTGTACTTGCAAATGA ACTCGCTCAGGGCTGAGGATACCGCGCTGTACTACTGCTCCGTGCATTCC TTCCTGGCCTACTGGGGACAGGGAACTCTGGTCACCGTGTCGAGCGCCTC CGGCGGCGGGGGCTCGGGTGGACGGGCCTCGGGCGGAGGGGGGTCCGACA TCGTGATGACCCAGACCCCGCTGAGCTTGCCCGTGACTCCCGGAGAGCCT GCATCCATCTCCTGCCGGTCATCCCAGTCCCTTCTCCACTCCAACGGATA CAACTACCTCGACTGGTACCTCCAGAAGCCGGGACAGAGCCCTCAGCTTC TGATCTACCTGGGGTCAAATAGAGCCTCAGGAGTGCCGGATCGGTTCAGC GGATCTGGTTCGGGAACTGATTTCACTCTGAAGATTTCCCGCGTGGAAGC CGAGGACGTGGGCGTCTACTACTGTATGCAGGCGCTGCAGACCCCCTATA CCTTCGGCCAAGGGACGAAAGTGGAGATCAAG
139105- aa VH	370	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSG ISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCSVHS FLAYWGQGTLVTVSS
139105- aa VL	385	DIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQ LLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTP YTFGQGTKVEIK
139111		
139111- aa ScFv domain	341	EVQLLESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSG IVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGG ESDVWGQGTTVTVSSASGGGGSGGRASGGGGSDIVMTQTPLSLSVTPGQP ASISCKSSQSLLRNDGKTPLYWYLQKAGQPPQLLIYEVSNRFSGVPDRFS GSGSGTDFTLKISRVEAEDVGAYYCMQNIQFPSFGGGTKLEIK
139111- nt ScFv domain	356	GAAGTGCAATTGTTGGAATCTGGAGGAGGACTTGTGCAGCCTGGAGGATC ACTGAGACTTTCGTGTGCGGTGTCAGGCTTCGCCCTGAGCAACCACGGCA TGAGCTGGGTGCGGAGAGCCCCGGGGAAGGGTCTGGAATGGGTGTCCGGG ATCGTCTACTCCGGTTCAACTTACTACGCCGCAAGCGTGAAGGGTCGCTT CACCATTTCCCGCGATAACTCCCGGAACACCCTGTACCTCCAAATGAACT CCCTGCGGCCCGAGGACACCGCCATCTACTACTGTTCCGCGCATGGAGGA GAGTCCGATGTCTGGGGACAGGGCACTACCGTGACCGTGTCGAGCGCCTC GGGGGGAGGAGGCTCCGGCGGTCGCGCCTCCGGGGGGGGTGGCAGCGACA TTGTGATGACGCAGACTCCACTCTCGCTGTCCGTGACCCCGGGACAGCCC GCGTCCATCTCGTGCAAGAGCTCCCAGAGCCTGCTGAGGAACGACGGAAA GACTCCTCTGTATTGGTACCTCCAGAAGGCTGGACAGCCCCCGCAACTGC TCATCTACGAAGTGTCAAATCGCTTCTCCGGGGTGCCGGATCGGTTTTCC GGCTCGGGATCGGGCACCGACTTCACCCTGAAAATCTCCAGGGTCGAGGC CGAGGACGTGGGAGCCTACTACTGCATGCAAAACATCCAGTTCCCTTCCT TCGGCGGCGGCACAAAGCTGGAGATTAAG
139111- aa	371	EVQLLESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSG

VH		IVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGG ESDVWGQGTTVTVSS
139111- aa VL	386	DIVMTQTPLSLSVTPGQPASISCKSSQSLLRNDGKTPLYWYLQKAGQPPQ LLIYEVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGAYYCMQNIQFP SFGGGTKLEIK
139100		
139100- aa ScFv domain	342	QVQLVQSGAEVRKTGASVKVSCKASGYIFDNFGINWVRQAPGQGLEWMGW INPKNNNTNYAQKFQGRVTITADESTNTAYMEVSSLRSEDTAVYYCARGP YYYQSYMDVWGQGTMVTVSSASGGGGSGGRASGGGGSDIVMTQTPLSLPV TPGEPASISCRSSQSLLHSNGYNYLNWYLQKPGQSPQLLIYLGSKRASGV PDRFSGSGSGTDFTLHITRVGAEDVGVYYCMQALQTPYTFGQGTKLEIK
139100- nt ScFv domain	357	CAAGTCCAACTCGTCCAGTCCGGCGCAGAAGTCAGAAAAACCGGTGCTAG CGTGAAAGTGTCCTGCAAGGCCTCCGGCTACATTTTCGATAACTTCGGAA TCAACTGGGTCAGACAGGCCCCGGGCCAGGGGCTGGAATGGATGGGATGG ATCAACCCCAAGAACAACAACACCAACTACGCACAGAAGTTCCAGGGCCG CGTGACTATCACCGCCGATGAATCGACCAATACCGCCTACATGGAGGTGT CCTCCCTGCGGTCGGAGGACACTGCCGTGTATTACTGCGCGAGGGGCCCA TACTACTACCAAAGCTACATGGACGTCTGGGGACAGGGAACCATGGTGAC CGTGTCATCCGCCTCCGGTGGTGGAGGCTCCGGGGGGCGGGCTTCAGGAG GCGGAGGAAGCGATATTGTGATGACCCAGACTCCGCTTAGCCTGCCCGTG ACTCCTGGAGAACCGGCCTCCATTTCCTGCCGGTCCTCGCAATCACTCCT GCATTCCAACGGTTACAACTACCTGAATTGGTACCTCCAGAAGCCTGGCC AGTCGCCCCAGTTGCTGATCTATCTGGGCTCGAAGCGCGCCTCCGGGGTG CCTGACCGGTTTAGCGGATCTGGGAGCGGCACGGACTTCACTCTCCACAT CACCCGCGTGGGAGCGGAGGACGTGGGAGTGTACTACTGTATGCAGGCGC TGCAGACTCCGTACACATTCGGACAGGGCACCAAGCTGGAGATCAAG
139100- aa VH	372	QVQLVQSGAEVRKTGASVKVSCKASGYIFDNFGINWVRQAPGQGLEWMGW INPKNNNTNYAQKFQGRVTITADESTNTAYMEVSSLRSEDTAVYYCARGP YYYQSYMDVWGQGTMVTVSS
139100- aa VL	387	DIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGYNYLNWYLQKPGQSPQ LLIYLGSKRASGVPDRFSGSGSGTDFTLHITRVGAEDVGVYYCMQALQTP YTFGQGTKLEIK
139101		
139101- aa ScFv domain	343	QVQLQESGGGLVQPGGSLRLSCAASGFTFSSDAMTWVRQAPGKGLEWVSV ISGSGGTTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKLD SSGYYYARGPRYWGQGTLVTVSSASGGGGSGGRASGGGGSDIQLTQSPSS LSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYGASTLASGVPA RFSGSGSGTHFTLTINSLQSEDSATYYCQQSYKRASFGQGTKVEIK
139101- nt ScFv domain	358	CAAGTGCAACTTCAAGAATCAGGCGGAGGACTCGTGCAGCCCGGAGGATC ATTGCGGCTCTCGTGCGCCGCCTCGGGCTTCACCTTCTCGAGCGACGCCA TGACCTGGGTCCGCCAGGCCCCGGGGAAGGGGCTGGAATGGGTGTCTGTG ATTTCCGGCTCCGGGGGAACTACGTACTACGCCGATTCCGTGAAAGGTCG CTTCACTATCTCCCGGGACAACAGCAAGAACACCCTTTATCTGCAAATGA ATTCCCTCCGCGCCGAGGACACCGCCGTGTACTACTGCGCCAAGCTGGAC TCCTCGGGCTACTACTATGCCCGGGGTCCGAGATACTGGGGACAGGGAAC CCTCGTGACCGTGTCCTCCGCGTCCGGCGGAGGAGGGTCGGGAGGGCGGG CCTCCGGCGGCGGCGGTTCGGACATCCAGCTGACCCAGTCCCCATCCTCA CTGAGCGCAAGCGTGGGCGACAGAGTCACCATTACATGCAGGGCGTCCCA GAGCATCAGCTCCTACCTGAACTGGTACCAACAGAAGCCTGGAAAGGCTC CTAAGCTGTTGATCTACGGGGCTTCGACCCTGGCATCCGGGGTGCCCGCG AGGTTTAGCGGAAGCGGTAGCGGCACTCACTTCACTCTGACCATTAACAG

		CCTCCAGTCCGAGGATTCAGCCACTTACTACTGTCAGCAGTCCTACAAGC GGGCCAGCTTCGGACAGGGCACTAAGGTCGAGATCAAG
139101- aa VH	373	QVQLQESGGGLVQPGGSLRLSCAASGFTFSSDAMTWVRQAPGKGLEWVSV ISGSGGTTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKLD SSGYYYARGPRYWGQGTLVTVSS
139101- aa VL	388	DIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYG ASTLASGVPARFSGSGSGTHFTLTINSLQSEDSATYYCQQSYKRASFGQG TKVEIK
139102		
139102- aa ScFv domain	344	QVQLVQSGAEVKKPGASVKVSCKASGYTFSNYGITWVRQAPGQGLEWMGW ISAYNGNTNYAQKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYYCARGP YYYYMDVWGKGTMVTVSSASGGGGSGGRASGGGGSEIVMTQSPLSLPVTP GEPASISCRSSQSLLYSNGYNYVDWYLQKPGQSPQLLIYLGSNRASGVPD RFSGSGSGTDFKLQISRVEAEDVGIYYCMQGRQFPYSFGQGTKVEIK
139102- nt ScFv domain	359	CAAGTCCAACTGGTCCAGAGCGGTGCAGAAGTGAAGAAGCCCGGAGCGAG CGTGAAAGTGTCCTGCAAGGCTTCCGGGTACACCTTCTCCAACTACGGCA TCACTTGGGTGCGCCAGGCCCCGGGACAGGGCCTGGAATGGATGGGGTGG ATTTCCGCGTACAACGGCAATACGAACTACGCTCAGAAGTTCCAGGGTAG AGTGACCATGACTAGGAACACCTCCATTTCCACCGCCTACATGGAACTGT CCTCCCTGCGGAGCGAGGACACCGCCGTGTACTATTGCGCCCGGGGACCA TACTACTACTACATGGATGTCTGGGGGAAGGGGACTATGGTCACCGTGTC ATCCGCCTCGGGAGGCGGCGGATCAGGAGGACGCGCCTCTGGTGGTGGAG GATCGGAGATCGTGATGACCCAGAGCCCTCTCTCCTTGCCCGTGACTCCT GGGGAGCCCGCATCCATTTCATGCCGGAGCTCCCAGTCACTTCTCTACTC CAACGGCTATAACTACGTGGATTGGTACCTCCAAAAGCCGGGCCAGAGCC CGCAGCTGCTGATCTACCTGGGCTCGAACAGGGCCAGCGGAGTGCCTGAC CGGTTCTCCGGGTCGGGAAGCGGGACCGACTTCAAGCTGCAAATCTCGAG AGTGGAGGCCGAGGACGTGGGAATCTACTACTGTATGCAGGGCCGCCAGT TTCCGTACTCGTTCGGACAGGGCACCAAAGTGGAAATCAAG
139102- aa VH	374	QVQLVQSGAEVKKPGASVKVSCKASGYTFSNYGITWVRQAPGQGLEWMGW ISAYNGNTNYAQKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYYCARGP YYYYMDVWGKGTMVTVSS
139102- aa VL	389	EIVMTQSPLSLPVTPGEPASISCRSSQSLLYSNGYNYVDWYLQKPGQSPQ LLIYLGSNRASGVPDRFSGSGSGTDFKLQISRVEAEDVGIYYCMQGRQFP YSFGQGTKVEIK
139104		
139104- aa ScFv domain	345	EVQLLETGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSG IVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGG ESDVWGQGTTVTVSSASGGGGSGGRASGGGGSEIVLTQSPATLSVSPGES ATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGASTRASGIPDRFSGSGSG TDFTLTISSLQAEDVAVYYCQQYGSSLTFGGGTKVEIK
139104- nt ScFv domain	360	GAAGTGCAATTGCTCGAAACTGGAGGAGGTCTGGTGCAACCTGGAGGATC ACTTCGCCTGTCCTGCGCCGTGTCGGGCTTTGCCCTGTCCAACCATGGAA TGAGCTGGGTCCGCCGCGCGCCGGGGAAGGGCCTCGAATGGGTGTCCGGC ATCGTCTACTCCGGCTCCACCTACTACGCCGCGTCCGTGAAGGGCCGGTT CACGATTTCACGGGACAACTCGCGGAACACCCTGTACCTCCAAATGAATT CCCTTCGGCCGGAGGATACTGCCATCTACTACTGCTCCGCCCACGGTGGC GAATCCGACGTCTGGGGCCAGGGAACCACCGTGACCGTGTCCAGCGCGTC CGGGGGAGGAGGAAGCGGGGGTAGAGCATCGGGTGGAGGCGGATCAGAGA TCGTGCTGACCCAGTCCCCCGCCACCTTGAGCGTGTCACCAGGAGAGTCC GCCACCCTGTCATGCCGCGCCAGCCAGTCCGTGTCCTCCAACCTGGCTTG

		GTACCAGCAGAAGCCGGGGCAGGCCCCTAGACTCCTGATCTATGGGGCGT CGACCCGGGCATCTGGAATTCCCGATAGGTTCAGCGGATCGGGCTCGGGC ACTGACTTCACTCTGACCATCTCCTCGCTGCAAGCCGAGGACGTGGCTGT GTACTACTGTCAGCAGTACGGAAGCTCCCTGACTTTCGGTGGCGGGACCA AAGTCGAGATTAAG
139104- aa VH	375	EVQLLETGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSG IVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGG ESDVWGQGTTVTVSS
139104- aa VL	390	EIVLTQSPATLSVSPGESATLSCRASQSVSSNLAWYQQKPGQAPRLLIYG ASTRASGIPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYGSSLTFGGG TKVEIK
139106		
139106- aa ScFv domain	346	EVQLVETGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSG IVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGG ESDVWGQGTTVTVSSASGGGGSGGRASGGGGSEIVMTQSPATLSVSPGER ATLSCRASQSVSSKLAWYQQKPGQAPRLLMYGASIRATGIPDRFSGSGSG TEFTLTISSLEPEDFAVYYCQQYGSSSWTFGQGTKVEIK
139106- nt ScFv domain	361	GAAGTGCAATTGGTGGAAACTGGAGGAGGACTTGTGCAACCTGGAGGATC ATTGAGACTGAGCTGCGCAGTGTCGGGATTCGCCCTGAGCAACCATGGAA TGTCCTGGGTCAGAAGGGCCCCTGGAAAAGGCCTCGAATGGGTGTCAGGG ATCGTGTACTCCGGTTCCACTTACTACGCCGCCTCCGTGAAGGGGCGCTT CACTATCTCACGGGATAACTCCCGCAATACCCTGTACCTCCAAATGAACA GCCTGCGGCCGGAGGATACCGCCATCTACTACTGTTCCGCCCACGGTGGA GAGTCTGACGTCTGGGGCCAGGGAACTACCGTGACCGTGTCCTCCGCGTC CGGCGGTGGAGGGAGCGGCGGCCGCGCCAGCGGCGGCGGAGGCTCCGAGA TCGTGATGACCCAGAGCCCCGCTACTCTGTCGGTGTCGCCCGGAGAAAGG GCGACCCTGTCCTGCCGGGCGTCGCAGTCCGTGAGCAGCAAGCTGGCTTG GTACCAGCAGAAGCCGGGCCAGGCACCACGCCTGCTTATGTACGGTGCCT CCATTCGGGCCACCGGAATCCCGGACCGGTTCTCGGGGTCGGGGTCCGGT ACCGAGTTCACACTGACCATTTCCTCGCTCGAGCCCGAGGACTTTGCCGT CTATTACTGCCAGCAGTACGGCTCCTCCTCATGGACGTTCGGCCAGGGGA CCAAGGTCGAAATCAAG
139106- aa VH	376	EVQLVETGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSG IVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGG ESDVWGQGTTVTVSS
139106- aa VL	391	EIVMTQSPATLSVSPGERATLSCRASQSVSSKLAWYQQKPGQAPRLLMYG ASIRATGIPDRFSGSGSGTEFTLTISSLEPEDFAVYYCQQYGSSSWTFGQ GTKVEIK
139107		
139107- aa ScFv domain	347	EVQLVETGGGVVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSG IVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGG ESDVWGQGTTVTVSSASGGGGSGGRASGGGGSEIVLTQSPGTLSLSPGER ATLSCRASQSVGSTNLAWYQQKPGQAPRLLIYDASNRATGIPDRFSGGGS GTDFTLTISRLEPEDFAVYYCQQYGSSPPWTFGQGTKVEIK
139107- nt ScFv domain	362	GAAGTGCAATTGGTGGAGACTGGAGGAGGAGTGGTGCAACCTGGAGGAAG CCTGAGACTGTCATGCGCGGTGTCGGGCTTCGCCCTCTCCAACCACGGAA TGTCCTGGGTCCGCCGGGCCCCTGGGAAAGGACTTGAATGGGTGTCCGGC ATCGTGTACTCGGGTTCCACCTACTACGCGGCCTCAGTGAAGGGCCGGTT TACTATTAGCCGCGACAACTCCAGAAACACACTGTACCTCCAAATGAACT CGCTGCGGCCGGAAGATACCGCTATCTACTACTGCTCCGCCCATGGGGGA GAGTCGGACGTCTGGGGACAGGGCACCACTGTCACTGTGTCCAGCGCTTC

		CGGCGGTGGTGGAAGCGGGGGACGGGCCTCAGGAGGCGGTGGCAGCGAGA TTGTGCTGACCCAGTCCCCCGGGACCCTGAGCCTGTCCCCGGGAGAAAGG GCCACCCTCTCCTGTCGGGCATCCCAGTCCGTGGGGTCTACTAACCTTGC ATGGTACCAGCAGAAGCCCGGCCAGGCCCCTCGCCTGCTGATCTACGACG CGTCCAATAGAGCCACCGGCATCCCGGATCGCTTCAGCGGAGGCGGATCG GGCACCGACTTCACCCTCACCATTTCAAGGCTGGAACCGGAGGACTTCGC CGTGTACTACTGCCAGCAGTATGGTTCGTCCCCACCCTGGACGTTCGGCC AGGGGACTAAGGTCGAGATCAAG
139107- aa VH	377	EVQLVETGGGVVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSG IVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGG ESDVWGQGTTVTVSS
139107- aa VL	392	EIVLTQSPGTLSLSPGERATLSCRASQSVGSTNLAWYQQKPGQAPRLLIY DASNRATGIPDRFSGGGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPWTF GQGTKVEIK
139108		
139108- aa ScFv domain	348	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVSY ISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARES GDGMDVWGQGTTVTVSSASGGGGSGGRASGGGGSDIQMTQSPSSLSASVG DRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSG SGTDFTLTISSLQPEDFATYYCQQSYTLAFGQGTKVDIK
139108- nt ScFv domain	363	CAAGTGCAACTCGTGGAATCTGGTGGAGGACTCGTGAAACCTGGAGGATC ATTGAGACTGTCATGCGCGGCCTCGGGATTCACGTTCTCCGATTACTACA TGAGCTGGATTCGCCAGGCTCCGGGGAAGGGACTGGAATGGGTGTCCTAC ATTTCCTCATCCGGCTCCACCATCTACTACGCGGACTCCGTGAAGGGGAG ATTCACCATTAGCCGCGATAACGCCAAGAACAGCCTGTACCTTCAGATGA ACTCCCTGCGGGCTGAAGATACTGCCGTCTACTACTGCGCAAGGGAGAGC GGAGATGGGATGGACGTCTGGGGACAGGGTACCACTGTGACCGTGTCGTC GGCCTCCGGCGGAGGGGGTTCGGGTGGAAGGGCCAGCGGCGGCGGAGGCA GCGACATCCAGATGACCCAGTCCCCCTCATCGCTGTCCGCCTCCGTGGGC GACCGCGTCACCATCACATGCCGGGCCTCACAGTCGATCTCCTCCTACCT CAATTGGTATCAGCAGAAGCCCGGAAAGGCCCCTAAGCTTCTGATCTACG CAGCGTCCTCCCTGCAATCCGGGGTCCCATCTCGGTTCTCCGGCTCGGGC AGCGGTACCGACTTCACTCTGACCATCTCGAGCCTGCAGCCGGAGGACTT CGCCACTTACTACTGTCAGCAAAGCTACACCCTCGCGTTTGGCCAGGGCA CCAAAGTGGACATCAAG
139108- aa VH	378	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVSY ISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARES GDGMDVWGQGTTVTVSS
139108- aa VL	393	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYA ASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYTLAFGQGT KVDIK
139110		
139110- aa ScFv domain	350	QVQLVQSGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVSY ISSSGNTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARST MVREDYWGQGTLVTVSSASGGGGSGGRASGGGGSDIVLTQSPLSLPVTLG QPASISCKSSESLVHNSGKTYLNWFHQRPGQSPRRLIYEVSNRDSGVPDR FTGSGSGTDFTLKISRVEAEDVGVYYCMQGTHWPGTFGQGTKLEIK
139110- nt ScFv domain	365	CAAGTGCAACTGGTGCAAAGCGGAGGAGGATTGGTCAAACCCGGAGGAAG CCTGAGACTGTCATGCGCGGCCTCTGGATTCACCTTCTCCGATTACTACA TGTCATGGATCAGACAGGCCCCGGGGAAGGGCCTCGAATGGGTGTCCTAC ATCTCGTCCTCCGGGAACACCATCTACTACGCCGACAGCGTGAAGGGCCG

		CTTTACCATTTCCCGCGACAACGCAAAGAACTCGCTGTACCTTCAGATGA ATTCCCTGCGGGCTGAAGATACCGCGGTGTACTATTGCGCCCGGTCCACT ATGGTCCGGGAGGACTACTGGGGACAGGGCACACTCGTGACCGTGTCCAG CGCGAGCGGGGGTGGAGGCAGCGGTGGACGCGCCTCCGGCGGCGGCGGTT CAGACATCGTGCTGACTCAGTCGCCCCTGTCGCTGCCGGTCACCCTGGGC CAACCGGCCTCAATTAGCTGCAAGTCCTCGGAGAGCCTGGTGCACAACTC AGGAAAGACTTACCTGAACTGGTTCCATCAGCGGCCTGGACAGTCCCCAC GGAGGCTCATCTATGAAGTGTCCAACAGGGATTCGGGGGTGCCCGACCGC TTCACTGGCTCCGGGTCCGGCACCGACTTCACCTTGAAAATCTCCAGAGT GGAAGCCGAGGACGTGGGCGTGTACTACTGTATGCAGGGTACCCACTGGC CTGGAACCTTTGGACAAGGAACTAAGCTCGAGATTAAG
139110- aa VH	380	QVQLVQSGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVSY ISSSGNTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARST MVREDYWGQGTLVTVSS
139110- aa VL	395	DIVLTQSPLSLPVTLGQPASISCKSSESLVHNSGKTYLNWFHQRPGQSPR RLIYEVSNRDSGVPDRFTGSGSGTDFTLKISRVEAEDVGVYYCMQGTHWP GTFGQGTKLEIK
139112		
139112- aa ScFv domain	351	QVQLVESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSG IVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGG ESDVWGQGTTVTVSSASGGGGSGGRASGGGGSDIRLTQSPSPLSASVGDR VTITCQASEDINKFLNWYHQTPGKAPKLLIYDASTLQTGVPSRFSGSGSG TDFTLTINSLQPEDIGTYYCQQYESLPLTFGGGTKVEIK
139112- nt ScFv domain	366	CAAGTGCAACTCGTGGAATCTGGTGGAGGACTCGTGCAACCCGGTGGAAG CCTTAGGCTGTCGTGCGCCGTCAGCGGGTTTGCTCTGAGCAACCATGGAA TGTCCTGGGTCCGCCGGGCACCGGGAAAAGGGCTGGAATGGGTGTCCGGC ATCGTGTACAGCGGGTCAACCTATTACGCCGCGTCCGTGAAGGGCAGATT CACTATCTCAAGAGACAACAGCCGGAACACCCTGTACTTGCAAATGAATT CCCTGCGCCCCGAGGACACCGCCATCTACTACTGCTCCGCCCACGGAGGA GAGTCGGACGTGTGGGGCCAGGGAACGACTGTGACTGTGTCCAGCGCATC AGGAGGGGGTGGTTCGGGCGGCCGGGCCTCGGGGGGAGGAGGTTCCGACA TTCGGCTGACCCAGTCCCCGTCCCCACTGTCGGCCTCCGTCGGCGACCGC GTGACCATCACTTGTCAGGCGTCCGAGGACATTAACAAGTTCCTGAACTG GTACCACCAGACCCCTGGAAAGGCCCCCAAGCTGCTGATCTACGATGCCT CGACCCTTCAAACTGGAGTGCCTAGCCGGTTCTCCGGGTCCGGCTCCGGC ACTGATTTCACTCTGACCATCAACTCATTGCAGCCGGAAGATATCGGGAC CTACTATTGCCAGCAGTACGAATCCCTCCCGCTCACATTCGGCGGGGGAA CCAAGGTCGAGATTAAG
139112- aa VH	381	QVQLVESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSG IVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGG ESDVWGQGTTVTVSS
139112- aa VL	396	DIRLTQSPSPLSASVGDRVTITCQASEDINKFLNWYHQTPGKAPKLLIYD ASTLQTGVPSRFSGSGSGTDFTLTINSLQPEDIGTYYCQQYESLPLTFGG GTKVEIK
139113		
139113- aa ScFv domain	352	EVQLVETGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSG IVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGG ESDVWGQGTTVTVSSASGGGGSGGRASGGGGSETTLTQSPATLSVSPGER ATLSCRASQSVGSNLAWYQQKPGQGPRLLIYGASTRATGIPARFSGSGSG TEFTLTISSLQPEDFAVYYCQQYNDWLPVTFGQGTKVEIK
139113- nt	367	GAAGTGCAATTGGTGGAAACTGGAGGAGGACTTGTGCAACCTGGAGGATC

ScFv domain		ATTGCGGCTCTCATGCGCTGTCTCCGGCTTCGCCCTGTCAAATCACGGGA TGTCGTGGGTCAGACGGGCCCCGGGAAAGGGTCTGGAATGGGTGTCGGGG ATTGTGTACAGCGGCTCCACCTACTACGCCGCTTCGGTCAAGGGCCGCTT CACTATTTCACGGGACAACAGCCGCAACACCCTCTATCTGCAAATGAACT CTCTCCGCCCGGAGGATACCGCCATCTACTACTGCTCCGCACACGGCGGC GAATCCGACGTGTGGGGACAGGGAACCACTGTCACCGTGTCGTCCGCATC CGGTGGCGGAGGATCGGGTGGCCGGGCCTCCGGGGGCGGCGGCAGCGAGA CTACCCTGACCCAGTCCCCTGCCACTCTGTCCGTGAGCCCGGGAGAGAGA GCCACCCTTAGCTGCCGGGCCAGCCAGAGCGTGGGCTCCAACCTGGCCTG GTACCAGCAGAAGCCAGGACAGGGTCCCAGGCTGCTGATCTACGGAGCCT CCACTCGCGCGACCGGCATCCCCGCGAGGTTCTCCGGGTCGGGTTCCGGG ACCGAGTTCACCCTGACCATCTCCTCCCTCCAACCGGAGGACTTCGCGGT GTACTACTGTCAGCAGTACAACGATTGGCTGCCCGTGACATTTGGACAGG GGACGAAGGTGGAAATCAAA
139113- aa VH	382	EVQLVETGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSG IVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGG ESDVWGQGTTVTVSS
139113- aa VL	397	ETTLTQSPATLSVSPGERATLSCRASQSVGSNLAWYQQKPGQGPRLLIYG ASTRATGIPARFSGSGSGTEFTLTISSLQPEDFAVYYCQQYNDWLPVTFG QGTKVEIK
139114		
139114- aa ScFv domain	353	EVQLVESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSG IVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGG ESDVWGQGTTVTVSSASGGGGSGGRASGGGGSEIVLTQSPGTLSLSPGER ATLSCRASQSIGSSSLAWYQQKPGQAPRLLMYGASSRASGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYCQQYAGSPPFTFGQGTKVEIK
139114- nt ScFv domain	368	GAAGTGCAATTGGTGGAATCTGGTGGAGGACTTGTGCAACCTGGAGGATC ACTGAGACTGTCATGCGCGGTGTCCGGTTTTGCCCTGAGCAATCATGGGA TGTCGTGGGTCCGGCGCGCCCCCGGAAAGGGTCTGGAATGGGTGTCGGGT ATCGTCTACTCCGGGAGCACTTACTACGCCGCGAGCGTGAAGGGCCGCTT CACCATTTCCCGCGATAACTCCCGCAACACCCTGTACTTGCAAATGAACT CGCTCCGGCCTGAGGACACTGCCATCTACTACTGCTCCGCACACGGAGGA GAATCCGACGTGTGGGGCCAGGGAACTACCGTGACCGTCAGCAGCGCCTC CGGCGGCGGGGGCTCAGGCGGACGGGCTAGCGGCGGCGGTGGCTCCGAGA TCGTGCTGACCCAGTCGCCTGGCACTCTCTCGCTGAGCCCCGGGGAAAGG GCAACCCTGTCCTGTCGGGCCAGCCAGTCCATTGGATCATCCTCCCTCGC CTGGTATCAGCAGAAACCGGGACAGGCTCCGCGGCTGCTTATGTATGGGG CCAGCTCAAGAGCCTCCGGCATTCCCGACCGGTTCTCCGGGTCCGGTTCC GGCACCGATTTCACCCTGACTATCTCGAGGCTGGAGCCAGAGGACTTCGC CGTGTACTACTGCCAGCAGTACGCGGGGTCCCCGCCGTTCACGTTCGGAC AGGGAACCAAGGTCGAGATCAAG
139114- aa VH	383	EVQLVESGGGLVQPGGSLRLSCAVSGFALSNHGMSWVRRAPGKGLEWVSG IVYSGSTYYAASVKGRFTISRDNSRNTLYLQMNSLRPEDTAIYYCSAHGG ESDVWGQGTTVTVSS
139114- aa VL	398	EIVLTQSPGTLSLSPGERATLSCRASQSIGSSSLAWYQQKPGQAPRLLMY GASSRASGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYAGSPPFTF GQGTKVEIK
149362		
149362-aa ScFv domain	429	QVQLQESGPGLVKPSETLSLTCTVSGGSISSSYYYWGWIRQPPGKGLEWI GSIYYSGSAYYNPSLKSRVTISVDTSKNQFSLRLSSVTAADTAVYYCARH WQEWPDAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSETTLTQSPAFMSAT

		PGDKVIISCKASQDIDDAMNWYQQKPGEAPLFIIQSATSPVPGIPPRFSG SGFGTDFSLTINNIESEDAAYYFCLQHDNFPLTFGQGTKLEIK
149362-nt ScFv domain	450	CAAGTGCAGCTTCAGGAAAGCGGACCGGGCCTGGTCAAGCCATCCGAAAC TCTCTCCCTGACTTGCACTGTGTCTGGCGGTTCCATCTCATCGTCGTACT ACTACTGGGGCTGGATTAGGCAGCCGCCCGGAAAGGGACTGGAGTGGATC GGAAGCATCTACTATTCCGGCTCGGCGTACTACAACCCTAGCCTCAAGTC GAGAGTGACCATCTCCGTGGATACCTCCAAGAACCAGTTTTCCCTGCGCC TGAGCTCCGTGACCGCCGCTGACACCGCCGTGTACTACTGTGCTCGGCAT TGGCAGGAATGGCCCGATGCCTTCGACATTTGGGGCCAGGGCACTATGGT CACTGTGTCATCCGGGGGTGGAGGCAGCGGGGGAGGAGGGTCCGGGGGGG GAGGTTCAGAGACAACCTTGACCCAGTCACCCGCATTCATGTCCGCCACT CCGGGAGACAAGGTCATCATCTCGTGCAAAGCGTCCCAGGATATCGACGA TGCCATGAATTGGTACCAGCAGAAGCCTGGCGAAGCGCCGCTGTTCATTA TCCAATCCGCAACCTCGCCCGTGCCTGGAATCCCACCGCGGTTCAGCGGC AGCGGTTTCGGAACCGACTTTTCCCTGACCATTAACAACATTGAGTCCGA GGACGCCGCCTACTACTTCTGCCTGCAACACGACAACTTCCCTCTCACGT TCGGCCAGGGAACCAAGCTGGAAATCAAG
149362-aa VH	471	QVQLQESGPGLVKPSETLSLTCTVSGGSISSSYYYWGWIRQPPGKGLEWI GSIYYSGSAYYNPSLKSRVTISVDTSKNQFSLRLSSVTAADTAVYYCARH WQEWPDAFDIWGQGTMVTVSS
149362-aa VL	492	ETTLTQSPAFMSATPGDKVIISCKASQDIDDAMNWYQQKPGEAPLFIIQS ATSPVPGIPPRFSGSGFGTDFSLTINNIESEDAAYYFCLQHDNFPLTFGQ GTKLEIK
149363		
149363-aa ScFv domain	430	QVNLRESGPALVKPTQTLTLTCTFSGFSLRTSGMCVSWIRQPPGKALEWL ARIDWDEDKFYSTSLKTRLTISKDTSDNQVVLRMTNMDPADTATYYCARS GAGGTSATAFDIWGPGTMVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLS ASVGDRVTITCRASQDIYNNLAWFQLKPGSAPRSLMYAANKSQSGVPSRF SGSASGTDFTLTISSLQPEDFATYYCQHYYRFPYSFGQGTKLEIK
149363-nt ScFv domain	451	CAAGTCAATCTGCGCGAATCCGGCCCCGCCTTGGTCAAGCCTACCCAGAC CCTCACTCTGACCTGTACTTTCTCCGGCTTCTCCCTGCGGACTTCCGGGA TGTGCGTGTCCTGGATCAGACAGCCTCCGGGAAAGGCCCTGGAGTGGCTC GCTCGCATTGACTGGGATGAGGACAAGTTCTACTCCACCTCACTCAAGAC CAGGCTGACCATCAGCAAAGATACCTCTGACAACCAAGTGGTGCTCCGCA TGACCAACATGGACCCAGCCGACACTGCCACTTACTACTGCGCGAGGAGC GGAGCGGGCGGAACCTCCGCCACCGCCTTCGATATTTGGGGCCCGGGTAC CATGGTCACCGTGTCAAGCGGAGGAGGGGGGTCCGGGGGCGGCGGTTCCG GGGGAGGCGGATCGGACATTCAGATGACTCAGTCACCATCGTCCCTGAGC GCTAGCGTGGGCGACAGAGTGACAATCACTTGCCGGGCATCCCAGGACAT CTATAACAACCTTGCGTGGTTCCAGCTGAAGCCTGGTTCCGCACCGCGGT CACTTATGTACGCCGCCAACAAGAGCCAGTCGGGAGTGCCGTCCCGGTTT TCCGGTTCGGCCTCGGGAACTGACTTCACCCTGACGATCTCCAGCCTGCA ACCCGAGGATTTCGCCACCTACTACTGCCAGCACTACTACCGCTTTCCCT ACTCGTTCGGACAGGGAACCAAGCTGGAAATCAAG
149363-aa VH	472	QVNLRESGPALVKPTQTLTLTCTFSGFSLRTSGMCVSWIRQPPGKALEWL ARIDWDEDKFYSTSLKTRLTISKDTSDNQVVLRMTNMDPADTATYYCARS GAGGTSATAFDIWGPGTMVTVSS
149363-aa VL	493	DIQMTQSPSSLSASVGDRVTITCRASQDIYNNLAWFQLKPGSAPRSLMYA ANKSQSGVPSRFSGSASGTDFTLTISSLQPEDFATYYCQHYYRFPYSFGQ GTKLEIK
149364		

149364-aa ScFv domain	431	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSS ISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKTI AAVYAFDIWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSPLSLPVTPE EPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDR FSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPYTFGQGTKLEIK
149364-nt ScFv domain	452	GAAGTGCAGCTTGTCGAATCCGGGGGGGGACTGGTCAAGCCGGGCGGATC ACTGAGACTGTCCTGCGCCGCGAGCGGCTTCACGTTCTCCTCCTACTCCA TGAACTGGGTCCGCCAAGCCCCCGGGAAGGGACTGGAATGGGTGTCCTCT ATCTCCTCGTCGTCGTCCTACATCTACTACGCCGACTCCGTGAAGGGAAG ATTCACCATTTCCCGCGACAACGCAAAGAACTCACTGTACTTGCAAATGA ACTCACTCCGGGCCGAAGATACTGCTGTGTACTATTGCGCCAAGACTATT GCCGCCGTCTACGCTTTCGACATCTGGGGCCAGGGAACCACCGTGACTGT GTCGTCCGGTGGTGGTGGCTCGGGCGGAGGAGGAAGCGGCGGCGGGGGGT CCGAGATTGTGCTGACCCAGTCGCCACTGAGCCTCCCTGTGACCCCCGAG GAACCCGCCAGCATCAGCTGCCGGTCCAGCCAGTCCCTGCTCCACTCCAA CGGATACAATTACCTCGATTGGTACCTTCAGAAGCCTGGACAAAGCCCGC AGCTGCTCATCTACTTGGGATCAAACCGCGCGTCAGGAGTGCCTGACCGG TTCTCCGGCTCGGGCAGCGGTACCGATTTCACCCTGAAAATCTCCAGGGT GGAGGCAGAGGACGTGGGAGTGTATTACTGTATGCAGGCGCTGCAGACTC CGTACACATTTGGGCAGGGCACCAAGCTGGAGATCAAG
149364-aa VH	473	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSS ISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKTI AAVYAFDIWGQGTTVTVSS
149364-aa VL	494	EIVLTQSPLSLPVTPEEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQ LLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTP YTFGQGTKLEIK
149365		
149365-aa ScFv domain	432	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVSY ISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDL RGAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSSYVLTQSPSVSAAPGYTA TISCGGNNIGTKSVHWYQQKPGQAPLLVIRDDSVRPSKIPGRFSGSNSGN MATLTISGVQAGDEADFYCQVWDSDSEHVVFGGGTKLTVL
149365-nt ScFv domain	453	GAAGTCCAGCTCGTGGAGTCCGGCGGAGGCCTTGTGAAGCCTGGAGGTTC GCTGAGACTGTCCTGCGCCGCCTCCGGCTTCACCTTCTCCGACTACTACA TGTCCTGGATCAGACAGGCCCCGGGAAAGGGCCTGGAATGGGTGTCCTAC ATCTCGTCATCGGGCAGCACTATCTACTACGCGGACTCAGTGAAGGGCG GTTCACCATTTCCCGGGATAACGCGAAGAACTCGCTGTATCTGCAAATGA ACTCACTGAGGGCCGAGGACACCGCCGTGTACTACTGCGCCCGCGATCTC CGCGGGGCATTTGACATCTGGGGACAGGGAACCATGGTCACAGTGTCCAG CGGAGGGGGAGGATCGGGTGGCGGAGGTTCCGGGGGTGGAGGCTCCTCCT ACGTGCTGACTCAGAGCCCAAGCGTCAGCGCTGCGCCCGGTTACACGGCA ACCATCTCCTGTGGCGGAAACAACATTGGGACCAAGTCTGTGCACTGGTA TCAGCAGAAGCCGGGCCAAGCTCCCCTGTTGGTGATCCGCGATGACTCCG TGCGGCCTAGCAAAATTCCGGGACGGTTCTCCGGCTCCAACAGCGGCAAT ATGGCCACTCTCACCATCTCGGGAGTGCAGGCCGGAGATGAAGCCGACTT CTACTGCCAAGTCTGGGACTCAGACTCCGAGCATGTGGTGTTCGGGGGCG GAACCAAGCTGACTGTGCTC
149365-aa VH	474	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVSY ISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDL RGAFDIWGQGTMVTVSS
149365-aa VL	495	SYVLTQSPSVSAAPGYTATISCGGNNIGTKSVHWYQQKPGQAPLLVIRDD SVRPSKIPGRFSGSNSGNMATLTISGVQAGDEADFYCQVWDSDSEHVVFG

		GGTKLTVL
149366		
149366-aa ScFv domain	433	QVQLVQSGAEVKKPGASVKVSCKPSGYTVTSHYIHWVRRAPGQGLEWMGM INPSGGVTAYSQTLQGRVTMTSDTSSSTVYMELSSLRSEDTAMYYCAREG SGSGWYFDFWGRGTLVTVSSGGGGSGGGGSGGGGSSYVLTQPPSVSVSPG QTASITCSGDGLSKKYVSWYQQKAGQSPVVLISRDKERPSGIPDRFSGSN SADTATLTISGTQAMDEADYYCQAWDDTTVVFGGGTKLTVL
149366-nt ScFv domain	454	CAAGTGCAGCTGGTGCAGAGCGGGGCCGAAGTCAAGAAGCCGGGAGCCTC CGTGAAAGTGTCCTGCAAGCCTTCGGGATACACCGTGACCTCCCACTACA TTCATTGGGTCCGCCGCGCCCCCGGCCAAGGACTCGAGTGGATGGGCATG ATCAACCCTAGCGGCGGAGTGACCGCGTACAGCCAGACGCTGCAGGGACG CGTGACTATGACCTCGGATACCTCCTCCTCCACCGTCTATATGGAACTGT CCAGCCTGCGGTCCGAGGATACCGCCATGTACTACTGCGCCCGGGAAGGA TCAGGCTCCGGGTGGTATTTCGACTTCTGGGGAAGAGGCACCCTCGTGAC TGTGTCATCTGGGGGAGGGGGTTCCGGTGGTGGCGGATCGGGAGGAGGCG GTTCATCCTACGTGCTGACCCAGCCACCCTCCGTGTCCGTGAGCCCCGGC CAGACTGCATCGATTACATGTAGCGGCGACGGCCTCTCCAAGAAATACGT GTCGTGGTACCAGCAGAAGGCCGGACAGAGCCCGGTGGTGCTGATCTCAA GAGATAAGGAGCGGCCTAGCGGAATCCCGGACAGGTTCTCGGGTTCCAAC TCCGCGGACACTGCTACTCTGACCATCTCGGGGACCCAGGCTATGGACGA AGCCGATTACTACTGCCAAGCCTGGGACGACACTACTGTCGTGTTTGGAG GGGGCACCAAGTTGACCGTCCTT
149366-aa VH	475	QVQLVQSGAEVKKPGASVKVSCKPSGYTVTSHYIHWVRRAPGQGLEWMGM INPSGGVTAYSQTLQGRVTMTSDTSSSTVYMELSSLRSEDTAMYYCAREG SGSGWYFDFWGRGTLVTVSS
149366-aa VL	496	SYVLTQPPSVSVSPGQTASITCSGDGLSKKYVSWYQQKAGQSPVVLISRD KERPSGIPDRFSGSNSADTATLTISGTQAMDEADYYCQAWDDTTVVFGGG TKLTVL
149367		
149367-aa ScFv domain	434	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARA GIAARLRGAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSDIVMTQSPSSVS ASVGDRVIITCRASQGIRNWLAWYQQKPGKAPNLLIYAASNLQSGVPSRF SGSGSGADFTLTISSLQPEDVATYYCQKYNSAPFTFGPGTKVDIK
149367-nt ScFv domain	455	CAAGTGCAGCTTCAGGAGAGCGGCCCGGGACTCGTGAAGCCGTCCCAGAC CCTGTCCCTGACTTGCACCGTGTCGGGAGGAAGCATCTCGAGCGGAGGCT ACTATTGGTCGTGGATTCGGCAGCACCCTGGAAAGGGCCTGGAATGGATC GGCTACATCTACTACTCCGGCTCGACCTACTACAACCCATCGCTGAAGTC CAGAGTGACAATCTCAGTGGACACGTCCAAGAATCAGTTCAGCCTGAAGC TCTCTTCCGTGACTGCGGCCGACACCGCCGTGTACTACTGCGCACGCGCT GGAATTGCCGCCCGGCTGAGGGGTGCCTTCGACATTTGGGGACAGGGCAC CATGGTCACCGTGTCCTCCGGCGGCGGAGGTTCCGGGGGTGGAGGCTCAG GAGGAGGGGGGTCCGACATCGTCATGACTCAGTCGCCCTCAAGCGTCAGC GCGTCCGTCGGGGACAGAGTGATCATCACCTGTCGGGCGTCCCAGGGAAT TCGCAACTGGCTGGCCTGGTATCAGCAGAAGCCCGGAAAGGCCCCCAACC TGTTGATCTACGCCGCCTCAAACCTCCAATCCGGGGTGCCGAGCCGCTTC AGCGGCTCCGGTTCGGGTGCCGATTTCACTCTGACCATCTCCTCCCTGCA ACCTGAAGATGTGGCTACCTACTACTGCCAAAAGTACAACTCCGCACCTT TTACTTTCGGACCGGGGACCAAAGTGGACATTAAG
149367-aa VH	476	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARA

		GIAARLRGAFDIWGQGTMVTVSS
149367-aa VL	497	DIVMTQSPSSVSASVGDRVIITCRASQGIRNWLAWYQQKPGKAPNLLIYA ASNLQSGVPSRFSGSGSGADFTLTISSLQPEDVATYYCQKYNSAPFTFGP GTKVDIK
149368		
149368-aa ScFv domain	435	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGG IIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARRG GYQLLRWDVGLLRSAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSSYVLTQ PPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVLYGKNNRPSG VPDRFSGSRSGTTASLTITGAQAEDEADYYCSSRDSSGDHLRVFGTGTKV TVL
149368-nt ScFv domain	456	CAAGTGCAGCTGGTCCAGTCGGGCGCCGAGGTCAAGAAGCCCGGGAGCTC TGTGAAAGTGTCCTGCAAGGCCTCCGGGGGCACCTTTAGCTCCTACGCCA TCTCCTGGGTCCGCCAAGCACCGGGTCAAGGCCTGGAGTGGATGGGGGGA ATTATCCCTATCTTCGGCACTGCCAACTACGCCCAGAAGTTCCAGGGACG CGTGACCATTACCGCGGACGAATCCACCTCCACCGCTTATATGGAGCTGT CCAGCTTGCGCTCGGAAGATACCGCCGTGTACTACTGCGCCCGGAGGGGT GGATACCAGCTGCTGAGATGGGACGTGGGCCTCCTGCGGTCGGCGTTCGA CATCTGGGGCCAGGGCACTATGGTCACTGTGTCCAGCGGAGGAGGCGGAT CGGGAGGCGGCGGATCAGGGGGAGGCGGTTCCAGCTACGTGCTTACTCAA CCCCCTTCGGTGTCCGTGGCCCCGGGACAGACCGCCAGAATCACTTGCGG AGGAAACAACATTGGGTCCAAGAGCGTGCATTGGTACCAGCAGAAGCCAG GACAGGCCCCTGTGCTGGTGCTCTACGGGAAGAACAATCGGCCCAGCGGA GTGCCGGACAGGTTCTCGGGTTCACGCTCCGGTACAACCGCTTCACTGAC TATCACCGGGGCCCAGGCAGAGGATGAAGCGGACTACTACTGTTCCTCCC GGGATTCATCCGGCGACCACCTCCGGGTGTTCGGAACCGGAACGAAGGTC ACCGTGCTG
149368-aa VH	477	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGG IIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARRG GYQLLRWDVGLLRSAFDIWGQGTMVTVSS
149368-aa VL	498	SYVLTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVLYGK NNRPSGVPDRFSGSRSGTTASLTITGAQAEDEADYYCSSRDSSGDHLRVF GTGTKVTVL
149369		
149369-aa ScFv domain	436	EVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEWL GRTYYRSKWYSFYAISLKSRIIINPDTSKNQFSLQLKSVTPEDTAVYYCA RSSPEGLFLYWFDPWGQGTLVTVSSGGDGSGGGGSGGGGSSSELTQDPAV SVALGQTIRITCQGDSLGNYYATWYQQKPGQAPVLVIYGTNNRPSGIPDR FSASSSGNTASLTITGAQAEDEADYYCNSRDSSGHHLLFGTGTKVTVL
149369-nt ScFv domain	457	GAAGTGCAGCTCCAACAGTCAGGACCGGGGCTCGTGAAGCCATCCCAGAC CCTGTCCCTGACTTGTGCCATCTCGGGAGATAGCGTGTCATCGAACTCCG CCGCCTGGAACTGGATTCGGCAGAGCCCGTCCCGCGGACTGGAGTGGCTT GGAAGGACCTACTACCGGTCCAAGTGGTACTCTTTCTACGCGATCTCGCT GAAGTCCCGCATTATCATTAACCCTGATACCTCCAAGAATCAGTTCTCCC TCCAACTGAAATCCGTCACCCCCGAGGACACAGCAGTGTATTACTGCGCA CGGAGCAGCCCCGAAGGACTGTTCCTGTATTGGTTTGACCCCTGGGGCCA GGGGACTCTTGTGACCGTGTCGAGCGGCGGAGATGGGTCCGGTGGCGGTG GTTCGGGGGGCGGCGGATCATCATCCGAACTGACCCAGGACCCGGCTGTG TCCGTGGCGCTGGGACAAACCATCCGCATTACGTGCCAGGGAGACTCCCT GGGCAACTACTACGCCACTTGGTACCAGCAGAAGCCGGGCCAAGCCCCTG TGTTGGTCATCTACGGGACCAACAACAGACCTTCCGGCATCCCCGACCGG

		TTCAGCGCTTCGTCCTCCGGCAACACTGCCAGCCTGACCATCACTGGAGC GCAGGCCGAAGATGAGGCCGACTACTACTGCAACAGCAGAGACTCCTCGG GTCATCACCTCTTGTTCGGAACTGGAACCAAGGTCACCGTGCTG
149369-aa VH	478	EVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEWL GRTYYRSKWYSFYAISLKSRIIINPDTSKNQFSLQLKSVTPEDTAVYYCA RSSPEGLFLYWFDPWGQGTLVTVSS
149369-aa VL	499	SSELTQDPAVSVALGQTIRITCQGDSLGNYYATWYQQKPGQAPVLVIYGT NNRPSGIPDRFSASSSGNTASLTITGAQAEDEADYYCNSRDSSGHHLLFG TGTKVTVL
BCMA_EBB-C1978-A4		
BCMA_EBB-C1978-A4 - aa ScFv domain	437	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKVE GSGSLDYWGQGTLVTVSSGGGGSGGGGSGGGGSEIVMTQSPGTLSLSPGE RATLSCRASQSVSSAYLAWYQQKPGQPPRLLISGASTRATGIPDRFGGSG SGTDFTLTISRLEPEDFAVYYCQHYGSSFNGSSLFTFGQGTRLEIK
BCMA_EBB-C1978-A4 - nt ScFv domain	458	GAAGTGCAGCTCGTGGAGTCAGGAGGCGGCCTGGTCCAGCCGGGAGGGTC CCTTAGACTGTCATGCGCCGCAAGCGGATTCACTTTCTCCTCCTATGCCA TGAGCTGGGTCCGCCAAGCCCCCGGAAAGGGACTGGAATGGGTGTCCGCC ATCTCGGGGTCTGGAGGCTCAACTTACTACGCTGACTCCGTGAAGGGACG GTTCACCATTAGCCGCGACAACTCCAAGAACACCCTCTACCTCCAAATGA ACTCCCTGCGGGCCGAGGATACCGCCGTCTACTACTGCGCCAAAGTGGAA GGTTCAGGATCGCTGGACTACTGGGGACAGGGTACTCTCGTGACCGTGTC ATCGGGCGGAGGAGGTTCCGGCGGTGGCGGCTCCGGCGGCGGAGGGTCGG AGATCGTGATGACCCAGAGCCCTGGTACTCTGAGCCTTTCGCCGGGAGAA AGGGCCACCCTGTCCTGCCGCGCTTCCCAATCCGTGTCCTCCGCGTACTT GGCGTGGTACCAGCAGAAGCCGGGACAGCCCCCTCGGCTGCTGATCAGCG GGGCCAGCACCCGGGCAACCGGAATCCCAGACAGATTCGGGGGTTCCGGC AGCGGCACAGATTTCACCCTGACTATTTCGAGGTTGGAGCCCGAGGACTT TGCGGTGTATTACTGTCAGCACTACGGGTCGTCCTTTAATGGCTCCAGCC TGTTCACGTTCGGACAGGGGACCCGCCTGGAAATCAAG
BCMA_EBB-C1978-A4 - aa VH	479	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKVE GSGSLDYWGQGTLVTVSS
BCMA_EBB-C1978-A4 - aa VL	500	EIVMTQSPGTLSLSPGERATLSCRASQSVSSAYLAWYQQKPGQPPRLLIS GASTRATGIPDRFGGSGSGTDFTLTISRLEPEDFAVYYCQHYGSSFNGSS LFTFGQGTRLEIK
BCMA_EBB-C1978-G1		
BCMA_EBB-C1978-G1 - aa ScFv domain	438	EVQLVETGGGLVQPGGSLRLSCAASGITFSRYPMSWVRQAPGKGLEWVSG ISDSGVSTYYADSAKGRFTISRDNSKNTLFLQMSSLRDEDTAVYYCVTRA GSEASDIWGQGTMVTVSSGGGGSGGGGSGGGGSEIVLTQSPATLSLSPGE RATLSCRASQSVSNSLAWYQQKPGQAPRLLIYDASSRATGIPDRFSGSGS GTDFTLTISRLEPEDFAIYYCQQFGTSSGLTFGGGTKLEIK
BCMA_EBB-C1978-G1 - nt ScFv domain	459	GAAGTGCAACTGGTGGAAACCGGTGGCGGCCTGGTGCAGCCTGGAGGATC ATTGAGGCTGTCATGCGCGGCCAGCGGTATTACCTTCTCCCGGTACCCCA TGTCCTGGGTCAGACAGGCCCCGGGGAAAGGGCTTGAATGGGTGTCCGGG ATCTCGGACTCCGGTGTCAGCACTTACTACGCCGACTCCGCCAAGGGACG CTTCACCATTTCCCGGGACAACTCGAAGAACACCCTGTTCCTCCAAATGA GCTCCCTCCGGGACGAGGATACTGCAGTGTACTACTGCGTGACCCGCGCC GGGTCCGAGGCGTCTGACATTTGGGGACAGGGCACTATGGTCACCGTGTC

		GTCCGGCGGAGGGGGCTCGGGAGGCGGTGGCAGCGGAGGAGGAGGGTCCG AGATCGTGCTGACCCAATCCCCGGCCACCCTCTCGCTGAGCCCTGGAGAA AGGGCAACCTTGTCCTGTCGCGCGAGCCAGTCCGTGAGCAACTCCCTGGC CTGGTACCAGCAGAAGCCCGGACAGGCTCCGAGACTTCTGATCTACGACG CTTCGAGCCGGGCCACTGGAATCCCCGACCGCTTTTCGGGGTCCGGCTCA GGAACCGATTTCACCCTGACAATCTCACGGCTGGAGCCAGAGGATTTCGC CATCTATTACTGCCAGCAGTTCGGTACTTCCTCCGGCCTGACTTTCGGAG GCGGCACGAAGCTCGAAATCAAG
BCMA_EBB-C1978-G1 - aa VH	480	EVQLVETGGGLVQPGGSLRLSCAASGITFSRYPMSWVRQAPGKGLEWVSG ISDSGVSTYYADSAKGRFTISRDNSKNTLFLQMSSLRDEDTAVYYCVTRA GSEASDIWGQGTMVTVSS
BCMA_EBB-C1978-G1 - aa VL	501	EIVLTQSPATLSLSPGERATLSCRASQSVSNSLAWYQQKPGQAPRLLIYD ASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAIYYCQQFGTSSGLTFG GGTKLEIK
BCMA_EBB-C1979-C1		
BCMA_EBB-C1979-C1 - aa ScFv domain	439	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA ISGSGGSTYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCARAT YKRELRYYYGMDVWGQGTMVTVSSGGGGSGGGGSGGGGSEIVMTQSPGTV SLSPGERATLSCRASQSVSSSFLAWYQQKPGQAPRLLIYGASSRATGIPD RFSGSGSGTDFTLTISRLEPEDSAVYYCQQYHSSPSWTFGQGTRLEIK
BCMA_EBB-C1979-C1 - nt ScFv domain	460	CAAGTGCAGCTCGTGGAATCGGGTGGCGGACTGGTGCAGCCGGGGGGCTC ACTTAGACTGTCCTGCGCGGCCAGCGGATTCACTTTCTCCTCCTACGCCA TGTCCTGGGTCAGACAGGCCCCTGGAAAGGGCCTGGAATGGGTGTCCGCA ATCAGCGGCAGCGGCGGCTCGACCTATTACGCGGATTCAGTGAAGGGCAG ATTCACCATTTCCCGGGACAACGCCAAGAACTCCTTGTACCTTCAAATGA ACTCCCTCCGCGCGGAAGATACCGCAATCTACTACTGCGCTCGGGCCACT TACAAGAGGGAACTGCGCTACTACTACGGGATGGACGTCTGGGGCCAGGG AACCATGGTCACCGTGTCCAGCGGAGGAGGAGGATCGGGAGGAGGCGGTA GCGGGGGTGGAGGGTCGGAGATCGTGATGACCCAGTCCCCCGGCACTGTG TCGCTGTCCCCCGGCGAACGGGCCACCCTGTCATGTCGGGCCAGCCAGTC AGTGTCGTCAAGCTTCCTCGCCTGGTACCAGCAGAAACCGGGACAAGCTC CCCGCCTGCTGATCTACGGAGCCAGCAGCCGGGCCACCGGTATTCCTGAC CGGTTCTCCGGTTCGGGGTCCGGGACCGACTTTACTCTGACTATCTCTCG CCTCGAGCCAGAGGACTCCGCCGTGTATTACTGCCAGCAGTACCACTCCT CCCCGTCCTGGACGTTCGGACAGGGCACAAGGCTGGAGATTAAG
BCMA_EBB-C1979-C1 - aa VH	481	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA ISGSGGSTYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIYYCARAT YKRELRYYYGMDVWGQGTMVTVSS
BCMA_EBB-C1979-C1 - aa VL	502	EIVMTQSPGTVSLSPGERATLSCRASQSVSSSFLAWYQQKPGQAPRLLIY GASSRATGIPDRFSGSGSGTDFTLTISRLEPEDSAVYYCQQYHSSPSWTF GQGTRLEIK
BCMA_EBB-C1978-C7		
BCMA_EBB-C1978-C7 - aa ScFv domain	440	EVQLVETGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNTLKAEDTAVYYCARAT YKRELRYYYGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSPSTL SLSPGESATLSCRASQSVSTTFLAWYQQKPGQAPRLLIYGSSNRATGIPD RFSGSGSGTDFTLTIRRLEPEDFAVYYCQQYHSSPSWTFGQGTKVEIK

BCMA_EBB-C1978-C7 - nt ScFv domain	461	GAGGTGCAGCTTGTGGAAACCGGTGGCGGACTGGTGCAGCCCGGAGGAAG CCTCAGGCTGTCCTGCGCCGCGTCCGGCTTCACCTTCTCCTCGTACGCCA TGTCCTGGGTCCGCCAGGCCCCCGGAAAGGGCCTGGAATGGGTGTCCGCC ATCTCTGGAAGCGGAGGTTCCACGTACTACGCGGACAGCGTCAAGGGAAG GTTCACAATCTCCCGCGATAATTCGAAGAACACTCTGTACCTTCAAATGA ACACCCTGAAGGCCGAGGACACTGCTGTGTACTACTGCGCACGGGCCACC TACAAGAGAGAGCTCCGGTACTACTACGGAATGGACGTCTGGGGCCAGGG AACTACTGTGACCGTGTCCTCGGGAGGGGGTGGCTCCGGGGGGGGCGGCT CCGGCGGAGGCGGTTCCGAGATTGTGCTGACCCAGTCACCTTCAACTCTG TCGCTGTCCCCGGGAGAGAGCGCTACTCTGAGCTGCCGGGCCAGCCAGTC CGTGTCCACCACCTTCCTCGCCTGGTATCAGCAGAAGCCGGGGCAGGCAC CACGGCTCTTGATCTACGGGTCAAGCAACAGAGCGACCGGAATTCCTGAC CGCTTCTCGGGGAGCGGTTCAGGCACCGACTTCACCCTGACTATCCGGCG CCTGGAACCCGAAGATTTCGCCGTGTATTACTGTCAACAGTACCACTCCT CGCCGTCCTGGACCTTTGGCCAAGGAACCAAAGTGGAAATCAAG
BCMA_EBB-C1978-C7 - aa VH	482	EVQLVETGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNTLKAEDTAVYYCARAT YKRELRYYYGMDVWGQGTTVTVSS
BCMA_EBB-C1978-C7 - aa VL	503	EIVLTQSPSTLSLSPGESATLSCRASQSVSTTFLAWYQQKPGQAPRLLIY GSSNRATGIPDRFSGSGSGTDFTLTIRRLEPEDFAVYYCQQYHSSPSWTF GQGTKVEIK
BCMA_EBB-C1978-D10		
BCMA_EBB-C1978-D10 - aa ScFv domain	441	EVQLVETGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSG ISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCARVG KAVPDVWGQGTTVTVSSGGGGSGGGGSGGGGSDIVMTQTPSSLSASVGDR VTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQSYSTPYSFGQGTRLEIK
BCMA_EBB-C1978-D10-nt ScFv domain	462	GAAGTGCAGCTCGTGGAAACTGGAGGTGGACTCGTGCAGCCTGGACGGTC GCTGCGGCTGAGCTGCGCTGCATCCGGCTTCACCTTCGACGATTATGCCA TGCACTGGGTCAGACAGGCGCCAGGGAAGGGACTTGAGTGGGTGTCCGGT ATCAGCTGGAATAGCGGCTCAATCGGATACGCGGACTCCGTGAAGGGAAG GTTCACCATTTCCCGCGACAACGCCAAGAACTCCCTGTACTTGCAAATGA ACAGCCTCCGGGATGAGGACACTGCCGTGTACTACTGCGCCCGCGTCGGA AAAGCTGTGCCCGACGTCTGGGGCCAGGGAACCACTGTGACCGTGTCCAG CGGCGGGGGTGGATCGGGCGGTGGAGGGTCCGGTGGAGGGGGCTCAGATA TTGTGATGACCCAGACCCCCTCGTCCCTGTCCGCCTCGGTCGGCGACCGC GTGACTATCACATGTAGAGCCTCGCAGAGCATCTCCAGCTACCTGAACTG GTATCAGCAGAAGCCGGGGAAGGCCCCGAAGCTCCTGATCTACGCGGCAT CATCACTGCAATCGGGAGTGCCGAGCCGGTTTTCCGGGTCCGGCTCCGGC ACCGACTTCACGCTGACCATTTCTTCCCTGCAACCCGAGGACTTCGCCAC TTACTACTGCCAGCAGTCCTACTCCACCCCTTACTCCTTCGGCCAAGGAA CCAGGCTGGAAATCAAG
BCMA_EBB-C1978-D10 - aa VH	483	EVQLVETGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSG ISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCARVG KAVPDVWGQGTTVTVSS
BCMA_EBB-C1978-D10-aa	504	DIVMTQTPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYA ASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPYSFGQ GTRLEIK

VL		
BCMA_EBB-C1979-C12		
BCMA_EBB-C1979-C12-aa ScFv domain	442	EVQLVESGGGLVQPGRSLRLSCTASGFTFDDYAMHWVRQRPGKGLEWVAS INWKGNSLAYGDSVKGRFAISRDNAKNTVFLQMNSLRTEDTAVYYCASHQ GVAYYNYAMDVWGRGTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSL SPGERATLSCRATQSIGSSFLAWYQQRPGQAPRLLIYGASQRATGIPDRF SGRGSGTDFTLTISRVEPEDSAVYYCQHYESSPSWTFGQGTKVEIK
BCMA_EBB-C1979-C12 - nt ScFv domain	463	GAAGTGCAGCTCGTGGAGAGCGGGGGAGGATTGGTGCAGCCCGGAAGGTC CCTGCGGCTCTCCTGCACTGCGTCTGGCTTCACCTTCGACGACTACGCGA TGCACTGGGTCAGACAGCGCCCGGGAAAGGGCCTGGAATGGGTCGCCTCA ATCAACTGGAAGGGAAACTCCCTGGCCTATGGCGACAGCGTGAAGGGCCG CTTCGCCATTTCGCGCGACAACGCCAAGAACACCGTGTTTCTGCAAATGA ATTCCCTGCGGACCGAGGATACCGCTGTGTACTACTGCGCCAGCCACCAG GGCGTGGCATACTATAACTACGCCATGGACGTGTGGGGAAGAGGGACGCT CGTCACCGTGTCCTCCGGGGGCGGTGGATCGGGTGGAGGAGGAAGCGGTG GCGGGGGCAGCGAAATCGTGCTGACTCAGAGCCCGGGAACTCTTTCACTG TCCCCGGGAGAACGGGCCACTCTCTCGTGCCGGGCCACCCAGTCCATCGG CTCCTCCTTCCTTGCCTGGTACCAGCAGAGGCCAGGACAGGCGCCCCGCC TGCTGATCTACGGTGCTTCCCAACGCGCCACTGGCATTCCTGACCGGTTC AGCGGCAGAGGGTCGGGAACCGATTTCACACTGACCATTTCCCGGGTGGA GCCCGAAGATTCGGCAGTCTACTACTGTCAGCATTACGAGTCCTCCCCTT CATGGACCTTCGGTCAAGGGACCAAAGTGGAGATCAAG
BCMA_EBB-C1979-C12 - aa VH	484	EVQLVESGGGLVQPGRSLRLSCTASGFTFDDYAMHWVRQRPGKGLEWVAS INWKGNSLAYGDSVKGRFAISRDNAKNTVFLQMNSLRTEDTAVYYCASHQ GVAYYNYAMDVWGRGTLVTVSS
BCMA_EBB-C1979-C12 - aa VL	505	EIVLTQSPGTLSLSPGERATLSCRATQSIGSSFLAWYQQRPGQAPRLLIY GASQRATGIPDRFSGRGSGTDFTLTISRVEPEDSAVYYCQHYESSPSWTF GQGTKVEIK
BCMA_EBB-C1980-G4		
BCMA_EBB-C1980-G4- aa ScFv domain	443	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKVV RDGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSPATLSLSPGER ATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGNGS GTDFTLTISRLEPEDFAVYYCQQYGSPPRFTFGPGTKVDIK
BCMA_EBB-C1980-G4- nt ScFv domain	464	GAGGTGCAGTTGGTCGAAAGCGGGGGCGGGCTTGTGCAGCCTGGCGGATC ACTGCGGCTGTCCTGCGCGGCATCAGGCTTCACGTTTTCTTCCTACGCCA TGTCCTGGGTGCGCCAGGCCCCTGGAAAGGGACTGGAATGGGTGTCCGCG ATTTCGGGGTCCGGCGGGAGCACCTACTACGCCGATTCCGTGAAGGGCCG CTTCACTATCTCGCGGGACAACTCCAAGAACACCCTCTACCTCCAAATGA ATAGCCTGCGGGCCGAGGATACCGCCGTCTACTATTGCGCTAAGGTCGTG CGCGACGGAATGGACGTGTGGGGACAGGGTACCACCGTGACAGTGTCCTC GGGGGGAGGCGGTAGCGGCGGAGGAGGAAGCGGTGGTGGAGGTTCCGAGA TTGTGCTGACTCAATCACCCGCGACCCTGAGCCTGTCCCCCGGCGAAAGG GCCACTCTGTCCTGTCGGGCCAGCCAATCAGTCTCCTCCTCGTACCTGGC CTGGTACCAGCAGAAGCCAGGACAGGCTCCGAGACTCCTTATCTATGGCG CATCCTCCCGCGCCACCGGAATCCCGGATAGGTTCTCGGGAAACGGATCG GGGACCGACTTCACTCTCACCATCTCCCGGCTGGAACCGGAGGACTTCGC CGTGTACTACTGCCAGCAGTACGGCAGCCCGCCTAGATTCACTTTCGGCC CCGGCACCAAAGTGGACATCAAG

BCMA_EBB-C1980-G4- aa VH	485	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKVV RDGMDVWGQGTTVTVSS
BCMA_EBB-C1980-G4- aa VL	506	EIVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIY GASSRATGIPDRFSGNGSGTDFTLTISRLEPEDFAVYYCQQYGSPPRFTF GPGTKVDIK
BCMA_EBB-C1980-D2		
BCMA_EBB-C1980-D2- aa ScFv domain	444	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIP QTGTFDYWGQGTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSLSPGE RATLSCRASQSVSSSYLAWYQQRPGQAPRLLIYGASSRATGIPDRFSGSG SGTDFTLTISRLEPEDFAVYYCQHYGSSPSWTFGQGTRLEIK
BCMA_EBB-C1980-D2- nt ScFv domain	465	GAAGTGCAGCTGCTGGAGTCCGGCGGTGGATTGGTGCAACCGGGGGGATC GCTCAGACTGTCCTGTGCGGCGTCAGGCTTCACCTTCTCGAGCTACGCCA TGTCATGGGTCAGACAGGCCCCTGGAAAGGGTCTGGAATGGGTGTCCGCC ATTTCCGGGAGCGGGGGATCTACATACTACGCCGATAGCGTGAAGGGCCG CTTCACCATTTCCCGGGACAACTCCAAGAACACTCTCTATCTGCAAATGA ACTCCCTCCGCGCTGAGGACACTGCCGTGTACTACTGCGCCAAAATCCCT CAGACCGGCACCTTCGACTACTGGGGACAGGGGACTCTGGTCACCGTCAG CAGCGGTGGCGGAGGTTCGGGGGGAGGAGGAAGCGGCGGCGGAGGGTCCG AGATTGTGCTGACCCAGTCACCCGGCACTTTGTCCCTGTCGCCTGGAGAA AGGGCCACCCTTTCCTGCCGGGCATCCCAATCCGTGTCCTCCTCGTACCT GGCCTGGTACCAGCAGAGGCCCGGACAGGCCCCACGGCTTCTGATCTACG GAGCAAGCAGCCGCGCGACCGGTATCCCGGACCGGTTTTCGGGCTCGGGC TCAGGAACTGACTTCACCCTCACCATCTCCCGCCTGGAACCCGAAGATTT CGCTGTGTATTACTGCCAGCACTACGGCAGCTCCCCGTCCTGGACGTTCG GCCAGGGAACTCGGCTGGAGATCAAG
BCMA_EBB-C1980-D2- aa VH	486	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIP QTGTFDYWGQGTLVTVSS
BCMA_EBB-C1980-D2- aa VL	507	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQRPGQAPRLLIY GASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQHYGSSPSWTF GQGTRLEIK
BCMA_EBB-C1978-A10		
BCMA_EBB-C1978-A10- aa ScFv domain	445	EVQLVETGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA ISGSGGSTYYADSVKGRFTMSRENDKNSVFLQMNSLRVEDTGVYYCARAN YKRELRYYYGMDVWGQGTMVTVSSGGGGSGGGGSGGGGSEIVMTQSPGTL SLSPGESATLSCRASQRVASNYLAWYQHKPGQAPSLLISGASSRATGVPD RFSGSGSGTDFTLAISRLEPEDSAVYYCQHYDSSPSWTFGQGTKVEIK
BCMA_EBB-C1978-A10- nt ScFv domain	466	GAAGTGCAACTGGTGGAAACCGGTGGAGGACTCGTGCAGCCTGGCGGCAG CCTCCGGCTGAGCTGCGCCGCTTCGGGATTCACCTTTTCCTCCTACGCGA TGTCTTGGGTCAGACAGGCCCCCGGAAAGGGGCTGGAATGGGTGTCAGCC ATCTCCGGCTCCGGCGGATCAACGTACTACGCCGACTCCGTGAAAGGCCG GTTCACCATGTCGCGCGAGAATGACAAGAACTCCGTGTTCCTGCAAATGA ACTCCCTGAGGGTGGAGGACACCGGAGTGTACTATTGTGCGCGCGCCAAC TACAAGAGAGAGCTGCGGTACTACTACGGAATGGACGTCTGGGGACAGGG AACTATGGTGACCGTGTCATCCGGTGGAGGGGGAAGCGGCGGTGGAGGCA GCGGGGGCGGGGGTTCAGAAATTGTCATGACCCAGTCCCCGGGAACTCTT TCCCTCTCCCCCGGGGAATCCGCGACTTTGTCCTGCCGGGCCAGCCAGCG CGTGGCCTCGAACTACCTCGCATGGTACCAGCATAAGCCAGGCCAAGCCC CTTCCCTGCTGATTTCCGGGGCTAGCAGCCGCGCCACTGGCGTGCCGGAT

		AGGTTCTCGGGAAGCGGCTCGGGTACCGATTTCACCCTGGCAATCTCGCG GCTGGAACCGGAGGATTCGGCCGTGTACTACTGCCAGCACTATGACTCAT CCCCCTCCTGGACATTCGGACAGGGCACCAAGGTCGAGATCAAG
BCMA_EBB-C1978-A10-aa VH	487	EVQLVETGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA ISGSGGSTYYADSVKGRFTMSRENDKNSVFLQMNSLRVEDTGVYYCARAN YKRELRYYYGMDVWGQGTMVTVSS
BCMA_EBB-C1978-A10-aa VL	508	EIVMTQSPGTLSLSPGESATLSCRASQRVASNYLAWYQHKPGQAPSLLIS GASSRATGVPDRFSGSGSGTDFTLAISRLEPEDSAVYYCQHYDSSPSWTF GQGTKVEIK
BCMA_EBB-C1978-D4		
BCMA_EBB-C1978-D4- aa ScFv domain	446	EVQLLETGGGLVQPGGSLRLSCAASGFSFSSYAMSWVRQAPGKGLEWVSA ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKAL VGATGAFDIWGQGTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSLSP GERATLSCRASQSLSSNFLAWYQQKPGQAPGLLIYGASNWATGTPDRFSG SGSGTDFTLTITRLEPEDFAVYYCQYYGTSPMYTFGQGTKVEIK
BCMA_EBB-C1978-D4- nt ScFv domain	467	GAAGTGCAGCTGCTCGAAACCGGTGGAGGGCTGGTGCAGCCAGGGGGCTC CCTGAGGCTTTCATGCGCCGCTAGCGGATTCTCCTTCTCCTCTTACGCCA TGTCGTGGGTCCGCCAAGCCCCTGGAAAAGGCCTGGAATGGGTGTCCGCG ATTTCCGGGAGCGGAGGTTCGACCTATTACGCCGACTCCGTGAAGGGCCG CTTTACCATCTCCCGGGATAACTCCAAGAACACTCTGTACCTCCAAATGA ACTCGCTGAGAGCCGAGGACACCGCCGTGTATTACTGCGCGAAGGCGCTG GTCGGCGCGACTGGGGCATTCGACATCTGGGGACAGGGAACTCTTGTGAC CGTGTCGAGCGGAGGCGGCGGCTCCGGCGGAGGAGGGAGCGGGGGCGGTG GTTCCGAAATCGTGTTGACTCAGTCCCCGGGAACCCTGAGCTTGTCACCC GGGGAGCGGGCCACTCTCTCCTGTCGCGCCTCCCAATCGCTCTCATCCAA TTTCCTGGCCTGGTACCAGCAGAAGCCCGGACAGGCCCCGGGCCTGCTCA TCTACGGCGCTTCAAACTGGGCAACGGGAACCCCTGATCGGTTCAGCGGA AGCGGATCGGGTACTGACTTTACCCTGACCATCACCAGACTGGAACCGGA GGACTTCGCCGTGTACTACTGCCAGTACTACGGCACCTCCCCCATGTACA CATTCGGACAGGGTACCAAGGTCGAGATTAAG
BCMA_EBB-C1978-D4- aa VH	488	EVQLLETGGGLVQPGGSLRLSCAASGFSFSSYAMSWVRQAPGKGLEWVSA ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKAL VGATGAFDIWGQGTLVTVSS
BCMA_EBB-C1978-D4- aa VL	509	EIVLTQSPGTLSLSPGERATLSCRASQSLSSNFLAWYQQKPGQAPGLLIY GASNWATGTPDRFSGSGSGTDFTLTITRLEPEDFAVYYCQYYGTSPMYTF GQGTKVEIK
BCMA_EBB-C1980-A2		
BCMA_EBB-C1980-A2- aa ScFv domain	447	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVLWF GEGFDPWGQGTLVTVSSGGGGSGGGGSGGGGSDIVLTQSPLSLPVTPGEP ASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFS GSGSGTDFTLKISRVEAEDVGVYYCMQALQTPLTFGGGTKVDIK
BCMA_EBB-C1980-A2- nt ScFv domain	468	GAAGTGCAGCTGCTTGAGAGCGGTGGAGGTCTGGTGCAGCCCGGGGGATC ACTGCGCCTGTCCTGTGCCGCGTCCGGTTTCACTTTCTCCTCGTACGCCA TGTCGTGGGTCAGACAGGCACCGGGAAAGGGACTGGAATGGGTGTCAGCC ATTTCGGGTTCGGGGGGCAGCACCTACTACGCTGACTCCGTGAAGGGCCG GTTCACCATTTCCCGCGACAACTCCAAGAACACCTTGTACCTCCAAATGA ACTCCCTGCGGGCCGAAGATACCGCCGTGTATTACTGCGTGCTGTGGTTC GGAGAGGGATTCGACCCGTGGGGACAAGGAACACTCGTGACTGTGTCATC

		CGGCGGAGGCGGCAGCGGTGGCGGCGGTTCCGGCGGCGGCGGATCTGACA TCGTGTTGACCCAGTCCCCTCTGAGCCTGCCGGTCACTCCTGGCGAACCA GCCAGCATCTCCTGCCGGTCGAGCCAGTCCCTCCTGCACTCCAATGGGTA CAACTACCTCGATTGGTATCTGCAAAAGCCGGGCCAGAGCCCCCAGCTGC TGATCTACCTTGGGTCAAACCGCGCTTCCGGGGTGCCTGATAGATTCTCC GGGTCCGGGAGCGGAACCGACTTTACCCTGAAAATCTCGAGGGTGGAGGC CGAGGACGTCGGAGTGTACTACTGCATGCAGGCGCTCCAGACTCCCCTGA CCTTCGGAGGAGGAACGAAGGTCGACATCAAGA
BCMA_EBB-C1980-A2- aa VH	489	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVLWF GEGFDPWGQGTLVTVSS
BCMA_EBB-C1980-A2- aa VL	510	DIVLTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQ LLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTP LTFGGGTKVDIK
BCMA_EBB-C1981-C3		
BCMA_EBB-C1981-C3- aa ScFv domain	448	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKVG YDSSGYYRDYYGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSPG TLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGTSSRATGI SDRFSGSGSGTDFTLTISRLEPEDFAVYYCQHYGNSPPKFTFGPGTKLEI K
BCMA_EBB-C1981-C3- nt ScFv domain	469	CAAGTGCAGCTCGTGGAGTCAGGCGGAGGACTGGTGCAGCCCGGGGGCTC CCTGAGACTTTCCTGCGCGGCATCGGGTTTTACCTTCTCCTCCTATGCTA TGTCCTGGGTGCGCCAGGCCCCGGGAAAGGGACTGGAATGGGTGTCCGCA ATCAGCGGTAGCGGGGGCTCAACATACTACGCCGACTCCGTCAAGGGTCG CTTCACTATTTCCCGGGACAACTCCAAGAATACCCTGTACCTCCAAATGA ACAGCCTCAGGGCCGAGGATACTGCCGTGTACTACTGCGCCAAAGTCGGA TACGATAGCTCCGGTTACTACCGGGACTACTACGGAATGGACGTGTGGGG ACAGGGCACCACCGTGACCGTGTCAAGCGGCGGAGGCGGTTCAGGAGGGG GAGGCTCCGGCGGTGGAGGGTCCGAAATCGTCCTGACTCAGTCGCCTGGC ACTCTGTCGTTGTCCCCGGGGGAGCGCGCTACCCTGTCGTGTCGGGCGTC GCAGTCCGTGTCGAGCTCCTACCTCGCGTGGTACCAGCAGAAGCCCGGAC AGGCCCCTAGACTTCTGATCTACGGCACTTCTTCACGCGCCACCGGGATC AGCGACAGGTTCAGCGGCTCCGGCTCCGGGACCGACTTCACCCTGACCAT TAGCCGGCTGGAGCCTGAAGATTTCGCCGTGTATTACTGCCAACACTACG GAAACTCGCCGCCAAAGTTCACGTTCGGACCCGGAACCAAGCTGGAAATC AAG
BCMA_EBB-C1981-C3- aa VH	490	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKVG YDSSGYYRDYYGMDVWGQGTTVTVSS
BCMA_EBB-C1981-C3- aa VL	511	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIY GTSSRATGISDRFSGSGSGTDFTLTISRLEPEDFAVYYCQHYGNSPPKFT FGPGTKLEIK
BCMA_EBB-C1978-G4		
BCMA_EBB-C1978-G4- aa ScFv domain	449	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKMG WSSGYLGAFDIWGQGTTVTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSL SPGERATLSCRASQSVASSFLAWYQQKPGQAPRLLIYGASGRATGIPDRF SGSGSGTDFTLTISRLEPEDFAVYYCQHYGGSPRLTFGGGTKVDIK
BCMA_EBB-C1978-G4- nt	470	GAAGTCCAACTGGTGGAGTCCGGGGGAGGGCTCGTGCAGCCCGGAGGCAG CCTTCGGCTGTCGTGCGCCGCCTCCGGGTTCACGTTCTCATCCTACGCGA

ScFv domain		TGTCGTGGGTCAGACAGGCACCAGGAAAGGGACTGGAATGGGTGTCCGCC ATTAGCGGCTCCGGCGGTAGCACCTACTATGCCGACTCAGTGAAGGGAAG GTTCACTATCTCCCGCGACAACAGCAAGAACACCCTGTACCTCCAAATGA ACTCTCTGCGGGCCGAGGATACCGCGGTGTACTATTGCGCCAAGATGGGT TGGTCCAGCGGATACTTGGGAGCCTTCGACATTTGGGGACAGGGCACTAC TGTGACCGTGTCCTCCGGGGGTGGCGGATCGGGAGGCGGCGGCTCGGGTG GAGGGGGTTCCGAAATCGTGTTGACCCAGTCACCGGGAACCCTCTCGCTG TCCCCGGGAGAACGGGCTACACTGTCATGTAGAGCGTCCCAGTCCGTGGC TTCCTCGTTCCTGGCCTGGTACCAGCAGAAGCCGGGACAGGCACCCCGCC TGCTCATCTACGGAGCCAGCGGCCGGGCGACCGGCATCCCTGACCGCTTC TCCGGTTCCGGCTCGGGCACCGACTTTACTCTGACCATTAGCAGGCTTGA GCCCGAGGATTTTGCCGTGTACTACTGCCAACACTACGGGGGGAGCCCTC GCCTGACCTTCGGAGGCGGAACTAAGGTCGATATCAAAA
BCMA_EBB-C1978-G4- aa VH	491	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA ISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKMG WSSGYLGAFDIWGQGTTVTVSS
BCMA_EBB-C1978-G4- aa VL	512	EIVLTQSPGTLSLSPGERATLSCRASQSVASSFLAWYQQKPGQAPRLLIY GASGRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQHYGGSPRLTF GGGTKVDIK

[00293] In embodiments, additional exemplary BCMA CAR constructs are generated using the 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 the 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 the 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 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 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 VH and VL sequences from PCT Publication WO2014/140248 (the contents of which are hereby incorporated by reference in its entirety).

[00294] In embodiments, additional exemplary BCMA CAR constructs can also be generated using the VH and VL sequences found in Table 13. The amino acid sequences of

exemplary scFv domains comprising the VH and VL domains and a linker sequence, and full-length CARs are also found in Table 13.

Table 13. Additional exemplary BCMA binding domain sequences

Name	Sequence	SEQ ID NO:
A7D12.2 VH	QIQLVQSGPDLKKPGETVKLSCKASGYTFTNFGMNWVKQAPGKGFKWMAWINTYTGESYFA DDFKGRFAFSVETSATTAYLQINNLKTEDTATYFCARGEIYYGYDGGFAYWGQGTLVTVSA	555
A7D12.2 VL	DVVMTQSHRFMSTSVGDRVSITCRASQDVNTAVSWYQQKPGQSPKLLIFSASYRYTGVPDR FTGSGSGADFTLTISSVQAEDLAVYYCQQHYSTPWTFGGGTKLDIK	559
A7D12.2 scFv domain	QIQLVQSGPDLKKPGETVKLSCKASGYTFTNFGMNWVKQAPGKGFKWMAWINTYTGESYFA DDFKGRFAFSVETSATTAYLQINNLKTEDTATYFCARGEIYYGYDGGFAYWGQGTLVTVSA GGGGSGGGGSGGGGSDVVMTQSHRFMSTSVGDRVSITCRASQDVNTAVSWYQQKPGQSPKL LIFSASYRYTGVPDRFTGSGSGADFTLTISSVQAEDLAVYYCQQHYSTPWTFGGGTKLDIK	563
C11D5.3 VH	QIQLVQSGPELKKPGETVKISCKASGYTFTDYSINWVKRAPGKGLKWMGWINTETREPAYA YDFRGRFAFSLETSASTAYLQINNLKYEDTATYFCALDYSYAMDYWGQGTSVTVSS	556
C11D5.3 VL	DIVLTQSPASLAMSLGKRATISCRASESVSVIGAHLIHWYQQKPGQPPKLLIYLASNLETG VPARFSGSGSGTDFTLTIDPVEEDDVAIYSCLQSRIFPRTFGGGTKLEIK	560
C11D5.3 scFv domain	QIQLVQSGPELKKPGETVKISCKASGYTFTDYSINWVKRAPGKGLKWMGWINTETREPAYA YDFRGRFAFSLETSASTAYLQINNLKYEDTATYFCALDYSYAMDYWGQGTSVTVSSGGGGS GGGGSGGGGSQIQLVQSGPELKKPGETVKISCKASGYTFTDYSINWVKRAPGKGLKWMGWI NTETREPAYAYDFRGRFAFSLETSASTAYLQINNLKYEDTATYFCALDYSYAMDYWGQGTS VTVSS	564
C12A3.2 VH	QIQLVQSGPELKKPGETVKISCKASGYTFRHYSMNWVKQAPGKGLKWMGRINTESGVPIYA DDFKGRFAFSVETSASTAYLVINNLKDEDTASYFCSNDYLYSLDFWGQGTALTVSS	557
C12A3.2 VL	DIVLTQSPPSLAMSLGKRATISCRASESVTILGSHLIYWYQQKPGQPPTLLIQLASNVQTG VPARFSGSGSRTDFTLTIDPVEEDDVAVYYCLQSRTIPRTFGGGTKLEIK	561
C12A3.2 scFv domain	QIQLVQSGPELKKPGETVKISCKASGYTFRHYSMNWVKQAPGKGLKWMGRINTESGVPIYA DDFKGRFAFSVETSASTAYLVINNLKDEDTASYFCSNDYLYSLDFWGQGTALTVSSGGGGS GGGGSGGGGSDIVLTQSPPSLAMSLGKRATISCRASESVTILGSHLIYWYQQKPGQPPTLL IQLASNVQTGVPARFSGSGSRTDFTLTIDPVEEDDVAVYYCLQSRTIPRTFGGGTKLEIK	565
C13F12.1 VH	QIQLVQSGPELKKPGETVKISCKASGYTFTHYSMNWVKQAPGKGLKWMGRINTETGEPLYA DDFKGRFAFSLETSASTAYLVINNLKNEDTATFFCSNDYLYSCDYWGQGTTLTVSS	558
C13F12.1 VL	DIVLTQSPPSLAMSLGKRATISCRASESVTILGSHLIYWYQQKPGQPPTLLIQLASNVQTG VPARFSGSGSRTDFTLTIDPVEEDDVAVYYCLQSRTIPRTFGGGTKLEIK	562
C13F12.1 scFv	QIQLVQSGPELKKPGETVKISCKASGYTFTHYSMNWVKQAPGKGLKWMGRINTETGEPLYA DDFKGRFAFSLETSASTAYLVINNLKNEDTATFFCSNDYLYSCDYWGQGTTLTVSSGGGGS GGGGSGGGGSDIVLTQSPPSLAMSLGKRATISCRASESVTILGSHLIYWYQQKPGQPPTLL	566

domain	IQLASNVQTGVPARFSGSGSRTDFTLTIDPVEEDDVAVYYCLQSRTIPRTFGGGTKLEIK	

[00295] The sequences of human CDR sequences of the scFv domains are shown in Table 14 for the heavy chain variable domains and in Table 15 for the light chain variable domains. "ID" stands for the respective SEQ ID NO for each CDR. The CDRs are shown according to the Kabat definition, however, the CDRs under other convention, for example, Chothia or the combined Kabat/Chothia definitions may be readily deduced based on the VH and VL sequences above.

Table 14: Heavy Chain Variable Domain CDRs according to the Kabat numbering scheme (Kabat et al. (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD)

Candidate	**HCDR1**	**SEQ ID NO:**	**HCDR2**	**SEQ ID NO:**	**HCDR3**	**SEQ ID NO:**
139109	NHGMS	694	GIVYSGSTYYAASVKG	734	HGGESDV	774
139103	NYAMS	684	GISRSGENTYYADSVKG	724	SPAHYYGGMDV	764
139105	DYAMH	685	GISWNSGSIGYADSVKG	725	HSFLAY	765
139111	NHGMS	686	GIVYSGSTYYAASVKG	726	HGGESDV	766
139100	NFGIN	687	WINPKNNNTNYAQKFQG	727	GPYYYQSYMDV	767
139101	SDAMT	688	VISGSGGTTYYADSVKG	728	LDSSGYYYARGPRY	768
139102	NYGIT	689	WISAYNGNTNYAQKFQG	729	GPYYYYMDV	769
139104	NHGMS	690	GIVYSGSTYYAASVKG	730	HGGESDV	770
139106	NHGMS	691	GIVYSGSTYYAASVKG	731	HGGESDV	771
139107	NHGMS	692	GIVYSGSTYYAASVKG	732	HGGESDV	772
139108	DYYMS	693	YISSSGSTIYYADSVKG	733	ESGDGMDV	773
139110	DYYMS	695	YISSSGNTIYYADSVKG	735	STMVREDY	775
139112	NHGMS	696	GIVYSGSTYYAASVKG	736	HGGESDV	776
139113	NHGMS	697	GIVYSGSTYYAASVKG	737	HGGESDV	777
139114	NHGMS	698	GIVYSGSTYYAASVKG	738	HGGESDV	778
149362	SSYYYWG	699	SIYYSGSAYYNPSLKS	739	HWQEWPDAFDI	779
149363	TSGMCVS	700	RIDWDEDKFYSTS	740	SGAGGTSATAFDI	780

			LKT			
149364	SYSMN	701	SISSSSSYIYYADSVKG	741	TIAAVYAFDI	781
149365	DYYMS	702	YISSSGSTIYYADSVKG	742	DLRGAFDI	782
149366	SHYIH	703	MINPSGGVTAYSQTLQG	743	EGSGSGWYFDF	783
149367	SGGYYWS	704	YIYYSGSTYYNPSLKS	744	AGIAARLRGAFDI	784
149368	SYAIS	705	GIIPIFGTANYAQKFQG	745	RGGYQLLRWDVGLLRSAFDI	785
149369	SNSAAWN	706	RTYYRSKWYSFYAISLKS	746	SSPEGLFLYWFDP	786
BCMA_EBB-C1978-A4	SYAMS	707	AISGSGGSTYYADSVKG	747	VEGSGSLDY	787
BCMA_EBB-C1978-G1	RYPMS	708	GISDSGVSTYYADSAKG	748	RAGSEASDI	788
BCMA_EBB-C1979-C1	SYAMS	709	AISGSGGSTYYADSVKG	749	ATYKRELRYYYGMDV	789
BCMA_EBB-C1978-C7	SYAMS	710	AISGSGGSTYYADSVKG	750	ATYKRELRYYYGMDV	790
BCMA_EBB-C1978-D10	DYAMH	711	GISWNSGSIGYADSVKG	751	VGKAVPDV	791
BCMA_EBB-C1979-C12	DYAMH	712	SINWKGNSLAYGDSVKG	752	HQGVAYYNYAMDV	792
BCMA_EBB-C1980-G4	SYAMS	713	AISGSGGSTYYADSVKG	753	VVRDGMDV	793
BCMA_EBB-C1980-D2	SYAMS	714	AISGSGGSTYYADSVKG	754	IPQTGTFDY	794
BCMA_EBB-C1978-A10	SYAMS	715	AISGSGGSTYYADSVKG	755	ANYKRELRYYYGMDV	795
BCMA_EBB-C1978-D4	SYAMS	716	AISGSGGSTYYADSVKG	756	ALVGATGAFDI	796
BCMA_EBB-C1980-A2	SYAMS	717	AISGSGGSTYYADSVKG	757	WFGEGFDP	797
BCMA_EBB-C1981-C3	SYAMS	718	AISGSGGSTYYADSVKG	758	VGYDSSGYYRDYYGMDV	798
BCMA_EBB-C1978-G4	SYAMS	719	AISGSGGSTYYADSVKG	759	MGWSSGYLGAFDI	799
A7D12.2	NFGMN	720	WINTYTGESYFADDFKG	760	GEIYYGYDGGFAY	800
C11D5.3	DYSIN	721	WINTETREPAYAYDFRG	761	DYSYAMDY	801
C12A3.2	HYSMN	722	RINTESGVPIYADDFKG	762	DYLYSLDF	802
C13F12.1	HYSMN	723	RINTETGEPLYADDFKG	763	DYLYSCDY	803

Table 15: Light Chain Variable Domain CDRs according to the Kabat numbering scheme (Kabat et al. (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD)

Candidate	LCDR1	SE	LCDR2	SEQ	LCDR3	SE

		Q ID NO:		ID NO:		Q ID NO:
139109	RASQSISSYLN	814	AASSLQS	854	QQSYSTPYT	894
139103	RASQSISSSFLA	804	GASRRAT	844	QQYHSSPSWT	884
139105	RSSQSLLHSNGYNYLD	805	LGSNRAS	845	MQALQTPYT	885
139111	KSSQSLLRNDGKTPLY	806	EVSNRFS	846	MQNIQFPS	886
139100	RSSQSLLHSNGYNYLN	807	LGSKRAS	847	MQALQTPYT	887
139101	RASQSISSYLN	808	GASTLAS	848	QQSYKRAS	888
139102	RSSQSLLYSNGYNYVD	809	LGSNRAS	849	MQGRQFPYS	889
139104	RASQSVSSNLA	810	GASTRAS	850	QQYGSSLT	890
139106	RASQSVSSKLA	811	GASIRAT	851	QQYGSSSWT	891
139107	RASQSVGSTNLA	812	DASNRAT	852	QQYGSSPPWT	892
139108	RASQSISSYLN	813	AASSLQS	853	QQSYTLA	893
139110	KSSESLVHNSGKTYLN	815	EVSNRDS	855	MQGTHWPGT	895
139112	QASEDINKFLN	816	DASTLQT	856	QQYESLPLT	896
139113	RASQSVGSNLA	817	GASTRAT	857	QQYNDWLPVT	897
139114	RASQSIGSSSLA	818	GASSRAS	858	QQYAGSPPFT	898
149362	KASQDIDDAMN	819	SATSPVP	859	LQHDNFPLT	899
149363	RASQDIYNNLA	820	AANKSQS	860	QHYYRFPYS	900
149364	RSSQSLLHSNGYNYLD	821	LGSNRAS	861	MQALQTPYT	901
149365	GGNNIGTKSVH	822	DDSVRPS	862	QVWDSDSEHVV	902
149366	SGDGLSKKYVS	823	RDKERPS	863	QAWDDTTVV	903
149367	RASQGIRNWLA	824	AASNLQS	864	QKYNSAPFT	904
149368	GGNNIGSKSVH	825	GKNNRPS	865	SSRDSSGDHLRV	905
149369	QGDSLGNYYAT	826	GTNNRPS	866	NSRDSSGHHLL	906
BCMA_EBB-C1978-A4	RASQSVSSAYLA	827	GASTRAT	867	QHYGSSFNGSSLFT	907
BCMA_EBB-C1978-G1	RASQSVSNSLA	828	DASSRAT	868	QQFGTSSGLT	908
BCMA_EBB-C1979-C1	RASQSVSSSFLA	829	GASSRAT	869	QQYHSSPSWT	909
BCMA_EBB-C1978-C7	RASQSVSTTFLA	830	GSSNRAT	870	QQYHSSPSWT	910
BCMA_EBB-C1978-D10	RASQSISSYLN	831	AASSLQS	871	QQSYSTPYS	911
BCMA_EBB-C1979-C12	RATQSIGSSFLA	832	GASQRAT	872	QHYESSPSWT	912
BCMA_EBB-C1980-G4	RASQSVSSSYLA	833	GASSRAT	873	QQYGSPPRFT	913
BCMA_EBB-C1980-D2	RASQSVSSSYLA	834	GASSRAT	874	QHYGSSPSWT	914
BCMA_EBB-C1978-A10	RASQRVASNYLA	835	GASSRAT	875	QHYDSSPSWT	915
BCMA_EBB-C1978-D4	RASQSLSSNFLA	836	GASNWAT	876	QYYGTSPMYT	916

BCMA_EBB-C1980-A2	RSSQSLLHSNGYNYLD	837	LGSNRAS	877	MQALQTPLT	917
BCMA_EBB-C1981-C3	RASQSVSSSYLA	838	GTSSRAT	878	QHYGNSPPKFT	918
BCMA_EBB-C1978-G4	RASQSVASSFLA	839	GASGRAT	879	QHYGGSPRLT	919
A7D12.2	RASQDVNTAVS	840	SASYRYT	880	QQHYSTPWT	920
C11D5.3	RASESVSVIGAHLIH	841	LASNLET	881	LQSRIFPRT	921
C12A3.2	RASESVTILGSHLIY	842	LASNVQT	882	LQSRTIPRT	922
C13F12.1	RASESVTILGSHLIY	843	LASNVQT	883	LQSRTIPRT	923

[00296] In one embodiment, the BCMA binding domain comprises one or more (e.g., all three) light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and light chain complementary determining region 3 (LC CDR3) of a BCMA binding domain described herein, e.g., provided in Table 12, 13 or 15, and/or one or more (e.g., all three) heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of a BCMA binding domain described herein, e.g., provided in Table 12, 13 or 14. In one embodiment, the BCMA binding domain comprises one, two, or all of LC CDR1, LC CDR2, and LC CDR3 of any amino acid sequences as provided in Table 12, incorporated herein by reference; and one, two or all of HC CDR1, HC CDR2, and HC CDR3 of any amino acid sequences as provided in Table 12.

[00297] In one embodiment, the BCMA antigen binding domain comprises:

(v) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 814, a LC CDR2 amino acid sequence of SEQ ID NO: 854, and a LC CDR3 amino acid sequence of SEQ ID NO: 894; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 694, a HC CDR2 amino acid sequence of SEQ ID NO: 734, and a HC CDR3 amino acid sequence of SEQ ID NO: 774

(vi) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 804, a LC CDR2 amino acid sequence of SEQ ID NO: 844, and a LC CDR3 amino acid sequence of SEQ ID NO: 884; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 684, a HC CDR2 amino acid sequence of SEQ ID NO: 724, and a HC CDR3 amino acid sequence of SEQ ID NO: 764

(vii) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 805, a LC CDR2 amino acid sequence of SEQ ID NO: 845, and a LC CDR3 amino acid sequence of SEQ ID NO: 885; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 685, a HC CDR2 amino acid sequence of SEQ ID NO: 725, and a HC CDR3 amino acid sequence of SEQ ID NO: 765

(viii) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 806, a LC CDR2 amino acid sequence of SEQ ID NO: 846, and a LC CDR3 amino acid sequence of SEQ ID NO: 886; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 686, a HC CDR2 amino acid sequence of SEQ ID NO: 726, and a HC CDR3 amino acid sequence of SEQ ID NO: 766

(ix) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 807, a LC CDR2 amino acid sequence of SEQ ID NO: 847, and a LC CDR3 amino acid sequence of SEQ ID NO: 887; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 687, a HC CDR2 amino acid sequence of SEQ ID NO: 727, and a HC CDR3 amino acid sequence of SEQ ID NO: 767

(x) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 808, a LC CDR2 amino acid sequence of SEQ ID NO: 848, and a LC CDR3 amino acid sequence of SEQ ID NO: 888; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 688, a HC CDR2 amino acid sequence of SEQ ID NO: 728, and a HC CDR3 amino acid sequence of SEQ ID NO: 768

(xi) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 809, a LC CDR2 amino acid sequence of SEQ ID NO: 849, and a LC CDR3 amino acid sequence of SEQ ID NO: 889; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 689, a HC CDR2 amino acid sequence of SEQ ID NO: 729, and a HC CDR3 amino acid sequence of SEQ ID NO: 769

(xii) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 810, a LC CDR2 amino acid sequence of SEQ ID NO: 850, and a LC CDR3 amino acid sequence of SEQ ID NO: 890; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 690, a HC CDR2 amino acid sequence of SEQ ID NO: 730, and a HC CDR3 amino acid sequence of SEQ ID NO: 770

(xiii) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 811, a LC CDR2 amino acid sequence of SEQ ID NO: 851, and a LC CDR3 amino acid sequence of SEQ ID NO: 891; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 691, a HC CDR2 amino acid sequence of SEQ ID NO: 731, and a HC CDR3 amino acid sequence of SEQ ID NO: 771

(xiv) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 812, a LC CDR2 amino acid sequence of SEQ ID NO: 852, and a LC CDR3 amino acid sequence of SEQ ID NO: 892; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 692, a HC CDR2 amino acid sequence of SEQ ID NO: 732, and a HC CDR3 amino acid sequence of SEQ ID NO: 772

(xv) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 813, a LC CDR2 amino acid sequence of SEQ ID NO: 853, and a LC CDR3 amino acid sequence of SEQ ID NO: 893; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 693, a HC CDR2 amino acid sequence of SEQ ID NO: 733, and a HC CDR3 amino acid sequence of SEQ ID NO: 773

(xvi) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 815, a LC CDR2 amino acid sequence of SEQ ID NO: 855, and a LC CDR3 amino acid sequence of SEQ ID NO: 895; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 695, a HC CDR2 amino acid sequence of SEQ ID NO: 735, and a HC CDR3 amino acid sequence of SEQ ID NO: 775

(xvii) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 816, a LC CDR2 amino acid sequence of SEQ ID NO: 856, and a LC CDR3 amino acid sequence of SEQ ID NO: 896; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 696, a HC CDR2 amino acid sequence of SEQ ID NO: 736, and a HC CDR3 amino acid sequence of SEQ ID NO: 776

(xviii) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 817, a LC CDR2 amino acid sequence of SEQ ID NO: 857, and a LC CDR3 amino acid sequence of SEQ ID NO: 897; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 697, a HC CDR2 amino acid sequence of SEQ ID NO: 737, and a HC CDR3 amino acid sequence of SEQ ID NO: 777

(xix) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 818, a LC CDR2 amino acid sequence of SEQ ID NO: 858, and a LC CDR3 amino acid sequence of SEQ ID NO: 898; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 698, a HC CDR2 amino acid sequence of SEQ ID NO: 738, and a HC CDR3 amino acid sequence of SEQ ID NO: 778

(xx) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 819, a LC CDR2 amino acid sequence of SEQ ID NO: 859, and a LC CDR3 amino acid sequence of SEQ ID NO: 899; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 699, a HC CDR2 amino acid sequence of SEQ ID NO: 739, and a HC CDR3 amino acid sequence of SEQ ID NO: 779

(xxi) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 820, a LC CDR2 amino acid sequence of SEQ ID NO: 860, and a LC CDR3 amino acid sequence of SEQ ID NO: 900; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 700, a HC CDR2 amino acid sequence of SEQ ID NO: 740, and a HC CDR3 amino acid sequence of SEQ ID NO: 780

(xxii) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 821, a LC CDR2 amino acid sequence of SEQ ID NO: 861, and a LC CDR3 amino acid sequence of SEQ ID NO: 901; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 701, a HC CDR2 amino acid sequence of SEQ ID NO: 741, and a HC CDR3 amino acid sequence of SEQ ID NO: 781

(xxiii) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 822, a LC CDR2 amino acid sequence of SEQ ID NO: 862, and a LC CDR3 amino acid sequence of SEQ ID NO: 902; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 702, a HC CDR2 amino acid sequence of SEQ ID NO: 742, and a HC CDR3 amino acid sequence of SEQ ID NO: 782

(xxiv) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 823, a LC CDR2 amino acid sequence of SEQ ID NO: 863, and a LC CDR3 amino acid sequence of SEQ ID NO: 903; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 703, a HC CDR2 amino acid sequence of SEQ ID NO: 743, and a HC CDR3 amino acid sequence of SEQ ID NO: 783

(xxv) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 824, a LC CDR2 amino acid sequence of SEQ ID NO: 864, and a LC CDR3 amino acid sequence of SEQ ID NO: 904; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 704, a HC CDR2 amino acid sequence of SEQ ID NO: 744, and a HC CDR3 amino acid sequence of SEQ ID NO: 784

(xxvi) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 825, a LC CDR2 amino acid sequence of SEQ ID NO: 865, and a LC CDR3 amino acid sequence of SEQ ID NO: 905; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 705, a HC CDR2 amino acid sequence of SEQ ID NO: 745, and a HC CDR3 amino acid sequence of SEQ ID NO: 785 or

(xxvii) (a) a LC CDR1 amino acid sequence of SEQ ID NO: 826, a LC CDR2 amino acid sequence of SEQ ID NO: 866, and a LC CDR3 amino acid sequence of SEQ ID NO: 906; and

(b) a HC CDR1 amino acid sequence of SEQ ID NO: 706, a HC CDR2 amino acid sequence of SEQ ID NO: 746, and a HC CDR3 amino acid sequence of SEQ ID NO: 786.

[00298] In one embodiment, the BCMA binding domain comprises a light chain variable region described herein (e.g., in Table 12 or 13) and/or a heavy chain variable region described herein (e.g., in Table 12 or 13). In one embodiment, the BCMA binding domain is a scFv comprising a light chain and a heavy chain of an amino acid sequence listed in Table 12 or 13. In an embodiment, the BCMA binding domain (e.g., an scFv) comprises: a light chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a light chain variable region provided in Table 12 or 13, or a sequence with 95-99% identity with an amino acid sequence provided in Table 12 or 13; and/or a heavy chain variable region comprising an amino acid sequence having at least one, two or three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of a heavy chain variable region provided in Table 12 or 13, or a sequence with 95-99% identity to an amino acid sequence provided in Table 12 or 13.

[00299] In one embodiment, the BCMA binding domain comprises an amino acid sequence selected from a group consisting of SEQ ID NO: 349; SEQ ID NO: 339, SEQ ID NO: 340; SEQ ID NO: 341; SEQ ID NO: 342; SEQ ID NO: 343; SEQ ID NO: 344, SEQ ID NO: 345, SEQ ID NO: 346, SEQ ID NO: 347, SEQ ID NO: 348, SEQ ID NO: 350, SEQ ID NO: 351, SEQ ID NO: 352, SEQ ID NO: 353, SEQ ID NO: 429, SEQ ID NO: 430, SEQ ID NO: 431, SEQ ID NO: 432, SEQ ID NO: 433, SEQ ID NO: 434, SEQ ID NO: 435, SEQ ID NO: 436, SEQ ID NO: 437, SEQ ID NO: 438, SEQ ID NO: 439, SEQ ID NO: 440, SEQ ID NO: 441, SEQ ID NO: 442, SEQ ID NO: 443, SEQ ID NO: 444, SEQ ID NO: 445, SEQ ID NO: 446, SEQ ID NO: 447, SEQ ID NO: 448, SEQ ID NO: 449, SEQ ID NO: 563, SEQ ID NO: 564, SEQ ID NO: 565 and SEQ ID NO: 566; or an amino acid sequence having at least one, two or

three modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 30, 20 or 10 modifications (e.g., substitutions, e.g., conservative substitutions) to any of the aforesaid sequences; or a sequence with 95-99% identity to any of the aforesaid sequences. In one embodiment, the BCMA binding domain is a scFv, and a light chain variable region comprising an amino acid sequence described herein, e.g., in Table 12 or 13, is attached to a heavy chain variable region comprising an amino acid sequence described herein, e.g., in Table 12 or 13, via a linker, e.g., a linker described herein. In one embodiment, the BCMA binding domain includes a (Gly4-Ser)n linker, wherein n is 1, 2, 3, 4, 5, or 6, preferably 4 (SEQ ID NO: 80). The light chain variable region and heavy chain variable region of a scFv can be, e.g., in any of the following orientations: light chain variable region-linker-heavy chain variable region or heavy chain variable region-linker-light chain variable region.

[00300] Any known BCMA CAR, e.g., the BMCA antigen binding domain of any known BCMA CAR, in the art can be used in accordance with the instant invention to construct a CAR. For example, those described herein.

[00301] 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.

[00302] 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).

[00303] 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, or derivatives thereof.

[00304] 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 that binds a tumor antigen or a B cell antigen 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 that binds a tumor antigen or a B cell antigen listed above.

[00305] 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.)

[00306] Examples of solid tumor associated antigens (i.e., solid tumor antigens) include, without limitation: EGFRvIII, mesothelin, GD2, Tn antigen, sTn antigen, Tn-O-Glycopeptides, sTn-O-Glycopeptides, PSMA, CD97, TAG72, CD44v6, CEA, EPCAM, KIT, IL-13Ra2, leguman, GD3, CD171, IL-11Ra, PSCA, MAD-CT-1, MAD-CT-2, VEGFR2, LewisY, CD24, PDGFR-beta, SSEA-4, folate receptor alpha, ERBBs (e.g., ERBB2), Her2/neu, MUC1, EGFR,

NCAM, Ephrin B2, CAIX, LMP2, sLe, HMWMAA, o-acetyl-GD2, folate receptor beta, TEM1/CD248, TEM7R, FAP, Legumain, HPV E6 or E7, ML-IAP, CLDN6, TSHR, GPRC5D, ALK, Polysialic acid, Fos-related antigen, neutrophil elastase, TRP-2, CYP1B1, sperm protein 17, beta human chorionic gonadotropin, AFP, thyroglobulin, PLAC1, globoH, RAGE1, MN-CA IX, human telomerase reverse transcriptase, intestinal carboxyl esterase, mut hsp 70-2, NA-17, NY-BR-1, UPK2, HAVCR1, ADRB3, PANX3, NY-ESO-1, GPR20, Ly6k, OR51E2, TARP, GFRα4, and a peptide of any of these antigens presented on MHC.

[00307] In one aspect, the CAR comprises an antigen binding domain that binds to a B cell antigen. In one embodiment, the CAR comprises a CD19 antigen binding domain (e.g., a murine, human or humanized antibody or antibody fragment that specifically binds to CD19), a transmembrane domain, and an intracellular signaling domain (e.g., an intracellular signaling domain comprising a costimulatory domain and/or a primary signaling domain).

[00308] Exemplary CAR molecules described herein are provided in Table 10. The CAR molecules in Table 10 comprise a CD19 antigen binding domain, e.g., an amino acid sequence of any CD19 antigen binding domain provided in Table 6.

Table 10. Exemplary CD19 CAR molecules

B cell antigen	Name	Amino Acid Sequence	SEQ ID NO:
CD19	CTL019	MALPVTALLLPLALLLHAARPDIQMTQTTSSLSASLGDRVTISCRASQDISKYL NWYQQKPDGTVKLLIYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYF CQQGNTLPYTFGGGTKLEITGGGGSGGGGSGGGGSEVKLQESGPGLVAPSQSLS VTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTIIKDN SKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSSTTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKF SRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGL YNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	281
CD19	CAR 1	MALPVTALLLPLALLLHAARPEIVMTQSPATLSLSPGERATLSCRASQDISKYL NWYQQKPGQAPRLLIYHTSRLHSGIPARFSGSGSGTDYTLTISSLQPEDFAVYF CQQGNTLPYTFGQGTKLEIKGGGGSGGGGSGGGGSQVQLQESGPGLVKPSETLS LTCTVSGVSLPDYGVSWIRQPPGKGLEWIGVIWGSETTYYSSSLKSRVTISKDN SKNQVSLKLSSVTAADTAVYYCAKHYYYGGSYAMDYWGQGTLVTVSSTTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKF SRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGL YNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	269
CD19	CAR 2	MALPVTALLLPLALLLHAARPEIVMTQSPATLSLSPGERATLSCRASQDISKYL NWYQQKPGQAPRLLIYHTSRLHSGIPARFSGSGSGTDYTLTISSLQPEDFAVYF CQQGNTLPYTFGQGTKLEIKGGGGSGGGGSGGGGSQVQLQESGPGLVKPSETLS LTCTVSGVSLPDYGVSWIRQPPGKGLEWIGVIWGSETTYYQSSLKSRVTISKDN SKNQVSLKLSSVTAADTAVYYCAKHYYYGGSYAMDYWGQGTLVTVSSTTTPAPR	270

		PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKF SRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGL YNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	
CD19	CAR 3	MALPVTALLLPLALLLHAARPQVQLQESGPGLVKPSETLSLTCTVSGVSLPDYG VSWIRQPPGKGLEWIGVIWGSETTYYSSSLKSRVTISKDNSKNQVSLKLSSVTA ADTAVYYCAKHYYYGGSYAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSEIVMTQ SPATLSLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIYHTSRLHSGIPA RFSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTFGQGTKLEIKTTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKF SRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGL YNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	**271**
CD19	CAR 4	MALPVTALLLPLALLLHAARPQVQLQESGPGLVKPSETLSLTCTVSGVSLPDYG VSWIRQPPGKGLEWIGVIWGSETTYYQSSLKSRVTISKDNSKNQVSLKLSSVTA ADTAVYYCAKHYYYGGSYAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSEIVMTQ SPATLSLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIYHTSRLHSGIPA RFSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTFGQGTKLEIKTTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKF SRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGL YNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	**272**
CD19	CAR 5	MALPVTALLLPLALLLHAARPEIVMTQSPATLSLSPGERATLSCRASQDISKYL NWYQQKPGQAPRLLIYHTSRLHSGIPARFSGSGSGTDYTLTISSLQPEDFAVYF CQQGNTLPYTFGQGTKLEIKGGGGSGGGGSGGGGSGGGGSQVQLQESGPGLVKP SETLSLTCTVSGVSLPDYGVSWIRQPPGKGLEWIGVIWGSETTYYSSSLKSRVT ISKDNSKNQVSLKLSSVTAADTAVYYCAKHYYYGGSYAMDYWGQGTLVTVSSTT TPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTC GVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCE LRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKN PQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQ ALPPR	**273**
CD19	CAR 6	MALPVTALLLPLALLLHAARPEIVMTQSPATLSLSPGERATLSCRASQDISKYL NWYQQKPGQAPRLLIYHTSRLHSGIPARFSGSGSGTDYTLTISSLQPEDFAVYF CQQGNTLPYTFGQGTKLEIKGGGGSGGGGSGGGGSGGGGSQVQLQESGPGLVKP SETLSLTCTVSGVSLPDYGVSWIRQPPGKGLEWIGVIWGSETTYYQSSLKSRVT ISKDNSKNQVSLKLSSVTAADTAVYYCAKHYYYGGSYAMDYWGQGTLVTVSSTT TPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTC GVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCE LRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKN PQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQ ALPPR	**274**
CD19	CAR 7	MALPVTALLLPLALLLHAARPQVQLQESGPGLVKPSETLSLTCTVSGVSLPDYG VSWIRQPPGKGLEWIGVIWGSETTYYSSSLKSRVTISKDNSKNQVSLKLSSVTA ADTAVYYCAKHYYYGGSYAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSE IVMTQSPATLSLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIYHTSRLH SGIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTFGQGTKLEIKTT TPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTC GVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCE LRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKN PQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQ ALPPR	**275**
CD19	CAR 8	MALPVTALLLPLALLLHAARPQVQLQESGPGLVKPSETLSLTCTVSGVSLPDYG VSWIRQPPGKGLEWIGVIWGSETTYYQSSLKSRVTISKDNSKNQVSLKLSSVTA ADTAVYYCAKHYYYGGSYAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSE IVMTQSPATLSLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIYHTSRLH SGIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTFGQGTKLEIKTT	**276**

		TPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTC GVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCE LRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKN PQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQ ALPPR	
CD19	CAR 9	MALPVTALLLPLALLLHAARPEIVMTQSPATLSLSPGERATLSCRASQDISKYL NWYQQKPGQAPRLLIYHTSRLHSGIPARFSGSGSGTDYTLTISSLQPEDFAVYF CQQGNTLPYTFGQGTKLEIKGGGGSGGGGSGGGGSGGGGSQVQLQESGPGLVKP SETLSLTCTVSGVSLPDYGVSWIRQPPGKGLEWIGVIWGSETTYYNSSLKSRVT ISKDNSKNQVSLKLSSVTAADTAVYYCAKHYYYGGSYAMDYWGQGTLVTVSSTT TPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTC GVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCE LRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKN PQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQ ALPPR	**277**
CD19	CAR 10	MALPVTALLLPLALLLHAARPEIVMTQSPATLSLSPGERATLSCRASQDISKYL NWYQQKPGQAPRLLIYHTSRLHSGIPARFSGSGSGTDYTLTISSLQPEDFAVYF CQQGNTLPYTFGQGTKLEIKGGGGSGGGGSGGGGSGGGGSQVQLQESGPGLVKP SETLSLTCTVSGVSLPDYGVSWIRQPPGKGLEWIGVIWGSETTYYNSSLKSRVT ISKDNSKNQVSLKLSSVTAADTAVYYCAKHYYYGGSYAMDYWGQGTLVTVSSTT TPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTC GVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCE LRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKN PQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQ ALPPR	**278**
CD19	CAR 11	MALPVTALLLPLALLLHAARPQVQLQESGPGLVKPSETLSLTCTVSGVSLPDYG VSWIRQPPGKGLEWIGVIWGSETTYYNSSLKSRVTISKDNSKNQVSLKLSSVTA ADTAVYYCAKHYYYGGSYAMDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSE IVMTQSPATLSLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLLIYHTSRLH SGIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYTFGQGTKLEIKTT TPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTC GVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCE LRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKN PQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQ ALPPR	**279**
CD19	CAR 12	MALPVTALLLPLALLLHAARPEIVMTQSPATLSLSPGERATLSCRASQDISKYL NWYQQKPGQAPRLLIYHTSRLHSGIPARFSGSGSGTDYTLTISSLQPEDFAVYF CQQGNTLPYTFGQGTKLEIKGGGGSGGGGSGGGGSQVQLQESGPGLVKPSETLS LTCTVSGVSLPDYGVSWIRQPPGKGLEWIGVIWGSETTYYNSSLKSRVTISKDN SKNQVSLKLSSVTAADTAVYYCAKHYYYGGSYAMDYWGQGTLVTVSSTTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKF SRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGL YNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	**280**

[00309] In one embodiment, the CAR molecule comprises (e.g., consists of) an amino acid sequence as provided in Table 10, or in Table 3 of International Publication No. WO2014/153270, filed March 15, 2014; incorporated herein by reference. In one embodiment, the CAR molecule (e.g., consists of) an amino acid sequence of SEQ ID NO: 269, SEQ ID NO: 270, SEQ ID NO: 271, SEQ ID NO: 272, SEQ ID NO: 273, SEQ ID NO: 274, SEQ ID NO: 275, SEQ ID NO: 276, SEQ ID NO: 277, SEQ ID NO: 278, SEQ ID NO: 279, SEQ ID NO:

280, or SEQ ID NO: 281; or an amino acid sequence having at least one, two, three, four, five, 10, 15, 20 or 30 modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 60, 50, or 40 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of SEQ ID NO: 269, SEQ ID NO: 270, SEQ ID NO: 271, SEQ ID NO: 272, SEQ ID NO: 273, SEQ ID NO: 274, SEQ ID NO: 275, SEQ ID NO: 276, SEQ ID NO: 277, SEQ ID NO: 278, SEQ ID NO: 279, SEQ ID NO: 280, or SEQ ID NO: 281; or an amino acid sequence having 85%, 90%, 95%, 96%, 97%, 98%, 99% identity to an amino acid sequence of SEQ ID NO: 269, SEQ ID NO: 270, SEQ ID NO: 271, SEQ ID NO: 272, SEQ ID NO: 273, SEQ ID NO: 274, SEQ ID NO: 275, SEQ ID NO: 276, SEQ ID NO: 277, SEQ ID NO: 278, SEQ ID NO: 279, SEQ ID NO: 280, or SEQ ID NO: 281.

[00310] In one aspect, the CAR comprises an antigen binding domain that binds to a B cell antigen. In one embodiment, CAR comprises a BCMA antigen binding domain (e.g., a murine, human or humanized antibody or antibody fragment that specifically binds to BCMA, e.g., human BCMA), a transmembrane domain, and an intracellular signaling domain (e.g., an intracellular signaling domain comprising a costimulatory domain and/or a primary signaling domain).

[00311] Exemplary CAR molecules described herein are provided in Table 29, or Table 1 of WO2016/014565, or as otherwise described herein. The CAR molecules in Table 29 comprise a BCMA antigen binding domain, e.g., an amino acid sequence of any BCMA antigen binding domain provided in Table 12 or 13.

Table 29. Exemplary BCMA CAR molecules. Sequences are provided with a leader sequence.

Name/ Description	SEQ ID NO:	Sequence
139109		
139109- aa Full CAR	959	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAVSGFALS NHGMSWVRRAPGKGLEWVSGIVYSGSTYYAASVKGRFTISRDNSRNTLYLQ MNSLRPEDTAIYYCSAHGGESDVWGQGTTVTVSSASGGGGSGGRASGGGGS DIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAA SSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPYTFGQGT KVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDI YIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDK RRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDG LYQGLSTATKDTYDALHMQALPPR
139109- nt Full CAR	974	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCGAAGTGCAATTGGTGGAATCAGGGGGAGGACTTGTGCAG

		CCTGGAGGATCGCTGAGACTGTCATGTGCCGTGTCCGGCTTTGCCCTGTCC AACCACGGGATGTCCTGGGTCCGCCGCGCGCCTGGAAAGGGCCTCGAATGG GTGTCGGGTATTGTGTACAGCGGTAGCACCTACTATGCCGCATCCGTGAAG GGGAGATTCACCATCAGCCGGGACAACTCCAGGAACACTCTGTACCTCCAA ATGAATTCGCTGAGGCCAGAGGACACTGCCATCTACTACTGCTCCGCGCAT GGCGGAGAGTCCGACGTCTGGGGACAGGGGACCACCGTGACCGTGTCTAGC GCGTCCGGCGGAGGCGGCAGCGGGGGTCGGGCATCAGGGGGCGGCGGATCG GACATCCAGCTCACCCAGTCCCCGAGCTCGCTGTCCGCCTCCGTGGGAGAT CGGGTCACCATCACGTGCCGCGCCAGCCAGTCGATTTCCTCCTACCTGAAC TGGTACCAACAGAAGCCCGGAAAAGCCCCGAAGCTTCTCATCTACGCCGCC TCGAGCCTGCAGTCAGGAGTGCCCTCACGGTTCTCCGGCTCCGGTTCCGGT ACTGATTTCACCCTGACCATTTCCTCCCTGCAACCGGAGGACTTCGCTACT TACTACTGCCAGCAGTCGTACTCCACCCCCTACACTTTCGGACAAGGCACC AAGGTCGAAATCAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCT CCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCC GCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATC TACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTC GTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTT AAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGT TCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAA TTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAGCTC TACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGGACAAG CGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAATCCC CAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCCTAT AGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACGACGGA CTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTTCAC ATGCAGGCCCTGCCGCCTCGG
139103		
139103- aa Full CAR	949	MALPVTALLLPLALLLHAARPQVQLVESGGGLVQPGRSLRLSCAASGFTFS NYAMSWVRQAPGKGLGWVSGISRSGENTYYADSVKGRFTISRDNSKNTLYL QMNSLRDEDTAVYYCARSPAHYYGGMDVWGQGTTVTVSSASGGGGSGGRAS GGGGSDIVLTQSPGTLSLSPGERATLSCRASQSISSSFLAWYQQKPGQAPR LLIYGASRRATGIPDRFSGSGSGTDFTLTISRLEPEDSAVYYCQQYHSSPS WTFGQGTKLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRG LDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQT TQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRRE EYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERR RGKGHDGLYQGLSTATKDTYDALHMQALPPR
139103- nt Full CAR	964	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCCAAGTGCAACTCGTGGAATCTGGTGGAGGACTCGTGCAA CCCGGAAGATCGCTTAGACTGTCGTGTGCCGCCAGCGGGTTCACTTTCTCG AACTACGCGATGTCCTGGGTCCGCCAGGCACCCGGAAAGGGACTCGGTTGG GTGTCCGGCATTTCCCGGTCCGGCGAAAATACCTACTACGCCGACTCCGTG AAGGGCCGCTTCACCATCTCAAGGGACAACAGCAAAAACACCCTGTACTTG CAAATGAACTCCCTGCGGGATGAAGATACAGCCGTGTACTATTGCGCCCGG TCGCCTGCCCATTACTACGGCGGAATGGACGTCTGGGGACAGGGAACCACT GTGACTGTCAGCAGCGCGTCGGGTGGCGGCGGCTCAGGGGGTCGGGCCTCC GGGGGGGGAGGGTCCGACATCGTGCTGACCCAGTCCCCGGGAACCCTGAGC CTGAGCCCGGGAGAGCGCGCGACCCTGTCATGCCGGGCATCCCAGAGCATT AGCTCCTCCTTTCTCGCCTGGTATCAGCAGAAGCCCGGACAGGCCCCGAGG CTGCTGATCTACGGCGCTAGCAGAAGGGCTACCGGAATCCCAGACCGGTTC

		TCCGGCTCCGGTTCCGGGACCGATTTCACCCTTACTATCTCGCGCCTGGAA CCTGAGGACTCCGCCGTCTACTACTGCCAGCAGTACCACTCATCCCCGTCG TGGACGTTCGGACAGGGCACCAAGCTGGAGATTAAGACCACTACCCCAGCA CCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTG CGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGT CTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGC GGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGG AAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACT ACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGC GGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTAC AAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAG GAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGG AAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAG GATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGA AGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAG GACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
139105		
139105- aa Full CAR	950	MALPVTALLLPLALLLHAARPQVQLVESGGGLVQPGRSLRLSCAASGFTFD DYAMHWVRQAPGKGLEWVSGISWNSGSIGYADSVKGRFTISRDNAKNSLYL QMNSLRAEDTALYYCSVHSFLAYWGQGTLVTVSSASGGGGSGGRASGGGGS DIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQL LIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPYT FGQGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLD FACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQ EEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEY DVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRG KGHDGLYQGLSTATKDTYDALHMQALPPR
139105- nt Full CAR	965	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCCAAGTGCAACTCGTCGAATCCGGTGGAGGTCTGGTCCAA CCTGGTAGAAGCCTGAGACTGTCGTGTGCGGCCAGCGGATTCACCTTTGAT GACTATGCTATGCACTGGGTGCGGCAGGCCCCAGGAAAGGGCCTGGAATGG GTGTCGGGAATTAGCTGGAACTCCGGGTCCATTGGCTACGCCGACTCCGTG AAGGGCCGCTTCACCATCTCCCGCGACAACGCAAAGAACTCCCTGTACTTG CAAATGAACTCGCTCAGGGCTGAGGATACCGCGCTGTACTACTGCTCCGTG CATTCCTTCCTGGCCTACTGGGGACAGGGAACTCTGGTCACCGTGTCGAGC GCCTCCGGCGGCGGGGGCTCGGGTGGACGGGCCTCGGGCGGAGGGGGGTCC GACATCGTGATGACCCAGACCCCGCTGAGCTTGCCCGTGACTCCCGGAGAG CCTGCATCCATCTCCTGCCGGTCATCCCAGTCCCTTCTCCACTCCAACGGA TACAACTACCTCGACTGGTACCTCCAGAAGCCGGGACAGAGCCCTCAGCTT CTGATCTACCTGGGGTCAAATAGAGCCTCAGGAGTGCCGGATCGGTTCAGC GGATCTGGTTCGGGAACTGATTTCACTCTGAAGATTTCCCGCGTGGAAGCC GAGGACGTGGGCGTCTACTACTGTATGCAGGCGCTGCAGACCCCCTATACC TTCGGCCAAGGGACGAAAGTGGAGATCAAGACCACTACCCCAGCACCGAGG CCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCG GAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGAC TTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTC CTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAG CTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAA GAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGC GAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAG GGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTAC GACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCG

		CGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAG ATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGC AAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACC TATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
139111		
139111- aa Full CAR	951	MALPVTALLLPLALLLHAARPEVQLLESGGGLVQPGGSLRLSCAVSGFALS NHGMSWVRRAPGKGLEWVSGIVYSGSTYYAASVKGRFTISRDNSRNTLYLQ MNSLRPEDTAIYYCSAHGGESDVWGQGTTVTVSSASGGGGSGGRASGGGGS DIVMTQTPLSLSVTPGQPASISCKSSQSLLRNDGKTPLYWYLQKAGQPPQL LIYEVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGAYYCMQNIQFPSF GGGTKLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDF ACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQE EDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYD VLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGK GHDGLYQGLSTATKDTYDALHMQALPPR
139111- nt Full CAR	966	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCGAAGTGCAATTGTTGGAATCTGGAGGAGGACTTGTGCAG CCTGGAGGATCACTGAGACTTTCGTGTGCGGTGTCAGGCTTCGCCCTGAGC AACCACGGCATGAGCTGGGTGCGGAGAGCCCCGGGGAAGGGTCTGGAATGG GTGTCCGGGATCGTCTACTCCGGTTCAACTTACTACGCCGCAAGCGTGAAG GGTCGCTTCACCATTTCCCGCGATAACTCCCGGAACACCCTGTACCTCCAA ATGAACTCCCTGCGGCCCGAGGACACCGCCATCTACTACTGTTCCGCGCAT GGAGGAGAGTCCGATGTCTGGGGACAGGGCACTACCGTGACCGTGTCGAGC GCCTCGGGGGGAGGAGGCTCCGGCGGTCGCGCCTCCGGGGGGGGTGGCAGC GACATTGTGATGACGCAGACTCCACTCTCGCTGTCCGTGACCCCGGGACAG CCCGCGTCCATCTCGTGCAAGAGCTCCCAGAGCCTGCTGAGGAACGACGGA AAGACTCCTCTGTATTGGTACCTCCAGAAGGCTGGACAGCCCCCGCAACTG CTCATCTACGAAGTGTCAAATCGCTTCTCCGGGGTGCCGGATCGGTTTTCC GGCTCGGGATCGGGCACCGACTTCACCCTGAAAATCTCCAGGGTCGAGGCC GAGGACGTGGGAGCCTACTACTGCATGCAAAACATCCAGTTCCCTTCCTTC GGCGGCGGCACAAAGCTGGAGATTAAGACCACTACCCCAGCACCGAGGCCA CCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAG GCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTC GCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTG CTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTG CTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAG GAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAA CTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGG CAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGAC GTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGC AGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATG GCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAA GGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTAT GACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
139100		
139100- aa Full CAR	952	MALPVTALLLPLALLLHAARPQVQLVQSGAEVRKTGASVKVSCKASGYIFD NFGINWVRQAPGQGLEWMGWINPKNNNTNYAQKFQGRVTITADESTNTAYM EVSSLRSEDTAVYYCARGPYYYQSYMDVWGQGTMVTVSSASGGGGSGGRAS GGGGSDIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGYNYLNWYLQKPG QSPQLLIYLGSKRASGVPDRFSGSGSGTDFTLHITRVGAEDVGVYYCMQAL QTPYTFGQGTKLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVH TRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRP

		VQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKG ERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
139100- nt Full CAR	967	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCCAAGTCCAACTCGTCCAGTCCGGCGCAGAAGTCAGAAAA ACCGGTGCTAGCGTGAAAGTGTCCTGCAAGGCCTCCGGCTACATTTTCGAT AACTTCGGAATCAACTGGGTCAGACAGGCCCCGGGCCAGGGGCTGGAATGG ATGGGATGGATCAACCCCAAGAACAACAACACCAACTACGCACAGAAGTTC CAGGGCCGCGTGACTATCACCGCCGATGAATCGACCAATACCGCCTACATG GAGGTGTCCTCCCTGCGGTCGGAGGACACTGCCGTGTATTACTGCGCGAGG GGCCCATACTACTACCAAAGCTACATGGACGTCTGGGGACAGGGAACCATG GTGACCGTGTCATCCGCCTCCGGTGGTGGAGGCTCCGGGGGGCGGGCTTCA GGAGGCGGAGGAAGCGATATTGTGATGACCCAGACTCCGCTTAGCCTGCCC GTGACTCCTGGAGAACCGGCCTCCATTTCCTGCCGGTCCTCGCAATCACTC CTGCATTCCAACGGTTACAACTACCTGAATTGGTACCTCCAGAAGCCTGGC CAGTCGCCCCAGTTGCTGATCTATCTGGGCTCGAAGCGCGCCTCCGGGGTG CCTGACCGGTTTAGCGGATCTGGGAGCGGCACGGACTTCACTCTCCACATC ACCCGCGTGGGAGCGGAGGACGTGGGAGTGTACTACTGTATGCAGGCGCTG CAGACTCCGTACACATTCGGACAGGGCACCAAGCTGGAGATCAAGACCACT ACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCT CTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCAT ACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCT GGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAG CGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCT GTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAG GAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCT CCAGCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGT CGGAGAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAA ATGGGCGGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAG CTCCAAAAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGG GAACGCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACC GCCACCAAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
139101		
139101- aa Full CAR	953	MALPVTALLLPLALLLHAARPQVQLQESGGGLVQPGGSLRLSCAASGFTFS SDAMTWVRQAPGKGLEWVSVISGSGGTTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCAKLDSSGYYYARGPRYWGQGTLVTVSSASGGGGSGG RASGGGGSDIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKA PKLLIYGASTLASGVPARFSGSGSGTHFTLTINSLQSEDSATYYCQQSYKR ASFGQGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRG LDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQT TQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRRE EYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERR RGKGHDGLYQGLSTATKDTYDALHMQALPPR
139101- nt Full CAR	968	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCCAAGTGCAACTTCAAGAATCAGGCGGAGGACTCGTGCAG CCCGGAGGATCATTGCGGCTCTCGTGCGCCGCCTCGGGCTTCACCTTCTCG AGCGACGCCATGACCTGGGTCCGCCAGGCCCCGGGGAAGGGGCTGGAATGG GTGTCTGTGATTTCCGGCTCCGGGGGAACTACGTACTACGCCGATTCCGTG AAAGGTCGCTTCACTATCTCCCGGGACAACAGCAAGAACACCCTTTATCTG CAAATGAATTCCCTCCGCGCCGAGGACACCGCCGTGTACTACTGCGCCAAG CTGGACTCCTCGGGCTACTACTATGCCCGGGGTCCGAGATACTGGGGACAG GGAACCCTCGTGACCGTGTCCTCCGCGTCCGGCGGAGGAGGGTCGGGAGGG

		CGGGCCTCCGGCGGCGGCGGTTCGGACATCCAGCTGACCCAGTCCCCATCC TCACTGAGCGCAAGCGTGGGCGACAGAGTCACCATTACATGCAGGGCGTCC CAGAGCATCAGCTCCTACCTGAACTGGTACCAACAGAAGCCTGGAAAGGCT CCTAAGCTGTTGATCTACGGGGCTTCGACCCTGGCATCCGGGGTGCCCGCG AGGTTTAGCGGAAGCGGTAGCGGCACTCACTTCACTCTGACCATTAACAGC CTCCAGTCCGAGGATTCAGCCACTTACTACTGTCAGCAGTCCTACAAGCGG GCCAGCTTCGGACAGGGCACTAAGGTCGAGATCAAGACCACTACCCCAGCA CCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTG CGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGT CTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGC GGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGG AAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACT ACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGC GGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTAC AAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAG GAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGG AAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAG GATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGA AGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAG GACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
139102		
139102- aa Full CAR	954	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFS NYGITWVRQAPGQGLEWMGWISAYNGNTNYAQKFQGRVTMTRNTSISTAYM ELSSLRSEDTAVYYCARGPYYYYMDVWGKGTMVTVSSASGGGGSGGRASGG GGSEIVMTQSPLSLPVTPGEPASISCRSSQSLLYSNGYNYVDWYLQKPGQS PQLLIYLGSNRASGVPDRFSGSGSGTDFKLQISRVEAEDVGIYYCMQGRQF PYSFGQGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTR GLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQ TTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRR EEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGER RRGKGHDGLYQGLSTATKDTYDALHMQALPPR
139102- nt Full CAR	969	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCCAAGTCCAACTGGTCCAGAGCGGTGCAGAAGTGAAGAAG CCCGGAGCGAGCGTGAAAGTGTCCTGCAAGGCTTCCGGGTACACCTTCTCC AACTACGGCATCACTTGGGTGCGCCAGGCCCCGGGACAGGGCCTGGAATGG ATGGGGTGGATTTCCGCGTACAACGGCAATACGAACTACGCTCAGAAGTTC CAGGGTAGAGTGACCATGACTAGGAACACCTCCATTTCCACCGCCTACATG GAACTGTCCTCCCTGCGGAGCGAGGACACCGCCGTGTACTATTGCGCCCGG GGACCATACTACTACTACATGGATGTCTGGGGGAAGGGGACTATGGTCACC GTGTCATCCGCCTCGGGAGGCGGCGGATCAGGAGGACGCGCCTCTGGTGGT GGAGGATCGGAGATCGTGATGACCCAGAGCCCTCTCTCCTTGCCCGTGACT CCTGGGGAGCCCGCATCCATTTCATGCCGGAGCTCCCAGTCACTTCTCTAC TCCAACGGCTATAACTACGTGGATTGGTACCTCCAAAAGCCGGGCCAGAGC CCGCAGCTGCTGATCTACCTGGGCTCGAACAGGGCCAGCGGAGTGCCTGAC CGGTTCTCCGGGTCGGGAAGCGGGACCGACTTCAAGCTGCAAATCTCGAGA GTGGAGGCCGAGGACGTGGGAATCTACTACTGTATGCAGGGCCGCCAGTTT CCGTACTCGTTCGGACAGGGCACCAAAGTGGAAATCAAGACCACTACCCCA GCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCC CTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGG GGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACT TGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGT CGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAG

		ACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAA GGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCC TACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGA GAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGC GGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAA AAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGC AGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACC AAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
139104		
139104- aa Full CAR	955	MALPVTALLLPLALLLHAARPEVQLLETGGGLVQPGGSLRLSCAVSGFALS NHGMSWVRRAPGKGLEWVSGIVYSGSTYYAASVKGRFTISRDNSRNTLYLQ MNSLRPEDTAIYYCSAHGGESDVWGQGTTVTVSSASGGGGSGGRASGGGGS EIVLTQSPATLSVSPGESATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGA STRASGIPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYGSSLTFGGGTK VEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIY IWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCS CRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKR RGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGL YQGLSTATKDTYDALHMQALPPR
139104- nt Full CAR	970	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCGAAGTGCAATTGCTCGAAACTGGAGGAGGTCTGGTGCAA CCTGGAGGATCACTTCGCCTGTCCTGCGCCGTGTCGGGCTTTGCCCTGTCC AACCATGGAATGAGCTGGGTCCGCCGCGCGCCGGGGAAGGGCCTCGAATGG GTGTCCGGCATCGTCTACTCCGGCTCCACCTACTACGCCGCGTCCGTGAAG GGCCGGTTCACGATTTCACGGGACAACTCGCGGAACACCCTGTACCTCCAA ATGAATTCCCTTCGGCCGGAGGATACTGCCATCTACTACTGCTCCGCCCAC GGTGGCGAATCCGACGTCTGGGGCCAGGGAACCACCGTGACCGTGTCCAGC GCGTCCGGGGGAGGAGGAAGCGGGGGTAGAGCATCGGGTGGAGGCGGATCA GAGATCGTGCTGACCCAGTCCCCCGCCACCTTGAGCGTGTCACCAGGAGAG TCCGCCACCCTGTCATGCCGCGCCAGCCAGTCCGTGTCCTCCAACCTGGCT TGGTACCAGCAGAAGCCGGGGCAGGCCCCTAGACTCCTGATCTATGGGGCG TCGACCCGGGCATCTGGAATTCCCGATAGGTTCAGCGGATCGGGCTCGGGC ACTGACTTCACTCTGACCATCTCCTCGCTGCAAGCCGAGGACGTGGCTGTG TACTACTGTCAGCAGTACGGAAGCTCCCTGACTTTCGGTGGCGGGACCAAA GTCGAGATTAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCT ACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCA GCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTAC ATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTG ATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAG CAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCA TGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAATTC AGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAGCTCTAC AACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGGACAAGCGG AGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAATCCCCAA GAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCCTATAGC GAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACGACGGACTG TACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTTCACATG CAGGCCCTGCCGCCTCGG
139106		
139106- aa Full CAR	956	MALPVTALLLPLALLLHAARPEVQLVETGGGLVQPGGSLRLSCAVSGFALS NHGMSWVRRAPGKGLEWVSGIVYSGSTYYAASVKGRFTISRDNSRNTLYLQ MNSLRPEDTAIYYCSAHGGESDVWGQGTTVTVSSASGGGGSGGRASGGGGS

		EIVMTQSPATLSVSPGERATLSCRASQSVSSKLAWYQQKPGQAPRLLMYGA SIRATGIPDRFSGSGSGTEFTLTISSLEPEDFAVYYCQQYGSSSWTFGQGT KVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDI YIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDK RRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDG LYQGLSTATKDTYDALHMQALPPR
139106- nt Full CAR	971	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCGAAGTGCAATTGGTGGAAACTGGAGGAGGACTTGTGCAA CCTGGAGGATCATTGAGACTGAGCTGCGCAGTGTCGGGATTCGCCCTGAGC AACCATGGAATGTCCTGGGTCAGAAGGGCCCCTGGAAAAGGCCTCGAATGG GTGTCAGGGATCGTGTACTCCGGTTCCACTTACTACGCCGCCTCCGTGAAG GGGCGCTTCACTATCTCACGGGATAACTCCCGCAATACCCTGTACCTCCAA ATGAACAGCCTGCGGCCGGAGGATACCGCCATCTACTACTGTTCCGCCCAC GGTGGAGAGTCTGACGTCTGGGGCCAGGGAACTACCGTGACCGTGTCCTCC GCGTCCGGCGGTGGAGGGAGCGGCGGCCGCGCCAGCGGCGGCGGAGGCTCC GAGATCGTGATGACCCAGAGCCCCGCTACTCTGTCGGTGTCGCCCGGAGAA AGGGCGACCCTGTCCTGCCGGGCGTCGCAGTCCGTGAGCAGCAAGCTGGCT TGGTACCAGCAGAAGCCGGGCCAGGCACCACGCCTGCTTATGTACGGTGCC TCCATTCGGGCCACCGGAATCCCGGACCGGTTCTCGGGGTCGGGGTCCGGT ACCGAGTTCACACTGACCATTTCCTCGCTCGAGCCCGAGGACTTTGCCGTC TATTACTGCCAGCAGTACGGCTCCTCCTCATGGACGTTCGGCCAGGGGACC AAGGTCGAAATCAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCT CCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCC GCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATC TACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTC GTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTT AAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGT TCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAA TTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAGCTC TACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGGACAAG CGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAATCCC CAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCCTAT AGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACGACGGA CTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTTCAC ATGCAGGCCCTGCCGCCTCGG
139107		
139107- aa Full CAR	957	MALPVTALLLPLALLLHAARPEVQLVETGGGVVQPGGSLRLSCAVSGFALS NHGMSWVRRAPGKGLEWVSGIVYSGSTYYAASVKGRFTISRDNSRNTLYLQ MNSLRPEDTAIYYCSAHGGESDVWGQGTTVTVSSASGGGGSGGRASGGGGS EIVLTQSPGTLSLSPGERATLSCRASQSVGSTNLAWYQQKPGQAPRLLIYD ASNRATGIPDRFSGGGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPWTFGQ GTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFAC DIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEED GCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVL DKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGH DGLYQGLSTATKDTYDALHMQALPPR
139107- nt Full CAR	972	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCGAAGTGCAATTGGTGGAGACTGGAGGAGGAGTGGTGCAA CCTGGAGGAAGCCTGAGACTGTCATGCGCGGTGTCGGGCTTCGCCCTCTCC AACCACGGAATGTCCTGGGTCCGCCGGGCCCCTGGGAAAGGACTTGAATGG GTGTCCGGCATCGTGTACTCGGGTTCCACCTACTACGCGGCCTCAGTGAAG

		GGCCGGTTTACTATTAGCCGCGACAACTCCAGAAACACACTGTACCTCCAA ATGAACTCGCTGCGGCCGGAAGATACCGCTATCTACTACTGCTCCGCCCAT GGGGGAGAGTCGGACGTCTGGGGACAGGGCACCACTGTCACTGTGTCCAGC GCTTCCGGCGGTGGTGGAAGCGGGGGACGGGCCTCAGGAGGCGGTGGCAGC GAGATTGTGCTGACCCAGTCCCCCGGGACCCTGAGCCTGTCCCCGGGAGAA AGGGCCACCCTCTCCTGTCGGGCATCCCAGTCCGTGGGGTCTACTAACCTT GCATGGTACCAGCAGAAGCCCGGCCAGGCCCCTCGCCTGCTGATCTACGAC GCGTCCAATAGAGCCACCGGCATCCCGGATCGCTTCAGCGGAGGCGGATCG GGCACCGACTTCACCCTCACCATTTCAAGGCTGGAACCGGAGGACTTCGCC GTGTACTACTGCCAGCAGTATGGTTCGTCCCCACCCTGGACGTTCGGCCAG GGGACTAAGGTCGAGATCAAGACCACTACCCCAGCACCGAGGCCACCCACC CCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGT AGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGC GATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTT TCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTAC ATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGAC GGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGC GTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAAC CAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTG GACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAG AATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAA GCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCAC GACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCT CTTCACATGCAGGCCCTGCCGCCTCGG
139108		
139108- aa Full CAR	958	MALPVTALLLPLALLLHAARPQVQLVESGGGLVKPGGSLRLSCAASGFTFS DYYMSWIRQAPGKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYL QMNSLRAEDTAVYYCARESGDGMDVWGQGTTVTVSSASGGGGSGGRASGGG GSDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIY AASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYTLAFGQGT KVDIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDI YIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDK RRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDG LYQGLSTATKDTYDALHMQALPPR
139108- nt Full CAR	973	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCCAAGTGCAACTCGTGGAATCTGGTGGAGGACTCGTGAAA CCTGGAGGATCATTGAGACTGTCATGCGCGGCCTCGGGATTCACGTTCTCC GATTACTACATGAGCTGGATTCGCCAGGCTCCGGGGAAGGGACTGGAATGG GTGTCCTACATTTCCTCATCCGGCTCCACCATCTACTACGCGGACTCCGTG AAGGGGAGATTCACCATTAGCCGCGATAACGCCAAGAACAGCCTGTACCTT CAGATGAACTCCCTGCGGGCTGAAGATACTGCCGTCTACTACTGCGCAAGG GAGAGCGGAGATGGGATGGACGTCTGGGGACAGGGTACCACTGTGACCGTG TCGTCGGCCTCCGGCGGAGGGGGTTCGGGTGGAAGGGCCAGCGGCGGCGGA GGCAGCGACATCCAGATGACCCAGTCCCCCTCATCGCTGTCCGCCTCCGTG GGCGACCGCGTCACCATCACATGCCGGGCCTCACAGTCGATCTCCTCCTAC CTCAATTGGTATCAGCAGAAGCCCGGAAAGGCCCCTAAGCTTCTGATCTAC GCAGCGTCCTCCCTGCAATCCGGGGTCCCATCTCGGTTCTCCGGCTCGGGC AGCGGTACCGACTTCACTCTGACCATCTCGAGCCTGCAGCCGGAGGACTTC GCCACTTACTACTGTCAGCAAAGCTACACCCTCGCGTTTGGCCAGGGCACC AAAGTGGACATCAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCT CCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCC

		GCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATC TACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTC GTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTT AAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGT TCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAA TTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAGCTC TACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGGACAAG CGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAATCCC CAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCCTAT AGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACGACGGA CTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTTCAC ATGCAGGCCCTGCCGCCTCGG
139110		
139110- aa Full CAR	960	MALPVTALLLPLALLLHAARPQVQLVQSGGGLVKPGGSLRLSCAASGFTFS DYYMSWIRQAPGKGLEWVSYISSSGNTIYYADSVKGRFTISRDNAKNSLYL QMNSLRAEDTAVYYCARSTMVREDYWGQGTLVTVSSASGGGGSGGRASGGG GSDIVLTQSPLSLPVTLGQPASISCKSSESLVHNSGKTYLNWFHQRPGQSP RRLIYEVSNRDSGVPDRFTGSGSGTDFTLKISRVEAEDVGVYYCMQGTHWP GTFGQGTKLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRG LDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQT TQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRRE EYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERR RGKGHDGLYQGLSTATKDTYDALHMQALPPR
139110- nt Full CAR	975	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCCAAGTGCAACTGGTGCAAAGCGGAGGAGGATTGGTCAAA CCCGGAGGAAGCCTGAGACTGTCATGCGCGGCCTCTGGATTCACCTTCTCC GATTACTACATGTCATGGATCAGACAGGCCCCGGGGAAGGGCCTCGAATGG GTGTCCTACATCTCGTCCTCCGGGAACACCATCTACTACGCCGACAGCGTG AAGGGCCGCTTTACCATTTCCCGCGACAACGCAAAGAACTCGCTGTACCTT CAGATGAATTCCCTGCGGGCTGAAGATACCGCGGTGTACTATTGCGCCCGG TCCACTATGGTCCGGGAGGACTACTGGGGACAGGGCACACTCGTGACCGTG TCCAGCGCGAGCGGGGGTGGAGGCAGCGGTGGACGCGCCTCCGGCGGCGGC GGTTCAGACATCGTGCTGACTCAGTCGCCCCTGTCGCTGCCGGTCACCCTG GGCCAACCGGCCTCAATTAGCTGCAAGTCCTCGGAGAGCCTGGTGCACAAC TCAGGAAAGACTTACCTGAACTGGTTCCATCAGCGGCCTGGACAGTCCCCA CGGAGGCTCATCTATGAAGTGTCCAACAGGGATTCGGGGGTGCCCGACCGC TTCACTGGCTCCGGGTCCGGCACCGACTTCACCTTGAAAATCTCCAGAGTG GAAGCCGAGGACGTGGGCGTGTACTACTGTATGCAGGGTACCCACTGGCCT GGAACCTTTGGACAAGGAACTAAGCTCGAGATTAAGACCACTACCCCAGCA CCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTG CGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGT CTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGC GGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGG AAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACT ACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGC GGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTAC AAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAG GAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGG AAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAG GATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGA AGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAG GACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG

139112		
139112- aa Full CAR	961	MALPVTALLLPLALLLHAARPQVQLVESGGGLVQPGGSLRLSCAVSGFALS NHGMSWVRRAPGKGLEWVSGIVYSGSTYYAASVKGRFTISRDNSRNTLYLQ MNSLRPEDTAIYYCSAHGGESDVWGQGTTVTVSSASGGGGSGGRASGGGGS DIRLTQSPSPLSASVGDRVTITCQASEDINKFLNWYHQTPGKAPKLLIYDA STLQTGVPSRFSGSGSGTDFTLTINSLQPEDIGTYYCQQYESLPLTFGGGT KVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDI YIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDK RRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDG LYQGLSTATKDTYDALHMQALPPR
139112- nt Full CAR	976	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCCAAGTGCAACTCGTGGAATCTGGTGGAGGACTCGTGCAA CCCGGTGGAAGCCTTAGGCTGTCGTGCGCCGTCAGCGGGTTTGCTCTGAGC AACCATGGAATGTCCTGGGTCCGCCGGGCACCGGGAAAAGGGCTGGAATGG GTGTCCGGCATCGTGTACAGCGGGTCAACCTATTACGCCGCGTCCGTGAAG GGCAGATTCACTATCTCAAGAGACAACAGCCGGAACACCCTGTACTTGCAA ATGAATTCCCTGCGCCCCGAGGACACCGCCATCTACTACTGCTCCGCCCAC GGAGGAGAGTCGGACGTGTGGGGCCAGGGAACGACTGTGACTGTGTCCAGC GCATCAGGAGGGGGTGGTTCGGGCGGCCGGGCCTCGGGGGGAGGAGGTTCC GACATTCGGCTGACCCAGTCCCCGTCCCCACTGTCGGCCTCCGTCGGCGAC CGCGTGACCATCACTTGTCAGGCGTCCGAGGACATTAACAAGTTCCTGAAC TGGTACCACCAGACCCCTGGAAAGGCCCCCAAGCTGCTGATCTACGATGCC TCGACCCTTCAAACTGGAGTGCCTAGCCGGTTCTCCGGGTCCGGCTCCGGC ACTGATTTCACTCTGACCATCAACTCATTGCAGCCGGAAGATATCGGGACC TACTATTGCCAGCAGTACGAATCCCTCCCGCTCACATTCGGCGGGGGAACC AAGGTCGAGATTAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCT CCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCC GCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATC TACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTC GTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTT AAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGT TCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAA TTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAGCTC TACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGGACAAG CGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAATCCC CAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCCTAT AGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACGACGGA CTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTTCAC ATGCAGGCCCTGCCGCCTCGG
139113		
139113- aa Full CAR	962	MALPVTALLLPLALLLHAARPEVQLVETGGGLVQPGGSLRLSCAVSGFALS NHGMSWVRRAPGKGLEWVSGIVYSGSTYYAASVKGRFTISRDNSRNTLYLQ MNSLRPEDTAIYYCSAHGGESDVWGQGTTVTVSSASGGGGSGGRASGGGGS ETTLTQSPATLSVSPGERATLSCRASQSVGSNLAWYQQKPGQGPRLLIYGA STRATGIPARFSGSGSGTEFTLTISSLQPEDFAVYYCQQYNDWLPVTFGQG TKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD IYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLD KRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHD GLYQGLSTATKDTYDALHMQALPPR
139113- nt	977	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC

Full CAR		GCCGCTCGGCCCGAAGTGCAATTGGTGGAAACTGGAGGAGGACTTGTGCAA CCTGGAGGATCATTGCGGCTCTCATGCGCTGTCTCCGGCTTCGCCCTGTCA AATCACGGGATGTCGTGGGTCAGACGGGCCCCGGGAAAGGGTCTGGAATGG GTGTCGGGGATTGTGTACAGCGGCTCCACCTACTACGCCGCTTCGGTCAAG GGCCGCTTCACTATTTCACGGGACAACAGCCGCAACACCCTCTATCTGCAA ATGAACTCTCTCCGCCCGGAGGATACCGCCATCTACTACTGCTCCGCACAC GGCGGCGAATCCGACGTGTGGGGACAGGGAACCACTGTCACCGTGTCGTCC GCATCCGGTGGCGGAGGATCGGGTGGCCGGGCCTCCGGGGGCGGCGGCAGC GAGACTACCCTGACCCAGTCCCCTGCCACTCTGTCCGTGAGCCCGGGAGAG AGAGCCACCCTTAGCTGCCGGGCCAGCCAGAGCGTGGGCTCCAACCTGGCC TGGTACCAGCAGAAGCCAGGACAGGGTCCCAGGCTGCTGATCTACGGAGCC TCCACTCGCGCGACCGGCATCCCCGCGAGGTTCTCCGGGTCGGGTTCCGGG ACCGAGTTCACCCTGACCATCTCCTCCCTCCAACCGGAGGACTTCGCGGTG TACTACTGTCAGCAGTACAACGATTGGCTGCCCGTGACATTTGGACAGGGG ACGAAGGTGGAAATCAAAACCACTACCCCAGCACCGAGGCCACCCACCCCG GCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGA CCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGAT ATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCA CTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATC TTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGC TGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTG AAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAG CTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGGAC AAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAAT CCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCC TATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACGAC GGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTT CACATGCAGGCCCTGCCGCCTCGG
139114		
139114- aa Full CAR	963	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAVSGFALS NHGMSWVRRAPGKGLEWVSGIVYSGSTYYAASVKGRFTISRDNSRNTLYLQ MNSLRPEDTAIYYCSAHGGESDVWGQGTTVTVSSASGGGGSGGRASGGGGS EIVLTQSPGTLSLSPGERATLSCRASQSIGSSSLAWYQQKPGQAPRLLMYG ASSRASGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYAGSPPFTFGQ GTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFAC DIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEED GCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVL DKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGH DGLYQGLSTATKDTYDALHMQALPPR
139114- nt Full CAR	978	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCGAAGTGCAATTGGTGGAATCTGGTGGAGGACTTGTGCAA CCTGGAGGATCACTGAGACTGTCATGCGCGGTGTCCGGTTTTGCCCTGAGC AATCATGGGATGTCGTGGGTCCGGCGCGCCCCCGGAAAGGGTCTGGAATGG GTGTCGGGTATCGTCTACTCCGGGAGCACTTACTACGCCGCGAGCGTGAAG GGCCGCTTCACCATTTCCCGCGATAACTCCCGCAACACCCTGTACTTGCAA ATGAACTCGCTCCGGCCTGAGGACACTGCCATCTACTACTGCTCCGCACAC GGAGGAGAATCCGACGTGTGGGGCCAGGGAACTACCGTGACCGTCAGCAGC GCCTCCGGCGGCGGGGGCTCAGGCGGACGGGCTAGCGGCGGCGGTGGCTCC GAGATCGTGCTGACCCAGTCGCCTGGCACTCTCTCGCTGAGCCCCGGGGAA AGGGCAACCCTGTCCTGTCGGGCCAGCCAGTCCATTGGATCATCCTCCCTC GCCTGGTATCAGCAGAAACCGGGACAGGCTCCGCGGCTGCTTATGTATGGG GCCAGCTCAAGAGCCTCCGGCATTCCCGACCGGTTCTCCGGGTCCGGTTCC

		GGCACCGATTTCACCCTGACTATCTCGAGGCTGGAGCCAGAGGACTTCGCC GTGTACTACTGCCAGCAGTACGCGGGGTCCCCGCCGTTCACGTTCGGACAG GGAACCAAGGTCGAGATCAAGACCACTACCCCAGCACCGAGGCCACCCACC CCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGT AGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGC GATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTT TCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTAC ATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGAC GGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGC GTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAAC CAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTG GACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAG AATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAA GCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCAC GACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCT CTTCACATGCAGGCCCTGCCGCCTCGG
149362		
149362-aa Full CAR	979	MALPVTALLLPLALLLHAARPQVQLQESGPGLVKPSETLSLTCTVSGGSIS SSYYYWGWIRQPPGKGLEWIGSIYYSGSAYYNPSLKSRVTISVDTSKNQFS LRLSSVTAADTAVYYCARHWQEWPDAFDIWGQGTMVTVSSGGGGSGGGGSG GGGSETTLTQSPAFMSATPGDKVIISCKASQDIDDAMNWYQQKPGEAPLFI IQSATSPVPGIPPRFSGSGFGTDFSLTINNIESEDAAYYFCLQHDNFPLTF GQGTKLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDF ACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQE EDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYD VLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGK GHDGLYQGLSTATKDTYDALHMQALPPR
149362-nt Full CAR	1001	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCCAAGTGCAGCTTCAGGAAAGCGGACCGGGCCTGGTCAAG CCATCCGAAACTCTCTCCCTGACTTGCACTGTGTCTGGCGGTTCCATCTCA TCGTCGTACTACTACTGGGGCTGGATTAGGCAGCCGCCCGGAAAGGGACTG GAGTGGATCGGAAGCATCTACTATTCCGGCTCGGCGTACTACAACCCTAGC CTCAAGTCGAGAGTGACCATCTCCGTGGATACCTCCAAGAACCAGTTTTCC CTGCGCCTGAGCTCCGTGACCGCCGCTGACACCGCCGTGTACTACTGTGCT CGGCATTGGCAGGAATGGCCCGATGCCTTCGACATTTGGGGCCAGGGCACT ATGGTCACTGTGTCATCCGGGGGTGGAGGCAGCGGGGGAGGAGGGTCCGGG GGGGGAGGTTCAGAGACAACCTTGACCCAGTCACCCGCATTCATGTCCGCC ACTCCGGGAGACAAGGTCATCATCTCGTGCAAAGCGTCCCAGGATATCGAC GATGCCATGAATTGGTACCAGCAGAAGCCTGGCGAAGCGCCGCTGTTCATT ATCCAATCCGCAACCTCGCCCGTGCCTGGAATCCCACCGCGGTTCAGCGGC AGCGGTTTCGGAACCGACTTTTCCCTGACCATTAACAACATTGAGTCCGAG GACGCCGCCTACTACTTCTGCCTGCAACACGACAACTTCCCTCTCACGTTC GGCCAGGGAACCAAGCTGGAAATCAAGACCACTACCCCAGCACCGAGGCCA CCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAG GCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTC GCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTG CTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTG CTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAG GAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAA CTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGG CAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGAC GTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGC

		AGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATG GCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAA GGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTAT GACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
149363		
149363-aa Full CAR	980	MALPVTALLLPLALLLHAARPQVNLRESGPALVKPTQTLTLTCTFSGFSLR TSGMCVSWIRQPPGKALEWLARIDWDEDKFYSTSLKTRLTISKDTSDNQVV LRMTNMDPADTATYYCARSGAGGTSATAFDIWGPGTMVTVSSGGGGSGGGG SGGGGSDIQMTQSPSSLSASVGDRVTITCRASQDIYNNLAWFQLKPGSAPR SLMYAANKSQSGVPSRFSGSASGTDFTLTISSLQPEDFATYYCQHYYRFPY SFGQGTKLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGL DFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTT QEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREE YDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRR GKGHDGLYQGLSTATKDTYDALHMQALPPR
149363-nt Full CAR	1002	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCCAAGTCAATCTGCGCGAATCCGGCCCCGCCTTGGTCAAG CCTACCCAGACCCTCACTCTGACCTGTACTTTCTCCGGCTTCTCCCTGCGG ACTTCCGGGATGTGCGTGTCCTGGATCAGACAGCCTCCGGGAAAGGCCCTG GAGTGGCTCGCTCGCATTGACTGGGATGAGGACAAGTTCTACTCCACCTCA CTCAAGACCAGGCTGACCATCAGCAAAGATACCTCTGACAACCAAGTGGTG CTCCGCATGACCAACATGGACCCAGCCGACACTGCCACTTACTACTGCGCG AGGAGCGGAGCGGGCGGAACCTCCGCCACCGCCTTCGATATTTGGGGCCCG GGTACCATGGTCACCGTGTCAAGCGGAGGAGGGGGGTCCGGGGGCGGCGGT TCCGGGGGAGGCGGATCGGACATTCAGATGACTCAGTCACCATCGTCCCTG AGCGCTAGCGTGGGCGACAGAGTGACAATCACTTGCCGGGCATCCCAGGAC ATCTATAACAACCTTGCGTGGTTCCAGCTGAAGCCTGGTTCCGCACCGCGG TCACTTATGTACGCCGCCAACAAGAGCCAGTCGGGAGTGCCGTCCCGGTTT TCCGGTTCGGCCTCGGGAACTGACTTCACCCTGACGATCTCCAGCCTGCAA CCCGAGGATTTCGCCACCTACTACTGCCAGCACTACTACCGCTTTCCCTAC TCGTTCGGACAGGGAACCAAGCTGGAAATCAAGACCACTACCCCAGCACCG AGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGT CCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTT GACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGG GTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAG AAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACT CAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGC TGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAG CAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAG TACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAG CCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGAT AAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGA GGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGAC ACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
149364		
149364-aa Full CAR	981	MALPVTALLLPLALLLHAARPEVQLVESGGGLVKPGGSLRLSCAASGFTFS SYSMNWVRQAPGKGLEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYL QMNSLRAEDTAVYYCAKTIAAVYAFDIWGQGTTVTVSSGGGGSGGGGSGGG GSEIVLTQSPLSLPVTPEEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSP QLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTP YTFGQGTKLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRG LDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQT

		TQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRRE EYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERR RGKGHDGLYQGLSTATKDTYDALHMQALPPR
149364-nt Full CAR	1003	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCGAAGTGCAGCTTGTCGAATCCGGGGGGGGACTGGTCAAG CCGGGCGGATCACTGAGACTGTCCTGCGCCGCGAGCGGCTTCACGTTCTCC TCCTACTCCATGAACTGGGTCCGCCAAGCCCCCGGGAAGGGACTGGAATGG GTGTCCTCTATCTCCTCGTCGTCGTCCTACATCTACTACGCCGACTCCGTG AAGGGAAGATTCACCATTTCCCGCGACAACGCAAAGAACTCACTGTACTTG CAAATGAACTCACTCCGGGCCGAAGATACTGCTGTGTACTATTGCGCCAAG ACTATTGCCGCCGTCTACGCTTTCGACATCTGGGGCCAGGGAACCACCGTG ACTGTGTCGTCCGGTGGTGGTGGCTCGGGCGGAGGAGGAAGCGGCGGCGGG GGGTCCGAGATTGTGCTGACCCAGTCGCCACTGAGCCTCCCTGTGACCCCC GAGGAACCCGCCAGCATCAGCTGCCGGTCCAGCCAGTCCCTGCTCCACTCC AACGGATACAATTACCTCGATTGGTACCTTCAGAAGCCTGGACAAAGCCCG CAGCTGCTCATCTACTTGGGATCAAACCGCGCGTCAGGAGTGCCTGACCGG TTCTCCGGCTCGGGCAGCGGTACCGATTTCACCCTGAAAATCTCCAGGGTG GAGGCAGAGGACGTGGGAGTGTATTACTGTATGCAGGCGCTGCAGACTCCG TACACATTTGGGCAGGGCACCAAGCTGGAGATCAAGACCACTACCCCAGCA CCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTG CGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGT CTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGC GGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGG AAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACT ACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGC GGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTAC AAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAG GAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGG AAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAG GATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGA AGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAG GACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
149365		
149365-aa Full CAR	982	MALPVTALLLPLALLLHAARPEVQLVESGGGLVKPGGSLRLSCAASGFTFS DYYMSWIRQAPGKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYL QMNSLRAEDTAVYYCARDLRGAFDIWGQGTMVTVSSGGGGSGGGGSGGGGS SYVLTQSPSVSAAPGYTATISCGGNNIGTKSVHWYQQKPGQAPLLVIRDDS VRPSKIPGRFSGSNSGNMATLTISGVQAGDEADFYCQVWDSDSEHVVFGGG TKLTVLTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD IYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLD KRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHD GLYQGLSTATKDTYDALHMQALPPR
149365-nt Full CAR	1004	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCGAAGTCCAGCTCGTGGAGTCCGGCGGAGGCCTTGTGAAG CCTGGAGGTTCGCTGAGACTGTCCTGCGCCGCCTCCGGCTTCACCTTCTCC GACTACTACATGTCCTGGATCAGACAGGCCCCGGGAAAGGGCCTGGAATGG GTGTCCTACATCTCGTCATCGGGCAGCACTATCTACTACGCGGACTCAGTG AAGGGGCGGTTCACCATTTCCCGGGATAACGCGAAGAACTCGCTGTATCTG CAAATGAACTCACTGAGGGCCGAGGACACCGCCGTGTACTACTGCGCCCGC GATCTCCGCGGGGCATTTGACATCTGGGGACAGGGAACCATGGTCACAGTG TCCAGCGGAGGGGGAGGATCGGGTGGCGGAGGTTCCGGGGGTGGAGGCTCC

		TCCTACGTGCTGACTCAGAGCCCAAGCGTCAGCGCTGCGCCCGGTTACACG GCAACCATCTCCTGTGGCGGAAACAACATTGGGACCAAGTCTGTGCACTGG TATCAGCAGAAGCCGGGCCAAGCTCCCCTGTTGGTGATCCGCGATGACTCC GTGCGGCCTAGCAAAATTCCGGGACGGTTCTCCGGCTCCAACAGCGGCAAT ATGGCCACTCTCACCATCTCGGGAGTGCAGGCCGGAGATGAAGCCGACTTC TACTGCCAAGTCTGGGACTCAGACTCCGAGCATGTGGTGTTCGGGGGCGGA ACCAAGCTGACTGTGCTCACCACTACCCCAGCACCGAGGCCACCCACCCCG GCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGA CCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGAT ATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCA CTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATC TTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGC TGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTG AAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAG CTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGGAC AAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAAT CCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCC TATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACGAC GGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTT CACATGCAGGCCCTGCCGCCTCGG
149366		
149366-aa Full CAR	983	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKPSGYTVT SHYIHWVRRAPGQGLEWMGMINPSGGVTAYSQTLQGRVTMTSDTSSSTVYM ELSSLRSEDTAMYYCAREGSGSGWYFDFWGRGTLVTVSSGGGGSGGGGSGG GGSSYVLTQPPSVSVSPGQTASITCSGDGLSKKYVSWYQQKAGQSPVVLIS RDKERPSGIPDRFSGSNSADTATLTISGTQAMDEADYYCQAWDDTTVVFGG GTKLTVLTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFAC DIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEED GCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVL DKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGH DGLYQGLSTATKDTYDALHMQALPPR
149366-nt Full CAR	1005	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCCAAGTGCAGCTGGTGCAGAGCGGGGCCGAAGTCAAGAAG CCGGGAGCCTCCGTGAAAGTGTCCTGCAAGCCTTCGGGATACACCGTGACC TCCCACTACATTCATTGGGTCCGCCGCGCCCCCGGCCAAGGACTCGAGTGG ATGGGCATGATCAACCCTAGCGGCGGAGTGACCGCGTACAGCCAGACGCTG CAGGGACGCGTGACTATGACCTCGGATACCTCCTCCTCCACCGTCTATATG GAACTGTCCAGCCTGCGGTCCGAGGATACCGCCATGTACTACTGCGCCCGG GAAGGATCAGGCTCCGGGTGGTATTTCGACTTCTGGGGAAGAGGCACCCTC GTGACTGTGTCATCTGGGGGAGGGGGTTCCGGTGGTGGCGGATCGGGAGGA GGCGGTTCATCCTACGTGCTGACCCAGCCACCCTCCGTGTCCGTGAGCCCC GGCCAGACTGCATCGATTACATGTAGCGGCGACGGCCTCTCCAAGAAATAC GTGTCGTGGTACCAGCAGAAGGCCGGACAGAGCCCGGTGGTGCTGATCTCA AGAGATAAGGAGCGGCCTAGCGGAATCCCGGACAGGTTCTCGGGTTCCAAC TCCGCGGACACTGCTACTCTGACCATCTCGGGGACCCAGGCTATGGACGAA GCCGATTACTACTGCCAAGCCTGGGACGACACTACTGTCGTGTTTGGAGGG GGCACCAAGTTGACCGTCCTTACCACTACCCCAGCACCGAGGCCACCCACC CCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGT AGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGC GATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTT TCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTAC ATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGAC

		GGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGC GTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAAC CAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTG GACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAG AATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAA GCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCAC GACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCT CTTCACATGCAGGCCCTGCCGCCTCGG
149367		
149367-aa Full CAR	984	MALPVTALLLPLALLLHAARPQVQLQESGPGLVKPSQTLSLTCTVSGGSIS SGGYYWSWIRQHPGKGLEWIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFS LKLSSVTAADTAVYYCARAGIAARLRGAFDIWGQGTMVTVSSGGGGSGGGG SGGGGSDIVMTQSPSSVSASVGDRVIITCRASQGIRNWLAWYQQKPGKAPN LLIYAASNLQSGVPSRFSGSGSGADFTLTISSLQPEDVATYYCQKYNSAPF TFGPGTKVDIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGL DFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTT QEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREE YDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRR GKGHDGLYQGLSTATKDTYDALHMQALPPR
149367-nt Full CAR	1006	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCCAAGTGCAGCTTCAGGAGAGCGGCCCGGGACTCGTGAAG CCGTCCCAGACCCTGTCCCTGACTTGCACCGTGTCGGGAGGAAGCATCTCG AGCGGAGGCTACTATTGGTCGTGGATTCGGCAGCACCCTGGAAAGGGCCTG GAATGGATCGGCTACATCTACTACTCCGGCTCGACCTACTACAACCCATCG CTGAAGTCCAGAGTGACAATCTCAGTGGACACGTCCAAGAATCAGTTCAGC CTGAAGCTCTCTTCCGTGACTGCGGCCGACACCGCCGTGTACTACTGCGCA CGCGCTGGAATTGCCGCCCGGCTGAGGGGTGCCTTCGACATTTGGGGACAG GGCACCATGGTCACCGTGTCCTCCGGCGGCGGAGGTTCCGGGGGTGGAGGC TCAGGAGGAGGGGGGTCCGACATCGTCATGACTCAGTCGCCCTCAAGCGTC AGCGCGTCCGTCGGGGACAGAGTGATCATCACCTGTCGGGCGTCCCAGGGA ATTCGCAACTGGCTGGCCTGGTATCAGCAGAAGCCCGGAAAGGCCCCCAAC CTGTTGATCTACGCCGCCTCAAACCTCCAATCCGGGGTGCCGAGCCGCTTC AGCGGCTCCGGTTCGGGTGCCGATTTCACTCTGACCATCTCCTCCCTGCAA CCTGAAGATGTGGCTACCTACTACTGCCAAAAGTACAACTCCGCACCTTTT ACTTTCGGACCGGGGACCAAAGTGGACATTAAGACCACTACCCCAGCACCG AGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGT CCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTT GACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGG GTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAG AAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACT CAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGC TGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAG CAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAG TACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAG CCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGAT AAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGA GGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGAC ACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
149368		
149368-aa Full CAR	985	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGSSVKVSCKASGGTFS SYAISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYM ELSSLRSEDTAVYYCARRGGYQLLRWDVGLLRSAFDIWGQGTMVTVSSGGG

		GSGGGGSGGGGSSYVLTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKP GQAPVLVLYGKNNRPSGVPDRFSGSRSGTTASLTITGAQAEDEADYYCSSR DSSGDHLRVFGTGTKVTVLTTTPAPRPPTPAPTIASQPLSLRPEACRPAAG GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNE LNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEI GMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
149368-nt Full CAR	1007	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCCAAGTGCAGCTGGTCCAGTCGGGCGCCGAGGTCAAGAAG CCCGGGAGCTCTGTGAAAGTGTCCTGCAAGGCCTCCGGGGGCACCTTTAGC TCCTACGCCATCTCCTGGGTCCGCCAAGCACCGGGTCAAGGCCTGGAGTGG ATGGGGGGAATTATCCCTATCTTCGGCACTGCCAACTACGCCCAGAAGTTC CAGGGACGCGTGACCATTACCGCGGACGAATCCACCTCCACCGCTTATATG GAGCTGTCCAGCTTGCGCTCGGAAGATACCGCCGTGTACTACTGCGCCCGG AGGGGTGGATACCAGCTGCTGAGATGGGACGTGGGCCTCCTGCGGTCGGCG TTCGACATCTGGGGCCAGGGCACTATGGTCACTGTGTCCAGCGGAGGAGGC GGATCGGGAGGCGGCGGATCAGGGGGAGGCGGTTCCAGCTACGTGCTTACT CAACCCCCTTCGGTGTCCGTGGCCCCGGGACAGACCGCCAGAATCACTTGC GGAGGAAACAACATTGGGTCCAAGAGCGTGCATTGGTACCAGCAGAAGCCA GGACAGGCCCCTGTGCTGGTGCTCTACGGGAAGAACAATCGGCCCAGCGGA GTGCCGGACAGGTTCTCGGGTTCACGCTCCGGTACAACCGCTTCACTGACT ATCACCGGGGCCCAGGCAGAGGATGAAGCGGACTACTACTGTTCCTCCCGG GATTCATCCGGCGACCACCTCCGGGTGTTCGGAACCGGAACGAAGGTCACC GTGCTGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATC GCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGT GGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGG GCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACT CTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCC TTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGG TTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGC AGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAA CTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGA CGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGC CTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCCTATAGCGAGATT GGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACGACGGACTGTACCAG GGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTTCACATGCAGGCC CTGCCGCCTCGG
149369		
149369-aa Full CAR	986	MALPVTALLLPLALLLHAARPEVQLQQSGPGLVKPSQTLSLTCAISGDSVS SNSAAWNWIRQSPSRGLEWLGRTYYRSKWYSFYAISLKSRIIINPDTSKNQ FSLQLKSVTPEDTAVYYCARSSPEGLFLYWFDPWGQGTLVTVSSGGDGSGG GGSGGGGSSSELTQDPAVSVALGQTIRITCQGDSLGNYYATWYQQKPGQAP VLVIYGTNNRPSGIPDRFSASSSGNTASLTITGAQAEDEADYYCNSRDSSG HHLLFGTGTKVTVLTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPV QTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGR REEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGE RRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
149369-nt Full CAR	1008	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCGAAGTGCAGCTCCAACAGTCAGGACCGGGGCTCGTGAAG CCATCCCAGACCCTGTCCCTGACTTGTGCCATCTCGGGAGATAGCGTGTCA TCGAACTCCGCCGCCTGGAACTGGATTCGGCAGAGCCCGTCCCGCGGACTG

		GAGTGGCTTGGAAGGACCTACTACCGGTCCAAGTGGTACTCTTTCTACGCG ATCTCGCTGAAGTCCCGCATTATCATTAACCCTGATACCTCCAAGAATCAG TTCTCCCTCCAACTGAAATCCGTCACCCCCGAGGACACAGCAGTGTATTAC TGCGCACGGAGCAGCCCCGAAGGACTGTTCCTGTATTGGTTTGACCCCTGG GGCCAGGGGACTCTTGTGACCGTGTCGAGCGGCGGAGATGGGTCCGGTGGC GGTGGTTCGGGGGGCGGCGGATCATCATCCGAACTGACCCAGGACCCGGCT GTGTCCGTGGCGCTGGGACAAACCATCCGCATTACGTGCCAGGGAGACTCC CTGGGCAACTACTACGCCACTTGGTACCAGCAGAAGCCGGGCCAAGCCCCT GTGTTGGTCATCTACGGGACCAACAACAGACCTTCCGGCATCCCCGACCGG TTCAGCGCTTCGTCCTCCGGCAACACTGCCAGCCTGACCATCACTGGAGCG CAGGCCGAAGATGAGGCCGACTACTACTGCAACAGCAGAGACTCCTCGGGT CATCACCTCTTGTTCGGAACTGGAACCAAGGTCACCGTGCTGACCACTACC CCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTG TCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACC CGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGT ACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGC GGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTG CAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAG GAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCA GCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGG AGAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATG GGCGGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTC CAAAAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAA CGCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCC ACCAAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1978-A4		
BCMA_EBB-C1978-A4 - aa Full CART	987	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASGFTFS SYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCAKVEGSGSLDYWGQGTLVTVSSGGGGSGGGGSGGGG SEIVMTQSPGTLSLSPGERATLSCRASQSVSSAYLAWYQQKPGQPPRLLIS GASTRATGIPDRFGGSGSGTDFTLTISRLEPEDFAVYYCQHYGSSFNGSSL FTFGQGTRLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRG LDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQT TQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRRE EYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERR RGKGHDGLYQGLSTATKDTYDALHMQALPPR
BCMA_EBB-C1978-A4 - nt Full CART	1009	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCGAAGTGCAGCTCGTGGAGTCAGGAGGCGGCCTGGTCCAG CCGGGAGGGTCCCTTAGACTGTCATGCGCCGCAAGCGGATTCACTTTCTCC TCCTATGCCATGAGCTGGGTCCGCCAAGCCCCCGGAAAGGGACTGGAATGG GTGTCCGCCATCTCGGGGTCTGGAGGCTCAACTTACTACGCTGACTCCGTG AAGGGACGGTTCACCATTAGCCGCGACAACTCCAAGAACACCCTCTACCTC CAAATGAACTCCCTGCGGGCCGAGGATACCGCCGTCTACTACTGCGCCAAA GTGGAAGGTTCAGGATCGCTGGACTACTGGGGACAGGGTACTCTCGTGACC GTGTCATCGGGCGGAGGAGGTTCCGGCGGTGGCGGCTCCGGCGGCGGAGGG TCGGAGATCGTGATGACCCAGAGCCCTGGTACTCTGAGCCTTTCGCCGGGA GAAAGGGCCACCCTGTCCTGCCGCGCTTCCCAATCCGTGTCCTCCGCGTAC TTGGCGTGGTACCAGCAGAAGCCGGGACAGCCCCCTCGGCTGCTGATCAGC GGGGCCAGCACCCGGGCAACCGGAATCCCAGACAGATTCGGGGGTTCCGGC AGCGGCACAGATTTCACCCTGACTATTTCGAGGTTGGAGCCCGAGGACTTT GCGGTGTATTACTGTCAGCACTACGGGTCGTCCTTTAATGGCTCCAGCCTG TTCACGTTCGGACAGGGGACCCGCCTGGAAATCAAGACCACTACCCCAGCA

		CCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTG CGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGT CTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGC GGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGG AAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACT ACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGC GGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTAC AAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAG GAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGG AAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAG GATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGA AGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAG GACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1978-G1		
BCMA_EBB-C1978-G1 - aa Full CART	988	MALPVTALLLPLALLLHAARPEVQLVETGGGLVQPGGSLRLSCAASGITFS RYPMSWVRQAPGKGLEWVSGISDSGVSTYYADSAKGRFTISRDNSKNTLFL QMSSLRDEDTAVYYCVTRAGSEASDIWGQGTMVTVSSGGGGSGGGGSGGGG SEIVLTQSPATLSLSPGERATLSCRASQSVSNSLAWYQQKPGQAPRLLIYD ASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAIYYCQQFGTSSGLTFGG GTKLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFAC DIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEED GCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVL DKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGH DGLYQGLSTATKDTYDALHMQALPPR
BCMA_EBB-C1978-G1 - nt Full CART	1010	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCGAAGTGCAACTGGTGGAAACCGGTGGCGGCCTGGTGCAG CCTGGAGGATCATTGAGGCTGTCATGCGCGGCCAGCGGTATTACCTTCTCC CGGTACCCCATGTCCTGGGTCAGACAGGCCCCGGGGAAAGGGCTTGAATGG GTGTCCGGGATCTCGGACTCCGGTGTCAGCACTTACTACGCCGACTCCGCC AAGGGACGCTTCACCATTTCCCGGGACAACTCGAAGAACACCCTGTTCCTC CAAATGAGCTCCCTCCGGGACGAGGATACTGCAGTGTACTACTGCGTGACC CGCGCCGGGTCCGAGGCGTCTGACATTTGGGGACAGGGCACTATGGTCACC GTGTCGTCCGGCGGAGGGGGCTCGGGAGGCGGTGGCAGCGGAGGAGGAGGG TCCGAGATCGTGCTGACCCAATCCCCGGCCACCCTCTCGCTGAGCCCTGGA GAAAGGGCAACCTTGTCCTGTCGCGCGAGCCAGTCCGTGAGCAACTCCCTG GCCTGGTACCAGCAGAAGCCCGGACAGGCTCCGAGACTTCTGATCTACGAC GCTTCGAGCCGGGCCACTGGAATCCCCGACCGCTTTTCGGGGTCCGGCTCA GGAACCGATTTCACCCTGACAATCTCACGGCTGGAGCCAGAGGATTTCGCC ATCTATTACTGCCAGCAGTTCGGTACTTCCTCCGGCCTGACTTTCGGAGGC GGCACGAAGCTCGAAATCAAGACCACTACCCCAGCACCGAGGCCACCCACC CCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGT AGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGC GATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTT TCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTAC ATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGAC GGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGC GTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAAC CAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTG GACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAG AATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAA GCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCAC GACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCT

		CTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1979-C1		
BCMA_EBB-C1979-C1 - aa Full CART	989	MALPVTALLLPLALLLHAARPQVQLVESGGGLVQPGGSLRLSCAASGFTFS SYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNAKNSLYL QMNSLRAEDTAIYYCARATYKRELRYYYGMDVWGQGTMVTVSSGGGGSGGG GSGGGGSEIVMTQSPGTVSLSPGERATLSCRASQSVSSSFLAWYQQKPGQA PRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDSAVYYCQQYHSS PSWTFGQGTRLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPV QTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGR REEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGE RRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
BCMA_EBB-C1979-C1 - nt Full CART	1011	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCCAAGTGCAGCTCGTGGAATCGGGTGGCGGACTGGTGCAG CCGGGGGGCTCACTTAGACTGTCCTGCGCGGCCAGCGGATTCACTTTCTCC TCCTACGCCATGTCCTGGGTCAGACAGGCCCCTGGAAAGGGCCTGGAATGG GTGTCCGCAATCAGCGGCAGCGGCGGCTCGACCTATTACGCGGATTCAGTG AAGGGCAGATTCACCATTTCCCGGGACAACGCCAAGAACTCCTTGTACCTT CAAATGAACTCCCTCCGCGCGGAAGATACCGCAATCTACTACTGCGCTCGG GCCACTTACAAGAGGGAACTGCGCTACTACTACGGGATGGACGTCTGGGGC CAGGGAACCATGGTCACCGTGTCCAGCGGAGGAGGAGGATCGGGAGGAGGC GGTAGCGGGGGTGGAGGGTCGGAGATCGTGATGACCCAGTCCCCCGGCACT GTGTCGCTGTCCCCCGGCGAACGGGCCACCCTGTCATGTCGGGCCAGCCAG TCAGTGTCGTCAAGCTTCCTCGCCTGGTACCAGCAGAAACCGGGACAAGCT CCCCGCCTGCTGATCTACGGAGCCAGCAGCCGGGCCACCGGTATTCCTGAC CGGTTCTCCGGTTCGGGGTCCGGGACCGACTTTACTCTGACTATCTCTCGC CTCGAGCCAGAGGACTCCGCCGTGTATTACTGCCAGCAGTACCACTCCTCC CCGTCCTGGACGTTCGGACAGGGCACAAGGCTGGAGATTAAGACCACTACC CCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTG TCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACC CGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGT ACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGC GGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTG CAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAG GAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCA GCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGG AGAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATG GGCGGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTC CAAAAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAA CGCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCC ACCAAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1978-C7		
BCMA_EBB-C1978-C7 - aa Full CART	990	MALPVTALLLPLALLLHAARPEVQLVETGGGLVQPGGSLRLSCAASGFTFS SYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL QMNTLKAEDTAVYYCARATYKRELRYYYGMDVWGQGTTVTVSSGGGGSGGG GSGGGGSEIVLTQSPSTLSLSPGESATLSCRASQSVSTTFLAWYQQKPGQA PRLLIYGSSNRATGIPDRFSGSGSGTDFTLTIRRLEPEDFAVYYCQQYHSS PSWTFGQGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPV QTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGR REEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGE RRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

BCMA_EBB-C1978-C7 - nt Full CART	1012	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCGAGGTGCAGCTTGTGGAAACCGGTGGCGGACTGGTGCAG CCCGGAGGAAGCCTCAGGCTGTCCTGCGCCGCGTCCGGCTTCACCTTCTCC TCGTACGCCATGTCCTGGGTCCGCCAGGCCCCCGGAAAGGGCCTGGAATGG GTGTCCGCCATCTCTGGAAGCGGAGGTTCCACGTACTACGCGGACAGCGTC AAGGGAAGGTTCACAATCTCCCGCGATAATTCGAAGAACACTCTGTACCTT CAAATGAACACCCTGAAGGCCGAGGACACTGCTGTGTACTACTGCGCACGG GCCACCTACAAGAGAGAGCTCCGGTACTACTACGGAATGGACGTCTGGGGC CAGGGAACTACTGTGACCGTGTCCTCGGGAGGGGGTGGCTCCGGGGGGGGC GGCTCCGGCGGAGGCGGTTCCGAGATTGTGCTGACCCAGTCACCTTCAACT CTGTCGCTGTCCCCGGGAGAGAGCGCTACTCTGAGCTGCCGGGCCAGCCAG TCCGTGTCCACCACCTTCCTCGCCTGGTATCAGCAGAAGCCGGGGCAGGCA CCACGGCTCTTGATCTACGGGTCAAGCAACAGAGCGACCGGAATTCCTGAC CGCTTCTCGGGGAGCGGTTCAGGCACCGACTTCACCCTGACTATCCGGCGC CTGGAACCCGAAGATTTCGCCGTGTATTACTGTCAACAGTACCACTCCTCG CCGTCCTGGACCTTTGGCCAAGGAACCAAAGTGGAAATCAAGACCACTACC CCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTG TCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACC CGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGT ACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGC GGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTG CAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAG GAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCA GCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGG AGAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATG GGCGGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTC CAAAAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAA CGCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCC ACCAAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1978-D10		
BCMA_EBB-C1978-D10 - aa Full CART	991	MALPVTALLLPLALLLHAARPEVQLVETGGGLVQPGRSLRLSCAASGFTFD DYAMHWVRQAPGKGLEWVSGISWNSGSIGYADSVKGRFTISRDNAKNSLYL QMNSLRDEDTAVYYCARVGKAVPDVWGQGTTVTVSSGGGGSGGGGSGGGGS DIVMTQTPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAA SSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPYSFGQGT RLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDI YIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDK RRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDG LYQGLSTATKDTYDALHMQALPPR
BCMA_EBB-C1978-D10 - nt Full CART	1013	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCGAAGTGCAGCTCGTGGAAACTGGAGGTGGACTCGTGCAG CCTGGACGGTCGCTGCGGCTGAGCTGCGCTGCATCCGGCTTCACCTTCGAC GATTATGCCATGCACTGGGTCAGACAGGCGCCAGGGAAGGGACTTGAGTGG GTGTCCGGTATCAGCTGGAATAGCGGCTCAATCGGATACGCGGACTCCGTG AAGGGAAGGTTCACCATTTCCCGCGACAACGCCAAGAACTCCCTGTACTTG CAAATGAACAGCCTCCGGGATGAGGACACTGCCGTGTACTACTGCGCCCGC GTCGGAAAAGCTGTGCCCGACGTCTGGGGCCAGGGAACCACTGTGACCGTG TCCAGCGGCGGGGGTGGATCGGGCGGTGGAGGGTCCGGTGGAGGGGGCTCA GATATTGTGATGACCCAGACCCCCTCGTCCCTGTCCGCCTCGGTCGGCGAC CGCGTGACTATCACATGTAGAGCCTCGCAGAGCATCTCCAGCTACCTGAAC TGGTATCAGCAGAAGCCGGGGAAGGCCCCGAAGCTCCTGATCTACGCGGCA

		TCATCACTGCAATCGGGAGTGCCGAGCCGGTTTTCCGGGTCCGGCTCCGGC ACCGACTTCACGCTGACCATTTCTTCCCTGCAACCCGAGGACTTCGCCACT TACTACTGCCAGCAGTCCTACTCCACCCCTTACTCCTTCGGCCAAGGAACC AGGCTGGAAATCAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCT CCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCC GCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATC TACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTC GTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTT AAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGT TCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAA TTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAACCAGCTC TACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTGGACAAG CGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAATCCC CAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCCTAT AGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCACGACGGA CTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCTCTTCAC ATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1979-C12		
BCMA_EBB-C1979-C12 - aa Full CART	992	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGRSLRLSCTASGFTFD DYAMHWVRQRPGKGLEWVASINWKGNSLAYGDSVKGRFAISRDNAKNTVFL QMNSLRTEDTAVYYCASHQGVAYYNYAMDVWGRGTLVTVSSGGGGSGGGGS GGGGSEIVLTQSPGTLSLSPGERATLSCRATQSIGSSFLAWYQQRPGQAPR LLIYGASQRATGIPDRFSGRGSGTDFTLTISRVEPEDSAVYYCQHYESSPS WTFGQGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRG LDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQT TQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRRE EYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERR RGKGHDGLYQGLSTATKDTYDALHMQALPPR
BCMA_EBB-C1979-C12 - nt Full CART	1014	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCGAAGTGCAGCTCGTGGAGAGCGGGGGAGGATTGGTGCAG CCCGGAAGGTCCCTGCGGCTCTCCTGCACTGCGTCTGGCTTCACCTTCGAC GACTACGCGATGCACTGGGTCAGACAGCGCCCGGGAAAGGGCCTGGAATGG GTCGCCTCAATCAACTGGAAGGGAAACTCCCTGGCCTATGGCGACAGCGTG AAGGGCCGCTTCGCCATTTCGCGCGACAACGCCAAGAACACCGTGTTTCTG CAAATGAATTCCCTGCGGACCGAGGATACCGCTGTGTACTACTGCGCCAGC CACCAGGGCGTGGCATACTATAACTACGCCATGGACGTGTGGGGAAGAGGG ACGCTCGTCACCGTGTCCTCCGGGGGCGGTGGATCGGGTGGAGGAGGAAGC GGTGGCGGGGGCAGCGAAATCGTGCTGACTCAGAGCCCGGGAACTCTTTCA CTGTCCCCGGGAGAACGGGCCACTCTCTCGTGCCGGGCCACCCAGTCCATC GGCTCCTCCTTCCTTGCCTGGTACCAGCAGAGGCCAGGACAGGCGCCCCGC CTGCTGATCTACGGTGCTTCCCAACGCGCCACTGGCATTCCTGACCGGTTC AGCGGCAGAGGGTCGGGAACCGATTTCACACTGACCATTTCCCGGGTGGAG CCCGAAGATTCGGCAGTCTACTACTGTCAGCATTACGAGTCCTCCCCTTCA TGGACCTTCGGTCAAGGGACCAAAGTGGAGATCAAGACCACTACCCCAGCA CCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTG CGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGT CTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGC GGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGG AAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACT ACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGC GGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTAC AAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAG

		GAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGG AAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAG GATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGA AGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAG GACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1980-G4		
BCMA_EBB-C1980-G4-aa Full CART	993	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASGFTFS SYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCAKVVRDGMDVWGQGTTVTVSSGGGGSGGGGSGGGGS EIVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYG ASSRATGIPDRFSGNGSGTDFTLTISRLEPEDFAVYYCQQYGSPPRFTFGP GTKVDIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFAC DIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEED GCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVL DKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGH DGLYQGLSTATKDTYDALHMQALPPR
BCMA_EBB-C1980-G4-nt Full CART	1015	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCGAGGTGCAGTTGGTCGAAAGCGGGGGCGGGCTTGTGCAG CCTGGCGGATCACTGCGGCTGTCCTGCGCGGCATCAGGCTTCACGTTTTCT TCCTACGCCATGTCCTGGGTGCGCCAGGCCCCTGGAAAGGGACTGGAATGG GTGTCCGCGATTTCGGGGTCCGGCGGGAGCACCTACTACGCCGATTCCGTG AAGGGCCGCTTCACTATCTCGCGGGACAACTCCAAGAACACCCTCTACCTC CAAATGAATAGCCTGCGGGCCGAGGATACCGCCGTCTACTATTGCGCTAAG GTCGTGCGCGACGGAATGGACGTGTGGGGACAGGGTACCACCGTGACAGTG TCCTCGGGGGGAGGCGGTAGCGGCGGAGGAGGAAGCGGTGGTGGAGGTTCC GAGATTGTGCTGACTCAATCACCCGCGACCCTGAGCCTGTCCCCCGGCGAA AGGGCCACTCTGTCCTGTCGGGCCAGCCAATCAGTCTCCTCCTCGTACCTG GCCTGGTACCAGCAGAAGCCAGGACAGGCTCCGAGACTCCTTATCTATGGC GCATCCTCCCGCGCCACCGGAATCCCGGATAGGTTCTCGGGAAACGGATCG GGGACCGACTTCACTCTCACCATCTCCCGGCTGGAACCGGAGGACTTCGCC GTGTACTACTGCCAGCAGTACGGCAGCCCGCCTAGATTCACTTTCGGCCCC GGCACCAAAGTGGACATCAAGACCACTACCCCAGCACCGAGGCCACCCACC CCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGT AGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCCTGC GATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTGCTT TCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTGTAC ATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGAC GGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGC GTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAGAAC CAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTGCTG GACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAG AATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAA GCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGCCAC GACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGACGCT CTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1980-D2		
BCMA_EBB-C1980-D2-aa Full CART	994	MALPVTALLLPLALLLHAARPEVQLLESGGGLVQPGGSLRLSCAASGFTFS SYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCAKIPQTGTFDYWGQGTLVTVSSGGGGSGGGGSGGGG SEIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQRPGQAPRLLIY GASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQHYGSSPSWTFG QGTRLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFA

		CDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEE DGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDV LDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKG HDGLYQGLSTATKDTYDALHMQALPPR
BCMA_EBB-C1980-D2-nt Full CART	1016	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCGAAGTGCAGCTGCTGGAGTCCGGCGGTGGATTGGTGCAA CCGGGGGGATCGCTCAGACTGTCCTGTGCGGCGTCAGGCTTCACCTTCTCG AGCTACGCCATGTCATGGGTCAGACAGGCCCCTGGAAAGGGTCTGGAATGG GTGTCCGCCATTTCCGGGAGCGGGGGATCTACATACTACGCCGATAGCGTG AAGGGCCGCTTCACCATTTCCCGGGACAACTCCAAGAACACTCTCTATCTG CAAATGAACTCCCTCCGCGCTGAGGACACTGCCGTGTACTACTGCGCCAAA ATCCCTCAGACCGGCACCTTCGACTACTGGGGACAGGGGACTCTGGTCACC GTCAGCAGCGGTGGCGGAGGTTCGGGGGGAGGAGGAAGCGGCGGCGGAGGG TCCGAGATTGTGCTGACCCAGTCACCCGGCACTTTGTCCCTGTCGCCTGGA GAAAGGGCCACCCTTTCCTGCCGGGCATCCCAATCCGTGTCCTCCTCGTAC CTGGCCTGGTACCAGCAGAGGCCCGGACAGGCCCCACGGCTTCTGATCTAC GGAGCAAGCAGCCGCGCGACCGGTATCCCGGACCGGTTTTCGGGCTCGGGC TCAGGAACTGACTTCACCCTCACCATCTCCCGCCTGGAACCCGAAGATTTC GCTGTGTATTACTGCCAGCACTACGGCAGCTCCCCGTCCTGGACGTTCGGC CAGGGAACTCGGCTGGAGATCAAGACCACTACCCCAGCACCGAGGCCACCC ACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCA TGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGACTTCGCC TGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTCCTGCTG CTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTG TACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAG GACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTG CGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAGGGGCAG AACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTACGACGTG CTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGA AAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCA GAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGCAAAGGC CACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACCTATGAC GCTCTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1978-A10		
BCMA_EBB-C1978-A10-aa Full CART	995	MALPVTALLLPLALLLHAARPEVQLVETGGGLVQPGGSLRLSCAASGFTFS SYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTMSRENDKNSVFL QMNSLRVEDTGVYYCARANYKRELRYYYGMDVWGQGTMVTVSSGGGGSGGG GSGGGGSEIVMTQSPGTLSLSPGESATLSCRASQRVASNYLAWYQHKPGQA PSLLISGASSRATGVPDRFSGSGSGTDFTLAISRLEPEDSAVYYCQHYDSS PSWTFGQGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPV QTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGR REEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGE RRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
BCMA_EBB-C1978-A10-nt Full CART	1017	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCGAAGTGCAACTGGTGGAAACCGGTGGAGGACTCGTGCAG CCTGGCGGCAGCCTCCGGCTGAGCTGCGCCGCTTCGGGATTCACCTTTTCC TCCTACGCGATGTCTTGGGTCAGACAGGCCCCCGGAAAGGGGCTGGAATGG GTGTCAGCCATCTCCGGCTCCGGCGGATCAACGTACTACGCCGACTCCGTG AAAGGCCGGTTCACCATGTCGCGCGAGAATGACAAGAACTCCGTGTTCCTG CAAATGAACTCCCTGAGGGTGGAGGACACCGGAGTGTACTATTGTGCGCGC GCCAACTACAAGAGAGAGCTGCGGTACTACTACGGAATGGACGTCTGGGGA

		CAGGGAACTATGGTGACCGTGTCATCCGGTGGAGGGGGAAGCGGCGGTGGA GGCAGCGGGGGCGGGGGTTCAGAAATTGTCATGACCCAGTCCCCGGGAACT CTTTCCCTCTCCCCCGGGGAATCCGCGACTTTGTCCTGCCGGGCCAGCCAG CGCGTGGCCTCGAACTACCTCGCATGGTACCAGCATAAGCCAGGCCAAGCC CCTTCCCTGCTGATTTCCGGGGCTAGCAGCCGCGCCACTGGCGTGCCGGAT AGGTTCTCGGGAAGCGGCTCGGGTACCGATTTCACCCTGGCAATCTCGCGG CTGGAACCGGAGGATTCGGCCGTGTACTACTGCCAGCACTATGACTCATCC CCCTCCTGGACATTCGGACAGGGCACCAAGGTCGAGATCAAGACCACTACC CCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTG TCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACC CGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGT ACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGC GGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTG CAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAG GAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCA GCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGG AGAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATG GGCGGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTC CAAAAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAA CGCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCC ACCAAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1978-D4		
BCMA_EBB-C1978-D4-aa Full CART	996	MALPVTALLLPLALLLHAARPEVQLLETGGGLVQPGGSLRLSCAASGFSFS SYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCAKALVGATGAFDIWGQGTLVTVSSGGGGSGGGGSGG GGSEIVLTQSPGTLSLSPGERATLSCRASQSLSSNFLAWYQQKPGQAPGLL IYGASNWATGTPDRFSGSGSGTDFTLTITRLEPEDFAVYYCQYYGTSPMYT FGQGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLD FACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQ EEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEY DVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRG KGHDGLYQGLSTATKDTYDALHMQALPPR
BCMA_EBB-C1978-D4-nt Full CART	1018	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCGAAGTGCAGCTGCTCGAAACCGGTGGAGGGCTGGTGCAG CCAGGGGGCTCCCTGAGGCTTTCATGCGCCGCTAGCGGATTCTCCTTCTCC TCTTACGCCATGTCGTGGGTCCGCCAAGCCCCTGGAAAAGGCCTGGAATGG GTGTCCGCGATTTCCGGGAGCGGAGGTTCGACCTATTACGCCGACTCCGTG AAGGGCCGCTTTACCATCTCCCGGGATAACTCCAAGAACACTCTGTACCTC CAAATGAACTCGCTGAGAGCCGAGGACACCGCCGTGTATTACTGCGCGAAG GCGCTGGTCGGCGCGACTGGGGCATTCGACATCTGGGGACAGGGAACTCTT GTGACCGTGTCGAGCGGAGGCGGCGGCTCCGGCGGAGGAGGGAGCGGGGGC GGTGGTTCCGAAATCGTGTTGACTCAGTCCCCGGGAACCCTGAGCTTGTCA CCCGGGGAGCGGGCCACTCTCTCCTGTCGCGCCTCCCAATCGCTCTCATCC AATTTCCTGGCCTGGTACCAGCAGAAGCCCGGACAGGCCCCGGGCCTGCTC ATCTACGGCGCTTCAAACTGGGCAACGGGAACCCCTGATCGGTTCAGCGGA AGCGGATCGGGTACTGACTTTACCCTGACCATCACCAGACTGGAACCGGAG GACTTCGCCGTGTACTACTGCCAGTACTACGGCACCTCCCCCATGTACACA TTCGGACAGGGTACCAAGGTCGAGATTAAGACCACTACCCCAGCACCGAGG CCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCG GAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGAC TTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTC CTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAG

		CTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAA GAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGC GAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAG GGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTAC GACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCG CGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAG ATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGC AAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACC TATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1980-A2		
BCMA_EBB-C1980-A2-aa Full CART	997	MALPVTALLLPLALLLHAARPEVQLLESGGGLVQPGGSLRLSCAASGFTFS SYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCVLWFGEGFDPWGQGTLVTVSSGGGGSGGGGSGGGGS DIVLTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQL LIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPLT FGGGTKVDIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLD FACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQ EEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEY DVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRG KGHDGLYQGLSTATKDTYDALHMQALPPR
BCMA_EBB-C1980-A2-nt Full CART	1019	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCGAAGTGCAGCTGCTTGAGAGCGGTGGAGGTCTGGTGCAG CCCGGGGGATCACTGCGCCTGTCCTGTGCCGCGTCCGGTTTCACTTTCTCC TCGTACGCCATGTCGTGGGTCAGACAGGCACCGGGAAAGGGACTGGAATGG GTGTCAGCCATTTCGGGTTCGGGGGGCAGCACCTACTACGCTGACTCCGTG AAGGGCCGGTTCACCATTTCCCGCGACAACTCCAAGAACACCTTGTACCTC CAAATGAACTCCCTGCGGGCCGAAGATACCGCCGTGTATTACTGCGTGCTG TGGTTCGGAGAGGGATTCGACCCGTGGGGACAAGGAACACTCGTGACTGTG TCATCCGGCGGAGGCGGCAGCGGTGGCGGCGGTTCCGGCGGCGGCGGATCT GACATCGTGTTGACCCAGTCCCCTCTGAGCCTGCCGGTCACTCCTGGCGAA CCAGCCAGCATCTCCTGCCGGTCGAGCCAGTCCCTCCTGCACTCCAATGGG TACAACTACCTCGATTGGTATCTGCAAAAGCCGGGCCAGAGCCCCCAGCTG CTGATCTACCTTGGGTCAAACCGCGCTTCCGGGGTGCCTGATAGATTCTCC GGGTCCGGGAGCGGAACCGACTTTACCCTGAAAATCTCGAGGGTGGAGGCC GAGGACGTCGGAGTGTACTACTGCATGCAGGCGCTCCAGACTCCCCTGACC TTCGGAGGAGGAACGAAGGTCGACATCAAGACCACTACCCCAGCACCGAGG CCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCG GAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGTCTTGAC TTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGCGGGGTC CTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAG CTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAA GAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGCGGCTGC GAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTACAAGCAG GGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTAC GACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCG CGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAG ATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGAAGAGGC AAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAGGACACC TATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
BCMA_EBB-C1981-C3		
BCMA_EBB-C1981-C3-	998	MALPVTALLLPLALLLHAARPQVQLVESGGGLVQPGGSLRLSCAASGFTFS SYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL

aa Full CART		QMNSLRAEDTAVYYCAKVGYDSSGYYRDYYGMDVWGQGTTVTVSSGGGGSG GGGSGGGGSEIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPG QAPRLLIYGTSSRATGISDRFSGSGSGTDFTLTISRLEPEDFAVYYCQHYG NSPPKFTFGPGTKLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGA VHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFM RPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELN LGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGM KGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
BCMA_EBB-C1981-C3-nt Full CART	1020	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCCAAGTGCAGCTCGTGGAGTCAGGCGGAGGACTGGTGCAG CCCGGGGGCTCCCTGAGACTTTCCTGCGCGGCATCGGGTTTTACCTTCTCC TCCTATGCTATGTCCTGGGTGCGCCAGGCCCCGGGAAAGGGACTGGAATGG GTGTCCGCAATCAGCGGTAGCGGGGGCTCAACATACTACGCCGACTCCGTC AAGGGTCGCTTCACTATTTCCCGGGACAACTCCAAGAATACCCTGTACCTC CAAATGAACAGCCTCAGGGCCGAGGATACTGCCGTGTACTACTGCGCCAAA GTCGGATACGATAGCTCCGGTTACTACCGGGACTACTACGGAATGGACGTG TGGGGACAGGGCACCACCGTGACCGTGTCAAGCGGCGGAGGCGGTTCAGGA GGGGGAGGCTCCGGCGGTGGAGGGTCCGAAATCGTCCTGACTCAGTCGCCT GGCACTCTGTCGTTGTCCCCGGGGGAGCGCGCTACCCTGTCGTGTCGGGCG TCGCAGTCCGTGTCGAGCTCCTACCTCGCGTGGTACCAGCAGAAGCCCGGA CAGGCCCCTAGACTTCTGATCTACGGCACTTCTTCACGCGCCACCGGGATC AGCGACAGGTTCAGCGGCTCCGGCTCCGGGACCGACTTCACCCTGACCATT AGCCGGCTGGAGCCTGAAGATTTCGCCGTGTATTACTGCCAACACTACGGA AACTCGCCGCCAAAGTTCACGTTCGGACCCGGAACCAAGCTGGAAATCAAG ACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCC CAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCC GTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCT CTGGCTGGTACTTGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTAC TGTAAGCGCGGTCGGAAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATG AGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCA GAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCA GATGCTCCAGCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAAT CTTGGTCGGAGAGAGGAGTACGACGTGCTGGACAAGCGGAGAGGACGGGAC CCAGAAATGGGCGGGAAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTAC AACGAGCTCCAAAAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATG AAAGGGGAACGCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTC AGCACCGCCACCAAGGACACCTATGACGCTCTTCACATGCAGGCCCTGCCG CCTCGG
BCMA_EBB-C1978-G4		
BCMA_EBB-C1978-G4-aa Full CART	999	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASGFTFS SYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCAKMGWSSGYLGAFDIWGQGTTVTVSSGGGGSGGGGS GGGGSEIVLTQSPGTLSLSPGERATLSCRASQSVASSFLAWYQQKPGQAPR LLIYGASGRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQHYGGSPR LTFGGGTKVDIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRG LDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQT TQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRRE EYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERR RGKGHDGLYQGLSTATKDTYDALHMQALPPR
BCMA_EBB-C1978-G4-nt	1021	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCAC GCCGCTCGGCCCGAAGTCCAACTGGTGGAGTCCGGGGGAGGGCTCGTGCAG CCCGGAGGCAGCCTTCGGCTGTCGTGCGCCGCCTCCGGGTTCACGTTCTCA

Full CART		TCCTACGCGATGTCGTGGGTCAGACAGGCACCAGGAAAGGGACTGGAATGG GTGTCCGCCATTAGCGGCTCCGGCGGTAGCACCTACTATGCCGACTCAGTG AAGGGAAGGTTCACTATCTCCCGCGACAACAGCAAGAACACCCTGTACCTC CAAATGAACTCTCTGCGGGCCGAGGATACCGCGGTGTACTATTGCGCCAAG ATGGGTTGGTCCAGCGGATACTTGGGAGCCTTCGACATTTGGGGACAGGGC ACTACTGTGACCGTGTCCTCCGGGGGTGGCGGATCGGGAGGCGGCGGCTCG GGTGGAGGGGGTTCCGAAATCGTGTTGACCCAGTCACCGGGAACCCTCTCG CTGTCCCCGGGAGAACGGGCTACACTGTCATGTAGAGCGTCCCAGTCCGTG GCTTCCTCGTTCCTGGCCTGGTACCAGCAGAAGCCGGGACAGGCACCCCGC CTGCTCATCTACGGAGCCAGCGGCCGGGCGACCGGCATCCCTGACCGCTTC TCCGGTTCCGGCTCGGGCACCGACTTTACTCTGACCATTAGCAGGCTTGAG CCCGAGGATTTTGCCGTGTACTACTGCCAACACTACGGGGGGAGCCCTCGC CTGACCTTCGGAGGCGGAACTAAGGTCGATATCAAAACCACTACCCCAGCA CCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTG CGTCCGGAGGCATGTAGACCCGCAGCTGGTGGGGCCGTGCATACCCGGGGT CTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACTTGC GGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGG AAGAAGCTGCTGTACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACT ACTCAAGAGGAGGACGGCTGTTCATGCCGGTTCCCAGAGGAGGAGGAAGGC GGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCTCCAGCCTAC AAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAG GAGTACGACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGG AAGCCGCGCAGAAAGAATCCCCAAGAGGGCCTGTACAACGAGCTCCAAAAG GATAAGATGGCAGAAGCCTATAGCGAGATTGGTATGAAAGGGGAACGCAGA AGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAG GACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG

[00312] In one embodiment, the CAR molecule comprises (e.g., consists of) an amino acid sequence provided in Table 29, or Table 1 of WO2016/014565, or as otherwise described herein. In one embodiment, the CAR molecule comprises (e.g., consists of) an amino acid sequence of SEQ ID NO: 949, SEQ ID NO: 950, SEQ ID NO: 951, SEQ ID NO: 952, SEQ ID NO: 953, SEQ ID NO: 954, SEQ ID NO: 955, SEQ ID NO: 956, SEQ ID NO: 957, SEQ ID NO: 958, SEQ ID NO: 959, SEQ ID NO: 960, SEQ ID NO: 961, SEQ ID NO: 962, SEQ ID NO: 963, SEQ ID NO: 979, SEQ ID NO: 980, SEQ ID NO: 981, SEQ ID NO: 982, SEQ ID NO: 983, SEQ ID NO: 984, SEQ ID NO: 985, SEQ ID NO: 986, SEQ ID NO: 987, SEQ ID NO: 988, SEQ ID NO: 989, SEQ ID NO: 990, SEQ ID NO: 991, SEQ ID NO: 992, SEQ ID NO: 993, SEQ ID NO: 994, SEQ ID NO: 995, SEQ ID NO: 996, SEQ ID NO: 997, SEQ ID NO: 998, or SEQ ID NO: 999; or an amino acid sequence having at least one, two, three, four, five, 10, 15, 20 or 30 modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 60, 50, or 40 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of SEQ ID NO: 949, SEQ ID NO: 950, SEQ ID NO: 951, SEQ ID NO: 952, SEQ ID NO: 953, SEQ ID NO: 954, SEQ ID NO: 955, SEQ ID NO: 956, SEQ ID NO:

957, SEQ ID NO: 958, SEQ ID NO: 959, SEQ ID NO: 960, SEQ ID NO: 961, SEQ ID NO: 962, SEQ ID NO: 963, SEQ ID NO: 979, SEQ ID NO: 980, SEQ ID NO: 981, SEQ ID NO: 982, SEQ ID NO: 983, SEQ ID NO: 984, SEQ ID NO: 985, SEQ ID NO: 986, SEQ ID NO: 987, SEQ ID NO: 988, SEQ ID NO: 989, SEQ ID NO: 990, SEQ ID NO: 991, SEQ ID NO: 992, SEQ ID NO: 993, SEQ ID NO: 994, SEQ ID NO: 995, SEQ ID NO: 996, SEQ ID NO: 997, SEQ ID NO: 998, or SEQ ID NO: 999; or an amino acid sequence having 85%, 90%, 95%, 96%, 97%, 98%, 99% identity to an amino acid sequence of SEQ ID NO: 949, SEQ ID NO: 950, SEQ ID NO: 951, SEQ ID NO: 952, SEQ ID NO: 953, SEQ ID NO: 954, SEQ ID NO: 955, SEQ ID NO: 956, SEQ ID NO: 957, SEQ ID NO: 958, SEQ ID NO: 959, SEQ ID NO: 960, SEQ ID NO: 961, SEQ ID NO: 962, SEQ ID NO: 963, SEQ ID NO: 979, SEQ ID NO: 980, SEQ ID NO: 981, SEQ ID NO: 982, SEQ ID NO: 983, SEQ ID NO: 984, SEQ ID NO: 985, SEQ ID NO: 986, SEQ ID NO: 987, SEQ ID NO: 988, SEQ ID NO: 989, SEQ ID NO: 990, SEQ ID NO: 991, SEQ ID NO: 992, SEQ ID NO: 993, SEQ ID NO: 994, SEQ ID NO: 995, SEQ ID NO: 996, SEQ ID NO: 997, SEQ ID NO: 998, or SEQ ID NO: 999.

[00313] Exemplary CAR molecules that target mesothelin are described herein, and are provided in Table 11. The CAR molecules in Table 11 comprise a mesothelin antigen binding domain, e.g., an amino acid sequence of any mesothelin antigen binding domain provided in Table 2. The leader sequence is in bold and underlined, CDRs are underlined, and the linker sequence between the heavy and light chain of the antigen binding region is shaded in grey.

Table 11. Exemplary mesothelin CAR molecules

Name	Amino Acid Sequence	SEQ ID NO:
M5 CAR	**MALPVTALLLPLALLLHAARP**QVQLVQSGAEVEKPGASVKVSCKASGYTFTDYYMHWVRQ APGQGLEWMGWINPNSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCASG WDFDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIVMTQSPSSLSASVGDRVTITCR ASQSIRYYLSWYQQKPGKAPKLLIYTASILQNGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCLQTYTTPDFGPGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTR GLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCS CRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGG KPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQ ALPPR	**286**
M11 CAR	**MALPVTALLLPLALLLHAARP**QVQLQQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQ APGQGLEWMGWINPNSGGTNYAQNFQGRVTMTRDTSISTAYMELRRLRSDDTAVYYCASG WDFDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIRMTQSPSSLSASVGDRVTITCR ASQSIRYYLSWYQQKPGKAPKLLIYTASILQNGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCLQTYTTPDFGPGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTR GLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCS CRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGG	**292**

	KPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQ ALPPR	
SS1 CAR	**MALPVTALLLPLALLLHAARP**QVQLQQSGPELEKPGASVKISCKASGYSFTGYTMNWVK QSHGKSLEWIGLITPYNGASSYNQKFRGKATLTVDKSSSTAYMDLLSLTSEDSAVYFCA RGGYDGRGFDYWGQGTTVTVSSGGGGSGGGGSGGGGSDIELTQSPAIMSASPGEKVTMT CSASSSVSYMHWYQQKSGTSPKRWIYDTSKLASGVPGRFSGSGSGNSYSLTISSVEAED DATYYCQQWSGYPLTFGAGTKLEITTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAV HTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEE DGCSCRFPEEEEGGCELRVKFSRSADAPA	**306**
M1 CAR	**MALPVTALLLPLALLLHAARP**QVQLQQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQ APGQGLEWMGRINPNSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSEDTAVYYCARG RYYGMDVWGQGTMVTVSSGGGGSGGGGSGGGGSGGGGSEIVLTQSPATLSLSPGERATIS CRASQSVSSNFAWYQQRPGQAPRLLIYDASNRATGIPPRFSGSGSGTDFTLTISSLEPED FAAYYCHQRSNWLYTFGQGTKVDIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAV HTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEED GCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPE MGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDAL HMQALPPR	**282**
M2 CAR	**MALPVTALLLPLALLLHAARP**QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQ APGQGLEWMGWINPNSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCARD LRRTVVTPRAYYGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDIQLTQSPSTLSA SVGDRVTITCQASQDISNSLNWYQQKAGKAPKLLIYDASTLETGVPSRFSGSGSGTDFSF TISSLQPEDIATYYCQQHDNLPLTFGQGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEA CRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMR PVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVL DKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLST ATKDTYDALHMQALPPR	**283**
M3 CAR	**MALPVTALLLPLALLLHAARP**QVQLVQSGAEVKKPGAPVKVSCKASGYTFTGYYMHWVRQ APGQGLEWMGWINPNSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCARG EWDGSYYYDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIVLTQTPSSLSASVGDRV TITCRASQSINTYLNWYQHKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSFSPLTFGGGTKLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGG AVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQE EDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRD PEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYD ALHMQALPPR	**284**
M4 CAR	**MALPVTALLLPLALLLHAARP**QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMHWVRQ VPGKGLVWVSRINTDGSTTTYADSVEGRFTISRDNAKNTLYLQMNSLRDDDTAVYYCVGG HWAVWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSTLSASVGDRVTITCRA SQSISDRLAWYQQKPGKAPKLLIYKASSLESGVPSRFSGSGSGTEFTLTISSLQPDDFAV YYCQQYGHLPMYTFGQGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR	**285**
M6 CAR	**MALPVTALLLPLALLLHAARP**QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQ APGQGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARY RLIAVAGDYYYYGMDVWGQGTMVTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSA SVGDRVTITCRASQGVGRWLAWYQQKPGTAPKLLIYAASTLQSGVPSRFSGSGSGTDFTL TINNLQPEDFATYYCQQANSFPLTFGGGTRLEIKTTTPAPRPPTPAPTIASQPLSLRPEA CRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMR PVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVL DKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLST ATKDTYDALHMQALPPR	**287**
M7	**MALPVTALLLPLALLLHAARP**QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQ APGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARW	**288**

CAR	KVSSSSPAFDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSEIVLTQSPATLSLSPGER AILSCRASQSVYTKYLGWYQQKPGQAPRLLIYDASTRATGIPDRFSGSGSGTDFTLTINR LEPEDFAVYYCQHYGGSPLITFGQGTRLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRP AAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQ TTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKR RGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATK DTYDALHMQALPPR	
M8 CAR	**MALPVTALLLPLALLLHAARP**QVQLQQSGAEVKKPGASVKVSCKTSGYPFTGYSLHWVRQ APGQGLEWMGWINPNSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCARD HYGGNSLFYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIQLTQSPSSISASVGDTVS ITCRASQDSGTWLAWYQQKPGKAPNLLMYDASTLEDGVPSRFSGSASGTEFTLTVNRLQP EDSATYYCQQYNSYPLTFGGGTKVDIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGG AVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQE EDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRD PEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYD ALHMQALPPR	**289**
M9 CAR	**MALPVTALLLPLALLLHAARP**QVQLVQSGAEVKKPGASVEVSCKASGYTFTSYYMHWVRQ APGQGLEWMGIINPSGGSTGYAQKFQGRVTMTRDTSTSTVHMELSSLRSEDTAVYYCARG GYSSSSDAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQSPPSLSASVGDR VTITCRASQDISSALAWYQQKPGTPPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQFSSYPLTFGGGTRLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAA GGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTT QEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRG RDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDT YDALHMQALPPR	**290**
M10 CAR	**MALPVTALLLPLALLLHAARP**QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQ APGQGLEWMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARV AGGIYYYYGMDVWGQGTTITVSSGGGGSGGGGSGGGGSGGGGSDIVMTQTPDSLAVSLGE RATISCKSSHSVLYNRNNKNYLAWYQQKPGQPPKLLFYWASTRKSGVPDRFSGSGSGTDF TLTISSLQPEDFATYFCQQTQTFPLTFGQGTRLEINTTTPAPRPPTPAPTIASQPLSLRP EACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPF MRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYD VLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGL STATKDTYDALHMQALPPR	**291**
M12 CAR	**MALPVTALLLPLALLLHAARP**QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQ APGQGLEWMGRINPNSGGTNYAQKFQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCART TTSYAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSGGGGSDIQLTQSPSTLSASVGDRVTI TCRASQSISTWLAWYQQKPGKAPNLLIYKASTLESGVPSRFSGSGSGTEFTLTISSLQPD DFATYYCQQYNTYSPYTFGQGTKLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGG AVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQE EDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRD PEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYD ALHMQALPPR	**293**
M13 CAR	**MALPVTALLLPLALLLHAARP**QVQLVQSGGGLVKPGGSLRLSCEASGFIFSDYYMGWIRQ APGKGLEWVSYIGRSGSSMYYADSVKGRFTFSRDNAKNSLYLQMNSLRAEDTAVYYCAAS PVVAATEDFQHWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIVMTQTPATLSLSPGER ATLSCRASQSVTSNYLAWYQQKPGQAPRLLLFGASTRATGIPDRFSGSGSGTDFTLTINR LEPEDFAMYYCQQYGSAPVTFGQGTKLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPA AGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQT TQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRR GRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKD TYDALHMQALPPR	**294**
M14 CAR	**MALPVTALLLPLALLLHAARP**QVQLVQSGAEVRAPGASVKISCKASGFTFRGYYIHWVRQ APGQGLEWMGIINPSGGSRAYAQKFQGRVTMTRDTSTSTVYMELSSLRSDDTAMYYCART ASCGGDCYYLDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQSPPTLSASVGD RVTITCRASENVNIWLAWYQQKPGKAPKLLIYKSSSLASGVPSRFSGSGSGAEFTLTISS LQPDDFATYYCQQYQSYPLTFGGGTKVDIKTTTPAPRPPTPAPTIASQPLSLRPEACRPA	**295**

	AGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQT TQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRR GRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKD TYDALHMQALPPR	
M15 CAR	**MALPVTALLLPLALLLHAARP**QVQLVQSGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQ APGKGLEWVSGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKD GSSSWSWGYFDYWGQGTLVTVSSGGGGSGGGGSGGGGSSSELTQDPAVSVALGQTVRTTC QGDALRSYYASWYQQKPGQAPMLVIYGKNNRPSGIPDRFSGSDSGDTASLTITGAQAEDE ADYYCNSRDSSGYPVFGTGTKVTVLTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAV HTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEED GCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPE MGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDAL HMQALPPR	**296**
M16 CAR	**MALPVTALLLPLALLLHAARP**EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQ APGKGLEWVSGISWNSGSTGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKD SSSWYGGGSAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSSSELTQEPAVSVALGQTVRIT CQGDSLRSYYASWYQQKPGQAPVLVIFGRSRRPSGIPDRFSGSSSGNTASLIITGAQAED EADYYCNSRDNTANHYVFGTGTKLTVLTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGG AVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQE EDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRD PEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYD ALHMQALPPR	**297**
M17 CAR	**MALPVTALLLPLALLLHAARP**EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQ APGKGLEWVSGISWNSGSTGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKD SSSWYGGGSAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSSSELTQDPAVSVALGQTVRIT CQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPSGIPDRFSGSSSGNTASLTITGAQAED EADYYCNSRGSSGNHYVFGTGTKVTVLTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGG AVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQE EDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRD PEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYD ALHMQALPPR	**298**
M18 CAR	**MALPVTALLLPLALLLHAARP**QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYWMHWVRQ APGKGLVWVSRINSDGSSTSYADSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCVRT GWVGSYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGGGSEIVLTQSPGTLSLSPGE RATLSCRASQSVSSNYLAWYQQKPGQPPRLLIYDVSTRATGIPARFSGGGSGTDFTLTIS SLEPEDFAVYYCQQRSNWPPWTFGQGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACR PAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPV QTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDK RRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTAT KDTYDALHMQALPPR	**299**
M19 CAR	**MALPVTALLLPLALLLHAARP**QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQ APGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKG YSRYYYYGMDVWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSEIVMTQSPATLSLSPGER AILSCRASQSVYTKYLGWYQQKPGQAPRLLIYDASTRATGIPDRFSGSGSGTDFTLTINR LEPEDFAVYYCQHYGGSPLITFGQGTKVDIKTTTPAPRPPTPAPTIASQPLSLRPEACRP AAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQ TTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKR RGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATK DTYDALHMQALPPR	**300**
M20 CAR	**MALPVTALLLPLALLLHAARP**QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQ APGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKR EAAAGHDWYFDLWGRGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIRVTQSPSSLSASVGD RVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQSYSIPLTFGQGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPA AGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQT TQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRR GRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKD	**301**

	TYDALHMQALPPR	
M21 CAR	**MALPVTALLLPLALLLHAARP**QVQLVQSWAEVKKPGASVKVSCKASGYTFTSYYMHWVRQ APGQGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSNLRSEDTAVYYCARS PRVTTGYFDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIQLTQSPSTLSASVGDRV TITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLESGVPSRFSGSGSGTEFTLTISSLQ PDDFATYYCQQYSSYPLTFGGGTRLEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAG GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQ EEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGR DPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTY DALHMQALPPR	**302**
M22 CAR	**MALPVTALLLPLALLLHAARP**QVQLVQSGAEVRRPGASVKISCRASGDTSTRHYIHWLRQ APGQGPEWMGVINPTTGPATGSPAYAQMLQGRVTMTRDTSTRTVYMELRSLRFEDTAVYY CARSVVGRSAPYYFDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSLSA SVGDRVTITCRASQGISDYSAWYQQKPGKAPKLLIYAASTLQSGVPSRFSGSGSGTDFTL TISYLQSEDFATYYCQQYYSYPLTFGGGTKVDIKTTTPAPRPPTPAPTIASQPLSLRPEA CRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMR PVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVL DKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLST ATKDTYDALHMQALPPR	**303**
M23 CAR	**MALPVTALLLPLALLLHAARP**QVQLQQSGAEVKKPGASVKVSCKASGYTFTNYYMHWVRQ APGQGLEWMGIINPSGGYTTYAQKFQGRLTMTRDTSTSTVYMELSSLRSEDTAVYYCARI RSCGGDCYYFDNWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIQLTQSPSTLSASVGD RVTITCRASENVNIWLAWYQQKPGKAPKLLIYKSSSLASGVPSRFSGSGSGAEFTLTISS LQPDDFATYYCQQYQSYPLTFGGGTKVDIKTTTPAPRPPTPAPTIASQPLSLRPEACRPA AGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQT TQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRR GRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKD TYDALHMQALPPR	**304**
M24 CAR	**MALPVTALLLPLALLLHAARP**QITLKESGPALVKPTQTLTLTCTFSGFSLSTAGVHVGWI RQPPGKALEWLALISWADDKRYRPSLRSRLDITRVTSKDQVVLSMTNMQPEDTATYYCAL QGFDGYEANWGPGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIVMTQSPSSLSASAGDRVT ITCRASRGISSALAWYQQKPGKPPKLLIYDASSLESGVPSRFSGSGSGTDFTLTIDSLEP EDFATYYCQQSYSTPWTFGQGTKVDIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGG AVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQE EDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRD PEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYD ALHMQALPPR	**305**

[00314] In one embodiment, the cell of the invention comprises a CAR molecule that binds mesothelin, and comprises (e.g., consists of) an amino acid sequence as provided in Table 11 and Table 2 of International Publication No. WO2015/090230, filed December 19, 2014; incorporated herein by reference. In one embodiment, the CAR molecule comprises (e.g., consists of) an amino acid sequence of SEQ ID NO: 282, SEQ ID NO: 283, SEQ ID NO: 284, SEQ ID NO: 285, SEQ ID NO: 286, SEQ ID NO: 287, SEQ ID NO: 288, SEQ ID NO: 289, SEQ ID NO: 290, SEQ ID NO: 291, SEQ ID NO: 292, SEQ ID NO: 293, SEQ ID NO: 294, SEQ ID NO: 295, SEQ ID NO: 296, SEQ ID NO: 297, SEQ ID NO: 298, SEQ ID NO: 299, SEQ ID NO: 300, SEQ ID NO: 301, SEQ ID NO: 302, SEQ ID NO: 303, SEQ ID NO: 304, SEQ ID NO: 305, or SEQ ID NO: 306; or an amino acid sequence having at least one, two,

three, four, five, 10, 15, 20 or 30 modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 60, 50, or 40 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of SEQ ID NO: 282, SEQ ID NO: 283, SEQ ID NO: 284, SEQ ID NO: 285, SEQ ID NO: 286, SEQ ID NO: 287, SEQ ID NO: 288, SEQ ID NO: 289, SEQ ID NO: 290, SEQ ID NO: 291, SEQ ID NO: 292, SEQ ID NO: 293, SEQ ID NO: 294, SEQ ID NO: 295, SEQ ID NO: 296, SEQ ID NO: 297, SEQ ID NO: 298, SEQ ID NO: 299, SEQ ID NO: 300, SEQ ID NO: 301, SEQ ID NO: 302, SEQ ID NO: 303, SEQ ID NO: 304, SEQ ID NO: 305, or SEQ ID NO: 306; or an amino acid sequence having 85%, 90%, 95%, 96%, 97%, 98%, 99% identity to an amino acid sequence of SEQ ID NO: 282, SEQ ID NO: 283, SEQ ID NO: 284, SEQ ID NO: 285, SEQ ID NO: 286, SEQ ID NO: 287, SEQ ID NO: 288, SEQ ID NO: 289, SEQ ID NO: 290, SEQ ID NO: 291, SEQ ID NO: 292, SEQ ID NO: 293, SEQ ID NO: 294, SEQ ID NO: 295, SEQ ID NO: 296, SEQ ID NO: 297, SEQ ID NO: 298, SEQ ID NO: 299, SEQ ID NO: 300, SEQ ID NO: 301, SEQ ID NO: 302, SEQ ID NO: 303, SEQ ID NO: 304, SEQ ID NO: 305, or SEQ ID NO: 306.

[00315] In one aspect, the cell of the invention comprises a CAR molecule comprising an antigen binding domain that binds to a tumor antigen. In one embodiment, the CAR comprises a EGFRvIII antigen binding domain (e.g., a murine, human or humanized antibody or antibody fragment that specifically binds to mesothelin), a transmembrane domain, and an intracellular signaling domain (e.g., an intracellular signaling domain comprising a costimulatory domain and/or a primary signaling domain).

[00316] Exemplary CAR molecules that target EGFRvIII are described herein, and are provided in Table 30, or in Table 2 of WO/2014/130657 or as described in WO2016/014789.

Table 30. Humanized EGFRvIII CAR Constructs. Sequences are provided with a leader, and the CDRs are underlined. Nt stands for nucleic acid and aa stands for amino acid

Name	SEQ ID NO:	Sequence
CAR 1		
CAR 1 – Full – nt	1042	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccgagatcc agctggtgcagtcgggagctgaagtcaaaaagcctggcgcaaccgtcaagatctcgtgcaaaggatc agggttcaacatcgaggactactacatccattgggtgcaacaggcacccggaaaaggcctggagtgg atggggaggattgacccagaaaatgacgaaaccaagtacggaccgatcttccaaggacgggtgacca

		tcacggctgacacttccactaacaccgtctacatggaactctcgagccttcgctcggaagataccgcgg tgtactactgcgcctttagaggtggagtctactggggacaagggactaccgtcaccgtgtcgtcaggtg gcggaggatcaggcggaggcggctccggtggaggaggaagcggaggaggtggctccgacgtggt gatgacgcagtcaccggactccttggcggtgagcctgggtgaacgcgccactatcaactgcaagagct cccagagcttgctggactccgatggaaagacttatctcaattggctgcaacagaagcctggccagccg ccaaagagactcatctcactggtgagcaagctggatagcggagtgccagatcggttttcgggatcggg ctcaggcaccgacttcaccctgactatttcctccctccaagccgaggatgtggccgtctactactgttggc aggggactcacttcccggggaccttcggtggaggcactaaggtggagatcaaaaccactaccccagc accgaggccacccacccccggctcctaccatcgcctcccagcctctgtccctgcgtccggaggcatgta gacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctacatttgggccc ctctggctggtacttgcggggtcctgctgctttcactcgtgatcactctttactgtaagcgcggtcggaag aagctgctgtacatctttaagcaacccttcatgaggcctgtgcagactactcaagaggaggacggctgtt catgccggttcccagaggaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcag atgctccagcctacaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagagga gtacgacgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaag aatccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgagattg gtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcagcaccgcc accaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
CAR 1 – Full - aa	1043	malpvtalllplalllhaarpeiqlvqsgaevkkpgatvkisckgsgfnie**dyyih**wvqqapgkgle wmg**ridpendetkygpifqg**rvtitadtstntvymelsslrsedtavyycaf**rggv**ywgqgttvt vssggggsggggsggggsggggsdvvmtqspdslavslgeratinc**kssqslldsdgktyln**wlq qkpgqppkrlis**lvsklds**gvpdrfsgsgsgtdftltisslqaedvavyyc**wqgthfpgt**fgggtkv eikttpaprpptpaptiasqplslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlllslvitlyc krgrkkllyifkqpfmrpvqttqeedgcscrfpeeeeggcelrvkfsrsadapaykqgqnqlyneln lgrreeydvldkrrgrdpemggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdgl yqglstatkdtydalhmqalppr
CAR 2		
CAR 2 - Full - nt	1048	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccgacgtg gtcatgactcaaagcccagattccttggctgtctcccttggagaaagagcaacgatcaattgcaaaagct cgcagtccctgttggactccgatggaaaaacctacctcaactggctgcagcagaagccgggacaacc accaaagcggctgatttccctcgtgtccaagctggacagcggcgtgccggatcgcttctcgggcagcg gctcgggaaccgattttactctcactatttcgtcactgcaagcggaggacgtggcggtgtattactgctgg cagggcactcacttcccgggtacttttggtggaggtaccaaagtcgaaatcaagggtggaggcggga gcggaggaggcgggtcgggaggaggaggatcgggtggcggaggctcagaaatccagctggtgca

		gtcaggtgccgaagtgaagaagcctggggccacggtgaagatctcgtgcaaggggagcggattcaa catcgaggattactacatccattgggtgcaacaggcccctggcaaagggctggaatggatgggaagg atcgaccccgagaatgacgagactaagtacggcccgatcttccaaggacgggtgaccatcactgcag acacttcaaccaacaccgtctacatggaactctcctcgctgcgctccgaggacaccgccgtgtactact gtgctttcagaggaggagtctactggggacagggaacgaccgtgaccgtcagctcaaccactacccc agcaccgaggccacccaccccggctcctaccatcgcctcccagcctctgtccctgcgtccggaggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctacatttggg cccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactctttactgtaagcgcggtcgg aagaagctgctgtacatctttaagcaacccttcatgaggcctgtgcagactactcaagaggaggacggc tgttcatgccggttcccagaggaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcg cagatgctccagcctacaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagaga ggagtacgacgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaa aagaatccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgag attggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcagcacc gccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
CAR 2 - Full - aa	1049	malpvtalllplalllhaarpdvvmtqspdslavslgeratinc**kssqslldsdgktyln**wlqqkpgq ppkrlis**lvsklds**gvpdrfsgsgsgtdftltisslqaedvavyyc**wqgthfpgt**fgggtkveikggg gsggggsggggsggggseiqlvqsgaevkkpgatvkisckgsgfnie**dyyih**wvqqapgkgle wmg**ridpendetkygpifqg**rvtitadtstntvymelsslrsedtavyyca**frggvy**wgqgttvt vsstttpaprpptpaptiasqplslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlllslvitlyc krgrkkllyifkqpfmrpvqttqeedgcscrfpeeeeggcelrvkfsrsadapaykqgqnqlyneln lgrreeydvldkrrgrdpemggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdgl yqglstatkdtydalhmqalppr
CAR 3		
CAR 3 – Full - nt	1054	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccgaaatcc agctggtgcaaagcggagccgaggtgaagaagcccggagaatccctgcgcatctcgtgtaagggttc cggctttaacatcgaggattactacatccactgggtgagacagatgccgggcaaaggtctggaatggat gggccgcatcgacccggagaacgacgaaaccaaatacggaccaatcttccaaggacatgtgactattt ccgcggatacctccatcaacactgtctacttgcagtggagctcgctcaaggcgtcggataccgccatgt actactgcgcattcagaggaggtgtgtactggggccagggcactacggtcaccgtgtcctcgggaggt ggagggtcaggaggcggaggctcgggcggtggaggatcaggcggaggaggaagcgatgtggtca tgactcaatccccactgtcactgcctgtcactctggggcaaccggcttccatctcatgcaagtcaagcca atcgctgctcgactccgacggaaaaacctacctcaattggcttcagcagcgcccaggccagtcgcctc ggaggctgatctcactcgtgtcgaagcttgactccggggtgccggatcggtttagcggaagcggatcg

		gggaccgacttcacgttgaagattagccgggtggaagccgaggacgtgggagtctattactgctggca ggggacccacttcccggggactttcggaggaggcaccaaagtcgagattaagaccactaccccagca ccgaggccacccaccccggctcctaccatcgcctcccagcctctgtccctgcgtccggaggcatgtag acccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctacatttgggcccc tctggctggtacttgcggggtcctgctgctttcactcgtgatcactctttactgtaagcgcggtcggaaga agctgctgtacatctttaagcaacccttcatgaggcctgtgcagactactcaagaggaggacggctgttc atgccggttcccagaggaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcaga tgctccagcctacaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggag tacgacgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaaga atccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgagattgg tatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcagcaccgcca ccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
CAR 3 – Full - aa	1055	malpvtalllplalllhaarpeiqlvqsgaevkkpgeslrisckgsgfnie**dyyih**wvrqmpgkgle wmg**ridpendetkygpifqg**hvtisadtsintvylqwsslkasdtamyycaf**rggvy**wgqgttv tvssggggsggggsggggsggggsdvvmtqsplslpvtlgqpasisc**kssqslldsdgktyln**wl qqrpgqsprrlis**lvsklds**gvpdrfsgsgsgtdftlkisrveaedvgvyyc**wqgthfpgt**fgggtk veiktttpaprpptpaptiasqplslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlllslvitly ckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeeggcelrvkfsrsadapaykqgqnqlynel nlgrreeydvldkrrgrdpemggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdg lyqglstatkdtydalhmqalppr
CAR 4		
CAR 4 – Full - nt	1060	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccgacgtcg tcatgacccaatcccctctctccctgccggtcaccctgggtcagccggcgtcgatctcatgcaaaagctc acagtccctgctggattcggacggaaaaacctacttgaactggctccaacagaggccgggtcagtccc ctcgcagactgatctcgctggtgagcaagctcgactcgggtgtgccggatcggttctccgggtcaggat cgggcaccgactttacgctcaagatttcgagagtggaggccgaggatgtgggagtgtactattgctggc agggcacgcatttccccgggacctttggaggcgggactaaggtggaaatcaagggaggtggcggat caggcggaggaggcagcggcggaggtggatcaggaggcggagggtcagagatccagctggtcca aagcggagcagaggtgaagaagccaggcgagtcccttcgcatttcgtgcaaagggagcggcttcaac attgaagattactacatccactgggtgcggcaaatgccaggaaagggtctggaatggatgggacggat cgacccagaaaatgatgaaactaagtacggaccgatcttccaaggacacgtcactatctccgcggaca cttcgatcaacaccgtgtacctccagtggagcagcttgaaagcctccgacaccgctatgtactactgtgc cttccgcggaggagtctactggggacaggggactactgtgaccgtgtcgtccaccactaccccagcac cgaggccacccaccccggctcctaccatcgcctcccagcctctgtccctgcgtccggaggcatgtaga

		cccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctacatttgggcccct ctggctggtacttgcggggtcctgctgctttcactcgtgatcactctttactgtaagcgcggtcggaagaa gctgctgtacatctttaagcaacccttcatgaggcctgtgcagactactcaagaggaggacggctgttca tgccggttcccagaggaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagat gctccagcctacaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagt acgacgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaa tccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgagattggt atgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcagcaccgccac caaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
CAR 4 – Full - aa	1061	malpvtalllplalllhaarpdvvmtqsplslpvtlgqpasisc**kssqslldsdgktyln**wlqqrpgq sprrlis**lvsklds**gvpdrfsgsgsgtdftlkisrveaedvgvyyc**wqgthfpgt**fgggtkveikgg ggsggggsggggsggggseiqlvqsgaevkkpgeslrisckgsgfnie**dyyih**wvrqmpgkgle wmg**ridpendetkygpifqg**hvtisadtsintvylqwsslkasdtamyycaf**rggvy**wgqgttv tvsstttpaprpptpaptiasqplslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlllslvitly ckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeeggcelrvkfsrsadapaykqgqnqlynel nlgrreeydvldkrrgrdpemggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdg lyqglstatkdtydalhmqalppr
CAR 5		
CAR 5 – Full - nt	1066	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccgaaatcc agctcgtgcagagcggagccgaggtcaagaaaccgggtgctaccgtgaagatttcatgcaagggatc gggcttcaacatcgaggattactacatccactgggtgcagcaggcaccaggaaaaggacttgaatgga tgggccggatcgacccggaaaatgacgagactaagtacggccctatcttccaaggacgggtgacgat caccgcagacactagcaccaacaccgtctatatggaactctcgtccctgaggtccgaagatactgccgt gtactactgtgcgtttcgcggaggtgtgtactggggacagggtaccaccgtcaccgtgtcatcgggcg gtggaggctccggtggaggagggtcaggaggcggtggaagcggaggaggcggcagcgacgtggt catgactcaatcgccgctgtcgctgcccgtcactctgggacaacccgcgtccatcagctgcaaatcctc gcagtcactgcttgactccgatggaaagacctacctcaactggctgcagcaacgcccaggccaatccc caagacgcctgatctcgttggtgtcaaagctggactcaggggtgccggaccggttctccgggagcgg gtcgggcacggatttcactctcaagatctccagagtggaagccgaggatgtgggagtctactactgctg gcagggaacccatttccctggaacttttggcggaggaactaaggtcgagattaaaaccactaccccag caccgaggccacccaccccggctcctaccatcgcctcccagcctctgtccctgcgtccggaggcatgt agacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctacatttgggcc cctctggctggtacttgcggggtcctgctgctttcactcgtgatcactctttactgtaagcgcggtcggaa gaagctgctgtacatctttaagcaacccttcatgaggcctgtgcagactactcaagaggaggacggctg

		ttcatgccggttcccagaggaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgc agatgctccagcctacaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagag gagtacgacgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaa agaatccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgagat tggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcagcaccg ccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
CAR 5 – Full - aa	1067	malpvtalllplalllhaarpeiqlvqsgaevkkpgatvkisckgsgfnie**dyyih**wvqqapgkgle wmg**ridpendetkygpifqg**rvtitadtstntvymelsslrsedtavyycaf**rggvy**wgqgttvt vssggggsggggsggggsggggsdvvmtqsplslpvtlgqpasisc**kssqslldsdgktyln**wlq qrpgqsprrlis**lvsklds**gvpdrfsgsgsgtdftlkisrveaedvgvyyc**wqgthfpgt**fgggtkv eiktttpaprpptpaptiasqplslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlllslvitlyc krgrkkllyifkqpfmrpvqttqeedgcscrfpeeeeggcelrvkfsrsadapaykqgqnqlyneln lgrreeydvldkrrgrdpemggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdgl yqglstatkdtydalhmqalppr
CAR 6		
CAR6 – Full - nt	1072	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccgagattc agctcgtgcaatcgggagcggaagtcaagaagccaggagagtccttgcggatctcatgcaagggtag cggctttaacatcgaggattactacatccactgggtgaggcagatgccggggaagggactcgaatgga tgggacggatcgacccagaaaacgacgaaactaagtacggtccgatcttccaaggccatgtgactatt agcgccgatacttcaatcaataccgtgtatctgcaatggtcctcattgaaagcctcagataccgcgatgta ctactgtgctttcagaggaggggtctactggggacagggaactaccgtgactgtctcgtccggcggag gcgggtcaggaggtggcggcagcggaggaggagggtccggcggaggtgggtccgacgtcgtgat gacccagagccctgacagcctggcagtgagcctgggcgaaagagctaccattaactgcaaatcgtcg cagagcctgctggactcggacggaaaaacgtacctcaattggctgcagcaaaagcctggccagccac cgaagcgccttatctcactggtgtcgaagctggattcgggagtgcccgatcgcttctccggctcgggat cgggtactgacttcaccctcactatctcctcgcttcaagcagaggacgtggccgtctactactgctggca gggaacccactttccgggaaccttcggcggagggacgaaagtggagatcaagaccactaccccagc accgaggccacccaccccggctcctaccatcgcctcccagcctctgtccctgcgtccggaggcatgta gacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctacatttgggccc ctctggctggtacttgcggggtcctgctgctttcactcgtgatcactctttactgtaagcgcggtcggaag aagctgctgtacatctttaagcaacccttcatgaggcctgtgcagactactcaagaggaggacggctgtt catgccggttcccagaggaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcag atgctccagcctacaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagagga gtacgacgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaag

		aatccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgagattg gtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcagcaccgcc accaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
CAR6 – Full – aa	1073	malpvtalllplalllhaarpeiqlvqsgaevkkpgeslrisckgsgfnie**dyyih**wvrqmpgkgle wmg**ridpendetkygpifqg**hvtisadtsintvylqwsslkasdtamyycaf**rggvy**wgqgttv tvssggggsggggsggggsggggsdvvmtqspdslavslgeratinc**kssqslldsdgktyln**wl qqkpgqppkrlis**lvsklds**gvpdrfsgsgsgtdftltisslqaedvavyyc**wqgthfpgt**fgggtk veikttpaprpptpaptiasqplslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlllslvitly ckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeeggcelrvkfsrsadapaykqgqnqlynel nlgrreeydvldkrrgrdpemggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdg lyqglstatkdtydalhmqalppr
CAR 7		
CAR 7 Full - nt	1078	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccgacgtg gtgatgactcagtcgcctgactcgctggctgtgtcccttggagagcgggccactatcaattgcaagtcat cccagtcgctgctggattccgacgggaaaacctacctcaattggctgcagcaaaaaccgggacagcct ccaaagcggctcatcagcctggtgtccaagttggacagcggcgtgccagaccgcttctccggttcggg aagcggtactgatttcacgctgaccatctcatccctccaagcggaggatgtggcagtctactactgttgg cagggcacgcattttccgggcacttttggaggagggaccaaggtcgaaatcaagggaggaggtggct cgggcggaggaggctcgggaggaggaggatcaggaggcggtggaagcgagattcaactggtcca gagcggcgcagaagtcaagaagccgggtgaatcgctcagaatctcgtgcaaaggatcgggattcaac atcgaggactactacattcactgggtcagacaaatgccgggcaaagggctggaatggatggggagga tcgaccccgaaaacgatgaaaccaagtacggaccaatcttccaagggcacgtgaccatttcggcgga cacctcaatcaacactgtgtacctccagtggagctcacttaaggccagcgataccgccatgtactattgc gctttccgcggaggggtgtactggggacagggcactactgtgaccgtgtcatccaccactaccccagc accgaggccacccacccccggctcctaccatcgcctcccagcctctgtccctgcgtccggaggcatgta gacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctacatttgggccc ctctggctggtacttgcggggtcctgctgctttcactcgtgatcactctttactgtaagcgcggtcggaag aagctgctgtacatctttaagcaacccttcatgaggcctgtgcagactactcaagaggaggacggctgtt catgccggttcccagaggaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcag atgctccagcctacaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagagga gtacgacgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaag aatccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgagattg gtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcagcaccgcc accaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg

CAR 7 Full - aa	1079	malpvtalllplalllhaarpdvvmtqspdslavslgeratinc**kssqslldsdgktyln**wlqqkpgq ppkrlis**lvsklds**gvpdrfsgsgsgtdftltisslqaedvavyyc**wqgthfpgt**fgggtkveikggg gsggggsggggsggggseiqlvqsgaevkkpgeslrisckgsgfnie**dyyih**wvrqmpgkgle wmg**ridpendetkygpifqg**hvtisadtsintvylqwsslkasdtamyycaf**rggvy**wgqgttv tvsstttpaprpptpaptiasqplslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlllslvitly ckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeeggcelrvkfsrsadapaykqgqnqlynel nlgrreeydvldkrrgrdpemggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdg lyqglstatkdtydalhmqalppr
CAR 8		
CAR 8 – Full - nt	1084	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccgatgtgg tcatgacgcagtcaccactgtccctccccgtgacccttggacagccagcgtcgattagctgcaagtcat cccaatccctgctcgattcggatggaaagacctatctcaactggctgcagcaaagacccggtcagagc cctaggagactcatctcgttggtgtcaaagctggacagcggagtgccggaccggttttccggttcggga tcggggacggacttcactctgaagatttcacgggtggaagctgaggatgtgggagtgtactactgctgg cagggaacccatttccctggcacttttggcggaggaactaaggtcgaaatcaagggaggaggtggctc gggaggaggcggatcgggcggaggcgggagcggcggaggagggtccgaaatccaacttgtccag tcaggagccgaagtgaagaaaccgggagccaccgtcaaaatcagctgtaagggatcgggattcaata tcgaggactactacatccactgggtgcagcaagctccgggcaaaggactggagtggatggggcgcat cgacccagagaacgacgaaaccaaatacggcccgatcttccaagggcgggtgaccatcaccgcgga cacctcaactaacactgtgtacatggagctgagctccctgcgctccgaagatactgcagtctactactgc gccttccgcggtggtgtgtactggggacagggcaccactgtgactgtcagctcgaccactaccccagc accgaggccacccaccccggctcctaccatcgcctcccagcctctgtccctgcgtccggaggcatgta gacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctacatttgggccc ctctggctggtacttgcggggtcctgctgctttcactcgtgatcactctttactgtaagcgcggtcggaag aagctgctgtacatctttaagcaacccttcatgaggcctgtgcagactactcaagaggaggacggctgtt catgccggttcccagaggaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcag atgctccagcctacaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagagga gtacgacgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaag aatccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgagattg gtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcagcaccgcc accaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
CAR 8 – Full - aa	1085	malpvtalllplalllhaarpdvvmtqsplslpvtlgqpasisc**kssqslldsdgktyln**wlqqrpgq sprrlis**lvsklds**gvpdrfsgsgsgtdftlkisrveaedvgvyyc**wqgthfpgt**fgggtkveikgg ggsggggsggggsggggseiqlvqsgaevkkpgatvkisckgsgfnie**dyyih**wvqqapgkgle

		wmg**ridpendetkygpifqg**rvtitadtstntvymelsslrsedtavyycaf**rggvy**wgqgttvt vsstttpaprpptpaptiasqplslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlllslvitlyc krgrkkllyifkqpfmrpvqttqeedgcscrfpeeeeggcelrvkfsrsadapaykqgqnqlyneln lgrreeydvldkrrgrdpemggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdgl yqglstatkdtydalhmqalppr
CAR 9		Mouse anti-EGFRvIII clone 3C10
CAR 9 – Full - nt	1089	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccgagatcc agctccaacagagcggagccgaactggtcaaaccgggagcgtcggtgaagttgtcatgcactggatc gggcttcaacatcgaggattactacatccactgggtcaagcaacgcaccgagcaggggctggaatgg atcggacggatcgaccccgaaaacgatgaaaccaagtacgggcctatcttccaaggacgggccacca ttacggctgacacgtcaagcaataccgtctacctccagctttccagcctgacctccgaggacactgccgt gtactactgcgccttcagaggaggcgtgtactggggaccaggaaccactttgaccgtgtccagcggag gcggtggatcaggaggaggaggctcaggcggtggcggctcgcacatggacgtggtcatgactcagt ccccgctgaccctgtcggtggcaattggacagagcgcatccatctcgtgcaagagctcacagtcgctg ctggattccgacggaaagacttatctgaactggctgctccaaagaccagggcaatcaccgaaacgcctt atctccctggtgtcgaaactcgactcgggtgtgccggatcggtttaccggtagcgggtccggcacgga cttcactctccgcatttcgagggtggaagcggaggatctcgggatctactactgttggcagggaaccca cttccctgggacttttggaggcggaactaagctggaaatcaagaccactaccccagcaccgaggccac ccaccccggctcctaccatcgcctcccagcctctgtccctgcgtccggaggcatgtagacccgcagct ggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctacatttgggcccctctggctggta cttgcggggtcctgctgctttcactcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtac atctttaagcaacccttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcc cagaggaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcct acaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacgacgtgct ggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaaga gggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggg gaacgcagaagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggaca cctatgacgctcttcacatgcaggccctgccgcctcgg
CAR 9 – Full - aa	1090	malpvtalllplalllhaarpeiqlqqsgaelvkpgasvklsctgsgfnie**dyyih**wvkqrteqglew ig**ridpendetkygpifqg**ratitadtssntvylqlssltsedtavyyca**frggvy**wgpgttltvssgg ggsggggsggggshmdvvmtqspltlsvaigqsasisc**kssqslldsdgktyln**wllqrpgqspk rlis**lvsklds**gvpdrftgsgsgtdftlrisrveaedlgiyyc**wqgthfpgt**fgggtkleikttpaprpp tpaptiasqplslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlllslvitlyckrgrkkllyifk qpfmrpvqttqeedgcscrfpeeeeggcelrvkfsrsadapaykqgqnqlynelnlgrreeydvld

		krrgrdpemggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdglyqglstatkdt ydalhmqalppr
CAR10		Anti-EGFRvIII clone 139
CAR 10 Full - nt	1095	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccgatatcc aaatgactcagagcccttcatccctgagcgccagcgtcggagacagggtgaccatcacgtgccgggc atcccaaggcattagaaataacttggcgtggtatcagcaaaaaccaggaaaggccccgaagcgcctg atctacgcggcctccaaccttcagtcaggagtgccctcgcgcttcaccgggagcggtagcggaactga gtttacccttatcgtgtcgtccctgcagccagaggacttcgcgacctactactgcctccagcatcactcgt acccgttgacttcgggaggcggaaccaaggtcgaaatcaaacgcactggctcgacgtcagggtccgg taaaccgggatcgggagaaggatcggaagtccaagtgctggagagcggaggcggactcgtgcaac ctggcgggtcgctgcggctcagctgtgccgcgtcgggttttactttcagctcgtacgctatgtcatgggt gcggcaggctccgggaaaggggctggaatgggtgtccgctatttccggctcgggtggaagcaccaat tacgccgactccgtgaagggacgcttcaccatctcacgggataactccaagaatactctgtacctccag atgaactcgctgagagccgaggacaccgcagtgtactactgcgcagggtcaagcggctggtccgaat actggggacagggcaccctcgtcactgtcagctccaccactaccccagcaccgaggccacccacccc ggctcctaccatcgcctcccagcctctgtccctgcgtccggaggcatgtagacccgcagctggtgggg ccgtgcatacccggggtcttgacttcgcctgcgatatctacatttgggcccctctggctggtacttgcggg gtcctgctgctttcactcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaag caacccttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagagga ggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagca ggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaag cggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgt acaacgagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgca gaagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatgac gctcttcacatgcaggccctgccgcctcgg
CAR 10 Full - aa	1096	malpvtalllplalllhaarpdiqmtqspsslsasvgdrvtitcrasqgirnnlawyqqkpgkapkrli yaasnlqsgvpsrftgsgsgteftlivsslqpedfatyyclqhhsypltsgggtkveikrtgstsgsgkp gsgegsevqvlesggglvqpggslrlscaasgftfssyamswvrqapgkglewvsaisgsggstny adsvkgrftisrdnskntlylqmnslraedtavyycagssgwseywgqgtlvtvssttpaprpptpa ptiasqplslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpf mrpvqttqeedgcscrfpeeeeggcelrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrg rdpemggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdglyqglstatkdtydal hmqalppr

[00317] In one embodiment, the cell of the invention comprises a CAR molecule that binds EGFRvIII that comprises (e.g., consists of) an amino acid sequence as provided in Table 30. In one embodiment, the CAR that binds EGFRvIII comprises (e.g., consists of) an amino acid sequence of SEQ ID NO: 1043, SEQ ID NO: 1049, SEQ ID NO: 1055, SEQ ID NO: 1061, SEQ ID NO: 1067, SEQ ID NO: 1073, SEQ ID NO: 1079, SEQ ID NO: 1085, SEQ ID NO: 1090, or SEQ ID NO: 1096; or an amino acid sequence having at least one, two, three, four, five, 10, 15, 20 or 30 modifications (e.g., substitutions, e.g., conservative substitutions) but not more than 60, 50, or 40 modifications (e.g., substitutions, e.g., conservative substitutions) of an amino acid sequence of SEQ ID NO: 1043, SEQ ID NO: 1049, SEQ ID NO: 1055, SEQ ID NO: 1061, SEQ ID NO: 1067, SEQ ID NO: 1073, SEQ ID NO: 1079, SEQ ID NO: 1085, SEQ ID NO: 1090, or SEQ ID NO: 1096; or an amino acid sequence having 85%, 90%, 95%, 96%, 97%, 98%, 99% identity to an amino acid sequence of SEQ ID NO: 1043, SEQ ID NO: 1049, SEQ ID NO: 1055, SEQ ID NO: 1061, SEQ ID NO: 1067, SEQ ID NO: 1073, SEQ ID NO: 1079, SEQ ID NO: 1085, SEQ ID NO: 1090, or SEQ ID NO: 1096.

[00318] In one aspect, the cell of the invention comprises a CAR molecule comprising an antigen binding domain that binds to a tumor antigen. In one embodiment, the CAR comprises a CAR molecule comprising a CD123 antigen binding domain (e.g., a murine, human or humanized antibody or antibody fragment that specifically binds to mesothelin), a transmembrane domain, and an intracellular signaling domain (e.g., an intracellular signaling domain comprising a costimulatory domain and/or a primary signaling domain).

[00319] Exemplary CAR molecules that target CD123 are described herein (e.g., Table 26 or Table 27), and are provided in Tables 2, 6 and 9 of WO2016/028896. Other exemplary CAR molecules that target CD123 are described in WO/2014/130635 (e.g., Table 1 of WO/2014/130635). Other exemplary CAR molecules that target CD123 are described in WO/2014/144622.

[00320] In one aspect, the cell of the invention comprises a CAR molecule comprising an antigen binding domain that binds to a tumor antigen. In one embodiment, the CAR comprises CD33 antigen binding domain (e.g., a murine, human or humanized antibody or antibody fragment that specifically binds to CD33), a transmembrane domain, and an intracellular signaling domain (e.g., an intracellular signaling domain comprising a costimulatory domain

and/or a primary signaling domain). Exemplary CAR molecules that target CD33 are described herein, and are provided in WO2016/014576, e.g., in Table 2 of WO2016/014576.

[00321] In one aspect, the cell of the invention comprises a CAR molecule comprising an antigen binding domain that binds to a tumor antigen. In one embodiment, the CAR comprises CLL-1 antigen binding domain (e.g., a murine, human or humanized antibody or antibody fragment that specifically binds to CLL-1), a transmembrane domain, and an intracellular signaling domain (e.g., an intracellular signaling domain comprising a costimulatory domain and/or a primary signaling domain). Exemplary CAR molecules that target CLL-1 are described herein, and are provided in WO/2016/014535, e.g., in Table 2 of WO2016/014535.

[00322] In one embodiment, 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 efficacy, 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 K_D 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.

[00323] In one embodiment, the antigen binding domain comprises a non-human antibody or antibody fragment, e.g., a mouse antibody or antibody fragment.

[00324] In another embodiment, 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 compared to the murine sequence of the antibody or antibody fragment, e.g., scFv, from which it is derived.

[00325] 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.)

[00326] 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.

[00327] 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.

[00328] In some aspects, the portion of a CAR 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.

[00329] A humanized antibody or antibody fragment may retain a similar antigenic specificity as the original antibody, e.g., in the present disclosure, the ability to bind human a tumor antigen as described herein. In some embodiments, a humanized antibody or antibody fragment may have improved affinity and/or specificity of binding to a tumor antigen as described herein or a B cell antigen as described herein. In some embodiments, a humanized antibody or antibody fragment may have lower affinity and/or specificity of a tumor antigen as described herein or a B cell antigen as described herein.

[00330] 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 of the invention that comprises an antigen binding domain specifically binds a tumor antigen as described herein.

[00331] In one aspect, the antigen binding domain is a fragment, e.g., a single chain variable fragment (scFv). In one aspect, the anti- tumor 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 tumor antigen as described herein protein with wild-type or enhanced affinity.

[00332] 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.

[00333] 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.

[00334] In another aspect, the antigen binding domain is a T cell receptor ("TCR"), an engineered 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 intracellular, however, a fragment of such antigen (peptide) is presented on the surface of the cancer cells by MHC.

[00335] 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.

[00336] In one specific aspect, the CAR composition of the invention comprises an antibody fragment. In a further aspect, the antibody fragment comprises a scFv. In a further aspect, the antibody fragment comprises a variable heavy chain (VH) only.

[00337] 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.

[00338] 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.

[00339] 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).

[00340] 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.

[00341] 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).

[00342] 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.

[00343] 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.

[00344] In one aspect, the present disclosure 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 tumor 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 tumor antigen described herein, e.g., scFv. The present disclosure 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.

[00345] Bispecific CARs

[00346] 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.

[00347] 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.

[00348] 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: 80). 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.

[00349] In one aspect, the invention provides a chimeric antigen receptor comprising a bispecific antigen binding domain, a transmembrane domain (e.g., as described herein), and an intracellular signaling domain (e.g., as described herein). In another aspect, the invention provides a cell (e.g., a population of cells), e.g., an immune effector cell, e.g., a T cell or NK cell, e.g., as described herein, which is engineered to express (e.g., comprises) a bispecific CAR as described herein. Without being bound by any theory, it is believed that cells expressing such bispecific CARs are useful in the methods and compositions described herein.

[00350] Chimeric TCR

[00351] In one aspect, the antigen binding domains described herein, e.g., the antibodies and antibody fragments, e.g., provided in the Tables herein, can be grafted to one or more constant domain of a T cell receptor ("TCR") chain, for example, a TCR alpha or TCR beta chain, to create an chimeric TCR that binds specifically to a tumor antigen, e.g., a solid tumor antigen or antigen expressed on a tumor associated with TAMs, described herein. Without being bound by theory, it is believed that chimeric TCRs will signal through the TCR complex upon antigen binding. For example, a mesothelin or CD19 scFv or a fragment there of, e.g., a VL domain, or VH domain, as disclosed herein, can be grafted to the constant domain, e.g., at least a portion of the extracellular constant domain, the transmembrane domain and the cytoplasmic domain, of a TCR chain, for example, the TCR alpha chain and/or the TCR beta chain. As another example, the CDRs of an antibody or antibody fragment, e.g., the CDRs of anyantibody or antibody fragment as described in Tables provided herein may be grafted into a TCR alpha and/or beta chain to create a chimeric TCR that binds specifically to a tumor antigen, e.g., a solid tumor antigen or antigen expressed on a tumor associated with TAMs, described herein. For example, the LCDRs disclosed herein may be grafted into the variable domain of a TCR alpha chain and the HCDRs disclosed herein may be grafted to the variable domain of a TCR beta chain, or vice versa. Such chimeric TCRs may be produced by methods known in

the art (For example, Willemsen RA et al, Gene Therapy 2000; 7: 1369–1377; Zhang T et al, Cancer Gene Ther 2004; 11: 487–496; Aggen et al, Gene Ther. 2012 Apr;19(4):365-74).

[00352] Transmembrane domain

[00353] 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, e.g., the antigen binding domain. 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, for example, the transmembrane domain is from the same protein as the intracellular signalling domain, e.g., the costimulatory domain. 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.

[00354] 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.

[00355] 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, 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.

[00356] 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 SEQ ID NO: 6. In some embodiments, the hinge or spacer comprises a hinge encoded by a nucleotide sequence of 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 SEQ ID NO: 8. In some embodiments, the hinge or spacer comprises a hinge encoded by a nucleotide sequence of SEQ ID NO: 9.

[00357] 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.

[00358] 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).

[00359] In one aspect, the hinge or spacer comprises a KIR2DS2 hinge.

[00360] Cytoplasmic domain

[00361] 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.

[00362] 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.

[00363] 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).

[00364] 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.

[00365] Examples of ITAM containing primary intracellular signaling domains that are of particular use in the invention include those of TCR zeta, FcR gamma, FcR beta, CD3 gamma, CD3 delta , CD3 epsilon, CD5, CD22, CD79a, CD79b, CD278 (also known as "ICOS"), FcεRI, DAP10, DAP12,and CD66d. In one embodiment, a CAR of the invention comprises an intracellular signaling domain, e.g., a primary signaling domain of CD3-zeta, e.g., a CD3-zeta sequence described herein.

[00366] 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.

[00367] The intracellular signaling 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 an MHC class I molecule, a TNF receptor protein, an

Immunoglobulin-like protein, a cytokine receptor, an integrin, a signaling lymphocytic activation molecule (SLAM protein), an activating NK cell receptor, BTLA, a Toll ligand receptor, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, 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.

[00368] 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.

[00369] 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.

[00370] 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.

[00371] 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 SEQ ID NO:16. In one aspect, the signalling domain of CD27 is encoded by a nucleic acid sequence of SEQ ID NO:17.

[00372] In one aspect, the intracellular is designed to comprise the signaling domain of CD3-zeta and the signaling domain of CD28. In one aspect, the signaling domain of CD28 comprises an amino acid sequence of SEQ ID NO: 44. In one aspect, the signaling domain of CD28 is encoded by a nucleic acid sequence of SEQ ID NO: 45.

[00373] In one aspect, the intracellular is designed to comprise the signaling domain of CD3-zeta and the signaling domain of ICOS. In one aspect, the signaling domain of ICOS comprises an amino acid sequence of SEQ ID NO: 42. In one aspect, the signaling domain of ICOS is encoded by a nucleic acid sequence of SEQ ID NO: 43.

[00374] In one aspect, the cell of the invention, e.g., described herein, e.g., a cell expressing a CAR described herein, includes a CAR that includes an antigen binding domain that binds a target tumor antigen described herein (e.g., a solid tumor antigen or antigen expressed on a tumor associated with MDSCs or TAMs), a transmembrane domain, a primary signaling domain, and one or more (e.g., one) costimulatory signaling domain.

[00375] In one embodiment, the CAR-expressing cell may further comprise 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 the tumor antigen targeted by the CAR. 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, LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, or TGF beta.

[00376] In one embodiment, the antigen binding domains of the 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.

[00377] 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.

[00378] 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.

[00379] 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.

[00380] The SDAB molecules can be recombinant, CDR-grafted, humanized, camelized, de-immunized and/or in vitro generated (e.g., selected by phage display).

[00381] 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.

[00382] In some embodiments, the claimed invention comprises a first and second CAR, wherein the antigen binding domain of one of the first CAR and the second CAR does not comprise a variable light domain and a variable heavy domain. In some embodiments, the antigen binding domain of one of the first CAR and the second CAR is an scFv, and the other is not an scFv. In some embodiments, the antigen binding domain of one of the first CAR and the 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 the first CAR and the second CAR comprises a nanobody. In some embodiments, the antigen binding domain of one of the first CAR and the second CAR comprises a camelid VHH domain.

[00383] In some embodiments, the antigen binding domain of one of the first CAR and the 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 the first CAR and the second CAR comprises an scFv, and the other comprises a nanobody. In some embodiments, the antigen binding domain of one of the first CAR and the second CAR comprises comprises an scFv, and the other comprises a camelid VHH domain.

[00384] In some embodiments, when present on the surface of a cell, binding of the antigen binding domain of the first CAR to its cognate antigen is not substantially reduced by the presence of the second CAR. In some embodiments, binding of the antigen binding domain of

the first CAR to its cognate antigen in the presence of the second CAR is 85%, 90%, 95%, 96%, 97%, 98% or 99% of binding of the antigen binding domain of the first CAR to its cognate antigen in the absence of the second CAR.

[00385] In some embodiments, when present on the surface of a cell, the antigen binding domains of the first CAR and the 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.

[00386] 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, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGF beta.

[00387] 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, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and 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.

[00388] 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 in combinations 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. In one embodiment, the PD1 CAR comprises the amino acid sequence of SEQ ID NO:39).

[00389] 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 as SEQ ID NO: 27 in Table 1, with the sequence for PD1 ECD underlined.

[00390] In another aspect, the present disclosure provides a population of CAR-expressing 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 tumor 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 tumor antigen described herein, e.g., an antigen binding domain to a tumor antigen described herein that differs from the tumor 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 tumor antigen described herein, and a second cell expressing a CAR that includes an antigen binding domain to a target other than a tumor 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.

[00391] In another aspect, the present disclosure provides a population of cells wherein at least one cell in the population expresses a CAR having an antigen binding domain to a tumor 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, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, 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, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and 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).

[00392] In one aspect, the present disclosure provides methods comprising administering a population of CAR-expressing 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 disclosure 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 tumor 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.

[00393] Natural Killer Cell Receptor (NKR) CARs

[00394] In an embodiment, the CAR molecule described herein, e.g., the CAR molecule that targets a tumor antigen, e.g., a solid tumor antigen or antigen expressed on a tumor associated with MDSCs or TAMs, comprises one or more components of a natural killer cell receptor (NKR), thereby forming an NKR-CAR. The NKR component can be a transmembrane domain, a hinge domain, or a cytoplasmic domain from any of the following natural killer cell receptors: killer cell immunoglobulin-like receptor (KIR), e.g., KIR2DL1, KIR2DL2/L3, KIR2DL4, KIR2DL5A, KIR2DL5B, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, DIR2DS5, KIR3DL1/S1, KIR3DL2, KIR3DL3, KIR2DP1, and KIR3DP1; natural cyotoxicity receptor (NCR), e.g., NKp30, NKp44, NKp46; signaling lymphocyte activation molecule (SLAM) family of immune cell receptors, e.g., CD48, CD229, 2B4, CD84, NTB-A, CRACC, BLAME, and CD2F-10; Fc receptor (FcR), e.g., CD16, and CD64; and Ly49 receptors, e.g., LY49A, LY49C. The NKR-CAR molecules described herein may interact with an adaptor molecule or intracellular signaling domain, e.g., DAP12. Exemplary configurations and sequences of CAR molecules comprising NKR components are described in International Publication No. WO2014/145252, the contents of which are hereby incorporated by reference.

[00395]

[00396] Split CAR

[00397] 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, incorporated herein by reference. 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. In embodiments the first antigen binding domain recognizes the tumor antigen or B cell antigen described herein, e.g., comprises an antigen binding domain described herein, and the second antigen binding domain recognizes a second antigen, e.g., a second tumor antigen or a second B cell antigen described herein.

[00398] Strategies for Regulating Chimeric Antigen Receptors

[00399] There are many ways CAR activities can be regulated. 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. For example, inducing apoptosis using, e.g., a caspase fused to a dimerization domain (see, e.g., Di et al., N Engl. 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 another example, CAR-expressing cells can also express an inducible Caspase-9 (iCaspase-9) molecule that, upon administration of a dimerizer drug (e.g., rimiducid (also called AP1903 (Bellicum Pharmaceuticals) or AP20187 (Ariad)) leads to activation of the Caspase-9 and apoptosis of the cells. The iCaspase-9 molecule contains a chemical inducer of dimerization (CID) binding domain that mediates dimerization in the presence of a CID. This results in inducible and selective depletion of CAR-expressing cells. In some cases, the iCaspase-9 molecule is encoded by a nucleic acid molecule separate from the CAR-encoding vector(s). In some cases, the iCaspase-9 molecule is encoded by the same nucleic acid molecule as the CAR-encoding vector. The iCaspase-9 can provide a safety switch to avoid any toxicity of CAR-expressing cells. See, e.g., Song et al. Cancer Gene Ther. 2008; 15(10):667-75; Clinical Trial Id. No. NCT02107963; and Di Stasi et al. N. Engl. J. Med. 2011; 365:1673-83.

[00400] Alternative strategies for regulating the CAR therapy of the instant invention include utilizing small molecules or antibodies that deactivate or turn off CAR activity, e.g., by deleting CAR-expressing cells, e.g., by inducing antibody dependent cell-mediated cytotoxicity (ADCC). For example, CAR-expressing cells described herein may also express an antigen that

is recognized by molecules capable of inducing cell death, e.g., ADCC or complement-induced cell death. For example, CAR expressing cells described herein may also express a receptor capable of being targeted by an antibody or antibody fragment. Examples of such receptors include EpCAM, VEGFR, integrins (e.g., integrins αvβ3, α4, αI¾β3, α4β7, α5β1, αvβ3, αv), members of the TNF receptor superfamily (e.g., TRAIL-R1 , TRAIL-R2), PDGF Receptor, interferon receptor, folate receptor, GPNMB, ICAM-1 , HLA-DR, CEA, CA-125, MUC1 , TAG-72, IL-6 receptor, 5T4, GD2, GD3, CD2, CD3, CD4, CD5, CD1 1 , CD1 1 a/LFA-1 , CD15, CD18/ITGB2, CD19, CD20, CD22, CD23/lgE Receptor, CD25, CD28, CD30, CD33, CD38, CD40, CD41 , CD44, CD51 , CD52, CD62L, CD74, CD80, CD125, CD147/basigin, CD152/CTLA-4, CD154/CD40L, CD195/CCR5, CD319/SLAMF7, and EGFR, and truncated versions thereof (e.g., versions preserving one or more extracellular epitopes but lacking one or more regions within the cytoplasmic domain).

[00401] For example, a CAR-expressing cell described herein may also express a truncated epidermal growth factor receptor (EGFR) which lacks signaling capacity but retains the epitope that is recognized by molecules capable of inducing ADCC, e.g., cetuximab (ERBITUX®), such that administration of cetuximab induces ADCC and subsequent depletion of the CAR-expressing cells (see, e.g., WO2011/056894, and Jonnalagadda et al., Gene Ther. 2013; 20(8)853-860). Another strategy includes expressing a highly compact marker/suicide gene that combines target epitopes from both CD32 and CD20 antigens in the CAR-expressing cells described herein, which binds rituximab, resulting in selective depletion of the CAR-expressing cells, e.g., by ADCC (see, e.g., Philip et al., Blood. 2014; 124(8)1277-1287). Other methods for depleting CAR-expressing cells described herein include administration of CAMPATH, a monoclonal anti-CD52 antibody that selectively binds and targets mature lymphocytes, e.g., CAR-expressing cells, for destruction, e.g., by inducing ADCC. In other embodiments, the CAR-expressing cell can be selectively targeted using a CAR ligand, e.g., an anti-idiotypic antibody. In some embodiments, the anti-idiotypic antibody can cause effector cell activity, e.g, ADCC or ADC activities, thereby reducing the number of CAR-expressing cells. In other embodiments, the CAR ligand, e.g., the anti-idiotypic antibody, can be coupled to an agent that induces cell killing, e.g., a toxin, thereby reducing the number of CAR-expressing cells. Alternatively, the CAR molecules themselves can be configured such that the activity can be regulated, e.g., turned on and off, as described below.

[00402] In other embodiments, a CAR-expressing cell described herein may also express a target protein recognized by the T cell depleting agent. In one embodiment, the target protein is CD20 and the T cell depleting agent is an anti-CD20 antibody, e.g., rituximab. In such embodiment, the T cell depleting agent is administered once it is desirable to reduce or eliminate the CAR-expressing cell, e.g., to mitigate the CAR induced toxicity. In other embodiments, the T cell depleting agent is an anti-CD52 antibody, e.g., alemtuzumab.

[00403] In other embodiments, 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. Additional description and exemplary configurations of such regulatable CARs are provided herein and in International Publication No. WO 2015/090229, hereby incorporated by reference in its entirety.

[00404]

[00405] Co-expression of CAR with a Chemokine Receptor

[00406] In embodiments, the CAR-expressing cell described herein further comprises a chemokine receptor molecule. Transgenic expression of chemokine receptors CCR2b or CXCR2 in T cells enhances trafficking to CCL2- or CXCL1-secreting solid tumors including melanoma and neuroblastoma (Craddock et al., *J Immunother.* 2010 Oct; 33(8):780-8 and Kershaw et al.,*Hum Gene Ther.* 2002 Nov 1; 13(16):1971-80). Thus, without wishing to be bound by theory, it is believed that chemokine receptors expressed in CAR-expressing cells that recognize chemokines secreted by tumors, e.g., solid tumors, can improve homing of the CAR-expressing cell to the tumor, facilitate the infiltration of the CAR-expressing cell to the tumor, and enhances antitumor efficacy of the CAR-expressing cell. The chemokine receptor molecule can comprise a naturally occurring or recombinant chemokine receptor or a chemokine-binding fragment thereof. A chemokine receptor molecule suitable for expression in a CAR-expressing cell described herein include a CXC chemokine receptor (e.g., CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, or CXCR7), a CC chemokine receptor (e.g.,

CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, or CCR11), a CX3C chemokine receptor (e.g., CX3CR1), a XC chemokine receptor (e.g., XCR1), or a chemokine-binding fragment thereof. In one embodiment, the chemokine receptor molecule to be expressed with a CAR described herein is selected based on the chemokine(s) secreted by the tumor. In one embodiment, the CAR-expressing cell described herein further comprises, e.g., expresses, a CCR2b receptor or a CXCR2 receptor. In an embodiment, the CAR described herein and the chemokine receptor molecule are on the same vector or are on two different vectors. In embodiments where the CAR described herein and the chemokine receptor molecule are on the same vector, the CAR and the chemokine receptor molecule are each under control of two different promoters or are under the control of the same promoter.

[00407] Nucleic Acid Constructs Encoding a CAR

[00408] The present disclosure also provides nucleic acid molecules encoding one or more of the CAR constructs targeting a tumor antigen and/or a B cell antigen 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.

[00409] 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 , e.g., a solid tumor antigen or antigen expressed on a tumor associated with MDSCs or TAMs, 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 , NKG2D, and NKG2C.

[00410] 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, PAG/Cbp, NKG2D, and NKG2C. 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, 42, or 44, 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.

[00411] 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, a CD27 costimulatory domain having a sequence of SEQ ID NO:16 (or a sequence with 95-99% identity thereof), a ICOS costimulatory domain having a sequence of SEQ ID NO: 42 (or a sequence with 95-99% identity thereof) or a CD28 costimulatory domain having a sequence of SEQ ID NO:44, 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).

[00412] 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.

[00413] The present disclosure also provides vectors in which a nucleic acid of the present disclosure 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.

[00414] 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.

[00415] 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.

[00416] The expression constructs of the present disclosure 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.

[00417] 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.

[00418] 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).

[00419] 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.

[00420] 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.

[00421] 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.

[00422] 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.

[00423] Another example of a promoter is the phosphoglycerate kinase (PGK) promoter. In embodiments, a truncated PGK promoter (e.g., a PGK promoter with one or more, e.g., 1, 2, 5, 10, 100, 200, 300, or 400, nucleotide deletions when compared to the wild-type PGK promoter sequence) may be desired. The nucleotide sequences of exemplary PGK promoters are provided below.

[00424] WT PGK Promoter

[00425] ACCCCTCTCTCCAGCCACTAAGCCAGTTGCTCCCTCGGCTGACGGCTGCA CGCGAGGCCTCCGAACGTCTTACGCCTTGTGGCGCGCCCGTCCTTGTCCCGGGTGT GATGGCGGGGTGTGGGGCGGAGGGCGTGGCGGGGAAGGGCCGGCGACGAGAGCC GCGCGGGACGACTCGTCGGCGATAACCGGTGTCGGGTAGCGCCAGCCGCGCGACG GTAACGAGGGACCGCGACAGGCAGACGCTCCCATGATCACTCTGCACGCCGAAGG CAAATAGTGCAGGCCGTGCGGCGCTTGGCGTTCCTTGGAAGGGCTGAATCCCCGCC TCGTCCTTCGCAGCGGCCCCCCGGGTGTTCCCATCGCCGCTTCTAGGCCCACTGCG ACGCTTGCCTGCACTTCTTACACGCTCTGGGTCCCAGCCGCGGCGACGCAAAGGGC CTTGGTGCGGGTCTCGTCGGCGCAGGGACGCGTTTGGGTCCCGACGGAACCTTTTC CGCGTTGGGGTTGGGGCACCATAAGCT (SEQ ID NO: 101)

[00426] Exemplary truncated PGK Promoters:

[00427] PGK100:

[00428] ACCCCTCTCTCCAGCCACTAAGCCAGTTGCTCCCTCGGCTGACGGCTGCA CGCGAGGCCTCCGAACGTCTTACGCCTTGTGGCGCGCCCGTCCTTGTCCCGGGTGT GATGGCGGGGTG (SEQ ID NO: 102)

[00429] PGK200:

[00430] ACCCCTCTCTCCAGCCACTAAGCCAGTTGCTCCCTCGGCTGACGGCTGCA CGCGAGGCCTCCGAACGTCTTACGCCTTGTGGCGCGCCCGTCCTTGTCCCGGGTGT GATGGCGGGGTGTGGGGCGGAGGGCGTGGCGGGGAAGGGCCGGCGACGAGAGCC

GCGCGGGACGACTCGTCGGCGATAACCGGTGTCGGGTAGCGCCAGCCGCGCGACG GTAACG (SEQ ID NO: 103)

[00431] PGK300:

[00432] ACCCCTCTCTCCAGCCACTAAGCCAGTTGCTCCCTCGGCTGACGGCTGCA CGCGAGGCCTCCGAACGTCTTACGCCTTGTGGCGCGCCCGTCCTTGTCCCGGGTGT GATGGCGGGGTGTGGGGCGGAGGGCGTGGCGGGGAAGGGCCGGCGACGAGAGCC GCGCGGGACGACTCGTCGGCGATAACCGGTGTCGGGTAGCGCCAGCCGCGCGACG GTAACGAGGGACCGCGACAGGCAGACGCTCCCATGATCACTCTGCACGCCGAAGG CAAATAGTGCAGGCCGTGCGGCGCTTGGCGTTCCTTGGAAGGGCTGAATCCCCG (SEQ ID NO: 104)

[00433] PGK400:

[00434] ACCCCTCTCTCCAGCCACTAAGCCAGTTGCTCCCTCGGCTGACGGCTGCA CGCGAGGCCTCCGAACGTCTTACGCCTTGTGGCGCGCCCGTCCTTGTCCCGGGTGT GATGGCGGGGTGTGGGGCGGAGGGCGTGGCGGGGAAGGGCCGGCGACGAGAGCC GCGCGGGACGACTCGTCGGCGATAACCGGTGTCGGGTAGCGCCAGCCGCGCGACG GTAACGAGGGACCGCGACAGGCAGACGCTCCCATGATCACTCTGCACGCCGAAGG CAAATAGTGCAGGCCGTGCGGCGCTTGGCGTTCCTTGGAAGGGCTGAATCCCCGCC TCGTCCTTCGCAGCGGCCCCCCGGGTGTTCCCATCGCCGCTTCTAGGCCCACTGCG ACGCTTGCCTGCACTTCTTACACGCTCTGGGTCCCAGCCG (SEQ ID NO: 105)

[00435] 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).

[00436] 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.

[00437] 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.

[00438] In some embodiments, the a vector comprising a nuclei acid sequence encoding a CAR molecule described herein can further comprises a second nucleic acid sequence encoding a polypeptide, e.g., an agent that increases the activity of the CAR molecule. 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:

[00439] T2A: (GSG) E G R G S L L T C G D V E E N P G P (SEQ ID NO: 106)

[00440] P2A: (GSG) A T N F S L L K Q A G D V E E N P G P (SEQ ID NO: 107)

[00441] 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: 108)

[00442] 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: 109)

[00443] 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.

[00444] 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 or electroporation.

[00445] 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.

[00446] 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.

[00447] 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.

[00448] 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.

[00449] 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 disclosure, 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.

[00450] The present disclosure further provides a vector comprising a CAR encoding nucleic acid molecule. In one embodiment, the vector comprises a CAR encoding nucleic acid molecule, e.g., as described herein. In one aspect, the one or more CAR vectors 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).

[00451] In one embodiment, where stable expression of a CAR is desired, a vector comprising a CAR-encoding nucleic acid molecule is transduced into an immune effector cell. For example, immune effector cells with stable expression of a CAR can be generated using lentiviral vectors. Cells that exhibit stable expression of a CAR express the CAR for at least 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 6 months, 9 months, or 12 months after transduction.

[00452] In one embodiment, where transient expression of a CAR is desired, a CAR-encoding nucleic acid molecule is transfected into an immune effector cell. The CAR-encoding nucleic acid molecule may be a vector comprising a CAR encoding nucleic acid molecule, or an in vitro transcribed RNA encoding CAR. In vitro transcribed RNA CARs and methods for transfection into immune effector cells are further described below. Cells that exhibit transient expression of a CAR express the CAR for 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 days after transfection.

[00453]

[00454] RNA Transfection

[00455] Disclosed herein are methods for producing an in vitro transcribed RNA CAR, e.g., an in vitro transcribed RNA CAR. The present disclosure 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.

[00456] In one aspect, a CAR of the present disclosure is encoded by a messenger RNA (mRNA). In one aspect, the mRNA encoding a CAR described herein is introduced into a T cell or a NK cell for production of a cell that expresses a CAR.

[00457] 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 template 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 antigen, e.g., a solid tumor antigen or antigen expressed on a tumor associated with MDSCs or TAMs, 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.

[00458] 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.

[00459] 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.

[00460] 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.

[00461] 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.

[00462] 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.

[00463] 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.

[00464] 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.

[00465] 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.

[00466] 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).

[00467] 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.

[00468] 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: 2588)), 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 (e.g., SEQ ID NO: 34).

[00469] 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.

[00470] 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)).

[00471] 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.

[00472] 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).

[00473] Non-viral delivery methods

[00474] 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.

[00475] 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.

[00476] 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.

[00477] 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.*

[00478] 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.

[00479] 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.

[00480] 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.

[00481] 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).

[00482] 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.

[00483] Sources of Cells

[00484] Prior to expansion and genetic modification, e.g., to express a CAR described herein, a source of cells, e.g., T cell or 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, 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, any number of T cell lines available in the art, may be used. In certain aspects of the present disclosure, 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 to place the cells in an appropriate buffer or media for subsequent processing steps. In one aspect of the invention, the cells are washed with phosphate buffered saline (PBS). In an alternative aspect, 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.

[00485] 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.

[00486] 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 PERCOLLTM gradient or by counterflow centrifugal elutriation. A specific subpopulation of T cells, such as CD3+, CD28+, CD4+, CD8+, CD45RA+, and CD45RO+T cells, can be further isolated by positive or negative selection techniques. For example, in one aspect, T cells are 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 aspect, the time period is about 30 minutes. In a further aspect, the time period ranges from 30 minutes to 36 hours or longer and all integer values there between. In a further aspect, the time period is at least 1, 2, 3, 4, 5, or 6 hours. In yet another preferred aspect,

the time period is 10 to 24 hours. In one aspect, the incubation time period is 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. The skilled artisan would recognize that multiple rounds of selection can also be used in the context of this invention. In certain aspects, it may be desirable to perform the selection procedure and use the "unselected" cells in the activation and expansion process. "Unselected" cells can also be subjected to further rounds of selection.

[00487] Enrichment of a T cell population by negative selection can be accomplished with a combination of antibodies directed to surface markers unique to the negatively selected cells. One method is cell sorting and/or selection via negative magnetic immunoadherence or flow cytometry that uses a cocktail of monoclonal antibodies directed to cell surface markers present on the cells negatively selected. For example, to enrich for CD4+ cells by negative selection, a monoclonal antibody cocktail typically includes antibodies to CD14, CD20, CD11b, CD16, HLA-DR, and CD8. In certain aspects, it may be desirable to enrich for or positively select for regulatory T cells which typically express CD4+, CD25+, CD62Lhi, GITR+, and FoxP3+. Alternatively, in certain aspects, T regulatory cells are depleted by anti-C25 conjugated beads or other similar method of selection.

[00488] 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.

[00489] 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.

[00490] 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.

[00491] 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).

[00492] 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.

[00493] 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.

[00494] 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.

[00495] 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.

[00496] 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.

[00497] 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.

[00498] 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.

[00499] 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.

[00500] 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.

[00501] 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.

[00502] 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 2 billion cells/ml is used. In one aspect, a concentration of 1 billion cells/ml is used. In a further 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, 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.

[00503] 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.

[00504] 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.

[00505] 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.

[00506] 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 disclosure.

[00507] 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 T cell therapy for any number of diseases or conditions that would benefit from T 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.

[00508] In a further aspect of the present disclosure, 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 disclosure 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.

[00509] 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.

[00510] 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.

[00511] 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.

[00512] 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).

[00513] Allogeneic CAR Immune Effector Cells

[00514] 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.

[00515] 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.

[00516] 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 I and/or HLA class II, is downregulated.

[00517] 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.

[00518] 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).

[00519] In some embodiments, the allogeneic cell can be a cell which does not expresses 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, LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, 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.

[00520] siRNA and shRNA to inhibit TCR or HLA

[00521] 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, and/or an inhibitory molecule described herein (e.g., PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGF beta), in a cell, e.g., T cell.

[00522] Expression systems for siRNA and shRNAs, and exemplary shRNAs, are described, e.g., in paragraphs 649 and 650 of International Publication WO2015/142675, filed March 13, 2015, which is incorporated by reference in its entirety.

[00523] CRISPR to inhibit TCR or HLA

[00524] "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.

[00525] 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, and/or an inhibitory molecule described herein (e.g., PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (e.g., CEACAM-1,

CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGF beta), in a cell, e.g., T cell.

[00526] The CRISPR/Cas system, and uses thereof, are described, e.g., in paragraphs 651-658 of International Publication WO2015/142675, filed March 13, 2015, which is incorporated by reference in its entirety.

[00527] TALEN to inhibit TCR and/or HLA

[00528] 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, and/or an inhibitory molecule described herein (e.g., PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGF beta), in a cell, e.g., T cell.

[00529] TALENs, and uses thereof, are described, e.g., in paragraphs 659-665 of International Publication WO2015/142675, filed March 13, 2015, which is incorporated by reference in its entirety.

[00530] Zinc finger nuclease to inhibit HLA and/or TCR

[00531] "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, and/or an inhibitory molecule described herein (e.g., PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (e.g., CEACAM-1, CEACAM-3 and/or CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GAL9, adenosine, and TGF beta), in a cell, e.g., T cell.

[00532] ZFNs, and uses thereof, are described, e.g., in paragraphs 666-671 of International Publication WO2015/142675, filed March 13, 2015, which is incorporated by reference in its entirety.

[00533] **Telomerase expression**

[00534] 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.

[00535] 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.

[00536] 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.

[00537] 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:

[00538] MPRAPRCRAVRSLLRSHYREVLPLATFVRRLGPQGWRLVQRGDPAAFRAL
VAQCLVCVPWDARPPPAAPSFRQVSCLKELVARVLQRLCERGAKNVLAFGFALLDGA
RGGPPEAFTTSVRSYLPNTVTDALRGSGAWGLLLRRVGDDVLVHLLARCALFVLVAPS
CAYQVCGPPLYQLGAATQARPPPHASGPRRRLGCERAWNHSVREAGVPLGLPAPGAR
RRGGSASRSLPLPKRPRRGAAPEPERTPVGQGSWAHPGRTRGPSDRGFCVVSPARPAE
EATSLEGALSGTRHSHPSVGRQHHAGPPSTSRPPRPWDTPCPPVYAETKHFLYSSGDKE

QLRPSFLLSSLRPSLTGARRLVETIFLGSRPWMPGTPRRLPRLPQRYWQMRPLFLELLG
NHAQCPYGVLLKTHCPLRAAVTPAAGVCAREKPQGSVAAPEEEDTDPRRLVQLLRQH
SSPWQVYGFVRACLRRLVPPGLWGSRHNERRFLRNTKKFISLGKHAKLSLQELTWKM
SVRGCAWLRRSPGVGCVPAAEHRLREEILAKFLHWLMSVYVVELLRSFFYVTETTFQK
NRLFFYRKSVWSKLQSIGIRQHLKRVQLRELSEAEVRQHREARPALLTSRLRFIPKPDG
LRPIVNMDYVVGARTFRREKRAERLTSRVKALFSVLNYERARRPGLLGASVLGLDDIH
RAWRTFVLRVRAQDPPPELYFVKVDVTGAYDTIPQDRLTEVIASIIKPQNTYCVRRYAV
VQKAAHGHVRKAFKSHVSTLTDLQPYMRQFVAHLQETSPLRDAVVIEQSSSLNEASSG
LFDVFLRFMCHHAVRIRGKSYVQCQGIPQGSILSTLLCSLCYGDMENKLFAGIRRDGLL
LRLVDDFLLVTPHLTHAKTFLRTLVRGVPEYGCVVNLRKTVVNFPVEDEALGGTAFV
QMPAHGLFPWCGLLLDTRTLEVQSDYSSYARTSIRASLTFNRGFKAGRNMRRKLFGVL
RLKCHSLFLDLQVNSLQTVCTNIYKILLLQAYRFHACVLQLPFHQQVWKNPTFFLRVIS
DTASLCYSILKAKNAGMSLGAKGAAGPLPSEAVQWLCHQAFLLKLTRHRVTYVPLLG
SLRTAQTQLSRKLPGTTLTALEAAANPALPSDFKTILD (SEQ ID NO: 110)

[00539] 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: 110. In an embodiment, the hTERT has a sequence of SEQ ID NO: 110. 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.

[00540] 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) as follows:

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 gggggccccc 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
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: 111)

[00541] 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: 111. In an embodiment, the hTERT is encoded by a nucleic acid of SEQ ID NO: 111.

[00542]

[00543] Activation and Expansion of Immune Effector Cells (e.g., T Cells)

[00544] 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.

[00545] Generally, a population of immune effector cells, e.g., T 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 immune effector cells, e.g., 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. 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).

[00546] 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 disclosure.

[00547] 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 disclosure, 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 of the present disclosure, 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 of the invention, 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.

[00548] 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 disclosure. 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.

[00549] In further aspects of the present disclosure, 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.

[00550] 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 disclosure. 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 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.

[00551] 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 CAR-expressing 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 CAR-expressing 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 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 CAR-expressing cell described herein, expanded for 5 days show at least a one, two, three, four, five, tenfold 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.

[00552] In one aspect of the present disclosure, the mixture may be cultured for several hours (about 3 hours) to about 14 days or any hourly integer value in between. In one aspect, the mixture may be cultured for 21 days. In one aspect of the invention the beads and the T cells are cultured together for about eight days. In one aspect, the beads and T cells are cultured together for 2-3 days. 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).

[00553] 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 IL-15 and/or IL-7 (e.g., IL-15 and IL-7).

[00554] 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.

[00555] 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.

[00556] 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.

[00557] In one embodiment, the cells are cultured (e.g., expanded, simulated, and/or transduced) in media comprising serum. The serum may be, e.g., human AB serum (hAB). In some embodiments, the hAB serum is present at about 2%, about 5%, about 2-3%, about 3-4%, about 4-5%, or about 2-5%. 2% and 5% serum are each suitable levels that allow for many fold expansion of T cells. Furthermore, as shown 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, medium containing 2% human AB serum is suitable for *ex vivo* expansion of T cells.

[00558] 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.

[00559] 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.

[00560] In some embodiments, cells transduced with a nucleic acid encoding a CAR, e.g., a CAR described herein, can be selected for administration based upon, e.g., protein expression levels of one or more of CCL20, GM-CSF, IFNγ, IL-10, IL-13, IL-17a, IL-2, IL-21, IL-4, IL-5, IL-6, IL-9, TNFα and/or combinations thereof. In some embodiments, cells transduced with a nucleic acid encoding a CAR, e.g., a CAR described herein, can be selected for administration based upon, e.g., protein expression levels of CCL20, IL-17a, IL-6 and combinations thereof.

[00561] Once a CAR 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 CAR or a cell expressing a CAR (e.g., a cell of the invention) are described in further detail in paragraphs 695-703 of International Publication WO2015/142675, filed March 13, 2015, which is incorporated by reference in its entirety.

[00562] Assays to evaluate the effects of a CAR or CAR-expressing cell (e.g., a cell of the invention) are described in further detail below.

[00563] For example, the cytotoxicity assay described above can be modified to evaluate the cytotoxic activity of a CAR-expressing cell in vitro. Cells of the invention can be mixed with target cells, e.g., cells expressing the antigen targeted by the CAR, at varying ratios of effector to target (E:T). After sufficient incubation to allow cell-mediated cytolysis the supernatant from each ratio sample is harvested and then measured for released 51Cr. To monitor cell-mediated persistence or proliferation, the cells of the invention can be monitored by, for example, flow cytometry.

[00564] Furthermore, animal models similar to those described above can be administered a cell of the invention, to evaluate the ability of the cell.

[00565] 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 CAR constructs and methods of the invention.

Therapeutic Application

[00566] In accordance with any method described herein, in embodiments, a subject has a cancer, e.g., a solid tumor or tumor associated with MDSCs or TAMs. In embodiments, a composition described herein can be used to treat a cancer described herein. In embodiments, an inhibitor of a pro-M2 macrophage molecule, e.g., as described herein, e.g., an anti-IL-13 antibody, an anti-IL-4 antibody or an anti-IL-13Rα1 antibody, is used in combination with a CAR-expressing cell (e.g., CD123 CAR expressing cell) to treat a cancer, e.g., Hodgkin lymphoma.

[00567] The present invention provides, among other things, compositions and methods for treating a disease associated with expression of an antigen (e.g., a solid tumor antigen or antigen expressed on a tumor associated with MDSCs or TAMs) or condition associated with cells which express the antigen (e.g., a solid tumor antigen or antigen expressed on a tumor associated with MDSCs or TAMs) including, e.g., a proliferative disease 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 the antigen (e.g., a solid tumor antigen or antigen expressed on a tumor associated with MDSCs or TAMs). In one aspect, a cancer associated with expression of an antigen is a hematological cancer. In one aspect, a hematological cancer includes but is not limited to AML, myelodysplastic syndrome, ALL, chronic myeloid leukemia, blastic plasmacytoid dendritic cell neoplasm, myeloproliferative neoplasms, Hodgkin lymphoma, and the like. In embodiments, disease associated with expression of CD123 includes, but are not limited to, e.g., atypical and/or non-classical cancers, malignancies, precancerous conditions or proliferative diseases associated with expression of CD123. Non-cancer related indications associated with expression of an antigen (e.g., CD123) may also be included. In some embodiments, the disorder is a disease associated with expression of CD19, e.g., a CD19-expressing B cell malignancy as described herein.

[00568] In one aspect, the invention provides methods for treating a disease associated with expression of antigen (e.g., a solid tumor antigen or antigen expressed on a tumor associated with MDSCs or TAMs). In one aspect, the invention provides methods for treating a disease wherein part of the tumor is negative for the antigen (e.g., a solid tumor antigen or antigen expressed on a tumor associated with MDSCs or TAMs) and part of the tumor is positive for

the antigen (e.g., a solid tumor antigen or antigen expressed on a tumor associated with MDSCs or TAMs). For example, the CAR described herein is useful for treating subjects that have undergone treatment for a disease associated with elevated expression of the antigen (e.g., a solid tumor antigen or antigen expressed on a tumor associated with MDSCs or TAMs), wherein the subject that has undergone treatment for elevated levels of the antigen (e.g., a solid tumor antigen or antigen expressed on a tumor associated with MDSCs or TAMs) exhibits a disease associated with elevated levels of the antigen (e.g., a solid tumor antigen or antigen expressed on a tumor associated with MDSCs or TAMs). In embodiments, the CAR is useful for treating subjects that have undergone treatment for a disease associated with expression of the antigen (e.g., a solid tumor antigen or antigen expressed on a tumor associated with MDSCs or TAMs), wherein the subject that has undergone treatment related to expression of the antigen (e.g., a solid tumor antigen or antigen expressed on a tumor associated with MDSCs or TAMs) exhibits a disease associated with expression of the antigen (e.g., a solid tumor antigen or antigen expressed on a tumor associated with MDSCs or TAMs).

[00569] In one aspect, provided herein is a method of inhibiting growth of an antigen-expressing tumor cell (e.g., a solid tumor or tumor associated with MDSCs or TAMs), comprising contacting the tumor cell with a CAR-expressing cell (e.g., as described herein) such that the CAR-expressing cell is activated in response to the antigen and targets the cancer cell, wherein the growth of the tumor is inhibited. The method can comprise administration of a inhibitor of a pro-M2 macrophage molecule, e.g., described herein.

[00570] In one aspect, the invention pertains to a method of treating cancer in a subject. The method comprises administering to the subject a CAR-expressing cell described herein such that the cancer is treated in the subject. The cellular therapy is provided in combination with a inhibitor of a pro-M2 macrophage molecule, e.g., described herein.

[00571] The disclosure includes a type of cellular therapy where immune effector cells, e.g., T cells or NK cells, are genetically modified to express a chimeric antigen receptor (CAR) and the CAR-expressing cell is infused to a recipient in need thereof. The infused cell is able to kill tumor cells in the recipient. The cellular therapy is provided in combination with a inhibitor of a pro-M2 macrophage molecule, e.g., described herein. Unlike antibody therapies, CAR-modified immune effector cells, e.g., the CAR-modified T cells or CAR-modified 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 or 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 immune effector cell, e.g., T cell or NK cell, to the patient.

[00572] The invention also includes a type of cellular therapy where immune effector cells, e.g., T cells or NK cells, are modified, e.g., by in vitro transcribed RNA, to transiently express a chimeric antigen receptor (CAR) and the CAR-expressing cell, e.g., CAR T cell or CAR NK cell) is infused to a recipient in need thereof. The cellular therapy is provided in combination with a inhibitor of a pro-M2 macrophage molecule, e.g., described herein. The infused cell is able to kill tumor cells in the recipient. Thus, in various aspects, the immune effector cells, e.g., T cells or 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 immune effector cell, e.g., T cell or NK cell, to the patient.

[00573] 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 or 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 or NK cells, exhibit specific proinflammatory cytokine secretion and potent cytolytic activity in response to human cancer cells expressing the target antigen, resist soluble target antigen inhibition, mediate bystander killing and mediate regression of an established human tumor. For example, antigen-less tumor cells within a heterogeneous field of antigen-expressing tumor may be susceptible to indirect destruction by antigen-redirected immune effector cell, e.g., T cells or NK cells that has previously reacted against adjacent antigen-positive cancer cells.

[00574] In one aspect, the fully-human CAR-modified immune effector cells (e.g., T cells or 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.

[00575] With respect to ex vivo immunization, at least one of the following occurs in vitro prior to administering the cell, e.g., T cell or NK 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.

[00576] 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.

[00577] 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 T 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.

[00578] 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.

[00579] 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 or NK cells) of the invention are used in the treatment of diseases, disorders and conditions described herein, e.g., disorders or conditions associated with expression of an antigen described herein, e.g., a solid tumor antigen or antigen expressed on a tumor associated with MDSCs or TAMs. In certain aspects, the cells of the invention are used in the treatment of patients at risk for developing diseases, disorders and conditions described herein, e.g.,

disorders or conditions associated with expression of an antigen described herein, e.g., e.g., a solid tumor antigen or antigen expressed on a tumor associated with MDSCs or TAMs. Thus, the present invention provides methods for the treatment or prevention of diseases, disorders and conditions described herein, e.g., disorders or conditions associated with expression of an antigen described herein, e.g., e.g., a solid tumor antigen or antigen expressed on a tumor associated with MDSCs or TAMs, comprising administering to a subject in need thereof, a therapeutically effective amount of the CAR-modified immune effector cells (e.g., T cells or NK cells) described herein in combination with a inhibitor of a pro-M2 macrophage molecule, e.g., described herein.

[00580] In one aspect, the CAR-expressing cells (CART cells or CAR-expressing NK 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. In one aspect, the cancer is a hematological cancer preleukemia, a hyperproliferative disorder, a hyperplasia or a dysplasia, which is characterized by abnormal growth of cells.

[00581] In one aspect, the CAR-expressing cells (CART cells or CAR-expressing NK cells) of the invention are used to treat a cancer, wherein the cancer is a hematological cancer. Hematological cancer conditions are the types of cancer such as leukemia and malignant lymphoproliferative conditions that affect blood, bone marrow and the lymphatic system.

[00582] In one aspect, the compositions and CAR-expressing cells (CART cells or CAR-expressing NK cells) of the present invention are particularly useful for treating a solid tumor such as, for example, malignancies, e.g., sarcomas, adenocarcinomas, and carcinomas, of the various organ systems, such as those affecting pancreas, liver, lung, breast, ovary, lymphoid, gastrointestinal (e.g., colon), genitourinary tract (e.g., renal, urothelial cells), prostate, and pharynx. In one aspect, the compositions and CAR-expressing cells (CART cells or CAR-expressing NK cells) of the present invention are particularly useful for treating Hodgkin lymphoma.

[00583] Also provided herein are methods for inhibiting the proliferation of or reducing an antigen-expressing cell population (e.g., solid tumor cell population or tumor associated with MDSCs or TAMs cell population), the methods comprising contacting a population of cells

comprising an antigen-expressing cell with a CAR-expressing cell that binds to the antigen-expressing cell. In a specific aspect, the present invention provides methods for inhibiting the proliferation of or reducing the population of cancer cells expressing the antigen, the methods comprising contacting the antigen-expressing cancer cell population with a CAR-expressing cell that binds to the antigen-expressing cell, in combination with an inhibitor of a pro-M2 macrophage molecule, e.g., described herein. In one aspect, the present invention provides methods for inhibiting the proliferation or reducing the population of cancer cells expressing an antigen, the methods comprising contacting the antigen-expressing cancer cell population with a CAR-expressing cell that binds to the antigen-expressing cell, in combination with an inhibitor of a pro-M2 macrophage molecule, e.g., described herein. In certain aspects, the CAR-expressing cell, when administered in combination with an inhibitor of a pro-M2 macrophage molecule, e.g., described herein, 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 Hodgkin lymphoma or another cancer associated with the antigen-expressing cells relative to a negative control or relative to either monotherapy alone. In one aspect, the subject is a human.

[00584] The present invention also provides methods for preventing, treating and/or managing a disease associated with antigen expressing cell (e.g., a solid tumor or tumor associated with MDSCs or TAMs, e.g., Hodgkin lymphoma), the methods comprising administering to a subject in need a CAR-expressing cell that binds to the antigen-expressing cell in combination with an inhibitor of a pro-M2 macrophage molecule, e.g., described herein. I n one aspect, the subject is a human.

[00585] The present invention also provides methods for preventing, treating and/or managing a disease associated with antigen-expressing cells, the methods comprising administering to a subject in need a CAR-expressing cell that binds to the antigen-expressing cell, in combination with an inhibitor of a pro-M2 macrophage molecule, e.g., described herein. In one aspect, the subject is a human.

[00586] The present invention provides methods for preventing relapse of cancer associated with antigen-expressing cells, the methods comprising administering to a subject in need thereof a CAR-expressing cell of the invention that binds to the antigen-expressing cell, in

combination with a an inhibitor of a pro-M2 macrophage molecule, e.g., described herein. In one aspect, the methods comprise administering to the subject in need thereof an effective amount of a CAR-expressing cell described herein that binds to the antigen-expressing cell in combination with an effective amount of another therapy (e.g., an inhibitor of a pro-M2 macrophage molecule, e.g., described herein).

[00587] In another aspect, the invention provides a method of treating a subject having a disease associated with expression of a tumor antigen (e.g., a subject having a cancer (e.g., a solid tumor or a tumor associated with tumor-associated macrophages)). The method includes administering to the subject (i) a CAR therapy including a cell, e.g., a population of immune effector cells, including (e.g., expressing) a chimeric antigen receptor (CAR), wherein the CAR includes a tumor antigen binding domain that binds to CD123, a transmembrane domain, and an intracellular signaling domain; and (ii) a tumor targeting therapy. In some embodiments, the CD123 CAR is administered in an amount and/or time sufficient to result in inhibition of an M2 macrophage activity. In embodiments, the inhibition of the M2 macrophage activity comprises inhibition of polarization of a macrophage to an M2 phenotype, and/or reversal of a phenotype of an M2 macrophage.

[00588] In other embodiments, the tumor targeting therapy is or includes a CD19-inhibiting or depleting therapy, e.g., a therapy that includes a CD19 inhibitor. In some embodiments, the CD19 inhibitor is a CD19 antibody, e.g., a CD19 bispecific antibody (e.g., a bispecific T cell engager that targets CD19, e.g., blinatumomab). In some embodiments, the bispecific T cell engager antibody molecule is an antibody molecule described in Bargou et al., "Tumor regression in cancer patients by very low doses of a T cell-engaging antibody." Science. 2008 Aug 15;321(5891):974-7. doi: 10.1126/science.1158545.

[00589] In some embodiments, the tumor targeting therapy includes a CD19 CAR-expressing cell, e.g., a CD19 CART cell, or an anti-CD19 antibody (e.g., an anti-CD19 mono- or bispecific antibody) or a fragment or conjugate thereof. In one embodiment, the anti-CD19 antibody is a humanized antigen binding domain as described in WO2014/153270 (e.g., Table 3 of WO2014/153270) incorporated herein by reference, or a conjugate thereof. Other exemplary anti-CD19 antibodies or fragments or conjugates thereof, include but are not limited to, blinatumomab, SAR3419 (Sanofi), MEDI-551 (MedImmune LLC), Combotox, DT2219ARL (Masonic Cancer Center), MOR-208 (also called XmAb-5574; MorphoSys),

XmAb-5871 (Xencor), MDX-1342 (Bristol-Myers Squibb), SGN-CD19A (Seattle Genetics), and AFM11 (Affimed Therapeutics). See, e.g., Hammer. MAbs. 4.5(2012): 571–77. Blinatomomab is a bispecific antibody comprised of two scFvs—one that binds to CD19 and one that binds to CD3. Blinatomomab directs T cells to attack cancer cells. See, e.g., Hammer et al.; Clinical Trial Identifier No. NCT00274742 and NCT01209286. MEDI-551 is a humanized anti-CD19 antibody with a Fc engineered to have enhanced antibody-dependent cell-mediated cytotoxicity (ADCC). See, e.g., Hammer et al.; and Clinical Trial Identifier No. NCT01957579. Combotox is a mixture of immunotoxins that bind to CD19 and CD22. The immunotoxins are made up of scFv antibody fragments fused to a deglycosylated ricin A chain. See, e.g., Hammer et al.; and Herrera et al. J. Pediatr. Hematol. Oncol. 31.12(2009):936-41; Schindler et al. Br. J. Haematol. 154.4(2011):471-6. DT2219ARL is a bispecific immunotoxin targeting CD19 and CD22, comprising two scFvs and a truncated diphtheria toxin. See, e.g., Hammer et al.; and Clinical Trial Identifier No. NCT00889408. SGN-CD19A is an antibody-drug conjugate (ADC) comprised of an anti-CD19 humanized monoclonal antibody linked to a synthetic cytotoxic cell-killing agent, monomethyl auristatin F (MMAF). See, e.g., Hammer et al.; and Clinical Trial Identifier Nos. NCT01786096 and NCT01786135. SAR3419 is an anti-CD19 antibody-drug conjugate (ADC) comprising an anti-CD19 humanized monoclonal antibody conjugated to a maytansine derivative via a cleavable linker. See, e.g., Younes et al. J. Clin. Oncol. 30.2(2012): 2776-82; Hammer et al.; Clinical Trial Identifier No. NCT00549185; and Blanc et al. Clin Cancer Res. 2011;17:6448-58. XmAb-5871 is an Fc-engineered, humanized anti-CD19 antibody. See, e.g., Hammer et al. MDX-1342 is a human Fc-engineered anti-CD19 antibody with enhanced ADCC. See, e.g., Hammer et al. In embodiments, the antibody molecule is a bispecific anti-CD19 and anti-CD3 molecule. For instance, AFM11 is a bispecific antibody that targets CD19 and CD3. See, e.g., Hammer et al.; and Clinical Trial Identifier No. NCT02106091. In some embodiments, an anti-CD19 antibody described herein is conjugated or otherwise bound to a therapeutic agent, e.g., a chemotherapeutic agent, peptide vaccine (such as that described in Izumoto et al. 2008 J Neurosurg 108:963-971), immunosuppressive agent, or immunoablative agent, e.g., cyclosporin, azathioprine, methotrexate, mycophenolate, FK506, CAMPATH, anti-CD3 antibody, cytoxin, fludarabine, rapamycin, mycophenolic acid, steroid, FR901228, or cytokine.

Hematologic Cancers

[00590] 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.

[00591] In one embodiment, the hematologic cancer is leukemia. In one embodiment, the cancer is selected from the group consisting of one or more acute leukemias including but not limited to B-cell acute lymphoid leukemia (BALL), T-cell acute lymphoid leukemia (TALL), small lymphocytic leukemia (SLL), acute lymphoid leukemia (ALL); one or more chronic leukemias including but not limited to chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL); additional hematologic cancers or hematologic conditions including, but not limited to mantle cell lymphoma (MCL), 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, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin lymphoma, 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.

[00592] In an embodiment, the cancer is Hodgkin lymphoma. In embodiments, the CAR is a CD123 CAR, e.g., described herein.

[00593] Leukemia can be classified as acute leukemia and chronic leukemia. Acute leukemia can be further classified as acute myelogenous leukemia (AML) and acute lymphoid 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.

[00594] Lymphoma is a group of blood cell tumors that develop from lymphocytes. Exemplary lymphomas include non-Hodgkin lymphoma and Hodgkin lymphoma. In an

embodiment, the cancer is Hodgkin lymphoma. In embodiments, the CAR is a CD123 CAR, e.g., described herein.

[00595] In an aspect, the invention pertains to a method of treating a mammal having a hematological cancer, comprising administering to the mammal an effective amount of the cells expressing a CAR molecule and an inhibitor of a pro-M2 macrophage molecule described herein.

Solid cancers

[00596] It is particularly preferred that the methods and compositions of the invention be used to treat solid cancers and solid tumors. Exemplary solid cancers include but are not limited to: uterine cancer, colon cancer, ovarian cancer, rectal cancer, skin cancer, stomach cancer, lung cancer, non-small cell carcinoma of the lung, breast cancer, cancer of the small intestine, testicular cancer, cancer of the anal region, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, rectal cancer, renal-cell carcinoma, liver cancer, cancer of the esophagus, melanoma, cutaneous or intraocular malignant melanoma, uterine cancer, brain cancer, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, cancer of the adrenal gland, bone cancer, pancreatic cancer, cancer of the head or neck, epidermoid cancer, carcinoma of the endometrium, carcinoma of the vagina, cervical cancer, sarcoma, uterine cancer, stomach cancer, esophageal cancer, colorectal cancer, liver cancer, prostate cancer, carcinoma of the cervix squamous cell cancer, carcinoma of the fallopian tubes, sarcoma of soft tissue, cancer of the urethra, carcinoma of the vulva, cancer of the kidney or ureter, carcinoma of the renal pelvis, spinal axis tumor, cancer of the penis, cancer of the bladder, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, metastatic lesions of said cancers, and/or combinations thereof.

[00597] In one embodiment, the present disclosure provides therapy described herein wherein cells or compostions of the invention is administered to treat a solid tumor, e.g., to inhibit the growth of a solid tumor. In embodiments the cells comprise a CAR molecule that targets, e.g., binds, to a tumor antigen present on a cell or population of cells in the solid tumor. Examples of solid tumors that can be treated with methods disclosed herein include malignancies, e.g., sarcomas, adenocarcinomas, and carcinomas, of the various organ systems, such as those affecting pancreas, liver, lung, breast, ovary, 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 solid tumor is a mesothelioma. Metastatic lesions of the aforementioned cancers can also be treated or prevented using the methods and compositions of the invention.

[00598] In one embodiment, the combination therapy described herein is administered to treat a CD19 negative cancer. A CD19 negative cancer can be characterized by CD19 loss (*e.g.*, an antigen loss mutation) or other CD19 alteration that reduces the level of CD19 (*e.g.*, caused by clonal selection of CD19-negative clones). It shall be understood that a CD19-negative cancer need not have 100% loss of CD19, and may retain some partial CD19 expression (*e.g.*, retain some cancer cells that express CD19).

[00599] In one aspect, the present disclosure 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 CD123 CAR, wherein the cancer cells express CD123. In one embodiment, the cancer to be treated is Hodgkin lymphoma.

[00600] In one aspect, the present disclosure 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.

[00601] In one aspect, the present disclosure 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 mesothelin CAR, wherein the cancer cells express mesothelin. In one embodiment, the cancer to be treated is mesothelioma, malignant pleural mesothelioma, non-small cell lung cancer, small cell lung cancer, squamous cell lung cancer, or large cell lung cancer, pancreatic cancer, pancreatic ductal adenocarcinoma, pancreatic metatstatic, esophageal adenocarcinoma, breast cancer, ovarian cancer, colorectal cancer and bladder cancer, or any combination thereof.

[00602] In one aspect, the present disclosure 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.

[00603] In one aspect, the present disclosure 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, colon cancer, breast cancer, or pancreatic cancer.

[00604] In one aspect, the present disclosure 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 sTnCAR, wherein the cancer cells express sTn antigen. In one embodiment, the cancer to be treated is ovarian cancer, colon cancer, breast cancer, or pancreatic cancer.

[00605] In one aspect, the present disclosure 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.

[00606] In one aspect, the present disclosure 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.

[00607] In one aspect, the present disclosure 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.

[00608] In one aspect, the present disclosure 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.

[00609] In one aspect, the present disclosure 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.

[00610] In one aspect, the present disclosure 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 IL-13Ra2CAR, wherein the cancer cells express IL-13Ra2. In one embodiment, the cancer to be treated is glioblastoma.

[00611] In one aspect, the present disclosure 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).

[00612] In one aspect, the present disclosure 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.

[00613] In one aspect, the present disclosure 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.

[00614] In one aspect, the present disclosure 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.

[00615] In one aspect, the present disclosure 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.

[00616] In one aspect, the present disclosure 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.

[00617] In one aspect, the present disclosure 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.

[00618] In one aspect, the present disclosure 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.

[00619] In one aspect, the present disclosure 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.

[00620] In one aspect, the present disclosure 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.

[00621] In one aspect, the present disclosure 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.

[00622] In one aspect, the present disclosure 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.

[00623] In one aspect, the present disclosure 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.

[00624] In one aspect, the present disclosure 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.

[00625] In one aspect, the present disclosure 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.

[00626] In one aspect, the present disclosure 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.

[00627] In one aspect, the present disclosure 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 Plysialic acid CAR, wherein the cancer cells express Plysialic acid. In one embodiment, the cancer to be treated is small cell lung cancer.

[00628] In one aspect, the present disclosure 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).

[00629] In one aspect, the present disclosure 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.

[00630] In one aspect, the present disclosure 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.

[00631] In one aspect, the present disclosure 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.

[00632] In one aspect, the present disclosure 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.

[00633] In one aspect, the present disclosure 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.

[00634] In one aspect, the present disclosure 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.

[00635] In one aspect, the present disclosure 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.

[00636] In one aspect, the present disclosure 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.

[00637] In one aspect, the present disclosure 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.

[00638] In one aspect, the present disclosure 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

[00639] In one aspect, the present disclosure 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 transcriptaseCAR, wherein the cancer cells express human telomerase reverse transcriptase. In one embodiment, the cancer to be treated is solid tumors.

[00640] In one aspect, the present disclosure 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 esteraseCAR, 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.

[00641] In one aspect, the present disclosure 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.

Combination Therapies

[00642] A CAR-expressing cell described herein may be used in combination with an inhibitor of a pro-M2 macrophage molecule, e.g., described herein. The combination of the CAR-expressing cell and the inhibitor of a pro-M2 macrophage molecule can be used in further combination with other known agents and therapies (additional therapeutic agent). 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.

[00643] 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 inhibitor of a pro-M2 macrophage molecule can be administered before, concurrently with, or after the CAR-expressing cell or the additional agent.

[00644] 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.

[00645] 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.

Inhibitors of a pro-M2 macrophage molecule

[00646] Macrophages with the M2 phenotype are known to play a role in inhibiting T cell function, including cytotoxic function. Certain cytokines, such as IL-13, IL-4, IL-10, CSF-1, TGF-beta and GM-CSF are known to polarize macrophages to the M2 phenotype, for example (in the case of IL-13 and/or IL-4), by interaction with the IL-13Rα1 chain and/or IL-4Rα chain expressed on macrophages. Molecules that block such molecules are useful in the methods and compositions described herein. Preferred inhibitors of a pro-M2 macrophage molecule include inhibitors of IL-13, inhibitors of IL-4, inhibitors of IL-13Rα1, and/or inhibitors of IL-4Rα, e.g., as described herein.

[00647] Inhibitors of a pro-M2 macrophage molecule include, for example, small molecules. An example of a small molecule inhibitor that can be administered with a CAR-expressing cell is pterostilbene (see, e.g., Huang et al., Oncotarget. 2016 Jun 28; 7(26): 39363–39375), which is hereby incorporated by reference in its entirety.

[00648] Inhibitors of a pro-M2 macrophage molecule include, for example, an antibody molecule, a polypeptide, e.g., a fusion protein, or an inhibitory nucleic acid, e.g., a siRNA or

shRNA, or a CAR-expressing cell which binds one or more surface antigens on MDSCs or TAMs.

[00649] In one aspect, the inhibitor of a pro-M2 macrophage molecule is an anti-IL-13 antibody. Generation of such antibodies may be undertaken by methods known in the art. An example of anti-IL-13 antibodies includes, for example, lebrikizumab (see CAS number 953400-68-5). Another example of an anti-IL-13 antibody is, for example, tralokinumab (CAS number 1044515-88-9). Another example of an anti-IL-13 antibody is or comprises the anti-IL-13 binding domain of GSK2434735. Another example of an anti-IL-13 antibody is QAX576 (see, e.g., Rothenberg et al., *J. Allergy Clin. Immunol.*, 2015, 135(2), pp. 500-507).

[00650] In another aspect, the inhibitor of a pro-M2 macrophage molecule is an anti-IL-4 antibody or anti-IL-4Rα antibody. Generation of such antibodies may be undertaken by methods known in the art. An example of anti-IL-4 antibodies includes, for example, the anti-IL-4 binding domain of GSK2434735. Another example of an anti-IL-4 antibody is, for example, dupilumab (see CAS number 1190264-60-8).

[00651] In another embodiment, the inhibitor of a pro-M2 macrophage is an inhibitor of IL-13 and/or IL-4. An example of an inhibitor of IL-13 and IL-4 that can be administered with a CAR-expressing cell is the vitamin A derivative Fenretinide ((e.g., 4-HPR) see, e.g., Dong et al. Cancer Letters. March 1, 2017. Volume 388, Pages 43–53, which is hereby incorporated by reference in its entirety).

[00652] In another aspect, the inhibitor of a pro-M2 macrophage molecule is an anti-CSF-1 antibody or small molecule inhibitor of CSF-1. Generation of such antibodies may be undertaken by methods known in the art. An example of an anti-CSF-1 antibody is emactuzumab. Another example of a CSF-1 inhibitor is BLZ945 (see, e.g., Strachan, DC et al., Oncoimmunology, 2013 Dec. 1, 2(12): e26968). Another example of an inhibitor of CSF-1 that can be administered with a CAR-expressing cell is nintedanib (see, e.g., Tandon et al. American Journal of Respiratory and Critical Care Medicine 2017;195:A2397, which is hereby incorporated by reference in its entirety).

[00653] In another aspect, the inhibitor of a pro-M2 macrophage molecule is a CAR-expressing cell which binds an antigen expressed on the surface of a MDSC or TAM (i.e., a TAM antigen), e.g., an antigen that is upregulated on the surface of a MDSCs or TAM, relative

to other macrophages. In embodiments, the CAR-expressing cell which binds a MDSCs or TAM antigen binds to CD123 (e.g., is a CD123 CAR as described herein). In embodiments, the CAR-expressing cell which binds a MDSCs or TAM antigen binds to CSF1R. In embodiments, the CAR-expressing cell which binds a MDSCs or TAM antigen binds to CD68. In embodiments, the CAR-expressing cell which binds a MDSCs or TAM antigen binds to CD206.

[00654] In another embodiment, the inhibitor of a pro-M2 macrophage is a JAK2 inhibitor. An example of a JAK2 inhibitor that can be administered with a CAR-expressing cell is Ruxolitinib (see, e.g., Chen et al. Clinical Lymphoma, Myeloma and Leukemia , Volume 17 , Issue 1 , e93, 2017, which is hereby incorporated by reference in its entirety).

[00655] In another embodiment, the inhibitor of a pro-M2 macrophage molecule is a cell surface molecule. An example of a cell surface molecule that can be administered with a CAR-expressing cell is Dipeptidyl peptidase 4 (DPP-4) or CD26 (see, e.g., Zhuge et al. Diabetes 2016 Oct; 65(10): 2966-2979, which is hereby incorporated by reference in its entirety).

[00656] In another embodiment, the inhibitor of a pro-M2 macrophage molecule is an HDAC inhibitor. An example of an HDAC inhibitor that can be administered with a CAR-expressing cell is suberanilohydroxamic acid (SAHA).

[00657] In another embodiment, the inhibitor of a pro-M2 macrophage molecule is an inhibitor of the glycolytic pathway. An example of an inhibitor of the glycolytic pathway that can be administered with a CAR-expressing cell is 2-deoxy-d-glucose ((2-DG) see, e.g., Zanganeh, Nat Nanotechnol. 2016 Nov; 11(11): 986–994, which is hereby incorporated by reference in its entirety).

[00658] In another embodiment, the inhibitor of a pro-M2 macrophage molecule is a mitochondria-targeted antioxidant. An example of a mitochondria-targeted antioxidant that can be administered with a CAR-expressing cell is MitoQ (Formentini et al., Cell Reports, Volume 19, Issue 6, 9 May 2017, Pages 1202-1213, which is hereby incorporated by reference in its entirety).

[00659] In another embodiment, the inhibitor of a pro-M2 macrophage molecule is an iron oxide. An example of an iron oxide that can be administered with a CAR-expressing cell is

ferumoxytol (see, e.g., Zanganeh, Nat Nanotechnol. 2016 Nov; 11(11): 986–994, which is hereby incorporated by reference in its entirety).

[00660] In embodiments, the invention includes a composition comprising an inhibitor of a pro-M2 macrophage molecule, and a pharmaceutically acceptable carrier.

Further Combination Therapies

[00661] In further aspects, a CAR-expressing cell described herein may be used in a treatment regimen in combination with surgery, cytokines, radiation, or chemotherapy such as cytoxan, fludarabine, histone deacetylase inhibitors, demethylating agents, or peptide vaccine, such as that described in Izumoto et al. 2008 J Neurosurg 108:963-971.

[00662] In certain instances, compounds of the present invention are combined with other therapeutic agents, such as other anti-cancer agents, anti-allergic agents, anti-nausea agents (or anti-emetics), pain relievers, cytoprotective agents, and combinations thereof.

[00663] In one embodiment, a CAR-expressing cell and/or the inhibitor of a pro-M2 macrophage molecule, e.g., described herein, can be used further 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).

[00664] 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®).

[00665] Anti-cancer agents of particular interest for the combinations disclosed herein include: anthracyclines; alkylating agents; antimetabolites; drugs that inhibit either the calcium dependent phosphatase calcineurin or the p70S6 kinase FK506) or inhibit the p70S6 kinase; mTOR inhibitors; immunomodulators; anthracyclines; vinca alkaloids; proteosome inhibitors; GITR agonists; protein tyrosine phosphatase inhibitors; a CDK4 kinase inhibitor; a BTK inhibitor; a MKN kinase inhibitor; a DGK kinase inhibitor; or an oncolytic virus.

[00666] Exemplary antimetabolites include, without limitation, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors): methotrexate (Rheumatrex®, Trexall®), 5-fluorouracil (Adrucil®, Efudex®, Fluoroplex®), floxuridine (FUDF®), cytarabine (Cytosar-U®, Tarabine PFS), 6-mercaptopurine (Puri-Nethol®)), 6-thioguanine (Thioguanine Tabloid®), fludarabine phosphate (Fludara®), pentostatin (Nipent®), pemetrexed (Alimta®), raltitrexed (Tomudex®), cladribine (Leustatin®), clofarabine (Clofarex®, Clolar®), azacitidine (Vidaza®), decitabine and gemcitabine (Gemzar®). Preferred antimetabolites include, cytarabine, clofarabine and fludarabine.

[00667] 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®).

[00668] In embodiments, a CAR-expressing cell described herein, optionally in combination with an inhibitor of a pro-M2 macrophage molecule, is administered to a subject in combination with a BTK inhibitor. Inhibitors of BTK include a small molecule, an antibody molecule, a polypeptide, e.g., a fusion protein, or an inhibitory nucleic acid, e.g., a siRNA or shRNA.

[00669] 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.

[00670] 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 chemical name of ibrutinib is as follows: 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).

In some embodiments the BTK inhibitor is a BTK inhibitor described in International Application WO/2015/079417, which is herein incorporated by reference in its entirety.

[00671] In embodiments, a CAR-expressing cell described herein, optionally in combination with an inhibitor of a pro-M2 macrophage molecule, 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 chemical name of idelalisib is 5-Fluoro-3-phenyl-2-[(1*S*)-1-(7*H*-purin-6-ylamino)propyl]-4(3*H*)-quinazolinone.

Duvelisib is a small molecule that blocks PI3K-δ,γ. The chemical name of duvelisib is 8-Chloro-2-phenyl-3-[(1S)-1-(9H-purin-6-ylamino)ethyl]-1(2H)-isoquinolinone).
In some embodiments, a CAR-expressing cell is administered to a subject in combination with a phosphoinositide 3-kinase (PI3K) inhibitor. In certain embodiments, the PI3K inhibitor is tenalisib (RP6530) see, e.g., Locatell et al., Blood. July 07, 2016; 128 (1), which is incorporated herein by reference in its entirety).

[00672] 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.

[00673] In embodiments, a CAR-expressing cell described herein, optionally in combination with an inhibitor of a pro-M2 macrophage molecule, is administered to a subject in combination with an anaplastic lymphoma kinase (ALK) inhibitor. Exemplary ALK kinase inhibitors 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.

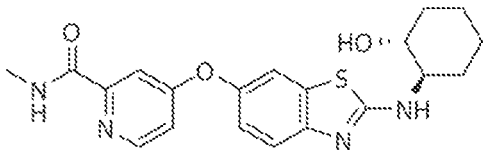
[00674] The chemical name of crizotinib is 3-[(1*R*)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]-5-(1-piperidin-4-ylpyrazol-4-yl)pyridin-2-amine. The chemical name of ceritinib is 5-Chloro-N^2-[2-isopropoxy-5-methyl-4-(4-piperidinyl)phenyl]-N^4-[2-(isopropylsulfonyl)phenyl]-2,4-pyrimidinediamine. The chemical 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.

[00675] In embodiments, a CAR-expressing cell described herein, optinally in combination with an inhibitor of a pro-M2 macrophage molecule, 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).

[00676] In embodiments, a CAR-expressing cell described herein, optionally in combination with an inhibitor of a pro-M2 macrophage molecule, 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 and WO2005/068503. 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. In embodiments the CAR targets mesothelin, e.g., comprises a mesothelin binding domain described herein, e.g., is a CAR of Table 11, e.g., is M5. In embodiments the CAR targets EGFRvIII, e.g., comprises a EGFRvIII binding domain described herein, e.g., is a CAR of Table 30. The structure of BLZ945 is shown below.



[00677] In some embodiments , a CAR-expressing cell described herein, optionally in combination with an inhibitor of a pro-M2 macrophage molecule, 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 some embodiments, a CAR-expressing cell described herein, optionally in combination with an inhibitor of a pro-M2 macrophage molecule, is administered to a subject in combination with an oncolytic virus. In embodiments, the oncolytic virus is Talimogene laherparepvec. In embodiments, the oncolytic virus is engineered to secrete one or more

cytokines, e.g., In embodiments, the oncolytic virus is Ad5-CMV-TNFa; In embodiments, the oncolytic virus is Ad5-CMV-IL2; In embodiments, the oncolytic virus is Ad5-CMV-IFNg; In embodiments, the oncolytic virus is Ad5-CMV-IFNb; or combinations thereof. In embodiments, the oncolytic virus is as described in WO2014/170389, which is incorporated herein by reference in its entirety, and is used in combination with a CAR-expressing cell, e.g., a CAR-expressing cell described herein, e.g., a mesoCAR-expressing cell, e.g., as described herein. In embodiments, the oncolytic virus is described in US2010/0178684 A1, which is incorporated herein by reference in its entirety. In some embodiments, a recombinant oncolytic virus comprises a nucleic acid sequence (e.g., heterologous nucleic acid sequence) encoding an inhibitor of an immune or inflammatory response, e.g., as described in US2010/0178684 A1, incorporated herein by reference in its entirety. In embodiments, the recombinant oncolytic virus, e.g., oncolytic NDV, comprises a pro-apoptotic protein (e.g., apoptin), a cytokine (e.g., GM-CSF, interferon-gamma, interleukin-2 (IL-2), tumor necrosis factor-alpha), an immunoglobulin (e.g., an antibody against ED-B firbonectin), tumor associated antigen, a bispecific adapter protein (e.g., bispecific antibody or antibody fragment directed against NDV HN protein and a T cell co-stimulatory receptor, such as CD3 or CD28; or fusion protein between human IL-2 and single chain antibody directed against NDV HN protein). See, e.g., Zamarin et al. Future Microbiol. 7.3(2012):347-67, incorporated herein by reference in its entirety. In some embodiments, the oncolytic virus is a chimeric oncolytic NDV described in US 8591881 B2, US 2012/0122185 A1, or US 2014/0271677 A1, each of which is incorporated herein by reference in their entireties. In some embodiments, the oncolytic virus comprises a conditionally replicative adenovirus (CRAd), which is designed to replicate exclusively in cancer cells. See, e.g., Alemany et al. Nature Biotechnol. 18(2000):723-27. In some embodiments, an oncolytic adenovirus comprises one described in Table 1 on page 725 of Alemany et al., incorporated herein by reference in its entirety.

Exemplary oncolytic viruses include but are not limited to the following:

Group B Oncolytic Adenovirus (ColoAd1) (PsiOxus Therapeutics Ltd.) (see, e.g., Clinical Trial Identifier: NCT02053220);

ONCOS-102 (previously called CGTG-102), which is an adenovirus comprising granulocyte-macrophage colony stimulating factor (GM-CSF) (Oncos Therapeutics) (see, e.g., Clinical Trial Identifier: NCT01598129);

VCN-01, which is a genetically modified oncolytic human adenovirus encoding human PH20 hyaluronidase (VCN Biosciences, S.L.) (see, e.g., Clinical Trial Identifiers: NCT02045602 and NCT02045589);

Conditionally Replicative Adenovirus ICOVIR-5, which is a virus derived from wild-type human adenovirus serotype 5 (Had5) that has been modified to selectively replicate in cancer cells with a deregulated retinoblastoma/E2F pathway (Institut Català d'Oncologia) (see, e.g., Clinical Trial Identifier: NCT01864759);

Celyvir, which comprises bone marrow-derived autologous mesenchymal stem cells (MSCs) infected with ICOVIR5, an oncolytic adenovirus (Hospital Infantil Universitario Niño Jesús, Madrid, Spain/ Ramon Alemany) (see, e.g., Clinical Trial Identifier: NCT01844661);

CG0070, which is a conditionally replicating oncolytic serotype 5 adenovirus (Ad5) in which human E2F-1 promoter drives expression of the essential E1a viral genes, thereby restricting viral replication and cytotoxicity to Rb pathway-defective tumor cells (Cold Genesys, Inc.) (see, e.g., Clinical Trial Identifier: NCT02143804); or

[00678] DNX-2401 (formerly named Delta-24-RGD), which is an adenovirus that has been engineered to replicate selectively in retinoblastoma (Rb)-pathway deficient cells and to infect cells that express certain RGD-binding integrins more efficiently (Clinica Universidad de Navarra, Universidad de Navarra/ DNAtrix, Inc.) (see, e.g., Clinical Trial Identifier: NCT01956734). In any of the embodiments incorporating an oncolytic virus, in an aspect, the CAR targets mesothelin, e.g., comprises a mesothelin binding domain described herein, e.g., is a CAR of Table 11, e.g., is M5. In any of the embodiments incorporating an oncolytic virus, in an aspect, the CAR targets EGFRvIII, e.g., comprises a EGFRvIII binding domain described herein, e.g., is a CAR of Table 30.

[00679] In some embodiments, a CAR-expressing cell described herein, optionally in combination with an inhibitor of a pro-M2 macrophage molecule, is administered to a subject in combination with human hyaluronidase, e.g., recombinant human hyaluronidase, e.g., is PEGPH20. See e.g., Clinical Trial Id. NCT02715804. In embodiments the CAR targets mesothelin, e.g., comprises a mesothelin binding domain described herein, e.g., is a CAR of Table 11, e.g., is M5. In embodiments the CAR targets EGFRvIII, e.g., comprises a EGFRvIII binding domain described herein, e.g., is a CAR of Table 30.

Pharmaceutical compositions and treatments

[00680] 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.

[00681] 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.

[00682] 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.

[00683] 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 T 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.

[00684] In some embodiments, a dose of CAR cells includes about 10^4 to about 10^9 cells/kg, e.g., about 10^4 to about 10^5 cells/kg, about 10^5 to about 10^6 cells/kg, about 10^6 to about 10^7 cells/kg, about 10^7 to about 10^8 cells/kg, or about 10^8 to about 10^9 cells/kg. In embodiments, the dose of CAR cells comprises about 0.6 x 10^6 cells/kg to about 2 x 10^7 cells/kg. In particular embodiments, a dose of CAR cells includes about 2 x 10^5, 1 x 10^6, 1.1 x 10^6, 2 x 10^6, 3 x 10^6, 3.6 x 10^6, 5 x 10^6, 1 x 10^7, 1.8 x 10^7, 2 x 10^7, 5 x 10^7, 1 x 10^8, 2 x 10^8, 3 x 10^8, or 5 x 10^8 cells/kg. In some embodiments, a dose of CAR cells comprises at least about 1 x 10^6, 1.1 x 10^6, 2 x 10^6, 3.6 x 10^6, 5 x 10^6, 1 x 10^7, 1.8 x 10^7, 2 x 10^7, 5 x 10^7, 1 x 10^8, 2 x 10^8, 3 x 10^8, or 5 x 10^8 cells/kg.

[00685] In some embodiments, a dose of CAR cells comprises about 1 x 10^6, 1.1 x 10^6, 2 x 10^6, 3.6 x 10^6, 5 x 10^6, 1 x 10^7, 1.8 x 10^7, 2 x 10^7, 5 x 10^7, 1 x 10^8, 2 x 10^8, or 5 x 10^8 cells/kg. In some embodiments, a dose of CAR cells comprises at least about 1 x 10^6, 1.1 x 10^6, 2 x 10^6, 3.6 x 10^6, 5 x 10^6, 1 x 10^7, 1.8 x 10^7, 2 x 10^7, 5 x 10^7, 1 x 10^8, 2 x 10^8, or 5 x 10^8 cells/kg. In some embodiments, a dose of CAR cells comprises up to about 1 x 10^6, 1.1 x 10^6, 2 x 10^6, 3.6 x 10^6, 5 x 10^6, 1 x 10^7, 1.8 x 10^7, 2 x 10^7, 5 x 10^7, 1 x 10^8, 2 x 10^8, or 5 x 10^8 cells/kg. In some embodiments, a dose of CAR cells comprises about 1.1 x 10^6 – 1.8 x 10^7 cells/kg. In some embodiments, a dose of CAR cells comprises about 1 x 10^7, 2 x 10^7, 5 x 10^7, 1 x 10^8, 2 x 10^8, 5 x 10^8, 1 x 10^9, 2 x 10^9, or 5 x 10^9 cells. In some embodiments, a dose of CAR cells comprises at least about 1 x 10^7, 2 x 10^7, 5 x 10^7, 1 x 10^8, 2 x 10^8, 5 x 10^8, 1 x 10^9, 2 x 10^9, or 5 x 10^9 cells. In some embodiments, a dose of CAR cells comprises up to about 1 x 10^7, 2 x 10^7, 5 x 10^7, 1 x 10^8, 2 x 10^8, 5 x 10^8, 1 x 10^9, 2 x 10^9, or 5 x 10^9 cells.

[00686] 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).

[00687] In certain aspects, it may be desired to administer activated T cells to a subject and then subsequently redraw blood (or have an apheresis performed), activate T cells therefrom according to the present invention, and reinfuse the patient with these activated and expanded T cells. This process can be carried out multiple times every few weeks. In certain aspects, T cells

can be activated from blood draws of from 10cc to 400cc. In certain aspects, T cells are activated from blood draws of 20cc, 30cc, 40cc, 50cc, 60cc, 70cc, 80cc, 90cc, or 100cc.

[00688] 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 CAR-expressing cell (e.g., T cell or NK cell) compositions of the present invention are administered to a patient by intradermal or subcutaneous injection. In one aspect, the the CAR-expressing cell (e.g., T cell or NK cell) compositions of the present invention are administered by i.v. injection. The compositions of the CAR-expressing cell (e.g., T cell or NK cell) may be injected directly into a tumor, lymph node, or site of infection.

[00689] 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., immune effector cells (e.g., T cells or NK cells). These immune effector cell (e.g., T cell or NK 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-expressing cell (e.g., CAR T cell or CAR-expressing NK 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-expressing cell (e.g., CAR T cell or CAR-expressing NK cell) of the present invention. In an additional aspect, expanded cells are administered before or following surgery.

[00690] 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).

[00691] In one embodiment, the CAR is introduced into immune effector cells (e.g., T cells or NK cells), e.g., using in vitro transcription, and the subject (e.g., human) receives an initial administration of a CAR-expressing cell (e.g., CAR T cell or CAR-expressing NK cell)of the invention, and one or more subsequent administrations of the CAR-expressing cell (e.g., CAR T cell or CAR-expressing NK cell) 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-expressing cell (e.g., CAR T cell or CAR-expressing NK cell)of the invention are administered to the subject (e.g., human) per week, e.g., 2, 3, or 4 administrations of the CAR-expressing cell (e.g., CAR T cell or CAR-expressing NK cell) of the invention are administered per week. In one embodiment, the subject (e.g., human subject) receives more than one administration of the CAR-expressing cell (e.g., CAR T cell or CAR-expressing NK cell)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-expressing cell (e.g., CAR T cell or CAR-expressing NK cell)administrations, and then one or more additional administration of the CAR-expressing cell (e.g., CAR T cell or CAR-expressing NK cell) (e.g., more than one administration of the CAR-expressing cell (e.g., CAR T cell or CAR-expressing NK cell)per week) is administered to the subject. In another embodiment, the subject (e.g., human subject) receives more than one cycle of CAR-expressing cell (e.g., CAR T cell or CAR-expressing NK cell), and the time between each cycle is less than 10, 9, 8, 7, 6, 5, 4, or 3 days. In one embodiment, the CAR-expressing cell (e.g., CAR T cell or CAR-expressing NK cell) are administered every other day for 3 administrations per week. In one embodiment, the CAR-expressing cell (e.g., CAR T cell or CAR-expressing NK cell)of the invention are administered for at least two, three, four, five, six, seven, eight or more weeks.

[00692] In one aspect, CAR-expressing cell (e.g., CAR T cell or CAR-expressing NK cell) (e.g., CD123 CAR-expressing cell) is generated using lentiviral viral vectors, such as lentivirus. CAR-expressing cell (e.g., CAR T cell or CAR-expressing NK cell) generated that way will have stable CAR expression.

[00693] In one aspect, CAR-expressing cells, e.g., CARTs or CAR-expressing NK cells, are generated using a viral vector such as a gammaretroviral vector, e.g., a gammaretroviral

vector described herein. CAR-expressing cells, e.g., CARTs or CAR-expressing NK cells, generated using these vectors can have stable CAR expression.

[00694] In one aspect, the CAR-expressing cell (e.g., CAR T cell or CAR-expressing NK cell) 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 cell (e.g., T cell or NK cell) by electroporation.

[00695] A potential issue that can arise in patients being treated using transiently expressing CAR cell (e.g., CAR T cell or CAR-expressing NK cell) (particularly with murine scFv bearing CARs) is anaphylaxis after multiple treatments.

[00696] 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.

[00697] 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), CAR-expressing cell (e.g., CAR T cell or CAR-expressing NK cell) infusion breaks should not last more than ten to fourteen days.

EXAMPLES

[00698] 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.

[00699] 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.

Example 1: Overcoming the Immunosuppressive Tumor Microenvironment of Hodgkin Lymphoma Using Chimeric Antigen Receptor T Cells

[00700] Despite modern treatment regimens, a subset of patients with Hodgkin lymphoma (HL) succumbs to this disease. In particular, 10-15% of patients with initially localized disease and 20-40% of patients with initially advanced stage disease will eventually relapse. Josting A, Franklin J, May M, Koch P, Beykirch MK, Heinz J, et al. New prognostic score based on treatment outcome of patients with relapsed Hodgkin's lymphoma registered in the database of the German Hodgkin's lymphoma study group. J Clin Oncol. 2002;20:221-30. Furthermore, 10-15% of patients have disease that is refractory to first-line therapy. Santoro A, Bonadonna G, Valagussa P, Zucali R, Viviani S, Villani F, et al. Long-term results of combined chemotherapy-radiotherapy approach in Hodgkin's disease: superiority of ABVD plus radiotherapy versus MOPP plus radiotherapy. J Clin Oncol. 1987;5:27-37. About half of patients relapsing after or refractory to first line therapy (r/r HL) can be successfully salvaged with chemotherapy followed by autologous stem cell transplantation (SCT). However, patients who fail to achieve a PET-negative status after salvage chemotherapy have a particularly poor prognosis and patients with primary refractory disease can expect an overall survival below 50%. Josting A, Franklin J, May M, Koch P, Beykirch MK, Heinz J, et al. New prognostic score based on treatment outcome of patients with relapsed Hodgkin's lymphoma registered in the database of the German Hodgkin's lymphoma study group. J Clin Oncol. 2002;20:221-30; Josting A, Rueffer U, Franklin J, Sieber M, Diehl V, Engert A. Prognostic factors and treatment outcome in primary progressive Hodgkin lymphoma: a report from the German Hodgkin Lymphoma Study Group. Blood. 2000;96:1280-6. Recent developments in biological therapy for r/r HL include the anti-CD30 antibody-drug conjugate brentuximab vedotin (BV). Although BV induces objective responses in 75% of patients with RR-HL after autologous SCT, responses are not durable and the median progression-free survival is 5.6 months. Younes A, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J

Clin Oncol. 2012;30:2183-9. These patients are often young and in dire need of alternative active therapies.

[00701] HL is an immune-responsive disease, as demonstrated by the activity of allogeneic transplantation in a subset of HL patients and, more recently, by the promising clinical results of the infusion of EBV-specific T cells. Bollard CM, Gottschalk S, Torrano V, Diouf O, Ku S, Hazrat Y, et al. Sustained complete responses in patients with lymphoma receiving autologous cytotoxic T lymphocytes targeting Epstein-Barr virus latent membrane proteins. J Clin Oncol. 2014;32:798-808. However, allogeneic transplantation carries a high treatment-related mortality and only approximately 30-40% of HL express EBV antigens. Staal SP, Ambinder R, Beschorner WE, Hayward GS, Mann R. A survey of Epstein-Barr virus DNA in lymphoid tissue. Frequent detection in Hodgkin's disease. American journal of clinical pathology. 1989;91:1-5; Weiss LM, Movahed LA, Warnke RA, Sklar J. Detection of Epstein-Barr viral genomes in Reed-Sternberg cells of Hodgkin's disease. The New England journal of medicine. 1989;320:502-6. Recent clinical trials indicate high response rates upon inhibition of the PD1-PDL1 axis in r/ HL, leading to the FDA approval of nivolumab for this indication. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. The New England journal of medicine. 2015;372:311-9; Moskowitz CH, Ribrag V, Michot J-M, Martinelli G, Zinzani PL, Gutierrez M, et al. PD-1 Blockade with the Monoclonal Antibody Pembrolizumab (MK-3475) in Patients with Classical Hodgkin Lymphoma after Brentuximab Vedotin Failure: Preliminary Results from a Phase 1b Study (KEYNOTE-013). Blood. 2014;124:290. Thus, T cell-based therapeutics have an important and growing role in HL. Chimeric antigen receptor T cells (CART) represent an exciting recent development in cancer immunotherapy. Ruella M, Kalos M. Adoptive immunotherapy for cancer. Immunological reviews. 2014;257:14-38. Our group and others have demonstrated the clinical efficacy of anti-CD19 chimeric antigen receptor redirected T cells (CART19, CTL019) for refractory B cell malignancies. Kalos M, Levine BL, Porter DL, Katz S, Grupp SA, Bagg A, et al. T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia. Science translational medicine. 2011;3:95ra73; Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. The New England journal of medicine. 2014;371:1507-17; Davila ML, Riviere I, Wang X, Bartido

S, Park J, Curran K, et al. Efficacy and Toxicity Management of 19-28z CAR T Cell Therapy in B Cell Acute Lymphoblastic Leukemia. Science translational medicine. 2014;6:224ra25; Turtle CJ, Hanafi LA, Berger C, Gooley TA, Cherian S, Hudecek M, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. The Journal of clinical investigation. 2016; Lee DW, Kochenderfer JN, Stetler-Stevenson M, Cui YK, Delbrook C, Feldman SA, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet. 2015;385:517-28. However, despite the B-cell origin of Hodgkin Reed-Sternberg (HRS) cells, B-cell antigens including CD19 are rarely expressed in HL. Herbst H, Tippelmann G, Anagnostopoulos I, Gerdes J, Schwarting R, Boehm T, et al. Immunoglobulin and T-cell receptor gene rearrangements in Hodgkin's disease and Ki-1-positive anaplastic large cell lymphoma: dissociation between phenotype and genotype. Leukemia research. 1989;13:103-16. While the CD30 antigen is known to be commonly expressed on HRS cells, outcomes of patients treated with anti-CD30 CART have been disappointing, with 1/8 complete responses (CR) and 4/8 stable disease (SD) and 3/8 progressive disease (PD) in r/r HL patients. Savoldo B, Rooney CM, Di Stasi A, Abken H, Hombach A, Foster AE, et al. Epstein Barr virus specific cytotoxic T lymphocytes expressing the anti-CD30zeta artificial chimeric T-cell receptor for immunotherapy of Hodgkin disease. Blood. 2007;110:2620-30; Di Stasi A, De Angelis B, Rooney CM, Zhang L, Mahendravada A, Foster AE, et al. T lymphocytes coexpressing CCR4 and a chimeric antigen receptor targeting CD30 have improved homing and antitumor activity in a Hodgkin tumor model. Blood. 2009;113:6392-402; Ramos CA, Ballard B, Liu E, Dakhova O, Mei Z, Liu H, et al. Chimeric T Cells for Therapy of CD30+ Hodgkin and Non-Hodgkin Lymphomas. Blood. 2015;126:185-. In HL the malignant cells represent only approximately 1-2% of cellularity, with the majority comprised of infiltrating immune cells (macrophages and myeloid-derived suppressive cells, basophils, mast cells, eosinophils, B and T lymphocytes, stromal cells and fibroblasts). The TME and in particular tumor-associated macrophages (TAM) and/or myeloid derived suppressor cells (MDSCs) have a key role in promoting tumor growth while also inhibiting the anti-tumor immune response. Steidl C, Connors JM, Gascoyne RD. Molecular pathogenesis of Hodgkin's lymphoma: increasing evidence of the importance of the microenvironment. J Clin Oncol. 2011;29:1812-26; Steidl C, Lee T, Shah SP, Farinha P, Han G, Nayar T, et al. Tumor-associated macrophages and survival in classic Hodgkin's lymphoma. The New England journal of medicine. 2010;362:875-85; Sanchez-Aguilera A, Montalban C, de la Cueva P, Sanchez-Verde L, Morente MM, Garcia-Cosio M, et al. Tumor microenvironment and mitotic checkpoint are key factors in the outcome of classic Hodgkin lymphoma. Blood. 2006;108:662-

8; Devilard E, Bertucci F, Trempat P, Bouabdallah R, Loriod B, Giaconia A, et al. Gene expression profiling defines molecular subtypes of classical Hodgkin's disease. Oncogene. 2002;21:3095-102; Mizuno H, Nakayama T, Miyata Y, Saito S, Nishiwaki S, Nakao N, et al. Mast cells promote the growth of Hodgkin's lymphoma cell tumor by modifying the tumor microenvironment that can be perturbed by bortezomib. Leukemia. 2012;26:2269-76; Huber S, Hoffmann R, Muskens F, Voehringer D. Alternatively activated macrophages inhibit T-cell proliferation by Stat6-dependent expression of PD-L2. Blood. 2010;116:3311-20. Thus, HL represents a unique opportunity to study the impact of the TME on immunotherapy. The development of an approach that could target the malignant cells as well as the supportive TME would likely represent an important advance in the field of CART immunotherapy, by providing robust stimulation of the CAR T cells while avoiding T cell inhibition. In this context we studied CD123, the α chain of the receptor for interleukin-3 (IL-3), whose expression has been previously described on Hodgkin Reed Sternberg (HRS) cells. Fromm JR. Flow cytometric analysis of CD123 is useful for immunophenotyping classical Hodgkin lymphoma. Cytometry B Clin Cytom. 2011;80:91-9; Liu K, Zhu M, Huang Y, Wei S, Xie J, Xiao Y. CD123 and its potential clinical application in leukemias. Life sciences. 2015;122:59-64; Hassanein NM, Alcancia F, Perkinson KR, Buckley PJ, Lagoo AS. Distinct expression patterns of CD123 and CD34 on normal bone marrow B-cell precursors ("hematogones") and B lymphoblastic leukemia blasts. American journal of clinical pathology. 2009;132:573-80; Djokic M, Bjorklund E, Blennow E, Mazur J, Soderhall S, Porwit A. Overexpression of CD123 correlates with the hyperdiploid genotype in acute lymphoblastic leukemia. Haematologica. 2009;94:1016-9; Aldinucci D, Poletto D, Gloghini A, Nanni P, Degan M, Perin T, et al. Expression of functional interleukin-3 receptors on Hodgkin and Reed-Sternberg cells. The American journal of pathology. 2002;160:585-96. In addition, in vitro data show that IL-3 rescues HL cells from apoptosis and promotes HL cell line growth. Aldinucci D, Olivo K, Lorenzon D, Poletto D, Gloghini A, Carbone A, et al. The role of interleukin-3 in classical Hodgkin's disease. Leukemia & lymphoma. 2005;46:303-11. Furthermore, since CD123 is expressed on myeloid cells, including macrophages, eosinophils, basophils and mast cells, we hypothesized that CD123 would be expressed extensively within HL tumor masses on both the malignant cells and the supportive TME. Pollard JW. Trophic macrophages in development and disease. Nat Rev Immunol. 2009;9:259-70.

[00702] The objective of this Example was therefore to develop an anti-HL CAR T cell immunotherapy that would also be able to overcome the immunosuppression of the HL microenvironment. We confirmed the presence of CD123 on HRS cells and found that many

immune cells in the HL TME, in particular immunosuppressive M2-type tumor-associated macrophages, express CD123. We previously developed anti-CD123 CAR T cells for the treatment of AML (Gill S, Tasian SK, Ruella M, Shestova O, Li Y, Porter DL, et al. Preclinical targeting of human acute myeloid leukemia and myeloablation using chimeric antigen receptor-modified T cells. Blood. 2014;123:2343-54) and we now find that CART123 cells can eliminate disseminated HL tumor xenografts leading to durable remissions and the formation of immune memory. Furthermore, through co-targeting of immunosuppressive CD123-expressing tumor-associated macrophages, CART123 (unlike CART19) are resistant to microenvironmental immunosuppression.

[00703] Materials and Methods

[00704] **Cell lines and primary samples.** Cell lines were originally obtained from ATCC (Manassas, VA) (K-562) or DSMZ (Braunschweig, Germany) (MOLM-14 and NALM-6). All cell lines were tested for the presence of mycoplasma contamination (MycoAlert™ Mycoplasma Detection Kit, LT07-318, Lonza, Basel, Switzerland). For some experiments, cell lines were transduced with luciferase (click-beetle green) or eGFP and then sorted to obtain a >99% positive population. MOLM-14 and K562 were used as controls as indicated in the relevant figures. The cell lines were maintained in culture with RPMI media 1640 (Gibco, 11875-085, LifeTechnologies, Grand Island, NY) supplemented with 10% fetal bovine serum (FBS, Gemini, 100-106, West Sacramento, CA), and 50 UI/ml penicillin/streptomycin (Gibco, LifeTechnologies,15070-063). For all functional studies, primary cells were thawed at least 12 hours before experiment and rested at 37°C. De-identified formalin-fixed primary human HL specimens were obtained from the clinical practices of University of Pennsylvania/Children's Hospital of Philadelphia under an Institutional Review Board (IRB)-protocol.

[00705] **Immunohistochemistry and immunofluorescence.** For formalin fixed paraffin embedded tissues immuno-histochemical (IHC) staining was performed on a Leica Bond-III instrument (Leica Biosystems, Buffalo Grove, IL, USA) using the Bond Polymer Refine Detection System. Antibodies against CD30, CD123 were used undiluted. Heat-induced epitope retrieval was done for 20 minutes with ER2 solution (Leica Microsystems, AR9640). Images were digitally acquired using the Aperio ScanScope™ (Leica Biosystems).

[00706] **RT-PCR.** HL and control cell lines were screened by RT-PCR analysis for CD123 (AB, Hs0060814) mRNA expression. RNA was extracted with RNAqueos-4PCR Kit (Ambion, LifeTechnologies, AM-1914) and cDNA was synthesized with iScript Reverse Transcription Supermix for RT-qPCR (BioRad, 170-8841). The relative target cDNA copies were quantified by relative qPCR (qPCR) with ABI TaqMan specific primers and probe set; TaqMan GUSB primers (AB, Hs00939627) and probe set were used for normalization.

[00707] **Multiparametric flow cytometry**. Flow cytometry was performed as previously described. Kenderian SS, Ruella M, Shestova O, Klichinsky M, Aikawa V, Morrissette JJ, et al. CD33 Specific Chimeric Antigen Receptor T Cells Exhibit Potent Preclinical Activity against Human Acute Myeloid Leukemia. Leukemia. 2015. Anti-human antibodies were purchased from Biolegend, eBioscience, or Becton Dickinson. For cell number quantitation, Countbright (Invitrogen) beads were used according to the manufacturer's instructions. In all analyses, the population of interest was gated based on forward vs. side scatter characteristics followed by singlet gating, and live cells were gated using Live Dead Fixable Aqua (Invitrogen). Time gating was included for quality control. Detection of CAR123 was performed using goat-anti-mouse antibody (Jackson Laboratories) or CD123-Fc/His (Sino Biologicals) and anti-His-APC (R&D) or PE (AbCam) or directly PE-conjugated CD123 protein. Flow cytometry was performed on a four-laser Fortessa-LSR II cytometer (Becton-Dickinson) and analyzed with FlowJo X 10.0.7r2 (Tree Star).

[00708] **Human macrophage differentiation.** Human macrophages (M0) were generated by differentiating positively selected CD14+ normal donor monocytes (Human CD14 MicroBeads, Miltenyi Biotec) for 7 days in X-VIVO 10 (Lonza) supplemented with 5% GemCell human serum AB (Gemini BioProducts), 1x Glutamax (Gibco), and penicillin/streptomycin (Lonza). Macrophages were polarized to M1 by adding 20ng/mL human IFNγ (Peprotech) and 100ng/mL LPS (LPS-EK, InvivoGen) to the differentiation media for an additional 24 hours. Macrophages were polarized to M2 by adding either 20ng/mL human IL-4, IL-10, or IL-13 (Peprotech) to the differentiation media for an additional 24 hours. The effect of Hodgkin lymphoma cells on macrophage phenotype was assessed by co-culturing M0 human macrophages with HDLM-2 cells at a 1:1 effector to target ratio for 5 days in RPMI media 1640 (Gibco, 11875-085, LifeTechnologies, Grand Island, NY) supplemented with 10%

fetal bovine serum (FBS, Gemini, 100-106, West Sacramento, CA), and 50 UI/ml penicillin/streptomycin (Gibco, LifeTechnologies,15070-063).

[00709] **Generation of CAR constructs and CAR T cells.** The 2nd generation anti-CD123 chimeric antigen receptor (CAR123) features an anti-CD123 scFv (clone 32716), CD8 hinge, 4-1BB costimulatory domain and CD3-ζ signaling domain. Gill S, Tasian SK, Ruella M, Shestova O, Li Y, Porter DL, et al. Preclinical targeting of human acute myeloid leukemia and myeloablation using chimeric antigen receptor-modified T cells. Blood. 2014;123:2343-54. This construct is currently used in a clinical trial for acute myeloid leukemia at the University of Pennsylvania (NCT02623582). The murine anti-CD19 chimeric antigen receptor (CD8 hinge, 4-1BB co-stimulatory domain and CD3 zeta signaling domain) was generated as previously described. Milone MC, Fish JD, Carpenito C, Carroll RG, Binder GK, Teachey D, et al. Chimeric receptors containing CD137 signal transduction domains mediate enhanced survival of T cells and increased antileukemic efficacy in vivo. Molecular therapy: the journal of the American Society of Gene Therapy. 2009;17:1453-64; Imai C, Mihara K, Andreansky M, Nicholson IC, Pui CH, Geiger TL, et al. Chimeric receptors with 4-1BB signaling capacity provoke potent cytotoxicity against acute lymphoblastic leukemia. Leukemia. 2004;18:676-84. This is the same construct currently used in the CTL019 clinical trials at the University of Pennsylvania. Production of CAR-expressing T cells was performed as previously described. Gill S, Tasian SK, Ruella M, Shestova O, Li Y, Porter DL, et al. Preclinical targeting of human acute myeloid leukemia and myeloablation using chimeric antigen receptor-modified T cells. Blood. 2014;123:2343-54. Normal donor CD4 and CD8 T cells or PB mononuclear cells (PBMC) were obtained from the Human Immunology Core of the University of Pennsylvania. Prior to all experiments, T cells were thawed and rested overnight at 37° C.

[00710] **In vitro T-cell effector function assays.** Degranulation, CFSE proliferation, cytotoxicity assays and cytokine measurements were performed as previously described. Kalos M, Levine BL, Porter DL, Katz S, Grupp SA, Bagg A, et al. T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia. Science translational medicine. 2011;3:95ra73; Gill S, Tasian SK, Ruella M, Shestova O, Li Y, Porter DL, et al. Preclinical targeting of human acute myeloid leukemia and myeloablation using chimeric antigen receptor-modified T cells. Blood. 2014;123:2343-54; Ruella M, Kenderian SS, Shestova O, Fraietta JA, Qayyum S, Zhang Q, et al. The Addition of

the BTK inhibitor Ibrutinib to Anti-CD19 Chimeric Antigen Receptor T Cells (CART19) Improves Responses against Mantle Cell Lymphoma. Clinical cancer research : an official journal of the American Association for Cancer Research. 2016. Phase contrast images of human macrophage and T cell co-culture (at 24 hours) were generated using the 20x lens on a Nikon Eclipse Ti-S microscope (Nikon Instruments, Inc.)

[00711] **Animal experiments.** In vivo experiments were performed as previously described. Kenderian SS, Ruella M, Shestova O, Klichinsky M, Aikawa V, Morrissette JJ, et al. CD33 Specific Chimeric Antigen Receptor T Cells Exhibit Potent Preclinical Activity against Human Acute Myeloid Leukemia. Leukemia. 2015. Schemas of the utilized xenograft models are discussed in details in the relevant figures. NOD-SCID gamma chain deficient (NSG) mice originally obtained from Jackson Laboratories were purchased from the Stem Cell and Xenograft Core of the University of Pennsylvania. Cells (HL cell lines or T cells) were injected in 100-200 ul of PBS at the indicated concentration into the tail veins of mice. Bioluminescent imaging was performed using a Xenogen IVIS-200 Spectrum camera and analyzed with LivingImage software v. 4.3.1 (Caliper LifeSciencies). Animals were euthanized at the end of the experiment or when they met pre-specified endpoints according to the IACUC protocols. **Study approval**. Animal experiments were performed according a protocol (#803230) approved by the Institutional Animal Care and Use Committee (IACUC) that adheres to the NIH Guide for the Care and Use of Laboratory Animals.

[00712] **Statistical Analysis.** All statistics were performed as indicated using GraphPad Prism 6 for Windows, version 6.05 (La Jolla, CA). Student's t-test was used to compare two groups; in analysis where multiple groups were compared, one-way analysis of variance (ANOVA) was performed with Holm-Sidak correction for multiple comparisons. When multiple groups at multiple time points/ratios were compared, the Student's t-test or ANOVA for each time points/ratios was used. Survival curves were compared using the log-rank test. In the figures asterisks are used to represent p-values (*=<0.05, **=<0.01, ***=<0.001, ****=<0.0001) and "ns" means "not significant" (p>0.05).

[00713] Results

[00714] The IL-3 receptor α, CD123, is expressed in Hodgkin Lymphoma cells and in tumor-associated macrophages

[00715] We sought to define a tumor-associated antigen expressed in the HRS but also on the microenvironment. For this purpose we evaluated the expression of CD123, the IL-3 receptor α, on histological specimens from patients with HL. As expected, in 10/10 patients the HRS cells were positive for the hallmark of HL, i.e. CD30; in 5/10 patients we also found CD123 on the HRS cells. Whereas CD30 was sparsely distributed on infiltrating immune cells, CD123 was highly expressed on the TME, in particular we found that TAM expressed CD123, as shown by dual-color immunofluorescence (**Figure 1A**). To define an appropriate human tumor model for further study we evaluated four HL cell lines (HDLM-2, KM-H2, SUP-HD1, and L-428) and found high-level expression at the mRNA and protein level (**Figure 1B and C**).

[00716] HL cells polarize normal macrophages to a M2-like phenotype and function via IL-13

[00717] Since TAMs have a relevant role in HL pathogenesis and prognosis (Steidl C, Lee T, Shah SP, Farinha P, Han G, Nayar T, et al. Tumor-associated macrophages and survival in classic Hodgkin's lymphoma. The New England journal of medicine. 2010;362:875-85), we sought to discover whether HL cells can directly mediate conversion of monocytes to an immunosuppressive phenotype. Human normal donor macrophages differentiated from peripheral blood monocytes were co-cultured with HDLM-2 cells or IL-4 (M2 positive control) or a control acute lymphoblastic leukemia cell line (NALM-6). After 24 hours of co-culture macrophage phenotype was analyzed by flow cytometry. As shown in **Figure 2 A**, HDLM-2 primed macrophages showed a M2-like phenotype, with expression of CD206 and CD163 similar to that of IL4 primed macrophages. Gordon S. Alternative activation of macrophages. Nat Rev Immunol. 2003;3:23-35; Murray PJ, Allen JE, Biswas SK, Fisher EA, Gilroy DW, Goerdt S, et al. Macrophage activation and polarization: nomenclature and experimental guidelines. Immunity. 2014;41:14-20; Qian BZ, Pollard JW. Macrophage diversity enhances tumor progression and metastasis. Cell. 2010;141:39-51; Roszer T. Understanding the Mysterious M2 Macrophage through Activation Markers and Effector Mechanisms. Mediators of inflammation. 2015;2015:816460; Georgoudaki AM, Prokopec KE, Boura VF, Hellqvist E, Sohn S, Ostling J, et al. Reprogramming Tumor-Associated Macrophages by Antibody Targeting Inhibits Cancer Progression and Metastasis. Cell reports. 2016;15:2000-11. As a control, macrophages co-cultured with a non-HL cell line, NALM-6, showed a non-M2-like

phenotype. Importantly, CD123 expression was high in both M2 and in HL-polarized macrophages (**Figure 2B**).

[00718] In order to test the function of the phenotypically-defined immunosuppressive macrophages we used a model where human CAR T cells were co-cultured under M0 (Human Serum, GM- or M-CSF), M1 (IFNγ/LPS) or M2 (IL-4) polarizing conditions, or with HL-polarized macrophages as a model of tumor-associated macrophages (TAM). In this experiment we used the gold-standard anti-CD19 CAR T cells as the "responder" cells and the CD19+ B leukemia cell line NALM-6 as the "stimulator" cells. Milone MC, Fish JD, Carpenito C, Carroll RG, Binder GK, Teachey D, et al. Chimeric receptors containing CD137 signal transduction domains mediate enhanced survival of T cells and increased antileukemic efficacy in vivo. Molecular therapy : the journal of the American Society of Gene Therapy. 2009;17:1453-64. As expected CART19 strongly proliferated in the presence of the target cell line, but this proliferation was inhibited in the presence of M2 macrophages or HL-polarized macrophages (**Figure 2C-E**). In order to probe the mechanism of macrophage polarization by HL cells, we collected the supernatant of HDLM-2 (or a control non-HL cell line, K562), co-cultured with human macrophages and analyzed the presence of 30 different cytokines by Luminex assay. IL-13 was the most overexpressed cytokine (**Figure 2F**). By blocking IL-13 signaling using a specific antibody we found partial reversal of immunosuppressive function of HL-primed macrophages (**Figure 2G**) and reduction in the expression of the inhibitory receptor ligand PDL-1. (**Figure 2H**).

[00719] Anti-CD123 chimeric antigen receptor T cells kill HL cells in vitro and in vivo

[00720] Having demonstrated the presence of CD123 in the HRS cells, we sought to demonstrate the extent to which anti-CD123 CAR T cells (CART123) can recognize HL cells, as measured by antigen-dependent CART proliferation, cytokine production and specific tumor lysis. We used the HDLM2 cell line as a model, given that it is impossible to propagate primary HL in culture and due to the lack of reliable primary HL xenograft models. CD123-expressing AML was used a positive control in these experiments, as we had previously demonstrated its sensitivity to CART123. In vitro, CART123 demonstrated specific CD107a degranulation and production of intracellular cytokines (IFNγ, IL-2, TNFα) when co-cultured with HL cells for 4-6 hours (**Figure 3A**). At 24 hours a potent cytotoxicity against HL cells is exerted by CART123 but not control untransduced T cells (UTD) (**Figure 3B**) and complete eradication of

HL cells by day 4 is associated with massive T cell proliferation (day 20) (**Figure 3C**). CART123 when co-cultured with HL cells (HDLM-2 or KM-H2) proliferate as demonstrated by absolute T cell number after 5 days (**Figure 3D**) and CFSE dilution (**Figure 3E**). Importantly, CART123 cells secrete effector cytokines like GM-CSF, IFNg, MIP1b and TNFa in the presence of HL cells (**Figure 3F**). In summary, CART123 cells were exquisitely responsive in vitro to malignant HRS cells despite the fact that both HRS and TAM express PDL1 and produce immunosuppressive cytokines by HRS.

[00721] We then developed a novel rigorous xenograft model of systemically advanced HL model by injecting $1x10^6$ luciferase+ HDLM-2 cells intravenously on day 0 in NSG mice (**Figure 4A**). Serial bioluminescent imaging (BLI) demonstrated tumor engraftment by day 7, which was followed by gradual increase in tumor burden over approximately 6 weeks, reproducing the indolent nature of the human disease. At day 42 when the tumor burden was 20-fold higher than baseline, mice were treated with $1.5x10^6$ CART123 cells or control T cells. CART123 induced complete and durable eradication of disseminated tumor within 14 days, leading to 100% relapse-free and 100% overall survival at 6 months (**Figure 4 B and C**). Mice were followed up for almost 1 year and no relapses were observed in CART123-treated mice while mice treated with control T cells had a median survival of 128 days (p=0.009). Tumor elimination was associated with extensive CAR T cell expansion in the peripheral blood, including both CD8+ and CD4+ cells as detected by flow cytometry in serial peripheral blood analyses, as seen in clinical studies of anti-CD19 CAR T cells (**Figure 4D**).

[00722] CART123 establish long-term immunological memory in mice with HL

[00723] Long-term persistence and T cell memory play an important role in immunosurveillance and prevention of relapse. In order to demonstrate the formation of immunological memory, at a long follow up time (day 250) CART123 treated mice were re-challenged with the HDLM-2 HL cells (see experiment schema **Figure 5 A**). Interestingly, in previously CART123 treated mice the tumor was rejected (**Figure 5 B**), associated with a re-expansion of previously undetectable CART123 cells in the peripheral blood (~10 months after T cell injection) (**Figure 5 C**). In contrast, in control mice HL cells engrafted and led to the death of these mice (**Figure 5D**).

[00724] CART123 are resistant to the inhibition of M2-macrophages

[00725] Lastly, as we demonstrated that CAR T cells can be inhibited by M2 and HL-polarized macrophages and that these macrophages are CD123-positive, we sought to understand if CART123 were also susceptible to macrophage inhibition, or conversely, due to the expression of CD123 in HL-macrophages, they would receive additional stimulation.

[00726] We generated immunosuppressive M2 macrophages using either IL-4, or exposure to HDLM-2 cells. Using the pre-established model of CART19 model in B-acute lymphoblastic leukemia we showed that M2 TAMs can potently inhibit CART19 proliferation following CAR stimulation at day 5 but, in stark contrast, CART123 were not affected (**Figure 6 A**). Importantly, CART123 actively recognize M2 macrophages and form aggregates around them at an early time point (24 hours) and exert significant cytotoxicity against TAMs by day 5, thereby overcoming TAM-mediated inhibition (**Figure 6 B**). HL-macrophages were able to inhibit cytokine production by CART19 but not by CART123 (**Figure 6 C**).

[00727] Discussion

We have previously described the activity of CART123 in human acute myeloid leukemia. Gill S, Tasian SK, Ruella M, Shestova O, Li Y, Porter DL, et al. Preclinical targeting of human acute myeloid leukemia and myeloablation using chimeric antigen receptor-modified T cells. Blood. 2014;123:2343-54. Here, we confirm previous findings that HRS cells and HL cell lines express CD123 (Fromm JR. Flow cytometric analysis of CD123 is useful for immunophenotyping classical Hodgkin lymphoma. Cytometry B Clin Cytom. 2011;80:91-9; Aldinucci D, Poletto D, Gloghini A, Nanni P, Degan M, Perin T, et al. Expression of functional interleukin-3 receptors on Hodgkin and Reed-Sternberg cells. The American journal of pathology. 2002;160:585-96) and show that CART123 specifically degranulate, proliferate, produce cytokines and kill HL cells in vitro. In vivo, we show that human CD123-redirected T cells display potent therapeutic activity against disseminated HL, persist long-term after eradication of disease and are capable of mounting a robust recall response to tumor challenge. To our knowledge, this is the first xenograft model of disseminated Hodgkin lymphoma, and the nodal localization and indolent progression recapitulate some aspects of the clinical disease. The xenograft system however does not permit an evaluation of the role of the tumor microenvironment (TME), since the murine NSG recipients lack lymphocytes and no human immune cells are transferred along with the HL cell line. Therefore, to investigate the role of the TME in resistance to CAR T cells we turned to an in vitro system.

[00728] We showed that HL cell lines produce several immunosuppressive cytokines, with the most highly elevated being interleukin-13. IL-13 has previously been reported to play a role in autocrine growth stimulation of HRS cells (Trieu Y, Wen XY, Skinnider BF, Bray MR, Li Z, Claudio JO, et al. Soluble interleukin-13Ralpha2 decoy receptor inhibits Hodgkin's lymphoma growth in vitro and in vivo. Cancer research. 2004;64:3271-5; Skinnider BF, Kapp U, Mak TW. The role of interleukin 13 in classical Hodgkin lymphoma. Leukemia & lymphoma. 2002;43:1203-10) and has been postulated to mediate recruitment of immune cells into the HL TME. We showed that exposure to HL polarizes macrophages towards an alternatively-activated "M2" phenotype with up-regulation of PD-L1 and a resultant immunosuppressive effect on T cells, in particular CAR T cells. This effect manifested as reduction of T cell proliferation and cytokine production. We used anti-CD19 CAR T cells (CART19) stimulated by the ALL cell line NALM-6 as a "gold standard". Milone MC, Fish JD, Carpenito C, Carroll RG, Binder GK, Teachey D, et al. Chimeric receptors containing CD137 signal transduction domains mediate enhanced survival of T cells and increased antileukemic efficacy in vivo. Molecular therapy : the journal of the American Society of Gene Therapy. 2009;17:1453-64; Brentjens RJ, Latouche JB, Santos E, Marti F, Gong MC, Lyddane C, et al. Eradication of systemic B-cell tumors by genetically targeted human T lymphocytes co-stimulated by CD80 and interleukin-15. Nature medicine. 2003;9:279-86. We found that HL-exposed macrophages, as a model of tumor-associated macrophages (TAM) are able to inhibit CART19. Although CD19 is not expressed on HL and CART19 therapy is not expected to have activity in HL, there is literature on clonotypic CD19+ B cells in HL and some groups including ours have attempted B cell-directed agents as therapy for HL (Younes A, Oki Y, McLaughlin P, Copeland AR, Goy A, Pro B, et al. Phase 2 study of rituximab plus ABVD in patients with newly diagnosed classical Hodgkin lymphoma. Blood. 2012;119:4123-8; Kasamon YL, Jacene HA, Gocke CD, Swinnen LJ, Gladstone DE, Perkins B, et al. Phase 2 study of rituximab-ABVD in classical Hodgkin lymphoma. Blood. 2012;119:4129-32) and a trial run at our institution evaluating CAR T cells against CD19 for HL (NCT02277522). More importantly, if our findings are generalizable to TAM in other malignancies, TAM may have a similar effect on CART19 in bone fide CD19-expressing B cell malignancies.

[00729] In this context, we sought to develop a relevant CART cell modality for HL. The most widely expressed HL antigen, CD30, is not expressed on most other cells in the TME and

specifically not on TAM. Following reports that CD123 is expressed on HRS cells we analyzed a series of clinical specimens from the pathology department of the University of Pennsylvania and observed that CD123 is present on the HRS cells in approximately 50% of patients. Equally importantly, we noted CD123 to be present on TAM. Since elevated numbers of CD68+ macrophages in the diagnostic specimens of patients with HL confer an unfavorable prognosis, we hypothesized that a modality that was able to ablate both TAM and HRS cells would represent a significant advance in the growing armamentarium against HL. Steidl C, Lee T, Shah SP, Farinha P, Han G, Nayar T, et al. Tumor-associated macrophages and survival in classic Hodgkin's lymphoma. The New England journal of medicine. 2010;362:875-85. Notably, recent advances in HL therapy include the PD1 antagonist nivolumab and although the presumed mechanism of action is reversal of inhibitory signaling from PD-L1 that is expressed on the HRS cells, the importance of PD-L1 expression on TAM in the response to nivolumab has not yet been investigated to our knowledge. The finding that TAM express CD123 and are targetable by CART123 adds to the growing body of literature on depletion of TAM using monoclonal antibodies directed against CSF1R. Pyonteck SM, Akkari L, Schuhmacher AJ, Bowman RL, Sevenich L, Quail DF, et al. CSF-1R inhibition alters macrophage polarization and blocks glioma progression. Nature medicine. 2013;19:1264-72.

[00730] Thus, in this work we highlight a lymphoma – macrophage – T cell axis that may be particularly vulnerable to anti-CD123 CAR T cells. Our previous publication on the anti-leukemia efficacy of anti-CD123 CAR T cells (CART123) also highlighted the potential for myeloablation resulting from targeting CD123 on normal hematopoieitic precursors. Thus, our current clinical trial utilizes short-acting mRNA-electroporated CAR T cells rather than permanently modified lentivirally transduced CAR T cells. (NCT02623582). Notably, there are currently 13 trials investigating CD123 as a target for hematological cancers using CAR T cells, bi-specific antibodies, monoclonal antibodies or antibody-drug conjugates. E.g., Liu K, Zhu M, Huang Y, Wei S, Xie J, Xiao Y. CD123 and its potential clinical application in leukemias. Life sciences. 2015;122:59-64; Gill S, Tasian SK, Ruella M, Shestova O, Li Y, Porter DL, et al. Preclinical targeting of human acute myeloid leukemia and myeloablation using chimeric antigen receptor-modified T cells. Blood. 2014;123:2343-54; Angelot-Delettre F, Roggy A, Frankel AE, Lamarthee B, Seilles E, Biichle S, et al. In vivo and in vitro sensitivity of blastic plasmacytoid dendritic cell neoplasm to SL-401, an interleukin-3 receptor

targeted biologic agent. Haematologica. 2015;100:223-30; Cohen KA, Liu TF, Cline JM, Wagner JD, Hall PD, Frankel AE. Safety evaluation of DT388IL3, a diphtheria toxin/interleukin 3 fusion protein, in the cynomolgus monkey. Cancer immunology, immunotherapy : CII. 2005;54:799-806; He SZ, Busfield S, Ritchie DS, Hertzberg MS, Durrant S, Lewis ID, et al. A Phase 1 study of the safety, pharmacokinetics and anti-leukemic activity of the anti-CD123 monoclonal antibody CSL360 in relapsed, refractory or high-risk acute myeloid leukemia. Leukemia & lymphoma. 2014:1-10; Zereshkian A, Leyton JV, Cai Z, Bergstrom D, Weinfeld M, Reilly RM. The human polynucleotide kinase/phosphatase (hPNKP) inhibitor A12B4C3 radiosensitizes human myeloid leukemia cells to Auger electron-emitting anti-CD123 (1)(1)(1)In-NLS-7G3 radioimmunoconjugates. Nuclear medicine and biology. 2014;41:377-83; Kuo SR, Wong L, Liu JS. Engineering a CD123xCD3 bispecific scFv immunofusion for the treatment of leukemia and elimination of leukemia stem cells. Protein engineering, design & selection : PEDS. 2012;25:561-9; Chichili GR, Huang L, Li H, Burke S, He L, Tang Q, et al. A CD3xCD123 bispecific DART for redirecting host T cells to myelogenous leukemia: Preclinical activity and safety in nonhuman primates. Science translational medicine. 2015;7:289ra82; Fan D, Li Z, Zhang X, Yang Y, Yuan X, Zhang X, et al. AntiCD3Fv fused to human interleukin-3 deletion variant redirected T cells against human acute myeloid leukemic stem cells. Journal of hematology & oncology. 2015;8:18; Mardiros A, Dos Santos C, McDonald T, Brown CE, Wang X, Budde LE, et al. T cells expressing CD123-specific chimeric antigen receptors exhibit specific cytolytic effector functions and antitumor effects against human acute myeloid leukemia. Blood. 2013;122:3138-48; Tettamanti S, Magnani CF, Biondi A, Biagi E. Acute myeloid leukemia and novel biological treatments: monoclonal antibodies and cell-based gene-modified immune effectors. Immunology letters. 2013;155:43-6. A recent case report described one patient treated with lentivirally-transduced CART123 showing the feasibility of this approach, supported by preliminary results from other CD123-targeted agents. Luo Y, Chang L-J, Hu Y, Dong L, Wei G, Huang H. First-in-Man CD123-Specific Chimeric Antigen Receptor-Modified T Cells for the Treatment of Refractory Acute Myeloid Leukemia. Blood. 2015;126:3778-; Frankel AE, Woo JH, Ahn C, Pemmaraju N, Medeiros BC, Carraway HE, et al. Activity of SL-401, a targeted therapy directed to interleukin-3 receptor, in blastic plasmacytoid dendritic cell neoplasm patients. Blood. 2014;124:385-92; He SZ, Busfield S, Ritchie DS, Hertzberg MS, Durrant S, Lewis ID, et al. A

Phase 1 study of the safety, pharmacokinetics and anti-leukemic activity of the anti-CD123 monoclonal antibody CSL360 in relapsed, refractory or high-risk acute myeloid leukemia. Leukemia & lymphoma. 2015;56:1406-15.

[00731] In summary, we showed that human CD123-redirected T cells display potent therapeutic activity against disseminated HL. Importantly CART123 can target both the HRS and the TAM. The observation that CART123 lead to myelosuppression in preclinical models, suggests that our findings could be translated to treat patients with refractory HL with a combined "short-acting" RNA-CAR123 or with depletable CART123 T cells followed by rescue autologous bone marrow transplantation. As well, this Example demonstrates that combination therapy of an IL-13 inhibitor together with CART cell therapy, for example, CART cells targeting a solid tumor, is a viable strategy for the treatment of solid tumors

EQUIVALENTS

[00732] 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.

Claims

1. A CAR therapy comprising a cell, e.g., a population of immune effector cells, comprising, e.g., expressing, a chimeric antigen receptor (CAR) for use in combination with an inhibitor of a pro-M2 macrophage molecule in treating a subject having a disease associated with expression of a tumor antigen, wherein the CAR comprises a tumor antigen binding domain, a transmembrane domain, and an intracellular signaling domain, and wherein the inhibitor of a pro-M2 macrophage molecule is chosen from: a modulator of myeloid-derived suppressor cells (MDSCs), a CSF-1 inhibitor, a CSF1R inhibitor, an IL-13 inhibitor, an IL-4 inhibitor, an IL-13Rα1 inhibitor, an IL-4Rα inhibitor, an IL-10 inhibitor, a TGF beta inhibitor, a JAK2 inhibitor, a cell surface molecule, an iron oxide, a small molecule inhibitor, a PI3K inhibitor, an HDAC inhibitor, an inhibitor of the glycolytic pathway, a mitochondria-targeted antioxidant, or combinations thereof.

2. An inhibitor of a pro-M2 macrophage molecule for use in combination with a CAR therapy comprising a cell, e.g., a population of immune effector cells, comprising, e.g., expressing, a chimeric antigen receptor (CAR) in treating a subject having a disease associated with expression of a tumor antigen, wherein the CAR comprises a tumor antigen binding domain, a transmembrane domain, and an intracellular signaling domain, and wherein the inhibitor of a pro-M2 macrophage molecule is chosen from: a modulator of myeloid-derived suppressor cells (MDSCs), a CSF-1 inhibitor, a CSF1R inhibitor, an IL-13 inhibitor, an IL-4 inhibitor, an IL-13Rα1 inhibitor, an IL-4Rα inhibitor, an IL-10 inhibitor, a TGF beta inhibitor, a JAK2 inhibitor, a cell surface molecule, an iron oxide, a small molecule inhibitor, a PI3K inhibitor, an HDAC inhibitor, an inhibitor of the glycolytic pathway, a mitochondria-targeted antioxidant, or combinations thereof.

3. The CAR therapy for use or the inhibitor of a pro-M2 macrophage molecule for use of claim 1 or 2, wherein:

(a) the CAR therapy and the inhibitor of a pro-M2 macrophage molecule are to be administered sequentially;

(b) the inhibitor of a pro-M2 macrophage molecule is to be administered prior to the CAR therapy; and/or

(c) the inhibitor of a pro-M2 macrophage molecule and the CAR therapy are to be administered simultaneously or concurrently.

4. The CAR therapy for use or the inhibitor of a pro-M2 macrophage molecule for use of any of claims 1-3, wherein:

(a) the CAR therapy is to be administered as (a) single infusion or (b) multiple infusions (e.g., a single dose split into multiple infusions), and wherein the inhibitor of a pro-M2 macrophage molecule is to be administered as (a) a single dose, or (b) multiple doses (e.g., a first and second, and optionally one or more subsequent doses);

(b) a dose of the CAR therapy is to be administered after (e.g., at least 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, or more, after) administration of a first dose of the inhibitor of a pro-M2 macrophage molecule, e.g., but before administration of the second dose of the inhibitor;

(c) a dose of the CAR therapy is to be administered concurrently with (e.g., within 2 days (e.g., within 2 days, 1 day, 24 hours, 12 hours, 6 hours, 4 hours, 2 hours, or less) of), the administration of a first dose of the inhibitor of a pro-M2 macrophage molecule;

(d) one or more subsequent doses of the inhibitor of a pro-M2 macrophage molecule are to be administered after a second dose of the inhibitor of a pro-M2 macrophage molecule;

(e) the inhibitor of a pro-M2 macrophage molecule is to be administered in more than one dose, and the doses are to be administered twice a day (BID), once a day, once a week, once every 14 days, or once every month;

(f) the administering of the inhibitor of a pro-M2 macrophage molecule comprises multiple doses comprising a duration of at least 7 days, e.g., at least 7 days, 8 days, 9 days, 10 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, or more; and/or

(g) wherein the CAR therapy is to be administered at a dose comprising at least about 5 x 10^6, 1 x 10^7, 1.5 x 10^7, 2 x 10^7, 2.5 x 10^7, 3 x 10^7, 3.5 x 10^7, 4 x 10^7, 5 x 10^7, 1 x 10^8, 1.5 x 10^8, 2 x 10^8, 2.5 x 10^8, 3 x 10^8, 3.5 x 10^8, 4 x 10^8, 5 x 10^8, 1 x 10^9, 2 x 10^9, or 5 x 10^9 cells, e.g., CAR positive cells.

5. The CAR therapy for use or the inhibitor of a pro-M2 macrophage molecule for use of any of claims 1-4, wherein the inhibitor of a pro-M2 macrophage molecule is a small molecule, an antibody or antigen-binding fragment thereof, a protein (e.g., a fusion protein), a nucleic acid (e.g., an shRNA or siRNA), or a gene editing system.

6. The CAR therapy for use or the inhibitor of a pro-M2 macrophage molecule for use of any of claims 1-5, wherein the tumor antigen binding domain of the CAR binds CD123.

7. A CAR therapy comprising a cell, e.g., a population of immune effector cells, comprising, e.g., expressing, a chimeric antigen receptor (CAR) for use in combination with a tumor targeting therapy in treating a subject having a disease associated with expression of a tumor antigen, wherein:

(i) the CAR comprises a tumor antigen binding domain that binds CD123 (CD123 CAR), a transmembrane domain, and an intracellular signaling domain; and

(ii) the tumor targeting therapy comprises a second CAR therapy that comprises a cell, e.g., a population of immune effector cells, comprising, e.g., expressing, a CAR comprising a tumor antigen binding domain that binds to a tumor antigen other than CD123 (e.g., a CAR that binds to a solid tumor antigen or a hematologic tumor antigen other than CD123),
wherein the CD123 CAR is to be administered in an amount and/or time sufficient to result in inhibition of an M2 macrophage activity.

8. A tumor targeting therapy for use in combination with a CAR therapy comprising a cell, e.g., a population of immune effector cells, comprising, e.g., expressing, a chimeric antigen receptor (CAR) in treating a subject having a disease associated with expression of a tumor antigen, wherein:

(i) the CAR comprises a tumor antigen binding domain that binds CD123 (CD123 CAR), a transmembrane domain, and an intracellular signaling domain; and

(ii) the tumor targeting therapy comprises a second CAR therapy that comprises a cell, e.g., a population of immune effector cells, comprising, e.g., expressing, a CAR comprising a tumor

antigen binding domain that binds to a tumor antigen other than CD123 (e.g., a CAR that binds to a solid tumor antigen or a hematologic tumor antigen other than CD123),
wherein the CD123 CAR is to be administered in an amount and/or time sufficient to result in inhibition of an M2 macrophage activity.

9. The pharmaceutical composition for use of claim 7 or 8, wherein the inhibition of the M2 macrophage activity comprises inhibition of polarization of a macrophage to an M2 phenotype, and/or reversal of a phenotype of an M2 macrophage.

10. The CAR therapy for use or the tumor targeting therapy for use of any of claims 7-9, wherein the tumor antigen binding domain of the second CAR therapy binds to CD19, mesothelin, or EGFRviii.

11. The CAR therapy for use or the tumor targeting therapy for use of any of claims 6-10, wherein the tumor antigen binding domain of the CAR that binds to CD123 comprises

a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of any CD123 heavy chain binding domain amino acid sequence listed in Table 16, Table 18, Table 20, Table 22, Table 24, Table 25, Table 26, Table 27 or Table 28; and

a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of any CD123 light chain binding domain amino acid sequence listed in Table 17, Table 19, Table 21, Table 23, Table 24, Table 25, Table 26, Table 27 or Table 28.

12. The CAR therapy for use or the tumor targeting therapy for use of any of claims 6-11, wherein:

(a) the CD123 binding domain comprises a CD123 binding domain (e.g., scFv) amino acid sequence listed in Table 26, Table 27 or Table 28; and/or

(b) the CAR comprises (e.g., consists of) a CAR amino acid sequence listed in Table 26 or Table 27.

13. The CAR therapy for use, the inhibitor of a pro-M2 macrophage molecule for use, or the tumor targeting therapy for use of any of claims 1-5, 7, or 8, wherein the tumor antigen binding domain of the CAR binds mesothelin, and wherein:

(a) the tumor antigen binding domain of the CAR comprises a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of any mesothelin heavy chain binding domain amino acid sequence listed in Table 2, Table 3 or Table 11; and

a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of any mesothelin light chain binding domain amino acid sequence listed in Table 2, Table 4 or Table 11;

(b) the mesothelin binding domain comprises a mesothelin binding domain (e.g., scFv) amino acid sequence listed in Table 2 or Table 11; and/or

(c) the CAR comprises (e.g., consists of) a CAR amino acid sequence listed in Table 11.

14. The CAR therapy for use, the inhibitor of a pro-M2 macrophage molecule for use, or the tumor targeting therapy for use of any of claims 1-5, 7, or 8, wherein the tumor antigen binding domain of the CAR binds EGFRvIII, and wherein:

(a) the tumor antigen binding domain of the CAR comprises:

a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of any EGFRvIII heavy chain binding domain amino acid sequence listed in Table 5; and

a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of any EGFRvIII light chain binding domain amino acid sequence listed in Table 5;

(b) the EGFRvIII binding domain comprises a EGFRvIII binding domain (e.g., scFv) amino acid sequence listed in Table 5; and/or

(c) the CAR comprises (e.g., consists of) a CAR amino acid sequence listed in Table 30.

15. The CAR therapy for use, the inhibitor of a pro-M2 macrophage molecule for use, or the tumor targeting therapy for use of claims 1-5, 7, or 8, wherein the tumor antigen binding domain of the CAR binds CD19, wherein:

(a) the tumor antigen binding domain of the CAR comprises a heavy chain complementary determining region 1 (HC CDR1), a heavy chain complementary determining region 2 (HC CDR2), and a heavy chain complementary determining region 3 (HC CDR3) of any CD19 heavy chain binding domain amino acid sequence listed in Table 6, Table 7, or Table 9; and a light chain complementary determining region 1 (LC CDR1), a light chain complementary determining region 2 (LC CDR2), and a light chain complementary determining region 3 (LC CDR3) of any CD19 light chain binding domain amino acid sequence listed in Table 6, Table 8, or Table 9;

(b) the CD19 binding domain comprises a CD19 binding domain (e.g., scFv) amino acid sequence listed in Table 6 or Table 9; and/or

(c) the CD19 binding domain comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 83; SEQ ID NO: 84, SEQ ID NO: 85; SEQ ID NO: 86; SEQ ID NO: 87; SEQ ID NO: 88; SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, and SEQ ID NO: 112.

16. The CAR therapy for use, the inhibitor of a pro-M2 macrophage molecule for use, or the tumor targeting therapy for use of any of the preceding claims, wherein the tumor antigen binding domain of the CAR binds a solid tumor antigen.

17. The CAR therapy for use, the inhibitor of a pro-M2 macrophage molecule for use, or the tumor targeting therapy for use of any of the preceding claims, wherein the tumor antigen binding domain of the CAR binds an antigen expressed on a tumor associated with tumor-associated macrophages (TAMs) and/or myeloid derived suppressor cells (MDSCs).

18. The CAR therapy for use, the inhibitor of a pro-M2 macrophage molecule for use, or the tumor targeting therapy for use of claim 16 or 17, wherein the solid tumor antigen or the antigen expressed on a tumor associated with tumor-associated macrophages (TAMs) and/or myeloid derived suppressor cells (MDSCs) is CD123, EGFRvIII, mesothelin, GD2, Tn antigen, sTn antigen, Tn-O-Glycopeptides, sTn-O-Glycopeptides, PSMA, CD97, TAG72, CD44v6, CEA, EPCAM, KIT, IL-13Ra2, leguman, GD3, CD171, IL-11Ra, PSCA, MAD-CT-1, MAD-CT-2, VEGFR2, LewisY, CD24, PDGFR-beta, SSEA-4, folate receptor alpha, ERBBs (e.g., ERBB2), Her2/neu, MUC1, EGFR, NCAM, Ephrin B2, CAIX, LMP2, sLe, HMWMAA, o-acetyl-GD2, folate receptor beta, TEM1/CD248, TEM7R, FAP, Legumain, HPV E6 or E7, ML-IAP, CLDN6, TSHR, GPRC5D, ALK, Polysialic acid, Fos-related antigen, neutrophil elastase, TRP-2, CYP1B1, sperm protein 17, beta human chorionic gonadotropin, AFP, thyroglobulin, PLAC1, globoH, RAGE1, MN-CA IX, human telomerase reverse transcriptase, intestinal carboxyl esterase, mut hsp 70-2, NA-17, NY-BR-1, UPK2, HAVCR1, ADRB3, PANX3, NY-ESO-1, GPR20, Ly6k, OR51E2, TARP, GFRα4, or a peptide of any of these antigens presented on MHC.

19. The CAR therapy for use, the inhibitor of a pro-M2 macrophage molecule for use, or the tumor targeting therapy for use of any of the preceding claims, wherein:

(a) the intracellular signaling domain comprises a primary signaling domain comprising a CD3-zeta stimulatory domain; and/or

(b) the intracellular signaling domain comprises a costimulatory domain which is an intracellular domain of a costimulatory protein selected from the group consisting of 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.

20. The CAR therapy for use, the inhibitor of a pro-M2 macrophage molecule for use, or the tumor targeting therapy for use of claim 19, wherein the costimulatory domain comprises:

(a) an intracellular domain of 4-1BB;

(b) an intracellular domain of CD28; and/or

(c) two costimulatory domains, e.g., a 4-1BB costimulatory domain and a CD28 costimulatory domain.

21. The CAR therapy for use, the inhibitor of a pro-M2 macrophage molecule for use, or the tumor targeting therapy for use of any of the preceding claims, wherein the disease associated with expression of a tumor antigen is cancer.

22. The CAR therapy for use, the inhibitor of a pro-M2 macrophage molecule for use, or the tumor targeting therapy for use of claim 21, wherein the cancer is Hodgkin lymphoma or a solid cancer.

23. The CAR therapy for use, the inhibitor of a pro-M2 macrophage molecule for use, or the tumor targeting therapy for use of any of the preceding claims, wherein the cell comprising a CAR comprises a nucleic acid encoding the CAR.

24. The CAR therapy for use, the inhibitor of a pro-M2 macrophage molecule for use, or the tumor targeting therapy for use of claim 23, wherein:

(a) the nucleic acid encoding the CAR is a lentiviral vector;

(b) the nucleic acid encoding the CAR is introduced into the cells by lentiviral transduction;

(c) wherein the nucleic acid encoding the CAR is an RNA, e.g., an in vitro transcribed RNA; and/or

(d) the nucleic acid encoding the CAR is introduced into the cells by electroporation.

25. The CAR therapy for use, the inhibitor of a pro-M2 macrophage molecule for use, or the tumor targeting therapy for use of any of claims 1-24, wherein the cell is a T cell or an NK cell.

26. The CAR therapy for use, the inhibitor of a pro-M2 macrophage molecule for use, or the tumor targeting therapy for use of claim 25, wherein the T cell is an autologous or allogeneic T cell.

27. The CAR therapy for use, the inhibitor of a pro-M2 macrophage molecule for use, or the tumor targeting therapy for use of any of claims 1-26, wherein the subject is a mammal, e.g., a human.

28. The CAR therapy for use, the inhibitor of a pro-M2 macrophage molecule for use, or the tumor targeting therapy for use of claims 7-27, wherein:

(a) the CD123 CAR therapy and the tumor targeting therapy are to be administered sequentially, simultaneously, or concurrently; and/or

(b) the CD123 CAR therapy is to be administered prior to the tumor targeting therapy.

29. The CAR therapy for use, the inhibitor of a pro-M2 macrophage molecule for use, or the tumor targeting therapy for use of claim 28, wherein:

(a) the CD123 CAR therapy is to be administered at least 5 days, at least 7 days, at least 10 days, at least 15 days, at least 20 days, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months or at least 10 months, prior to administration of the tumor targeting therapy;

(b) the CD123 CAR therapy is to be administered as (a) a single infusion or (b) multiple infusions (e.g., a single dose split into multiple infusions), and wherein the tumor targeting therapy is to be administered as (a) a single dose, or (b) multiple doses (e.g., a first and second, and optionally one or more subsequent doses); and/or

(c) the CAR therapy or the tumor targeting therapy is to be administered at a dose comprising at least about 5×10^6, 1×10^7, 1.5×10^7, 2×10^7, 2.5×10^7, 3×10^7, 3.5×10^7, 4×10^7, 5×10^7, 1×10^8, 1.5×10^8, 2×10^8, 2.5×10^8, 3×10^8, 3.5×10^8, 4×10^8, 5×10^8, 1×10^9, 2×10^9, or 5×10^9 cells, e.g., CAR positive cells.

30. The CAR therapy for use, the inhibitor of a pro-M2 macrophage molecule for use, or the tumor targeting therapy for use of claims 7-29, wherein the CAR therapy and the tumor targeting therapy are formulated in a pharmaceutical composition.

31. A pharmaceutical composition comprising (i) a cell, e.g., a population of immune effector cells, comprising, e.g., expressing, a chimeric antigen receptor (CAR), wherein the CAR

comprises a tumor antigen binding domain, a transmembrane domain, and an intracellular signaling domain; and (ii) an inhibitor of a pro-M2 macrophage molecule, which is chosen from: a modulator of myeloid-derived suppressor cells (MDSCs), a CSF1R inhibitor, an IL-13 inhibitor, an IL-4 inhibitor, an IL-13Rα1 inhibitor, an IL-4Rα inhibitor, an IL-10 inhibitor, a TGF beta inhibitor, a JAK2 inhibitor, a cell surface molecule, an iron oxide, a small molecule inhibitor, a PI3K inhibitor, an HDAC inhibitor, an inhibitor of the glycolytic pathway, a mitochondria-targeted antioxidant, or combinations thereof.

32. A pharmaceutical composition comprising (i) a cell, e.g., a population of immune effector cells, comprising, e.g., expressing, a chimeric antigen receptor (CAR), wherein the CAR comprises a tumor antigen binding domain, a transmembrane domain, and an intracellular signaling domain; and (ii) an inhibitor of a pro-M2 macrophage molecule which is for use in treating a disease or disorder, wherein the inhibitor of a pro-M2 macrophage molecule is chosen from: a modulator of myeloid-derived suppressor cells (MDSCs), a CSF-1 inhibitor, a CSF1R inhibitor, an IL-13 inhibitor, an IL-4 inhibitor, an IL-13Rα1 inhibitor, an IL-4Rα inhibitor, an IL-10 inhibitor, a TGF beta inhibitor, a JAK2 inhibitor, a cell surface molecule, an iron oxide, a small molecule inhibitor, a PI3K inhibitor, an HDAC inhibitor, an inhibitor of the glycolytic pathway, a mitochondria-targeted antioxidant, or combinations thereof.

33. The pharmaceutical composition of claim 31 for:

(a) stimulating a T cell-mediated immune response to a solid tumor cell in a mammal;

(b) providing an anti-solid tumor immunity in a mammal; or

(c) treating a mammal having a disease associated with expression of a solid tumor antigen.

34. The pharmaceutical composition for use of claim 32 or 33, wherein:

(a) the cell, e.g., the population of immune effector cells, and the inhibitor of a pro-M2 macrophage molecule are provided for separate administration (e.g., in two separate compositions); or

(b) the cell, e.g., the population of immune effector cells, and the inhibitor of a pro-M2 macrophage molecule are provided for simultaneous administration (e.g., in one composition).

35. The CAR therapy for use or the inhibitor of a pro-M2 macrophage molecule for use, or the pharmaceutical composition for use of any one of claims 1-5 or 32-34, wherein the MDSC modulator is:

(a) an M-CSF inhibitor;

(b) a CSF1R inhibitor;

(c) BLZ945; or

(d) MCS110.