

TACI/BCMA DUAL BINDING MOLECULES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 63/175,997, filed April 16, 2021, U.S. Provisional Application No. 63/209,869, filed June 11, 2021, U.S. Provisional Application No. 63/279,477 filed November 15, 2021 and U.S. Provisional Application No. 63/310,492 filed February 15, 2022, which are incorporated herein in their entireties for all purposes.

TECHNICAL FIELD

[0002] The present disclosure relates to the field of cell therapy, and more specifically, to antibodies, CARs and/or TCRs that target antigens present on multiple myeloma cells.

BACKGROUND

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

[0004] Current T cell therapies rely on enriched or modified human T cells to target and kill cancer cells in a patient. To increase the ability of T cells to target and kill a particular cancer cell, methods have been developed to engineer T cells to express constructs which direct T cells to a particular target cancer cell. Chimeric antigen receptors (CARs) and engineered T cell receptors (TCRs), which comprise binding domains capable of interacting with a particular tumor antigen, allow T cells to target and kill cancer cells that express the particular tumor antigen. A need exists for CARs and TCRs for targeting and killing cancer cells and, in particular, cells expressing transmembrane activator and CAML interactor (TACI) and/or B-cell maturation antigen (BCMA), such as multiple myeloma cells.

SUMMARY

[0005] Disclosed are antibodies, antigen binding fragments thereof, and nucleic acids encoding the same, comprising a dual TACI-BCMA binding domain. In embodiments, the dual TACI-BCMA binding domain comprises sequences of three heavy chain complementarity determining

regions (HCDRs) of any one of the heavy chain variable region (HCVR) from SEQ ID NOs: 1, 25, 49, 73, 97, 121, 145, 169, and 193 and sequences of three light chain CDRs (LCDRs) of any one of the light chain variable region (LCVR) from SEQ ID NOs: 12, 36, 60, 84, 108, 132, 156, 180, and 204.

[0006] In embodiments, the dual TACI-BCMA binding domain comprises a first domain comprising three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) and a second domain comprising three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3), wherein (i) the HCDR1 has a sequence according to any one of SEQ ID NOs: 3-5, 27-29, 51-53, 75-77, 99-101, 123-125, 147-149, 171-173, and 195-197; (ii) the HCDR2 has a sequence according to any one of SEQ ID NOs: 6-8, 30-32, 54-56, 78-80, 102-104, 126-128, 150-152, 174-176, and 198-200; (iii) the HCDR3 has a sequence according to any one of SEQ ID NOs: 9-11, 33-35, 57-59, 81-83, 105-107, 129-131, 153-155, 177-179, and 201-203; (iv) the LCDR1 has a sequence according to any one of SEQ ID NOs: 14-16, 38-40, 62-64, 86-88, 110-112, 134-136, 158-160, 182-184, and 206-208; (v) the LCDR2 has a sequence according to any one of SEQ ID NOs: 17-19, 41-43, 65-67, 89-91, 113-115, 137-139, 161-163, 185-187, and 209-211; and (vi) the LCDR3 has a sequence according to any one of SEQ ID NOs: 20-22, 44-46, 68-70, 92-94, 116-118, 140-142, 164-166, 188-190, and 212-214. In embodiments, the HCDRs comprise: (i) an HCDR1 according to any one of SEQ ID NOs: 3-5; an HCDR2 according to any one of SEQ ID NOs: 6-8; an HCDR3 according to any one of SEQ ID NOs: 9-11; (ii) an HCDR1 according to any one of SEQ ID NOs: 27-29; an HCDR2 according to any one of SEQ ID NOs: 30-32; an HCDR3 according to any one of SEQ ID NOs: 33-35; (iii) an HCDR1 according to any one of SEQ ID NOs: 51-53; an HCDR2 according to any one of SEQ ID NOs: 54-56; an HCDR3 according to any one of SEQ ID NOs: 57-59; (iv) an HCDR1 according to any one of SEQ ID NOs: 75-77; an HCDR2 according to any one of SEQ ID NOs: 78-80; an HCDR3 according to any one of SEQ ID NOs: 81-83; (v) an HCDR1 according to any one of SEQ ID NOs: 99-101; an HCDR2 according to any one of SEQ ID NOs: 102-104; an HCDR3 according to any one of SEQ ID NOs: 105-107; (vi) an HCDR1 according to any one of SEQ ID NOs: 123-125; an HCDR2 according to any one of SEQ ID NOs: 126-128; an HCDR3 according to any one of SEQ ID NOs: 129-131; (vii) an HCDR1 according to any one of SEQ ID NOs: 147-149; an HCDR2 according to any one of SEQ ID NOs: 150-152; an HCDR3 according to any one of SEQ ID NOs: 153-155; (viii) an HCDR1 according to any one of SEQ ID NOs: 171-173; an HCDR2 according to any of SEQ ID NOs: 174-176; an HCDR3 according to any one of SEQ ID NOs: 177-179; or (ix) an HCDR1 according to any one of SEQ ID NOs: 195-197; an HCDR2 according to any one of SEQ ID NOs: 198-200; an HCDR3 according to any one of SEQ ID NOs: 201-203;

and the LCDRs comprise: (i) an LCDR1 according to any one of SEQ ID NOs: 14-16; an LCDR2 according to any one of SEQ ID NOs: 17-19; an LCDR3 according to any one of SEQ ID NOs: 20-22; (ii) an LCDR1 according to any one of SEQ ID NOs: 38-40; an LCDR2 according to any one of SEQ ID NOs: 41-43; an LCDR3 according to any one of SEQ ID NOs: 44-46; (iii) an LCDR1 according to any one of SEQ ID NOs: 62-64; an LCDR2 according to any one of SEQ ID NOs: 65-67; an LCDR3 according to any one of SEQ ID NOs: 68-70; (iv) an LCDR1 according to any one of SEQ ID NOs: 86-88; an LCDR2 according to any one of SEQ ID NOs: 89-91; an LCDR3 according to any one of SEQ ID NOs: 92-94; (v) an LCDR1 according to any one of SEQ ID NOs: 110-112; an LCDR2 according to any one of SEQ ID NOs: 113-115; an LCDR3 according to any one of SEQ ID NOs: 116-118; (vi) an LCDR1 according to any one of SEQ ID NOs: 134-136; an LCDR2 according to any one of SEQ ID NOs: 137-139; an LCDR3 according to any one of SEQ ID NOs: 140-142; (vii) an LCDR1 according to any one of SEQ ID NOs: 158-160; an LCDR2 according to any one of SEQ ID NOs: 161-163; an LCDR3 according to any one of SEQ ID NOs: 164-166; (viii) an LCDR1 according to any one of SEQ ID NOs: 182-184; an LCDR2 according to any one of SEQ ID NOs: 185-187; an LCDR3 according to any one of SEQ ID NOs: 188-190; or (ix) an LCDR1 according to any one of SEQ ID NOs: 206-208; an LCDR2 according to any one of SEQ ID NOs: 209-211; an LCDR3 according to any one of SEQ ID NOs: 212-214.

[0007] In embodiment, the antibody, or antigen binding fragment thereof, comprises a first domain comprising three heavy chain complementarity determining regions (HCDRs) and a second domain comprising three light chain complementarity determining regions (LCDRs), wherein: the HCDRs and LCDRs comprise: (i) an HCDR1 according to any one of SEQ ID NOs: 3-5; an HCDR2 according to any one of SEQ ID NOs: 6-8; an HCDR3 according to any one of SEQ ID NOs: 9-11; an LCDR1 according to any one of SEQ ID NOs: 14-16; an LCDR2 according to any one of SEQ ID NOs: 17-19; an LCDR3 according to any one of SEQ ID NOs: 20-22; (ii) an HCDR1 according to any one of SEQ ID NOs: 27-29; an HCDR2 according to any one of SEQ ID NOs: 30-32; an HCDR3 according to any one of SEQ ID NOs: 33-35; an LCDR1 according to any one of SEQ ID NOs: 38-40; an LCDR2 according to any one of SEQ ID NOs: 41-43; an LCDR3 according to any one of SEQ ID NOs: 44-46; (iii) an HCDR1 according to any one of SEQ ID NOs: 51-53; an HCDR2 according to any one of SEQ ID NOs: 54-56; an HCDR3 according to any one of SEQ ID NOs: 57-59; an LCDR1 according to any one of SEQ ID NOs: 62-64; an LCDR2 according to any one of SEQ ID NOs: 65-67; an LCDR3 according to any one of SEQ ID NOs: 68-70; (iv) an HCDR1 according to any one of SEQ ID NOs: 75-77; an HCDR2 according to any one of SEQ ID NOs: 78-80; an HCDR3 according to any one of SEQ ID NOs:

81-83; an LCDR1 according to any one of SEQ ID NOs: 86-88; an LCDR2 according to any one of SEQ ID NOs: 89-91; an LCDR3 according to any one of SEQ ID NOs: 92-94; (v) an HCDR1 according to any one of SEQ ID NOs: 99-101; an HCDR2 according to any one of SEQ ID NOs: 102-104; an HCDR3 according to any one of SEQ ID NOs: 105-107; an LCDR1 according to any one of SEQ ID NOs: 110-112; an LCDR2 according to any one of SEQ ID NOs: 113-115; an LCDR3 according to any one of SEQ ID NOs: 116-118; (vi) an HCDR1 according to any one of SEQ ID NOs: 123-125; an HCDR2 according to any one of SEQ ID NOs: 126-128; an HCDR3 according to any one of SEQ ID NOs: 129-131; an LCDR1 according to any one of SEQ ID NOs: 134-136; an LCDR2 according to any one of SEQ ID NOs: 137-139; an LCDR3 according to any one of SEQ ID NOs: 140-142; (vii) an HCDR1 according to any one of SEQ ID NOs: 147-149; an HCDR2 according to any one of SEQ ID NOs: 150-152; an HCDR3 according to any one of SEQ ID NOs: 153-155; an LCDR1 according to any one of SEQ ID NOs: 158-160; an LCDR2 according to any one of SEQ ID NOs: 161-163; an LCDR3 according to any one of SEQ ID NOs: 164-166; (viii) an HCDR1 according to any one of SEQ ID NOs: 171-173; an HCDR2 according to any one of SEQ ID NOs: 174-176; an HCDR3 according to any one of SEQ ID NOs: 177-179; an LCDR1 according to any one of SEQ ID NOs: 182-184; an LCDR2 according to any one of SEQ ID NOs: 185-187; an LCDR3 according to any one of SEQ ID NOs: 188-190; or (ix) an HCDR1 according to any one of SEQ ID NOs: 195-197; an HCDR2 according to any one of SEQ ID NOs: 198-200; an HCDR3 according to any one of SEQ ID NOs: 201-203; an LCDR1 according to any one of SEQ ID NOs: 206-208; an LCDR2 according to any one of SEQ ID NOs: 209-211; an LCDR3 according to any one of SEQ ID NOs: 212-214.

[0008] In embodiments, the antibody, or antigen binding fragment thereof comprises a first heavy chain variable domain comprising the three HCDRs and a light chain variable domain comprising the three LCDRs, wherein: (i) the heavy chain variable domain is at least 80% identical to SEQ ID NO: 1, SEQ ID NO: 25, SEQ ID NO: 49, SEQ ID NO: 73, SEQ ID NO: 97, SEQ ID NO: 121, SEQ ID NO: 145, SEQ ID NO: 169, or SEQ ID NO: 193; and (ii) the light chain variable domain is at least 80% identical to SEQ ID NO: 12, SEQ ID NO: 36, SEQ ID NO: 60, SEQ ID NO: 84, SEQ ID NO: 108, SEQ ID NO: 132, SEQ ID NO: 156, SEQ ID NO: 180, or SEQ ID NO: 204. In embodiments, the antibody, or antigen binding fragment thereof comprises a first heavy chain variable domain comprising the three HCDRs and a light chain variable domain comprising the three LCDRs, wherein: (i) the heavy chain variable domain is at least 80% identical to SEQ ID NO: 1 and the light chain variable domain is at least 80% identical to SEQ ID NO: 12; (ii) the heavy chain variable domain is at least 80% identical to SEQ ID NO: 25 and the light chain variable domain is at least 80% identical to SEQ ID NO: 36; (iii) the heavy chain variable domain

is at least 80% identical to SEQ ID NO: 49 and the light chain variable domain is at least 80% identical to SEQ ID NO: 60; (iv) the heavy chain variable domain is at least 80% identical to SEQ ID NO: 73 and the light chain variable domain is at least 80% identical to SEQ ID NO: 84; (v) the heavy chain variable domain is at least 80% identical to SEQ ID NO: 97 and the light chain variable domain is at least 80% identical to SEQ ID NO: 108; (vi) the heavy chain variable domain is at least 80% identical to SEQ ID NO: 121 and the light chain variable domain is at least 80% identical to SEQ ID NO: 132; (vii) the heavy chain variable domain is at least 80% identical to SEQ ID NO: 145 and the light chain variable domain is at least 80% identical to SEQ ID NO: 156; (viii) the heavy chain variable domain is at least 80% identical to SEQ ID NO: 169 and the light chain variable domain is at least 80% identical to SEQ ID NO: 180; or (ix) the heavy chain variable domain is at least 80% identical to SEQ ID NO: 193 and the light chain variable domain is at least 80% identical to SEQ ID NO: 204. In certain embodiments, the three HCDRs and the three LCDRs are comprised by a single polypeptide. In certain embodiments, the antigen binding fragment thereof comprises an scFv.

[0009] Disclosed are chimeric antigen receptors and nucleic acids encoding the same, comprised by the antibody, or antigen binding fragment thereof of any of the antibodies, or an antigen binding fragments thereof, disclosed herein. In embodiments, the chimeric antigen receptor comprises a transmembrane domain of 4-1BB/CD137, an alpha chain of a T cell receptor, a beta chain of a T cell receptor, 2B4, CD3 epsilon, CD4, CD5, CD8 alpha, CD9, CD16, CD19, CD22, CD28, CD33, CD37, CD45, CD64, CD80, CD86, CD134, CD137, CD154, NKG2D, or a zeta chain of a T cell receptor, or any combination thereof.

[0010] Disclosed is a recombinant vector comprising the nucleic acids encoding a disclosed antibody, antigen binding fragment thereof, CAR or TCR. In embodiments, a recombinant vector or nucleic acid further comprises a nucleic acid encoding a dominant negative TGF β receptor (DN TGF β R). In embodiments, a DN TGF β R comprises an extracellular domain (ECD) from a TGF β receptor and a transmembrane domain (TMD), wherein the recombinant polypeptide lacks amino acid residues responsible for signaling and phosphorylation present in a wild-type TGF β receptor. In embodiments, the ECD is from TGF β RI or TGF β RII. In embodiments, the TMD is the transmembrane domain from TGF β RI, TGF β RII, PDGFR, CD4, CD8, CD28, CD127, CD132, CD3 ζ , 4-1BB, OX40, ICOS, CTLA-4, PD-1, LAG-3, 2B4, IL-5, IL-7, IL-7R α , BTLA or mutants of any of the foregoing. In embodiments, the DN TGF β R further comprises a heterologous intracellular domain (ICD) which lacks amino acid residues responsible for signaling and phosphorylation present in wild-type TGF β receptor.

[0011] Disclosed are host cells transformed with a disclosed nucleic acid or disclosed recombinant vector and pharmaceutical compositions comprising the same. In embodiments, a host cell is transformed with a nucleic acid encoding a disclosed CAR or TCR. In embodiments, a host cell is transformed with a nucleic acid encoding a disclosed CAR or TCR, and a nucleic acid encoding a dominant negative TGF β receptor (DN TGF β R). In certain embodiments, the host cell is transformed with a nucleic acid encoding a membrane bound IL-15-IL-15R α sushi domain chimeric receptor. In embodiment, the host cell comprises an iPSC, a T cell or a NK cell.

[0012] Disclosed is a method of treating disease in a patient in need of thereof, comprising administering a T cell and/or an NK cell or a pharmaceutical composition comprising the same, wherein the T cell and/or an NK cell comprises disclose CAR or TCR. In embodiments, the disease is multiple myeloma. Disclosed is a method of inducing an immune response in a subject or immunizing a subject against a multiple myeloma, the method comprising administering to the subject a T cell and/or an NK cell or a pharmaceutical composition comprising the same, wherein the T cell and/or an NK cell comprises disclose CAR or TCR. In embodiments, the T cell and/or an NK cell s allogeneic to the patient.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] **FIG. 1** shows enhanced efficacy with TGF β RII dominant-negative receptors (DNRs) observed with low dose CAR-T cell treatment in RPMI8226 myeloma model. (A) CAR targeted BCMA; (B) CAR targeted both TACI and BCMA (binder #1); and (C) CAR targeted both TACI and BCMA (binder #3).

[0014] **FIGS. 2A and 2B** show increased mean fluorescence intensity (MFI) for codon-optimized BCMA/TACI dual binders, indicating relatively increased expression of the codon-optimized CARs.

[0015] **FIGS. 3A and 3B** show increased MFI for codon-optimized BCMA/TACI dual binders linked to TGF β II DNR, indicating relatively increased expression of both the codon-optimized CARs and DNR.

[0016] **FIGS. 4A-4D** show results of 24-hour *in vitro* cytotoxicity assays of codon-optimized and noncodon-optimized CARs linked to TGF β II DNR. **FIGs. 4E-4H** show results of cytokine assays of codon-optimized and noncodon-optimized CARs linked to TGF β II DNR.

[0017] **FIGS. 5A and 5B** show *in vivo* data of codon-optimized and noncodon-optimized CARs linked to TGF β II DNR.

DETAILED DESCRIPTION

Terms

[0018] In order for the present disclosure to be more readily understood, certain terms are first defined below. Additional definitions for the following terms and other terms are set forth throughout the Specification.

[0019] As used in this Specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise.

[0020] Unless specifically stated or obvious from context, as used herein, the term “or” is understood to be inclusive and covers both “or” and “and”.

[0021] The term “and/or” where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term “and/or” as used in a phrase such as “A and/or B” herein is intended to include A and B; A or B; A (alone); and B (alone). Likewise, the term “and/or” as used in a phrase such as “A, B, and/or C” is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0022] The term “*e.g.*,” as used herein, is used merely by way of example, without limitation intended, and should not be construed as referring only those items explicitly enumerated in the specification.

[0023] The terms “or more”, “at least”, “more than”, and the like, *e.g.*, “at least one” are understood to include but not be limited to at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149 or 150, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000 or more than the stated value. Also included is any greater number or fraction in between.

[0024] Conversely, the term “no more than” includes each value less than the stated value. For example, “no more than 100 nucleotides” includes 100, 99, 98, 97, 96, 95, 94, 93, 92, 91, 90, 89, 88, 87, 86, 85, 84, 83, 82, 81, 80, 79, 78, 77, 76, 75, 74, 73, 72, 71, 70, 69, 68, 67, 66, 65, 64, 63,

62, 61, 60, 59, 58, 57, 56, 55, 54, 53, 52, 51, 50, 49, 48, 47, 46, 45, 44, 43, 42, 41, 40, 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, and 0 nucleotides. Also included is any lesser number or fraction in between.

[0025] The terms “plurality”, “at least two”, “two or more”, “at least second”, and the like, are understood to include but not limited to at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149 or 150, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000 or more. Also included is any greater number or fraction in between.

[0026] Throughout the specification the word “comprising,” or variations such as “comprises” or “comprising,” will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps. It is understood that wherever aspects are described herein with the language “comprising,” otherwise analogous aspects described in terms of “consisting of” and/or “consisting essentially of” are also provided.

[0027] Unless specifically stated or evident from context the term “about” refers to a value or composition that is within an acceptable error range for the particular value or composition as determined by one of ordinary skill in the art, which will depend in part on how the value or composition is measured or determined, *i.e.*, the limitations of the measurement system. For example, “about” or “comprising essentially of” can mean within one or more than one standard deviation per the practice in the art. “About” or “comprising essentially of” can mean a range of up to 10% (*i.e.*, $\pm 10\%$). Thus, “about” can be understood to be within 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, 0.05%, 0.01%, or 0.001% greater or less than the stated value. For example, about 5 mg can include any amount between 4.5 mg and 5.5 mg. Furthermore, particularly with respect to biological systems or processes, the terms can mean up to an order of magnitude or up to 5-fold of a value. When particular values or compositions are provided in the instant disclosure, unless otherwise stated, the meaning of “about” or “comprising essentially of” should be assumed to be within an acceptable error range for that particular value or composition.

[0028] As described herein, any concentration range, percentage range, ratio range or integer range is to be understood to be inclusive of the value of any integer within the recited range and, when appropriate, fractions thereof (such as one-tenth and one-hundredth of an integer), unless otherwise indicated.

[0029] Units, prefixes, and symbols used herein are provided using their Système International de Unites (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range.

[0030] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, Juo, “The Concise Dictionary of Biomedicine and Molecular Biology”, 2nd ed., (2001), CRC Press; “The Dictionary of Cell & Molecular Biology”, 5th ed., (2013), Academic Press; and “The Oxford Dictionary Of Biochemistry And Molecular Biology”, Cammack *et al.* eds., 2nd ed, (2006), Oxford University Press, provide those of skill in the art with a general dictionary for many of the terms used in this disclosure.

[0031] “Administering” refers to the physical introduction of an agent to a subject, such as a modified T cell disclosed herein, using any of the various methods and delivery systems known to those skilled in the art. Exemplary routes of administration for the formulations disclosed herein include intravenous, intramuscular, subcutaneous, intraperitoneal, spinal or other parenteral routes of administration, for example by injection or infusion. The phrase “parenteral administration” means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intralymphatic, intralesional, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion, as well as *in vivo* electroporation. In some embodiments, the formulation is administered via a non-parenteral route, *e.g.*, orally. Other non-parenteral routes include a topical, epidermal or mucosal route of administration, for example, intranasally, vaginally, rectally, sublingually or topically. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

[0032] The terms, “activated” and “activation” refer to the state of a T cell that has been sufficiently stimulated to induce detectable cellular proliferation. In one embodiment, activation may also be associated with induced cytokine production, and detectable effector functions. The term “activated T cells” refers to, among other things, T cells that are proliferating. Signals generated through the TCR alone may be insufficient for full activation of the T cell and one or more secondary or costimulatory signals may also be required. Thus, T cell activation comprises

a primary stimulation signal through the TCR/CD3 complex and one or more secondary costimulatory signals. Costimulation may be evidenced by proliferation and/or cytokine production by T cells that have received a primary activation signal, such as stimulation through the TCR/CD3 complex.

[0033] The term “agent” may refer to a molecule or entity of any class comprising, or a plurality of molecules or entities, any of which may be, for example, a polypeptide, nucleic acid, saccharide, lipid, small molecule, metal, cell (such as a T cell or NK cell or progenitor of such cells, for example an iPSC), or organism (for example, a fraction or extract thereof) or component thereof. In some embodiments, an agent may be utilized in isolated or pure form. In some embodiments, an agent may be utilized in a crude or impure form. In some embodiments, an agent may be provided as a population, collection, or library, for example that may be screened to identify or characterize members present therein.

[0034] The term “allogeneic” refers to any material derived from one individual which is then introduced to another individual of the same species, *e.g.*, allogeneic T cell or NK cell transplantation.

[0035] The term “antibody” (Ab) includes, without limitation, a glycoprotein immunoglobulin which binds specifically to an antigen. In general, an antibody can comprise at least two heavy (H) chains and two light (L) chains interconnected by disulfide bonds, or an antigen-binding molecule thereof. Each H chain comprises a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region comprises three constant domains, CH1, CH2 and CH3. Each light chain comprises a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region is comprises one constant domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL comprises three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the Abs may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e.g.*, effector cells) and the first component (C1q) of the classical complement system. In general, human antibodies are approximately 150 kD tetrameric agents composed of two identical heavy (H) chain polypeptides (about 50 kD each) and two identical light (L) chain polypeptides (about 25 kD each) that associate with each other into

what is commonly referred to as a “Y-shaped” structure. The heavy and light chains are linked or connected to one another by a single disulfide bond; two other disulfide bonds connect the heavy chain hinge regions to one another, so that the dimers are connected to one another and the tetramer is formed. Naturally-produced antibodies are also glycosylated, *e.g.*, on the CH2 domain.

[0036] The term “human antibody” is intended to comprise antibodies having variable and constant domain sequences generated, assembled, or derived from human immunoglobulin sequences, or sequences indistinguishable therefrom. In some embodiments, antibodies (or antibody components) may be considered to be “human” even though their amino acid sequences comprise residues or elements not encoded by human germline immunoglobulin sequences (*e.g.*, variations introduced by *in vitro* random or site-specific mutagenesis or introduced by *in vivo* somatic mutation). The term “humanized” is intended to comprise antibodies having a variable domain with a sequence derived from a variable domain of a non-human species (*e.g.*, a mouse), modified to be more similar to a human germline encoded sequence. In some embodiments, a “humanized” antibody comprises one or more framework domains having substantially the amino acid sequence of a human framework domain, and one or more complementary determining regions having substantially the amino acid sequence as that of a non-human antibody. In some embodiments, a humanized antibody comprises at least a portion of an immunoglobulin constant region (Fc), generally that of a human immunoglobulin constant domain. In some embodiments, a humanized antibodies may comprise a C_H1, hinge, C_H2, C_H3, and, optionally, a C_H4 region of a human heavy chain constant domain.

[0037] Antibodies can include, for example, monoclonal antibodies, recombinantly produced antibodies, monospecific antibodies, multispecific antibodies (including bispecific antibodies), human antibodies, engineered antibodies, humanized antibodies, chimeric antibodies, immunoglobulins, synthetic antibodies, tetrameric antibodies comprising two heavy chain and two light chain molecules, an antibody light chain monomer, an antibody heavy chain monomer, an antibody light chain dimer, an antibody heavy chain dimer, an antibody light chain- antibody heavy chain pair, intrabodies, antibody fusions (sometimes referred to herein as “antibody conjugates”), heteroconjugate antibodies, single domain antibodies, monovalent antibodies, single chain antibodies or single-chain Fvs (scFv), camelized antibodies, affybodies, Fab fragments, F(ab')₂ fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies (including, *e.g.*, anti-anti-Id antibodies), minibodies, domain antibodies, synthetic antibodies (sometimes referred to herein as “antibody mimetics”), and antigen binding fragments of any of the above. In certain embodiments, antibodies described herein refer to polyclonal antibody populations. Antibodies may also comprise, for example, Fab' fragments, Fd' fragments, Fd fragments, isolated CDRs,

single chain Fvs, polypeptide-Fc fusions, single domain antibodies (e.g., shark single domain antibodies such as IgNAR or fragments thereof), camelid antibodies, human heavy-chain antibodies (e.g. UniAbs) single chain or Tandem diabodies (TandAb®), Anticalins®, Nanobodies® minibodies, BiTE®, ankyrin repeat proteins or DARPINs®, Avimers®, DARTs, TCR-like antibodies, Adnectins®, Affilins®, Trans-bodies®, Affibodies®, TrimerX®, MicroProteins, Fynomers®, Centyrins®, and KALBITOR®s.

[0038] An immunoglobulin may derive from any of the commonly known isotypes, including but not limited to IgA, secretory IgA, IgG, IgE and IgM. IgG subclasses are also well known to those in the art and include but are not limited to human IgG1, IgG2, IgG3 and IgG4. “Isotype” refers to the Ab class or subclass (e.g., IgM or IgG1) that is encoded by the heavy chain constant region genes. The term “antibody” includes, by way of example, both naturally occurring and non-naturally occurring Abs; monoclonal and polyclonal Abs; chimeric and humanized Abs; human or nonhuman Abs; wholly synthetic Abs; and single chain Abs. A nonhuman Ab may be humanized by recombinant methods to reduce its immunogenicity in man. Where not expressly stated, and unless the context indicates otherwise, the term “antibody” also includes an antigen binding fragment or an antigen-binding portion of any of the aforementioned immunoglobulins, and includes a monovalent and a divalent fragment or portion, and a single chain Ab.

[0039] An “antigen binding molecule,” “antigen binding portion,” “antigen binding fragment,” or “antibody fragment” or “antigen binding domain” refers to any molecule that comprises the antigen binding parts (e.g., CDRs) of the antibody from which the molecule is derived. An antigen binding molecule can include the antigenic complementarity determining regions (CDRs). Examples of antibody fragments include, but are not limited to, Fab, Fab’, F(ab’)2, and Fv fragments, dAb, linear antibodies, scFv antibodies, and multispecific antibodies formed from antigen binding molecules. Peptibodies (i.e., Fc fusion molecules comprising peptide binding domains) are another example of suitable antigen binding molecules. In some embodiments, the antigen binding molecule binds to an antigen on a tumor cell. In some embodiments, the antigen binding molecule binds to an antigen on a cell involved in a hyperproliferative disease or to a viral or bacterial antigen. In certain embodiments, an antigen binding molecule is a chimeric antigen receptor (CAR) or an engineered T cell receptor (TCR). In certain embodiments, the antigen binding molecule or domain binds to transmembrane activator and CAML interactor (TACI) and/or B-cell maturation antigen (BCMA). In certain embodiments, the antigen binding molecule or domain is an antibody fragment that specifically binds to the antigen, including one or more of the complementarity determining regions (CDRs) thereof. In further embodiments, the antigen

binding molecule is a single chain variable fragment (scFv). In some embodiments, the antigen binding molecule or domain comprises or consists of avimers.

[0040] In some instances, a CDR is substantially identical to one found in a reference antibody (*e.g.*, an antibody of the present disclosure) and/or the sequence of a CDR provided in the present disclosure. In some embodiments, a CDR is substantially identical to a reference CDR (*e.g.*, a CDR provided in the present disclosure) in that it is either identical in sequence or contains between 1, 2, 3, 4, or 5 (*e.g.*, 1-5) amino acid substitutions as compared with the reference CDR. In some embodiments a CDR is substantially identical to a reference CDR in that it shows at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with the reference CDR (*e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%). In some embodiments a CDR is substantially identical to a reference CDR in that it shows at least 96%, 96%, 97%, 98%, 99%, or 100% sequence identity with the reference CDR. In some embodiments a CDR is substantially identical to a reference CDR in that one amino acid within the CDR is deleted, added, or substituted as compared with the reference CDR while the CDR has an amino acid sequence that is otherwise identical with that of the reference CDR. In some embodiments a CDR is substantially identical to a reference CDR in that 2, 3, 4, or 5 (*e.g.*, 2-5) amino acids within the CDR are deleted, added, or substituted as compared with the reference CDR while the CDR has an amino acid sequence that is otherwise identical to the reference CDR. In various embodiments, an antigen binding fragment binds a same antigen as a reference antibody. In various embodiments, an antigen binding fragment cross-competes with the reference antibody, for example, binding to substantially the same or identical epitope as the reference antibody

[0041] An antigen binding fragment may be produced by any means. For example, in some embodiments, an antigen binding fragment may be enzymatically or chemically produced by fragmentation of an intact antibody. In some embodiments, an antigen binding fragment may be recombinantly produced (such as by expression of an engineered nucleic acid sequence). In some embodiments, an antigen binding fragment may be wholly or partially synthetically produced. In some embodiments, an antigen binding fragment may have a length of at least about 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190 amino acids or more; in some embodiments at least about 200 amino acids (*e.g.*, 50-100, 50-150, 50-200, or 100-200 amino acids).

[0042] The term “variable region” or “variable domain” is used interchangeably. The variable region typically refers to a portion of an antibody, generally, a portion of a light or heavy chain,

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

[0043] The terms “VL” and “VL domain” are used interchangeably to refer to the light chain variable region of an antibody or an antigen-binding molecule thereof.

[0044] The terms “VH” and “VH domain” are used interchangeably to refer to the heavy chain variable region of an antibody or an antigen-binding molecule thereof.

[0045] A number of definitions of the CDRs are commonly in use: Kabat numbering, Chothia numbering, AbM numbering, or contact numbering. The AbM definition is a compromise between the two used by Oxford Molecular’s AbM antibody modelling software. The contact definition is based on an analysis of the available complex crystal structures.

Table 1. CDR Numbering

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

[0046] The term “Kabat numbering” and like terms are recognized in the art and refer to a system of numbering amino acid residues in the heavy and light chain variable regions of an antibody, or

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

[0047] In certain aspects, the CDRs of an antibody can be determined according to the Chothia numbering scheme, which refers to the location of immunoglobulin structural loops (*see, e.g.*, Chothia C & Lesk AM, (1987), *J Mol Biol* 196: 901-917; Al-Lazikani B *et al.*, (1997) *J Mol Biol* 273: 927-948; Chothia C *et al.*, (1992) *J Mol Biol* 227: 799-817; Tramontano A *et al.*, (1990) *J Mol Biol* 215(1): 175-82; and U.S. Patent No. 7,709,226). Typically, when using the Kabat numbering convention, the Chothia CDR-H1 loop is present at heavy chain amino acids 26 to 32, 33, or 34, the Chothia CDR-H2 loop is present at heavy chain amino acids 52 to 56, and the Chothia CDR-H3 loop is present at heavy chain amino acids 95 to 102, while the Chothia CDR-L1 loop is present at light chain amino acids 24 to 34, the Chothia CDR-L2 loop is present at light chain amino acids 50 to 56, and the Chothia CDR-L3 loop is present at light chain amino acids 89 to 97. The end of the Chothia CDR-HI loop when numbered using the Kabat numbering convention varies between H32 and H34 depending on the length of the loop (this is because the Kabat numbering scheme places the insertions at H35A and H35B; if neither 35A nor 35B is present, the loop ends at 32; if only 35A is present, the loop ends at 33; if both 35A and 35B are present, the loop ends at 34). In a specific embodiment, the CDRs of the antibodies described herein have been determined according to the Chothia numbering scheme.

[0048] The terms “constant region” and “constant domain” are interchangeable and have a meaning common in the art. The constant region is an antibody portion, *e.g.*, a carboxyl terminal portion of a light and/or heavy chain which is not directly involved in binding of an antibody to antigen but which can exhibit various effector functions, such as interaction with the Fc receptor. The constant region of an immunoglobulin molecule generally has a more conserved amino acid sequence relative to an immunoglobulin variable domain.

[0049] The term “heavy chain” when used in reference to an antibody can refer to any distinct type, *e.g.*, alpha (α), delta (δ), epsilon (ϵ), gamma (γ) and mu (μ), based on the amino acid sequence of the constant domain, which give rise to IgA, IgD, IgE, IgG and IgM classes of antibodies, respectively, including subclasses of IgG, *e.g.*, IgG₁, IgG₂, IgG₃ and IgG₄.

[0050] The term “light chain” when used in reference to an antibody can refer to any distinct type, *e.g.*, kappa (κ) or lambda (λ) based on the amino acid sequence of the constant domains. Light chain amino acid sequences are well known in the art. In specific embodiments, the light chain is a human light chain.

[0051] An “antigen” refers to a compound, composition, or substance that may stimulate the production of antibodies or a T cell response in a human or animal, including compositions (such as one that includes a tumor-specific protein) that are injected or absorbed into a human or animal. An antigen reacts with the products of specific humoral or cellular immunity, including those induced by heterologous antigens, such as the disclosed antigens. A “target antigen” or “target antigen of interest” is an antigen that is not substantially found on the surface of other normal (desired) cells and to which a binding domain of a TCR or CAR contemplated herein, is designed to bind. A person of skill in the art would readily understand that any macromolecule, including virtually all proteins or peptides, can serve as an antigen. An antigen can be endogenously expressed, *i.e.* expressed by genomic DNA, or can be recombinantly expressed. An antigen can be specific to a certain tissue, such as a cancer cell, or it can be broadly expressed. In addition, fragments of larger molecules can act as antigens. In one embodiment, antigens are tumor antigens. In one particular embodiment, the antigen is all or a fragment of transmembrane activator and CAML interactor (TACI) and/or B-cell maturation antigen (BCMA). A “target” is any molecule bound by a binding domain, antigen binding system, CAR or antigen binding agent, *e.g.*, an antibody.

[0052] “Antigen-specific targeting region” (ASTR) refers to the region of the CAR, antibody or TCR, which targets specific antigens. The targeting regions on a CAR or TCR are extracellular. In some embodiments, the antigen-specific targeting regions comprise an antibody or a functional equivalent thereof or a fragment thereof or a derivative thereof and each of the targeting regions target a different antigen. The targeting regions may comprise full length heavy chain, Fab fragments, single chain Fv (scFv) fragments, divalent single chain antibodies or diabodies, each of which are specific to the target antigen. There are, however, numerous alternatives, such as linked cytokines (which leads to recognition of cells bearing the cytokine receptor), affibodies, ligand binding domains from naturally occurring receptors, soluble protein/peptide ligand for a

receptor (for example on a tumor cell), peptides, and vaccines to prompt an immune response, which may each be used in various embodiments of this disclosure. In fact, almost any molecule that binds a given antigen with high affinity can be used as an antigen-specific targeting region, as will be appreciated by those of skill in the art.

[0053] “Antigen presenting cell” or “APC” refers to cells that process and present antigens to T cells. Exemplary APCs comprise dendritic cells, macrophages, B cells, certain activated epithelial cells, and other cell types capable of TCR stimulation and appropriate T cell costimulation.

[0054] An “anti-tumor effect” refers to a biological effect that can present as a decrease in tumor volume, a decrease in the number of tumor cells, a decrease in tumor cell proliferation, a decrease in the number of metastases, an increase in overall or progression-free survival, an increase in life expectancy, or amelioration of various physiological symptoms associated with the tumor. An anti-tumor effect can also refer to the prevention of the occurrence of a tumor.

[0055] Two events or entities are “associated” with one another if the presence, level, and/or form of one is correlated with that of the other. For example, an entity (*e.g.*, polypeptide, genetic signature, metabolite, microbe, etc.) is considered to be associated with a disease, disorder, or condition, if its presence, level, and/or form correlates with incidence of and/or susceptibility to the disease, disorder, or condition (*e.g.*, across a relevant population). For example, two or more entities are physically “associated” with one another if they interact, directly or indirectly, so that they are and/or remain in physical proximity with one another (*e.g.*, bind). In additional examples, two or more entities that are physically associated with one another are covalently linked or connected to one another, or non-covalently associated, for example by means of hydrogen bonds, van der Waals interaction, hydrophobic interactions, magnetism, and combinations thereof.

[0056] The term “autologous” refers to any material derived from the same individual to which it is later to be re-introduced. For example, the engineered autologous cell therapy (eACT™) method described herein involves collection of lymphocytes from a patient, which are then engineered to express, *e.g.*, a CAR construct, and then administered back to the same patient.

[0057] “Binding affinity” generally refers to the strength of the sum total of non-covalent interactions between a single binding site of a molecule (*e.g.*, an antibody) and its binding partner (*e.g.*, an antigen). Unless indicated otherwise “binding affinity” refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (*e.g.*, antibody and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (K_D). Affinity can be measured and/or expressed in a number of ways known in the art,

including, but not limited to, equilibrium dissociation constant (K_D), and equilibrium association constant (K_A). The K_D is calculated from the quotient of k_{off}/k_{on} , whereas K_A is calculated from the quotient of k_{on}/k_{off} . k_{on} refers to the association rate constant of, *e.g.*, an antibody to an antigen, and k_{off} refers to the dissociation of, *e.g.*, an antibody to an antigen. The k_{on} and k_{off} can be determined by techniques known to one of ordinary skill in the art, such as BIACORE® or KinExA.

[0058] The term “ K_D ” (M) refers to the dissociation equilibrium constant of a particular antibody-antigen interaction, or the dissociation equilibrium constant of an antibody or antibody-binding fragment binding to an antigen. There is an inverse relationship between K_D and binding affinity, therefore the smaller the K_D value, the higher, *i.e.* stronger, the affinity. Thus, the terms “higher affinity” or “stronger affinity” relate to a higher ability to form an interaction and therefore a smaller K_D value, and conversely the terms “lower affinity” or “weaker affinity” relate to a lower ability to form an interaction and therefore a larger K_D value. In some circumstances, a higher binding affinity (or K_D) of a particular molecule (*e.g.* antibody) to its interactive partner molecule (*e.g.* antigen X) compared to the binding affinity of the molecule (*e.g.* antibody) to another interactive partner molecule (*e.g.* antigen Y) may be expressed as a binding ratio determined by dividing the larger K_D value (lower, or weaker, affinity) by the smaller K_D (higher, or stronger, affinity), for example expressed as 5-fold or 10-fold greater binding affinity, as the case may be.

[0059] The term “ k_d ” (sec⁻¹ or 1/s) refers to the dissociation rate constant of a particular antibody-antigen interaction, or the dissociation rate constant of an antibody or antibody-binding fragment. Said value is also referred to as the k_{off} value.

[0060] The term “ k_a ” (M⁻¹ x sec⁻¹ or 1/M) refers to the association rate constant of a particular antibody-antigen interaction, or the association rate constant of an antibody or antibody-binding fragment.

[0061] The term “ K_A ” (M⁻¹ or 1/M) refers to the association equilibrium constant of a particular antibody-antigen interaction, or the association equilibrium constant of an antibody or antibody binding fragment. The association equilibrium constant is obtained by dividing the k_a by the k_d .

[0062] The term “binding” generally refers to a non-covalent association between or among two or more entities. Direct binding involves physical contact between entities or moieties. “Indirect” binding involves physical interaction by way of physical contact with one or more intermediate entities. Binding between two or more entities may be assessed in any of a variety of contexts, *e.g.*, where interacting entities or moieties are studied in isolation or in the context of more

complex systems (*e.g.*, while covalently or otherwise associated with a carrier entity and/or in a biological system such as a cell).

[0063] The terms “immunospecifically binds,” “immunospecifically recognizes,” “specifically binds,” and “specifically recognizes” are analogous terms in the context of antibodies and refer to molecules that bind to an antigen (*e.g.*, epitope or immune complex) as such binding is understood by one skilled in the art. For example, a molecule that specifically binds to an antigen may bind to other peptides or polypeptides, generally with lower affinity as determined by, *e.g.*, immunoassays, BIAcore®, KinExA 3000 instrument (Sapidyne Instruments, Boise, ID), or other assays known in the art. In a specific embodiment, molecules that specifically bind to an antigen bind to the antigen with a K_A that is at least 2 logs, 2.5 logs, 3 logs, 4 logs or greater than the K_A when the molecules bind to another antigen. Binding may comprise preferential association of a binding domain, antibody, or antigen binding system with a target of the binding domain, antibody, or antigen binding system as compared to association of the binding domain, antibody, or antigen binding system with an entity that is not the target (*i.e.* non-target). In some embodiments, the binding domain, antibody, or antigen binding system can bind two different but related targets, such as both TACI and BCMA. In some embodiments, a binding domain, antibody, or antigen binding system selectively binds a target if binding between the binding domain, antibody, or antigen binding system and the target is greater than 2-fold, greater than 5-fold, greater than 10-fold, 20-fold, 30-fold, 40-fold, 50-fold, 60-fold, 70-fold, 80-fold, 90-fold, or greater than 100-fold as compared with binding of the binding domain, antibody, or antigen binding system and a non-target. In some embodiments, a binding domain, antibody, or antigen binding system selectively binds a target if the binding affinity is less than about 10^{-5} M, less than about 10^{-6} M, less than about 10^{-7} M, less than about 10^{-8} M, or less than about 10^{-9} M.

[0064] In another embodiment, molecules that specifically bind to an antigen bind with a dissociation constant (K_d) of about 1×10^{-7} M. In some embodiments, the antigen binding molecule specifically binds an antigen with “high affinity” when the K_d is about 1×10^{-9} M to about 5×10^{-9} M. In some embodiments, the antigen binding molecule specifically binds an antigen with “very high affinity” when the K_d is 1×10^{-10} M to about 5×10^{-10} M. In one embodiment, the antigen binding molecule has a K_d of 10^{-9} M. In one embodiment, the off-rate is less than about 1×10^{-5} . In embodiments, the antigen binding molecule binds TACI and BCMA with a K_d of about 1×10^{-10} M to about 5×10^{-10} M.

[0065] In certain embodiments, provided herein is an antibody or an antigen binding molecule thereof that binds to the target human antigen, *e.g.*, In certain embodiments, the antigen binding

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

[0066] “Cancer” refers to a broad group of various diseases characterized by the uncontrolled growth of abnormal cells in the body. Unregulated cell division and growth results in the formation of malignant tumors that invade neighboring tissues and may also metastasize to distant parts of the body through the lymphatic system or bloodstream. A “cancer” or “cancer tissue” can include a tumor. In some embodiments, the methods of the present disclosure can be used to reduce the tumor size of a tumor derived from, for example, prostate cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, multiple myeloma, Hodgkin’s Disease, non-Hodgkin’s lymphoma (NHL), primary mediastinal large B cell lymphoma (PMBC), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), transformed follicular lymphoma, splenic marginal zone lymphoma (SMZL), cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, chronic or acute leukemia, acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia (ALL) (including non T cell ALL), chronic lymphocytic leukemia (CLL), solid tumors of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi’s sarcoma, epidermoid cancer, squamous cell cancer, T cell lymphoma, environmentally induced cancers including those induced by asbestos, other B cell malignancies, multiple myeloma, and combinations of said cancers. The particular cancer can be responsive to chemo- or radiation therapy or the cancer can be refractory. A refractory cancer refers to a cancer that is not amendable to surgical intervention and the cancer is either initially unresponsive to chemo- or radiation therapy or the cancer becomes unresponsive over time.

[0067] “Chemokines” are a type of cytokine that mediates cell chemotaxis, or directional movement. Examples of chemokines include, but are not limited to, IL-8, IL-16, eotaxin, eotaxin-3, macrophage-derived chemokine (MDC or CCL22), monocyte chemotactic protein 1 (MCP-1 or CCL2), MCP-4, macrophage inflammatory protein 1 α (MIP-1 α , MIP-1a), MIP-1 β (MIP-1b), gamma-induced protein 10 (IP-10), and thymus and activation regulated chemokine (TARC or CCL17).

[0068] “Chimeric antigen receptor” or “CAR” refers to a molecule engineered to comprise a binding domain and a means of activating immune cells (for example T cells such as naive T cells, central memory T cells, effector memory T cells, NK cells or combination thereof) upon antigen binding. CARs are also known as artificial T cell receptors, chimeric T cell receptors or chimeric immunoreceptors. In some embodiments, a CAR comprises a binding domain, an extracellular domain, a transmembrane domain, one or more co-stimulatory domains, and an intracellular signaling domain. A T cell that has been genetically engineered to express a chimeric antigen receptor may be referred to as a CAR T cell. Similarly, an NK cell that has been genetically engineered to express a chimeric antigen receptor may be referred to as a CAR NK cell.

[0069] By “decrease” or “lower,” or “lessen,” or “reduce,” or “abate” refers generally to the ability of a composition contemplated herein to produce, elicit, or cause a lesser physiological response (i.e., a downstream effect) compared to the response caused by either the vehicle alone (i.e., an active moiety) or a control molecule/composition. A “decrease” or “reduced” amount is typically a “statistically significant” amount, and may include an decrease that is 1.1, 1.2, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 15, 20, 30 or more times (e.g., 500, 1000 times) (including all integers and decimal points in between and above 1, e.g., 1.5, 1.6, 1.7, 1.8, etc.) the response (reference response) produced by vehicle, a control composition.

[0070] “Extracellular domain” (or “ECD”) refers to a portion of a polypeptide that, when the polypeptide is present in a cell membrane, is understood to reside outside of the cell membrane, in the extracellular space.

[0071] The term “extracellular ligand-binding domain,” as used herein, refers to an oligo- or polypeptide that is capable of binding a ligand, e.g., a cell surface molecule. For example, the extracellular ligand-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 (e.g., cancer). Examples of cell surface markers that may act as ligands include those associated with viral, bacterial and parasitic infections, autoimmune disease and cancer cells.

[0072] The binding domain of the CAR may be followed by a “spacer,” or, “hinge,” which refers to the region that moves the antigen binding domain away from the effector cell surface to enable proper cell/cell contact, antigen binding and activation (Patel et al., Gene Therapy, 1999; 6: 412-419). The hinge region in a CAR is generally between the transmembrane (TM) and the binding domain. In certain embodiments, a hinge region is an immunoglobulin hinge region and may be a wild type immunoglobulin hinge region or an altered wild type immunoglobulin hinge region. Other exemplary hinge regions used in the CARs described herein include the hinge region derived from the extracellular regions of type 1 membrane proteins such as CD8alpha, CD4, CD28 and CD7, which may be wild-type hinge regions from these molecules or may be altered.

[0073] The “transmembrane” region or domain is the portion of the CAR that anchors the extracellular binding portion to the plasma membrane of the immune effector cell, and facilitates binding of the binding domain to the target antigen. The transmembrane domain may be a CD3zeta transmembrane domain, however other transmembrane domains that may be employed include those obtained from CD8alpha, CD4, CD28, CD45, CD9, CD16, CD22, CD33, CD64, CD80, CD86, CD134, CD137, NKG2D, 2B4 and CD154. In certain embodiments, the transmembrane domain is synthetic in which case it would comprise predominantly hydrophobic residues such as leucine and valine.

[0074] The “intracellular signaling domain” or “signaling domain” refers to the part of the chimeric antigen receptor protein that participates in transducing the message of effective CAR binding to a target antigen into the interior of the immune effector cell to elicit effector cell function, e.g., activation, cytokine production, proliferation and cytotoxic activity, including the release of cytotoxic factors to the CAR-bound target cell, or other cellular responses elicited with antigen binding to the extracellular CAR domain. The term “effector function” refers to a specialized function of the cell. Effector function of the T cell, for example, may be cytolytic activity or help or activity including the secretion of a cytokine. Thus, the terms “intracellular signaling domain” or “signaling domain,” used interchangeably herein, refer to the portion of a protein which transduces the effector function signal and that 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 domain. To the extent that a truncated portion of an intracellular signaling domain is used, such truncated portion may be used in place of the entire domain as long as it transduces the effector function signal. The term intracellular signaling domain is meant to include any truncated portion of the intracellular signaling domain sufficient to transducing effector function signal. The intracellular signaling domain is also known as the,

“signal transduction domain,” and is typically derived from portions of the human CD3 or FcRγ chains.

[0075] It is known that signals generated through the T cell receptor alone are insufficient for full activation of the T cell and that a secondary, 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 T cell receptor (primary cytoplasmic signaling sequences) and those that act in an antigen independent manner to provide a secondary or costimulatory signal (secondary cytoplasmic signaling sequences). Cytoplasmic signaling sequences that act in a costimulatory manner may contain signaling domains which are known as immunoreceptor tyrosine-based activation domain or ITAMs.

[0076] Examples of ITAM containing primary cytoplasmic signaling sequences that are of particular use in the disclosure include those derived from DAP10, DAP12, TCRζeta, FcRγgamma, FcRβeta, CD3ζeta, CD3γgamma, CD3δdelta, CD3εepsilon, CD5, CD22, CD79a, CD79b and CD66d.

[0077] As used herein, the term, “costimulatory signaling domain,” or “costimulatory domain”, refers to the portion of the CAR comprising the intracellular domain of a costimulatory molecule. Costimulatory molecules are cell surface molecules other than antigen receptors or Fc receptors that provide a second signal required for efficient activation and function of T lymphocytes upon binding to antigen. Examples of such co-stimulatory molecules include CD27, CD28, 4-1 BB (CD137), OX40 (CD134), CD30, CD40, PD-1, ICOS (CD278), LFA-1, CD2, CD7, LIGHT, NKD2C, 2B4, CD137, DAP12, B7-H2 and a ligand that specifically binds CD83. Accordingly, while the present disclosure provides exemplary costimulatory domains derived from CD28, other costimulatory domains are contemplated for use with the CARs described herein. The inclusion of one or more co stimulatory signaling domains may enhance the efficacy and expansion of T cells and NK cells expressing CAR receptors. The intracellular signaling and costimulatory signaling domains may be linked in any order in tandem to the carboxyl terminus of the transmembrane domain.

[0078] Although scFv-based CARs engineered to contain a signaling domain from CD3 or FcRγgamma have been shown to deliver a potent signal for T cell activation and effector function, they are not sufficient to elicit signals that promote T cell survival and expansion in the absence of a concomitant costimulatory signal. Other CARs containing a binding domain, a hinge, a transmembrane and the signaling domain derived from CD3ζeta or FcRγgamma together with one or more costimulatory signaling domains (e.g., intracellular costimulatory domains derived from 4-1BB, CD28, CD134 and CD278) may more effectively direct antitumor activity as well as

increased cytokine secretion, lytic activity, survival and proliferation in CAR expressing T cells in vitro, and in animal models and cancer patients (Milone et al., Molecular Therapy, 2009; 17: 1453-1464; Zhong et al., Molecular Therapy, 2010; 18: 413-420; Carpenito et al., PNAS, 2009; 106:3360-3365).

[0079] A “costimulatory signal” refers to a signal, which in combination with a primary signal, such as TCR/CD3 ligation, leads to a T cell response, such as, but not limited to, proliferation and/or upregulation or down regulation of key molecules.

[0080] A “costimulatory ligand” includes a molecule on an antigen presenting cell that specifically binds a cognate co-stimulatory molecule on a T cell. Binding of the costimulatory ligand provides a signal that mediates a T cell response, including, but not limited to, proliferation, activation, differentiation, and the like. A costimulatory ligand induces a signal that is in addition to the primary signal provided by a stimulatory molecule, for instance, by binding of a T cell receptor (TCR)/CD3 complex with a major histocompatibility complex (MHC) molecule loaded with peptide. A co-stimulatory ligand can include, but is not limited to, 3/TR6, 4-1BB ligand, agonist or antibody that binds Toll ligand receptor, B7-1 (CD80), B7-2 (CD86), CD30 ligand, CD40, CD7, CD70, CD83, herpes virus entry mediator (HVEM), human leukocyte antigen G (HLA-G), ILT4, immunoglobulin-like transcript (ILT) 3, inducible costimulatory ligand (ICOS-L), intercellular adhesion molecule (ICAM), ligand that specifically binds with B7-H3, lymphotoxin beta receptor, MHC class I chain-related protein A (MICA), MHC class I chain-related protein B (MICB), OX40 ligand, PD-L2, or programmed death (PD) L1. A co-stimulatory ligand includes, without limitation, an antibody that specifically binds with a co-stimulatory molecule present on a T cell, such as, but not limited to, 4-1BB, B7-H3, CD2, CD27, CD28, CD30, CD40, CD7, ICOS, ligand that specifically binds with CD83, lymphocyte function-associated antigen-1 (LFA-1), natural killer cell receptor C (NKG2C), OX40, PD-1, or tumor necrosis factor superfamily member 14 (TNFSF14 or LIGHT).

[0081] A “costimulatory molecule” is a cognate binding partner on a T cell that specifically binds with a costimulatory ligand, thereby mediating a costimulatory response by the T cell, such as, but not limited to, proliferation. Costimulatory molecules include, but are not limited to, A “costimulatory molecule” is a cognate binding partner on a T cell that specifically binds with a costimulatory ligand, thereby mediating a costimulatory response by the T cell, such as, but not limited to, proliferation. Costimulatory molecules include, but are not limited to, 4-1BB/CD137, B7-H3, BAFFR, BLAME (SLAMF8), BTLA, CD 33, CD 45, CD100 (SEMA4D), CD103, CD134, CD137, CD154, CD16, CD160 (BY55), CD18, CD19, CD19a, CD2, CD22, CD247,

CD27, CD276 (B7-H3), CD28, CD29, CD3 (alpha; beta; delta; epsilon; gamma; zeta), CD30, CD37, CD4, CD40, CD49a, CD49D, CD49f, CD5, CD64, CD69, CD7, CD80, CD83 ligand, CD84, CD86, CD8alpha, CD8beta, CD9, CD96 (Tactile), CD1-la, CD1-lb, CD1-lc, CD1-ld, CDS, CEACAM1, CRT AM, DAP-10, DNAM1 (CD226), Fc gamma receptor, GADS, GITR, HVEM (LIGHTR), IA4, ICAM-1, ICAM-1, ICOS, Ig alpha (CD79a), IL2R beta, IL2R gamma, IL7R alpha, integrin, ITGA4, ITGA4, ITGA6, ITGAD, ITGAE, ITGAL, ITGAM, ITGAX, ITGB2, ITGB7, ITGB1, KIRDS2, LAT, LFA-1, LFA-1, LIGHT, LIGHT (tumor necrosis factor superfamily member 14; TNFSF14), LTBR, Ly9 (CD229), lymphocyte function-associated antigen-1 (LFA-1 (CD1 la/CD18), MHC class I molecule, NKG2C, NKG2D, NKp30, NKp44, NKp46, NKp80 (KLRF1), OX40, PAG/Cbp, PD-1, PSGL1, SELPLG (CD162), signaling lymphocytic activation molecule, SLAM (SLAMF1; CD150; IPO-3), SLAMF4 (CD244; 2B4), SLAMF6 (NTB-A; Lyl08), SLAMF7, SLP-76, TNF, TNFr, TNFR2, Toll ligand receptor, TRANCE/RANKL, VLA1, or VLA-6, or fragments, truncations, or combinations thereof.

[0082] A “conservative amino acid substitution” is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). In certain embodiments, one or more amino acid residues within a CDR(s) or within a framework region(s) of an antibody or antigen-binding molecule thereof can be replaced with an amino acid residue with a similar side chain. In general, two sequences are generally considered to be “substantially similar” if they contain a conservative amino acid substitution in corresponding positions. For example, certain amino acids are generally classified as “hydrophobic” or “hydrophilic” amino acids, and/or as having “polar” or “non-polar” side chains. Substitution of one amino acid for another of the same type may be considered a conservative substitution. Exemplary amino acid categorizations are summarized in Tables 2 and 3 below:

Table 2: Exemplary amino acid categorization

Amino Acid	3-Letter	1-Letter	Property	Property	Hydropathy Index
Alanine	Ala	A	nonpolar	neutral	1.8
Arginine	Arg	R	polar	positive	-4.5
Asparagine	Asn	N	polar	neutral	-3.5

Aspartic acid	Asp	D	polar	negative	-3.5
Cysteine	Cys	C	nonpolar	neutral	2.5
Glutamic acid	Glu	E	polar	negative	-3.5
Glutamine	Gln	Q	polar	neutral	-3.5
Glycine	Gly	G	nonpolar	neutral	-0.4
Histidine	His	H	polar	positive	-3.2
Isoleucine	Ile	I	nonpolar	neutral	4.5
Leucine	Leu	L	nonpolar	neutral	3.8
Lysine	Lys	K	polar	positive	-3.9
Methionine	Met	M	nonpolar	neutral	1.9
Phenylalanine	Phe	F	nonpolar	neutral	2.8
Proline	Pro	P	nonpolar	neutral	-1.6
Serine	Ser	S	polar	neutral	-0.8
Threonine	Thr	T	polar	neutral	-0.7
Tryptophan	Trp	W	nonpolar	neutral	-0.9
Tyrosine	Tyr	Y	polar	neutral	-1.3
Valine	Val	V	nonpolar	neutral	4.2

Table 3: Exemplary amino acid categorization

Ambiguous Amino Acids	3-Letter	1-Letter
Asparagine or aspartic acid	Asx	B
Glutamine or glutamic acid	Glx	Z
Leucine or Isoleucine	Xle	J
Unspecified or unknown amino acid	Xaa	X

[0083] “Combination therapy” refers to those situations in which a subject is simultaneously exposed to two or more therapeutic regimens (*e.g.*, two or more therapeutic moieties). In some embodiments, the two or more regimens may be administered simultaneously; in some embodiments, such regimens may be administered sequentially (*e.g.*, all “doses” of a first regimen are administered prior to administration of any doses of a second regimen); in some embodiments, such agents are administered in overlapping dosing regimens. In some embodiments, “administration” of combination therapy may involve administration of one or more agent(s) or modality(ies) to a subject receiving the other agent(s) or modality(ies) in the combination. For clarity, combination therapy does not require that individual agents be administered together in a single composition (or even necessarily at the same time), although in some embodiments, two or more agents, or active moieties thereof, may be administered together in a combination composition, or even in a combination compound (*e.g.*, as part of a single chemical complex or covalent entity).

[0084] “Corresponding to” may be used to designate the position/identity of a structural element in a molecule or composition through comparison with an appropriate reference molecule or composition. For example, in some embodiments, a monomeric residue in a polymer (*e.g.*, an

amino acid residue in a polypeptide or a nucleic acid residue in a polynucleotide) may be identified as “corresponding to” a residue in an appropriate reference polymer. For example, for purposes of simplicity, residues in a polypeptide may be designated using a canonical numbering system based on a reference related polypeptide, so that an amino acid “corresponding to” a residue at position 100, for example, need not actually be the 100th amino acid in an amino acid chain provided it corresponds to the residue found at position 100 in the reference polypeptide. Various sequence alignment strategies are available, comprising software programs such as, for example, BLAST, CS-BLAST, CUDASW++, DIAMOND, FASTA, GGSEARCH/GLSEARCH, Genoogle, HMMER, HHpred/HHsearch, IDF, Infernal, KLAST, USEARCH, parasail, PSI-BLAST, PSI-Search, ScalaBLAST, Sequilab, SAM, SSEARCH, SWAPHI, SWAPHI-LS, SWIMM, or SWIPE that may be utilized, for example, to identify “corresponding” residues in polypeptides and/or nucleic acids in accordance with the present disclosure.

[0085] An antigen binding molecule, such as an antibody, an antigen binding fragment thereof, CAR or TCR, “cross-competes” with a reference binding molecule, such as an antibody or an antigen binding fragment thereof, if the interaction between an antigen and the first antigen binding molecule blocks, limits, inhibits, or otherwise reduces the ability of the reference binding molecule to interact with the antigen. Cross competition can be complete, *e.g.*, binding of the antigen binding molecule to the antigen completely blocks the ability of the reference binding molecule to bind the antigen, or it can be partial, *e.g.*, binding of the antigen binding molecule to the antigen reduces the ability of the reference antigen binding molecule to bind the antigen. In certain embodiments, an antigen binding molecule that cross-competes with a reference antigen binding molecule binds the same or an overlapping epitope as the reference antigen binding molecule. In other embodiments, the antigen binding molecule that cross-competes with a reference antigen binding molecule binds a different epitope than the reference antigen binding molecule. Numerous types of competitive binding assays can be used to determine if one antigen binding molecule competes with another, for example: solid phase direct or indirect radioimmunoassay (RIA); solid phase direct or indirect enzyme immunoassay (EIA); sandwich competition assay (Stahli et al., 1983, *Methods in Enzymology* 9:242-253); solid phase direct biotin-avidin EIA (Kirkland et al., 1986, *J. Immunol.* 137:3614-3619); solid phase direct labeled assay, solid phase direct labeled sandwich assay (Harlow and Lane, 1988, *Antibodies, A Laboratory Manual*, Cold Spring Harbor Press); solid phase direct label RIA using 1-125 label (Morel et al., 1988, *Molec. Immunol.* 25:7-15); solid phase direct biotin-avidin EIA (Cheung, et al., 1990, *Virology* 176:546-552); and direct labeled RIA (Moldenhauer et al., 1990, *Scand. J. Immunol.* 32:77-82).

[0086] A “cytokine,” refers to a non-antibody protein that is released by one cell in response to contact with a specific antigen, wherein the cytokine interacts with a second cell to mediate a response in the second cell. A cytokine can be endogenously expressed by a cell or administered to a subject. Cytokines may be released by immune cells, including macrophages, B cells, T cells, and mast cells to propagate an immune response. Cytokines can induce various responses in the recipient cell. Cytokines can include homeostatic cytokines, chemokines, pro-inflammatory cytokines, effectors, and acute-phase proteins. For example, homeostatic cytokines, including interleukin (IL) 7 and IL-15, promote immune cell survival and proliferation, and pro-inflammatory cytokines can promote an inflammatory response. Examples of homeostatic cytokines include, but are not limited to, IL-2, IL-4, IL-5, IL-7, IL-10, IL-12p40, IL-12p70, IL-15, and interferon (IFN) gamma. Examples of pro-inflammatory cytokines include, but are not limited to, IL-1a, IL-1b, IL-6, IL-13, IL-17a, tumor necrosis factor (TNF)-alpha, TNF-beta, fibroblast growth factor (FGF) 2, granulocyte macrophage colony-stimulating factor (GM-CSF), soluble intercellular adhesion molecule 1 (sICAM-1), soluble vascular adhesion molecule 1 (sVCAM-1), vascular endothelial growth factor (VEGF), VEGF-C, VEGF-D, and placental growth factor (PLGF). Examples of effectors include, but are not limited to, granzyme A, granzyme B, soluble Fas ligand (sFasL), and perforin. Examples of acute phase-proteins include, but are not limited to, C-reactive protein (CRP) and serum amyloid A (SAA).

[0087] The term “domain” refers to a portion of an entity. In some embodiments, a “domain” is associated with a structural and/or functional feature of the entity, *e.g.*, so that, when the domain is physically separated from the rest of its parent entity, it substantially or entirely retains the structural and/or functional feature. In some embodiments, a domain may comprise a portion of an entity that, when separated from that (parent) entity and linked or connected with a different (recipient) entity, substantially retains and/or imparts on the recipient entity one or more structural and/or functional features, *e.g.*, that characterized it in the parent entity. In some embodiments, a domain is a portion of a molecule (*e.g.*, a small molecule, carbohydrate, lipid, nucleic acid, or polypeptide). In some embodiments, a domain is a section of a polypeptide; in some such embodiments, a domain is characterized by a structural element (*e.g.*, an amino acid sequence or sequence domain, α -helix character, β -sheet character, coiled-coil character, random coil character, etc.), and/or by a functional feature (*e.g.*, binding activity, enzymatic activity, folding activity, signaling activity, etc.).

[0088] The term “dosage form” may be used to refer to a physically discrete unit of an active agent (*e.g.*, an antigen binding system or antibody) for administration to a subject. Generally, each such unit contains a predetermined quantity of active agent. In some embodiments, such quantity

is a unit dosage amount (or a whole fraction thereof) appropriate for administration in accordance with a dosing regimen that has been determined to correlate with a desired or beneficial outcome when administered to a relevant population. The total amount of a therapeutic composition or agent administered to a subject is determined by one or more medical practitioners and may involve administration of more than one dosage forms.

[0089] The term “dosing regimen” may be used to refer to a set of one or more unit doses that are administered individually to a subject. In some embodiments, a given therapeutic agent has a recommended dosing regimen, which may involve one or more doses. In some embodiments, a dosing regimen comprises a plurality of doses each of which is separated in time from other doses. In some embodiments, a dosing regimen comprises a plurality of doses and consecutive doses are separated from one another by time periods of equal length; in some embodiments, a dosing regimen comprises a plurality of doses and consecutive doses are separated from one another by time periods of at least two different lengths. In some embodiments, all doses within a dosing regimen are of the same unit dose amount. In some embodiments, different doses within a dosing regimen are of different amounts. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount different from the first dose amount. In some embodiments, a dosing regimen is periodically adjusted to achieve a desired or beneficial outcome.

[0090] “Effector cell” refers to a cell of the immune system that expresses one or more Fc receptors and mediates one or more effector functions. In some embodiments, effector cells may comprise, without limitation, one or more of monocytes, macrophages, neutrophils, dendritic cells, eosinophils, mast cells, platelets, large granular lymphocytes, Langerhans’ cells, natural killer (NK) cells, T-lymphocytes, and B-lymphocytes. Effector cells may be of any organism comprising, without limitation, humans, mice, rats, rabbits, and monkeys.

[0091] “Effector function” refers to a biological result of interaction of an antibody Fc region with an Fc receptor or ligand. Effector functions comprise, without limitation, antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADCP), and complement-mediated cytotoxicity (CMC). An effector function may be antigen binding dependent, antigen binding independent, or both. ADCC refers to lysis of antibody-bound target cells by immune effector cells. Without wishing to be bound by any theory, ADCC is generally understood to involve Fc receptor (FcR)-bearing effector cells recognizing and subsequently killing antibody-coated target cells (*e.g.*, cells that express on their surface antigens to which an

antibody is bound). Effector cells that mediate ADCC may comprise immune cells, comprising yet not limited to, one or more of natural killer (NK) cells, macrophages, neutrophils, eosinophils.

[0092] The term “engineered Autologous Cell Therapy,” which can be abbreviated as “eACT™,” also known as adoptive cell transfer, is a process by which a patient’s own T cells are collected and subsequently genetically altered to recognize and target one or more antigens expressed on the cell surface of one or more specific tumor cells or malignancies. T cells can be engineered to express, for example, chimeric antigen receptors (CAR) or T cell receptor (TCR). CAR positive (+) T cells are engineered to express an extracellular single chain variable fragment (scFv) with specificity for a particular tumor antigen linked to an intracellular signaling part comprising at least one costimulatory domain and at least one activating domain. The costimulatory domain can be derived from a naturally-occurring costimulatory domain, or a variant thereof, *e.g.*, a variant having a truncated hinge domain (“THD”), and the activating domain can be derived from, *e.g.*, CD3-zeta. In certain embodiments, the CAR is designed to have two, three, four, or more costimulatory domains. The CAR scFv can be designed to target, for example, TACI and BCMA, which are transmembrane proteins expressed on multiple myeloma cells.

[0093] In some embodiments, the CAR is engineered such that the costimulatory domain is expressed as a separate polypeptide chain. Example CAR T cell therapies and constructs are described in U.S. Patent Publication Nos. 2013/0287748, 2014/0227237, 2014/0099309, and 2014/0050708, which are incorporated by reference in their entirety. “Adoptive cell therapy” or “ACT” involves transfer of immune cells with anti-tumor activity into a subject, *e.g.*, a cancer patient. In some embodiments, ACT is a treatment approach that involves the use of lymphocytes (*e.g.*, engineered lymphocytes) with anti-tumor activity.

[0094] An “epitope” refers to a localized region of an antigen to which an antibody can specifically bind. An epitope can be, for example, contiguous amino acids of a polypeptide (linear or contiguous epitope) or an epitope can, for example, come together from two or more non-contiguous regions of a polypeptide or polypeptides (conformational, non-linear, discontinuous, or non-contiguous epitope). In certain embodiments, the epitope to which an antibody binds can be determined by, *e.g.*, NMR spectroscopy, X-ray diffraction crystallography studies, ELISA assays, hydrogen/deuterium exchange coupled with mass spectrometry (*e.g.*, liquid chromatography electrospray mass spectrometry), array-based oligo-peptide scanning assays, and/or mutagenesis mapping (*e.g.*, site-directed mutagenesis mapping). For X-ray crystallography, crystallization may be accomplished using any of the known methods in the art (*e.g.*, Giegé R *et al.*, (1994) *Acta Crystallogr D Biol Crystallogr* 50(Pt 4): 339-350; McPherson A

(1990) Eur J Biochem 189: 1-23; Chayen NE (1997) Structure 5: 1269-1274; McPherson A (1976) J Biol Chem 251: 6300-6303). Antibody:antigen crystals may be studied using well known X-ray diffraction techniques and may be refined using computer software such as X-PLOR (Yale University, 1992, distributed by Molecular Simulations, Inc.; see e.g. Meth Enzymol (1985) volumes 114 & 115, eds Wyckoff HW *et al.*; U.S. 2004/0014194), and BUSTER (Bricogne G (1993) Acta Crystallogr D Biol Crystallogr 49(Pt 1): 37-60; Bricogne G (1997) Meth Enzymol 276A: 361-423, ed Carter CW; Roversi P *et al.*, (2000) Acta Crystallogr D Biol Crystallogr 56(Pt 10): 1316-1323). Mutagenesis mapping studies may be accomplished using any method known to one of skill in the art. *See, e.g.*, Champe M *et al.*, (1995) J Biol Chem 270: 1388-1394 and Cunningham BC & Wells JA (1989) Science 244: 1081-1085 for a description of mutagenesis techniques, including alanine scanning mutagenesis techniques.

[0095] “Endogenous” with reference to a gene, protein, and/or nucleic acid refers to the natural presence of that gene, protein, and/or nucleic acid in a cell, such as an immune cell.

[0096] “Exogenous” refers to an introduced agent, such as a nucleic acid, gene, or protein, into a cell, for example from an outside source. A nucleic acid introduced into a cell is exogenous even if it encodes a protein which is naturally found in the cell. Such exogenous introduction of a nucleic acid encoding a protein can be used to increase the expression of the protein over the level that would naturally be found in the cell under similar conditions, e.g. without introduction of the exogenous nucleic acid.

[0097] The term “excipient” refers to an agent that may be comprised in a composition, for example to provide or contribute to a desired consistency or stabilizing effect. In some embodiments, a suitable excipient may comprise, for example, starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol, or the like.

[0098] A “fragment” or “portion” of a material or entity as described herein has a structure that comprises a discrete portion of the whole, *e.g.*, of a physical entity or abstract entity. In some embodiments, a fragment lacks one or more moieties found in the whole. In some embodiments, a fragment consists of or comprises a characteristic structural element, domain or moiety found in the whole. In some embodiments, a polymer fragment comprises or consists of at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500 or more monomeric units (*e.g.*, residues) as found in the whole polymer. In some embodiments, a polymer fragment comprises or consists of at least about

5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more of the monomeric units (*e.g.*, residues) found in the whole polymer (*e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%). The whole material or entity may in some embodiments be referred to as the “parent” of the fragment.

[0099] The term “fusion polypeptide” or “fusion protein” generally refers to a polypeptide comprising at least two segments. Generally, a polypeptide containing at least two such segments is considered to be a fusion polypeptide if the two segments are moieties that (1) are not comprised in nature in the same peptide, and/or (2) have not previously been linked or connected to one another in a single polypeptide, and/or (3) have been linked or connected to one another through action of the hand of man. In embodiments, a CAR is a fusion protein. In embodiments, a TCR is a fusion protein.

[0100] The term “gene product” or “expression product” generally refers to an RNA transcribed from the gene (pre-and/or post-processing) or a polypeptide (pre- and/or post-modification) encoded by an RNA transcribed from the gene.

[0101] The term “genetically engineered” or “engineered” refers to a method of modifying the genome of a cell, including, but not limited to, deleting a coding or non-coding region or a portion thereof or inserting a coding region or a portion thereof. In some embodiments, the cell that is modified is a lymphocyte, *e.g.*, a T cell or NK cell, which can either be obtained from a patient or a donor. In some embodiments, the cell that is modified is an induced pluripotent stem cell (iPSC) which can be differentiated to a lymphocyte, such as a T cell or NK cell. The cell can be modified to express an exogenous construct, such as, *e.g.*, a chimeric antigen receptor (CAR) or a T cell receptor (TCR), which is incorporated into the cell’s genome. Other gene edits can also be done., for example to reduce rejection and/or enhance cell fitness. Engineering generally comprises manipulation by the hand of man. For example, a polynucleotide is considered to be “engineered” when two or more sequences, that are not linked or connected together in that order in nature, are manipulated by the hand of man to be directly linked or connected to one another in the engineered polynucleotide. In the context of manipulation of cells by techniques of molecular biology, a cell or organism is considered to be “engineered” if it has been manipulated so that its genetic information is altered (*e.g.*, new genetic material not previously present has been introduced, for example by transformation, somatic hybridization, transfection, transduction, or other mechanism, or previously present genetic material is altered or removed, for example by substitution or deletion mutation, or by other protocols). In some embodiments, a binding agent is a modified lymphocyte, *e.g.*, a T cell or NK cell, may be obtained from a patient or a donor. An engineered

cell may be modified to express an exogenous construct, such as, *e.g.*, a chimeric antigen receptor (CAR) or a T cell receptor (TCR), which is incorporated into the cell's genome. Progeny of an engineered polynucleotide or binding agent are generally referred to as "engineered" even though the actual manipulation was performed on a prior entity. In some embodiments, "engineered" refers to an entity that has been designed and produced. The term "designed" refers to an agent (i) whose structure is or was selected by the hand of man; (ii) that is produced by a process requiring the hand of man; and/or (iii) that is distinct from natural substances and other known agents.

[0102] A "T cell receptor" or "TCR" refers to antigen-recognition molecules present on the surface of T cells. During normal T cell development, each of the four TCR genes, α , β , γ , and δ , may rearrange leading to highly diverse TCR proteins.

[0103] The term "heterologous" means from any source other than naturally occurring sequences. For example, a heterologous sequence included as a part of a costimulatory protein is amino acids that do not naturally occur as, *i.e.*, do not align with, the wild type human costimulatory protein. For example, a heterologous nucleotide sequence refers to a nucleotide sequence other than that of the wild type human costimulatory protein-encoding sequence.

[0104] Term "identity" refers to the overall relatedness between polymeric molecules, *e.g.*, between nucleic acid molecules (*e.g.*, DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Methods for the calculation of a percent identity as between two provided polypeptide sequences are known. Calculation of the percent identity of two nucleic acid or polypeptide sequences, for example, may be performed by aligning the two sequences for optimal comparison purposes (*e.g.*, gaps may be introduced in one or both of a first and a second sequences for optimal alignment and non-identical sequences may be disregarded for comparison purposes). The nucleotides or amino acids at corresponding positions are then compared. When a position in the first sequence is occupied by the same residue (*e.g.*, nucleotide or amino acid) as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, optionally taking into account the number of gaps, and the length of each gap, which may need to be introduced for optimal alignment of the two sequences. Comparison or alignment of sequences and determination of percent identity between two sequences may be accomplished using a mathematical algorithm, such as BLAST (basic local alignment search tool). In some embodiments, polymeric molecules are considered to be "homologous" to one another if their sequences are at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%,

85%, 90%, 95%, or 99% identical (e.g., 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%).

[0105] To calculate percent identity, the sequences being compared are typically aligned in a way that gives the largest match between the sequences. One example of a computer program that can be used to determine percent identity is the GCG program package, which includes GAP (Devereux et al., 1984, Nucl. Acid Res. 12:387; Genetics Computer Group, University of Wisconsin, Madison, Wis.). The computer algorithm GAP is used to align the two polypeptides or polynucleotides for which the percent sequence identity is to be determined. The sequences are aligned for optimal matching of their respective amino acid or nucleotide (the “matched span,” as determined by the algorithm). In certain embodiments, a standard comparison matrix (*see*, Dayhoff et al., 1978, Atlas of Protein Sequence and Structure 5:345-352 for the PAM 250 comparison matrix; Henikoff et al., 1992, Proc. Natl. Acad. Sci. U.S.A. 89:10915-10919 for the BLOSUM 62 comparison matrix) is also used by the algorithm. Other algorithms are also available for comparison of amino acid or nucleic acid sequences, comprising those available in commercial computer programs such as BLASTN for nucleotide sequences and BLASTP, gapped BLAST, and PSI-BLAST for amino acid sequences. Exemplary such programs are described in Altschul, et al., Basic local alignment search tool, J. Mol. Biol., 215(3): 403-410, 1990; Altschul, et al., Methods in Enzymology; Altschul, et al., “Gapped BLAST and PSI-BLAST: a new generation of protein database search programs,” Nucleic Acids Res. 25:3389-3402, 1997; Baxevanis, et al., Bioinformatics : A Practical Guide to the Analysis of Genes and Proteins, Wiley, 1998; and Misener, et al., (eds.), Bioinformatics Methods and Protocols (Methods in Molecular Biology, Vol. 132), Humana Press, 1999. In addition to identifying similar sequences, the programs mentioned above generally provide an indication of the degree of similarity. In some embodiments, two sequences are considered to be substantially similar if at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or more of their corresponding residues are similar and/or identical over a relevant stretch of residues (e.g., 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%). In some embodiments, the relevant stretch is a complete sequence. In some embodiments, the relevant stretch is at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 95, at least 100, at least 125, at least 150, at least 175, at least 200, at least 225, at least 250, at least 275, at least 300, at least 325, at least 350, at least 375, at least 400,

at least 425, at least 450, at least 475, at least 500 or more residues. Sequences with substantial sequence similarity may be homologs of one another.

[0106] The term “substantial identity” or “substantially identical,” when referring to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 95%, and more preferably at least about 96%, 97%, 98% or 99% of the nucleotide bases, as measured by any well-known algorithm of sequence identity, such as FASTA, BLAST or Gap, as discussed below. A nucleic acid molecule having substantial identity to a reference nucleic acid molecule may, in certain instances, encode a polypeptide having the same or substantially similar amino acid sequence as the polypeptide encoded by the reference nucleic acid molecule.

[0107] As applied to polypeptides, the term “substantial similarity” or “substantially similar” means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 95% sequence identity, even more preferably at least 98% or 99% sequence identity. Preferably, residue positions which are not identical differ by conservative amino acid substitutions.

[0108] The terms “improve,” “increase,” “inhibit,” and “reduce” indicate values that are relative to a baseline or other reference measurement. In some embodiments, an appropriate reference measurement may comprise a measurement in certain system (*e.g.*, in a single individual) under otherwise comparable conditions absent presence of (*e.g.*, prior to and/or after) an agent or treatment, or in presence of an appropriate comparable reference agent. In some embodiments, an appropriate reference measurement may comprise a measurement in comparable system known or expected to respond in a comparable way, in presence of the relevant agent or treatment.

[0109] An “immune response” refers to the action of a cell of the immune system (for example, T lymphocytes, B lymphocytes, natural killer (NK) cells, macrophages, eosinophils, mast cells, dendritic cells and neutrophils) and soluble macromolecules produced by any of these cells or the liver (including Abs, cytokines, and complement) that results in selective targeting, binding to, damage to, destruction of, and/or elimination from a vertebrate’s body of invading pathogens, cells or tissues infected with pathogens, cancerous or other abnormal cells, or, in cases of autoimmunity or pathological inflammation, normal human cells or tissues.

[0110] The term “immunotherapy” refers to the treatment of a subject afflicted with, or at risk of contracting or suffering a recurrence of, a disease by a method comprising inducing, enhancing,

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

[0111] The T cells or NK cells of the immunotherapy can come from any source known in the art. For example, T cells and NK cells can be differentiated *in vitro* from a hematopoietic stem cell population (for example iPSCs) or can be obtained from a subject. T cells and NK cells can be obtained from, *e.g.*, peripheral blood mononuclear cells (PBMCs), bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion, spleen tissue, and tumors. In addition, the T cells can be derived from one or more T cell lines available in the art. T cells can also be obtained from a unit of blood collected from a subject using any number of techniques known to the skilled artisan, such as FICOLL™ separation and/or apheresis. Additional methods of isolating T cells for a T cell therapy are disclosed in U.S. Patent Publication No. 2013/0287748, which is herein incorporated by references in its entirety.

[0112] The term “*in vitro*” refers to events occurring in an artificial environment, *e.g.*, in a test tube, reaction vessel, cell culture, etc., rather than within a multi-cellular organism. The term “*in vitro* cell” refers to any cell which is cultured *ex vivo*. In particular, an *in vitro* cell can include a T cell or an NK cell. The term “*in vivo*” refers to events that occur within a multi-cellular organism, such as a human or a non-human animal.

[0113] The term “isolated” refers to a substance that (1) has been separated from at least some components with which it was associated at an earlier time or with which the substance would otherwise be associated, and/or (2) is present in a composition that comprises a limited or defined amount or concentration of one or more known or unknown contaminants. An isolated substance, in some embodiments, may be separated from about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% (*e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%) of other non-substance components with which the substance was associated at an earlier time, *e.g.*, other components or contaminants with which the substance was previously or otherwise would be associated. In

certain instances, a substance is isolated if it is present in a composition that comprises a limited or reduced amount or concentration of molecules of a same or similar type. For instance, in certain instances, a nucleic acid, DNA, or RNA substance is isolated if it is present in a composition that comprises a limited or reduced amount or concentration of non-substance nucleic acid, DNA, or RNA molecules. For instance, in certain instances, a polypeptide substance is isolated if it is present in a composition that comprises a limited or reduced amount or concentration of non-substance polypeptide molecules. In certain embodiments, an amount may be, *e.g.*, an amount measured relative to the amount of a desired substance present in a composition. In certain embodiments, a limited amount may be an amount that is no more than 100% of the amount of substance in a composition, *e.g.*, no more than 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95% of the amount of substance in a composition (*e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%). In certain instances, a composition is pure or substantially pure with respect to a selected substance. In some embodiments, an isolated substance is about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% pure (*e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%). A substance is “pure” if it is substantially free of other components or of contaminants. In some embodiments, a substance may still be considered “isolated” or even “pure,” after having been combined with certain other components such as, for example, one or more carriers or excipients (*e.g.*, buffer, solvent, water, etc.); in such embodiments, percent isolation or purity of the substance is calculated without comprising such carriers or excipients.

[0114] “Linker” (L) or “linker domain” or “linker region” refers to an oligo- or polypeptide region from about 1 to 100 amino acids in length, for example linking together any of the domains/regions of a CAR, TCR, a Dominant Negative TGF β receptor and/or scFv, or even one of more of those polypeptides together. Linkers may be composed of flexible residues like glycine and serine so that the adjacent protein domains are free to move relative to one another. Longer linkers may be used when it is desirable to ensure that two adjacent domains do not sterically interfere with one another. Linkers may be cleavable or non-cleavable. Examples of cleavable linkers include 2A linkers (for example T2A), 2A-like linkers or functional equivalents thereof and combinations thereof. In some embodiments, the linkers include the picornaviral 2A-like linker, CHYSEL (SEQ ID NO: 217) sequences of porcine teschovirus (P2A), virus (T2A) or combinations, variants and functional equivalents thereof. In other embodiments, the linker sequences may comprise Asp-Val/Ile-Glu-X-Asn-Pro-Gly^(2A)-Pro^(2B) domain (SEQ ID NO: 218), which results in cleavage between the 2A glycine and the 2B proline. In some examples, a cleavable linker is used to connect

a CAR or TCR with a Dominant Negative TGF β receptor. Other linkers will be apparent to those of skill in the art and may be used in connection with this disclosure. A linker may be a portion of a multi-element agent that connects different elements to one another. For example, a polypeptide comprises two or more functional or structural domains may comprise a stretch of amino acids between such domains that links them to one another. In some embodiments, a polypeptide comprising a linker element has an overall structure of the general form S1-L-S2, wherein S1 and S2 may be the same or different and represent two domains associated with one another by the linker. A linker may connect or link together any of the domains/regions of a CAR or TCR. In some embodiments, a polypeptide linker is at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 or more amino acids in length (*e.g.*, 1 to 10, 1 to 20, 1 to 30, 1 to 40, 1 to 50, 1 to 60, 1 to 70, 1 to 80, 1 to 90, 1 to 100, 10 to 20, 10 to 30, 10 to 40, 10 to 50, 10 to 60, 10 to 70, 10 to 80, 10 to 90, or 10 to 100 amino acids in length). In some embodiments, a linker is characterized in that it tends not to adopt a rigid three-dimensional structure, and instead provides flexibility to the polypeptide. In another example it may be used to connect to or more polypeptides to be expressed, such as a CAR or TCR and a TGF β -DNR. In some examples, the CAR, or and the TGF β - DNR are connected by a cleavable linker.

[0115] Other linkers include non-cleavable linkers. A number of linkers are employed to realize the subject invention including “flexible linkers.” The latter are rich in glycine. Klein et al., Protein Engineering, Design & Selection Vol. 27, No. 10, pp. 325–330, 2014; Priyanka et al., Protein Sci., 2013 Feb; 22(2): 153–167.

[0116] In some embodiments, the linker is a synthetic linker. A synthetic linker can have a length of from about 10 amino acids to about 200 amino acids, *e.g.*, from 10 to 25 amino acids, from 25 to 50 amino acids, from 50 to 75 amino acids, from 75 to 100 amino acids, from 100 to 125 amino acids, from 125 to 150 amino acids, from 150 to 175 amino acids, or from 175 to 200 amino acids. A synthetic linker can have a length of from 10 to 30 amino acids, *e.g.*, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 amino acids. A synthetic linker can have a length of from 30 to 50 amino acids, *e.g.*, from 30 to 35 amino acids, from 35 to 40 amino acids, from 40 to 45 amino acids, or from 45 to 50 amino acids.

[0117] In some embodiments, the linker is a flexible linker. In some embodiments, the linker is rich in glycine (Gly or G) residues. In some embodiments, the linker is rich in serine (Ser or S) residues. In some embodiments, the linker is rich in glycine and serine residues.

[0118] The term “lymphocyte” includes natural killer (NK) cells, T cells, or B cells. NK cells are a type of cytotoxic (cell toxic) lymphocyte that represent a component of the inherent immune system. NK cells reject tumors and cells infected by viruses. It works through the process of apoptosis or programmed cell death. They were termed “natural killers” because they do not require activation in order to kill cells. T cells play a role in cell-mediated-immunity (no antibody involvement). Its T cell receptors (TCR) differentiate themselves from other lymphocyte types. The thymus, a specialized organ of the immune system, is primarily responsible for the T cell’s maturation. There are six types of T cells, namely: Helper T cells (*e.g.*, CD4+ cells), Cytotoxic T cells (also known as TC, cytotoxic T lymphocyte, CTL, T-killer cell, cytolytic T cell, CD8+ T cells or killer T cell), Memory T cells ((i) stem memory T_{SCM} cells, like naive cells, are CD45RO–, CCR7+, CD45RA+, CD62L+ (L-selectin), CD27+, CD28+ and IL-7Rα+, but they also express large amounts of CD95, IL-2Rβ, CXCR3, and LFA-1, and show numerous functional attributes distinctive of memory cells); (ii) central memory T_{CM} cells express L-selectin and the CCR7, they secrete IL-2, but not IFNγ or IL-4, and (iii) effector memory T_{EM} cells, however, do not express L-selectin or CCR7 but produce effector cytokines like IFNγ and IL-4), Regulatory T cells (Tregs, suppressor T cells, or CD4+CD25+ regulatory T cells), Natural Killer T cells (NKT) and Gamma Delta T cells. B-cells, on the other hand, play a role in humoral immunity (with antibody involvement). It makes antibodies and antigens and performs the role of antigen-presenting cells (APCs) and turns into memory B-cells after activation by antigen interaction. In mammals, immature B-cells are formed in the bone marrow, where its name is derived from.

[0119] The term “neutralizing” refers to an antigen binding molecule, scFv, antibody, or a fragment thereof, that binds to a ligand and prevents or reduces the biological effect of that ligand. In some embodiments, the antigen binding molecule, scFv, antibody, or a fragment thereof, directly blocking a binding site on the ligand or otherwise alters the ligand’s ability to bind through indirect means (such as structural or energetic alterations in the ligand). In some embodiments, the antigen binding molecule, scFv, antibody, or a fragment thereof prevents the protein to which it is bound from performing a biological function.

[0120] “Nucleic acid” refers to any polymeric chain of nucleotides. A nucleic acid may be DNA, RNA, or a combination thereof. In some embodiments, a nucleic acid comprises one or more natural nucleic acid residues. In some embodiments, a nucleic acid comprises of one or more nucleic acid analogs. In some embodiments, nucleic acids are prepared by one or more of isolation from a natural source, enzymatic synthesis by polymerization based on a complementary template (*in vivo* or *in vitro*), reproduction in a recombinant cell or system, and chemical synthesis. In some embodiments, a nucleic acid is at least 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60,

65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 600, 700, 800, 900, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000 or more residues long (e.g., 20 to 100, 20 to 500, 20 to 1000, 20 to 2000, or 20 to 5000 or more residues). In some embodiments, a nucleic acid is partly or wholly single stranded; in some embodiments, a nucleic acid is partly or wholly double stranded. In some embodiments a nucleic acid has a nucleotide sequence comprising at least one element that encodes, or is the complement of a sequence that encodes, a polypeptide.

[0121] “Operably linked” refers to a juxtaposition where the components described are in a relationship permitting them to function in their intended manner. For example, a control element “*operably linked*” to a functional element is associated in such a way that expression and/or activity of the functional element is achieved under conditions compatible with the control element. In embodiments, a promoter is operably linked to nucleic acid.

[0122] A “patient” includes any human who is afflicted with a cancer (e.g., multiple myeloma). The terms “subject” and “patient” are used interchangeably herein.

[0123] The terms “peptide,” “polypeptide,” and “protein” are used interchangeably, and refer to a compound comprised of amino acid residues covalently linked by peptide bonds. A protein or peptide contains at least two amino acids, and no limitation is placed on the maximum number of amino acids that can comprise a protein’s or peptide’s sequence. Polypeptides include any peptide or protein comprising two or more amino acids joined to each other by peptide bonds. As used herein, the term refers to both short chains, which also commonly are referred to in the art as peptides, oligopeptides and oligomers, for example, and to longer chains, which generally are referred to in the art as proteins, of which there are many types. “Polypeptides” include, for example, biologically active fragments, substantially homologous polypeptides, oligopeptides, homodimers, heterodimers, variants of polypeptides, modified polypeptides, derivatives, analogs, fusion proteins, among others. The polypeptides include natural peptides, recombinant peptides, synthetic peptides, or a combination thereof.

[0124] The term “pharmaceutically acceptable” refers to a molecule or composition that, when administered to a recipient, is not deleterious to the recipient thereof, or that any deleterious effect is outweighed by a benefit to the recipient thereof. With respect to a carrier, diluent, or excipient used to formulate a composition as disclosed herein, a pharmaceutically acceptable carrier, diluent, or excipient must be compatible with the other ingredients of the composition and not deleterious to the recipient thereof, or any deleterious effect must be outweighed by a benefit to the recipient. The term “pharmaceutically acceptable carrier” means a pharmaceutically-

acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, or solvent encapsulating material, involved in carrying or transporting an agent from one portion of the body to another (*e.g.*, from one organ to another). Each carrier present in a pharmaceutical composition must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not deleterious to the patient, or any deleterious effect must be outweighed by a benefit to the recipient. Some examples of materials which may serve as pharmaceutically acceptable carriers comprise: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer’s solution; ethyl alcohol; pH buffered solutions; polyesters, polycarbonates and/or polyanhydrides; and other non-toxic compatible substances employed in pharmaceutical formulations.

[0125] The term “pharmaceutical composition” refers to a composition in which an active agent is formulated together with one or more pharmaceutically acceptable carriers. In some embodiments, the active agent is present in a unit dose amount appropriate for administration in a therapeutic regimen that shows a statistically significant probability of achieving a predetermined therapeutic effect when administered to a relevant subject or population. In some embodiments, a pharmaceutical composition may be formulated for administration in solid or liquid form, comprising, without limitation, a form adapted for the following: oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, *e.g.*, those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin, lungs, or oral cavity; intravaginally or intrarectally, for example, as a pessary, cream, or foam; sublingually; ocularly; transdermally; or nasally, pulmonary, and to other mucosal surfaces.

[0126] The term “proliferation” refers to an increase in cell division, either symmetric or asymmetric division of cells. In some embodiments, “proliferation” refers to the symmetric or

asymmetric division of T cells. “Increased proliferation” occurs when there is an increase in the number of cells in a treated sample compared to cells in a non-treated sample.

[0127] The term “reference” describes a standard or control relative to which a comparison is performed. For example, in some embodiments, an agent, animal, individual, population, sample, sequence, or value of interest is compared with a reference or control that is an agent, animal, individual, population, sample, sequence, or value. In some embodiments, a reference or control is tested, measured, and/or determined substantially simultaneously with the testing, measuring, or determination of interest. In some embodiments, a reference or control is a historical reference or control, optionally embodied in a tangible medium. Generally, a reference or control is determined or characterized under comparable conditions or circumstances to those under assessment. When sufficient similarities are present to justify reliance on and/or comparison to a selected reference or control.

[0128] “Regulatory T cells” (“Treg”, “Treg cells”, or “Tregs”) refer to a lineage of CD4+ T lymphocytes that participate in controlling certain immune activities, *e.g.*, autoimmunity, allergy, and response to infection. Regulatory T cells may regulate the activities of T cell populations, and may also influence certain innate immune system cell types. Tregs may be identified by the expression of the biomarkers CD4, CD25 and Foxp3, and low expression of CD127. Naturally occurring Treg cells normally constitute about 5-10% of the peripheral CD4+ T lymphocytes. However, Treg cells within a tumor microenvironment (*i.e.* tumor-infiltrating Treg cells), Treg cells may make up as much as 20-30% of the total CD4+ T lymphocyte population.

[0129] The term “sample” generally refers to an aliquot of material obtained or derived from a source of interest. In some embodiments, a source of interest is a biological or environmental source. In some embodiments, a source of interest may comprise a cell or an organism, such as a cell population, tissue, or animal (*e.g.*, a human). In some embodiments, a source of interest comprises biological tissue or fluid. In some embodiments, a biological tissue or fluid may comprise amniotic fluid, aqueous humor, ascites, bile, bone marrow, blood, breast milk, cerebrospinal fluid, cerumen, chyle, chime, ejaculate, endolymph, exudate, feces, gastric acid, gastric juice, lymph, mucus, pericardial fluid, perilymph, peritoneal fluid, pleural fluid, pus, rheum, saliva, sebum, semen, serum, smegma, sputum, synovial fluid, sweat, tears, urine, vaginal secretions, vitreous humour, vomit, and/or combinations or component(s) thereof. In some embodiments, a biological fluid may comprise an intracellular fluid, an extracellular fluid, an intravascular fluid (blood plasma), an interstitial fluid, a lymphatic fluid, and/or a transcellular fluid. In some embodiments, a biological fluid may comprise a plant exudate. In some

embodiments, a biological tissue or sample may be obtained, for example, by aspirate, biopsy (*e.g.*, fine needle or tissue biopsy), swab (*e.g.*, oral, nasal, skin, or vaginal swab), scraping, surgery, washing or lavage (*e.g.*, bronchoalveolar, ductal, nasal, ocular, oral, uterine, vaginal, or other washing or lavage). In some embodiments, a biological sample comprises cells obtained from an individual. In some embodiments, a sample is a “primary sample” obtained directly from a source of interest by any appropriate means. In some embodiments, as will be clear from context, the term “sample” refers to a preparation that is obtained by processing (*e.g.*, by removing one or more components of and/or by adding one or more agents to) a primary sample. Such a “processed sample” may comprise, for example nucleic acids or proteins extracted from a sample or obtained by subjecting a primary sample to one or more techniques such as amplification or reverse transcription of nucleic acid, isolation and/or purification of certain components, *etc.*

[0130] “Single chain variable fragment”, “single-chain antibody variable fragments” or “scFv” antibodies refer to forms of antibodies comprising the variable regions of only the heavy and light chains, connected by a linker peptide.

[0131] The term “stage of cancer” refers to a qualitative or quantitative assessment of the level of advancement of a cancer. In some embodiments, criteria used to determine the stage of a cancer may comprise, without limitation, one or more of where the cancer is located in a body, tumor size, whether the cancer has spread to lymph nodes, whether the cancer has spread to one or more different parts of the body, *etc.* In some embodiments, cancer may be staged using the so-called TNM System, according to which T refers to the size and extent of the main tumor, usually called the primary tumor; N refers to the number of nearby lymph nodes that have cancer; and M refers to whether the cancer has metastasized. In some embodiments, a cancer may be referred to as Stage 0 (abnormal cells are present without having spread to nearby tissue, also called carcinoma *in situ*, or CIS; CIS is not cancer, though could become cancer), Stage I-III (cancer is present; the higher the number, the larger the tumor and the more it has spread into nearby tissues), or Stage IV (the cancer has spread to distant parts of the body). In some embodiments, a cancer may be assigned to a stage selected from the group consisting of: *in situ*; localized (cancer is limited to the place where it started, with no sign that it has spread); regional (cancer has spread to nearby lymph nodes, tissues, or organs); distant (cancer has spread to distant parts of the body); and unknown (there is not enough information to determine the stage).

[0132] “Stimulation,” refers to a primary response induced by binding of a stimulatory molecule with its cognate ligand, wherein the binding mediates a signal transduction event. A “stimulatory molecule” is a molecule on a T cell, *e.g.*, the T cell receptor (TCR)/CD3 complex, that specifically

binds with a cognate stimulatory ligand present on an antigen present cell. A “stimulatory ligand” is a ligand that when present on an antigen presenting cell (*e.g.*, an APC, a dendritic cell, a B-cell, and the like) can specifically bind with a stimulatory molecule on a T cell, thereby mediating a primary response by the T cell, including, but not limited to, activation, initiation of an immune response, proliferation, and the like. Stimulatory ligands include, but are not limited to, an anti-CD3 antibody (such as OKT3), an MHC Class I molecule loaded with a peptide, a superagonist anti-CD2 antibody, and a superagonist anti-CD28 antibody.

[0133] The phrase “therapeutic agent” may refer to any agent that elicits a desired pharmacological effect when administered to an organism. In some embodiments, an agent is considered to be a therapeutic agent if it demonstrates a statistically significant effect across an appropriate population. In some embodiments, the appropriate population may be a population of model organisms or human subjects. In some embodiments, an appropriate population may be defined by various criteria, such as a certain age group, gender, genetic background, preexisting clinical conditions, in accordance with presence or absence of a biomarker, etc. In some embodiments, a therapeutic agent is a substance that may be used to alleviate, ameliorate, relieve, inhibit, prevent, delay onset of, reduce severity of, and/or reduce incidence of one or more symptoms or features of a disease, disorder, and/or condition. In some embodiments, a therapeutic agent is an agent that has been or is required to be approved by a government agency before it may be marketed for administration to humans. In some embodiments, a therapeutic agent is an agent for which a medical prescription is required for administration to humans.

[0134] A “therapeutically effective amount,” “effective dose,” “effective amount,” or “therapeutically effective dosage” of a therapeutic agent, *e.g.*, engineered CAR T cells or NK cells, is any amount that, when used alone or in combination with another therapeutic agent, protects a subject against the onset of a disease or promotes disease regression evidenced by a decrease in severity of disease symptoms, an increase in frequency and duration of disease symptom-free periods, or a prevention of impairment or disability due to the disease affliction. The ability of a therapeutic agent to promote disease regression can be evaluated using a variety of methods known to the skilled practitioner, such as in human subjects during clinical trials, in animal model systems predictive of efficacy in humans, or by assaying the activity of the agent in *in vitro* assays.

[0135] The terms “transduction” and “transduced” refer to the process whereby foreign DNA is introduced into a cell via viral vector (*see* Jones et al., “Genetics: principles and analysis,” Boston: Jones & Bartlett Publ. (1998)). In some embodiments, the vector is a retroviral vector, a DNA

vector, a RNA vector, an adenoviral vector, a baculoviral vector, an Epstein Barr viral vector, a papovaviral vector, a vaccinia viral vector, a herpes simplex viral vector, an adenovirus associated vector, a lentiviral vector, or any combination thereof.

[0136] “Transformation” refers to any process by which exogenous DNA is introduced into a host cell. Transformation may occur under natural or artificial conditions using various methods. Transformation may be achieved using any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. In some embodiments, some transformation methodology is selected based on the host cell being transformed and/or the nucleic acid to be inserted. Methods of transformation may comprise, yet are not limited to, viral infection, electroporation, and lipofection. In some embodiments, a “transformed” cell is stably transformed in that the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome. In some embodiments, a transformed cell may express introduced nucleic acid.

[0137] “Treatment” or “treating” of a subject refers to any type of intervention or process performed on, or the administration of an active agent to, the subject with the objective of reversing, alleviating, ameliorating, inhibiting, slowing down or preventing the onset, progression, development, severity or recurrence of a symptom, complication or condition, or biochemical indicia associated with a disease. In one embodiment, “treatment” or “treating” includes a partial remission. In another embodiment, “treatment” or “treating” includes a complete remission. In some embodiments, treatment may be of a subject who does not exhibit signs of the relevant disease, disorder and/or condition and/or of a subject who exhibits only early signs of the disease, disorder, and/or condition. In some embodiments, such treatment may be of a subject who exhibits one or more established signs of the relevant disease, disorder and/or condition. In some embodiments, treatment may be of a subject who has been diagnosed as suffering from the relevant disease, disorder, and/or condition. In some embodiments, treatment may be of a subject known to have one or more susceptibility factors that are statistically correlated with increased risk of development of the relevant disease, disorder, and/or condition.

[0138] The term “vector” refers to a recipient nucleic acid molecule modified to comprise or incorporate a provided nucleic acid sequence. One type of vector is a “plasmid,” which refers to a circular double stranded DNA molecule into which additional DNA may be ligated. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian

vectors). Other vectors (e.g., non-episomal mammalian vectors) may be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors comprise sequences that direct expression of inserted genes to which they are operatively linked. Such vectors may be referred to herein as “expression vectors.” Standard techniques may be used for engineering of vectors, e.g., as found in Sambrook et al., *Molecular Cloning: A Laboratory Manual* (2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)), which is incorporated herein by reference.

[0139] The term “sequence” refers to a nucleotide sequence of any length, which can be DNA or RNA; can be linear, circular or branched and can be either single-stranded or double stranded. The term “donor sequence” refers to a nucleotide sequence that is inserted into a genome. A donor sequence can be of any length, for example between 2 and 10,000 nucleotides in length (or any integer value therebetween or thereabove), preferably between about 100 and 1,000 nucleotides in length (or any integer therebetween), more preferably between about 200 and 500 nucleotides in length.

[0140] A “gene,” for the purposes of the present disclosure, includes a DNA region encoding a gene product (see *infra*), as well as all DNA regions which regulate the production of the gene product, whether or not such regulatory sequences are adjacent to coding and/or transcribed sequences. Accordingly, a gene includes, but is not necessarily limited to, promoter sequences, terminators, translational regulatory sequences such as ribosome binding sites and internal ribosome entry sites, enhancers, silencers, insulators, boundary elements, replication origins, matrix attachment sites and locus control regions.

[0141] A “transmembrane domain” is a domain of a polypeptide that includes at least one contiguous amino acid sequence that traverses a lipid bilayer when present in the corresponding endogenous polypeptide when expressed in a mammalian cell. For example, a transmembrane domain can include one, two, three, four, five, six, seven, eight, nine, or ten contiguous amino acid sequences that each traverse a lipid bilayer when present in the corresponding endogenous polypeptide when expressed in a mammalian cell. A transmembrane domain can, e.g., include at least one (e.g., two, three, four, five, six, seven, eight, nine, or ten) contiguous amino acid sequence (that traverses a lipid bilayer when present in the corresponding endogenous polypeptide when expressed in a mammalian cell) that has α -helical secondary structure in the lipid bilayer. In some embodiments, a transmembrane domain can include two or more contiguous amino acid sequences (that each traverse a lipid bilayer when present in the corresponding endogenous polypeptide when expressed in a mammalian cell) that form a β -barrel secondary structure in the

lipid bilayer. Non-limiting examples of transmembrane domains are described herein. Additional examples of transmembrane domains are known in the art.

[0142] The phrase “extracellular side of the plasma membrane” when used to describe the location of a polypeptide means that the polypeptide includes at least one transmembrane domain that traverses the plasma membrane and at least one domain (e.g., at least one antigen-binding domain) that is located in the extracellular space.

[0143] The disclosure may employ, unless indicated specifically to the contrary, methods of chemistry, biochemistry, organic chemistry, molecular biology, microbiology, recombinant DNA techniques, genetics, immunology, and cell biology that are within the skill of the art, many of which are described below for the purpose of illustration. Such techniques are explained fully in the literature. See, e.g., Sambrook, *et al.*, *Molecular Cloning: A Laboratory Manual* (3rd Edition, 2001); Maniatis *et al.*, *Molecular Cloning: A Laboratory Manual* (1982); Ausubel *et al.*, *Current Protocols in Molecular Biology* (John Wiley and Sons, updated July 2008); *Short Protocols in Molecular Biology: A Compendium of Methods from Current Protocols in Molecular Biology*, Greene Pub. Associates and Wiley-Interscience; Glover, *DNA Cloning: A Practical Approach*, vol. I & II (IRL Press, Oxford, 1985); Anand, *Techniques for the Analysis of Complex Genomes*, (Academic Press, New York, 1992); *Transcription and Translation* (B. Hames & S. Higgins, Eds., 1984); Perbal, *A Practical Guide to Molecular Cloning* (1984); Harlow and Lane, *Antibodies*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1998) *Current Protocols in Immunology* Q. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach and W. Strober, eds., 1991); *Annual Review of Immunology*; as well as monographs in journals such as *Advances in Immunology*.

TACI and BCMA Binding Agents

[0144] The present disclosure provides antigen binding agents, such as antibodies, chimeric antigen receptors (CARs) and T cell receptors (TCRs) comprising at least a single antigen binding domain that binds to both transmembrane activator and CAML interactor (TACI) and B-cell maturation antigen (BCMA), referred to herein as a dual TACI-BCMA binding domain. Among other things, the present disclosure provides methods and compositions useful for treatment of cancer and/or for initiating or modulating immune responses. In various embodiments, the dual TACI-BCMA binding domain is an scFv. Exemplary dual TACI-BCMA binding domain amino acid sequences, and nucleic acid sequences encoding the same, are provided herein, for example in Tables 4-12. In some embodiments, the dual TACI-BCMA binding domain of the present disclosure is comprised by a chimeric antigen receptor (CAR). In some embodiments, the dual

TACI-BCMA binding domain of the present disclosure is comprised by a T cell receptor (TCR). In some embodiments, an antigen binding agent of the present disclosure is an engineered T cell receptor (TCR). In some embodiments, the CARs and/or TCRs are expressed with a dominant negative TFG β Receptor (DN TFG β R). In some embodiments, the CARs and/or TCRs are expressed with a membrane bound interleukin 15 (IL-15), IL-15R α sushi-domain chimeric receptor. Disclosed are antibodies and fragments thereof that include a dual TACI-BCMA binding domain, such as disclosed in Tables 4-12.

[0145] Various embodiments of the present disclosure provide a vector encoding a dual TACI-BCMA binding domain or dual TACI-BCMA binding agent provided herein, *e.g.*, a vector encoding a dual TACI-BCMA binding CAR or TCR. Various embodiments of the present disclosure provide a vector encoding a DN TFG β R, *e.g.*, a vector encoding a dual TACI-BCMA binding CAR and a DN TFG β R. In some embodiments the DN TFG β R is encoded in a separate vector from the vector encoding the a dual TACI-BCMA binding CAR or TCR. In some embodiments the DN TFG β R is encoded in the same vector encoding the dual TACI-BCMA binding CAR or TCR. Various embodiments of the present disclosure provide a vector encoding an IL-15- IL-15R α sushi-domain chimeric receptor, *e.g.*, a vector encoding a dual TACI-BCMA binding CAR and an IL-15-IL-15R α sushi-domain chimeric receptor. In some embodiments the IL-15-IL-15R α sushi-domain chimeric receptor is encoded in a separate vector from the vector encoding the a dual TACI-BCMA binding CAR or TCR. In some embodiments the IL-15-IL-15R α sushi-domain chimeric receptor is encoded in the same vector encoding the dual TACI-BCMA binding CAR or TCR.

[0146] Various embodiments of the present disclosure provide a dual TACI-BCMA binding agent that is a cell encoding or expressing a dual TACI-BCMA binding CAR or TCR, *e.g.*, a T cell or NK cell engineered to encode or express a dual TACI-BCMA binding CAR or TCR. The present disclosure provides immune cells genetically modified with an integrated gene, *e.g.*, a nucleotide sequence of interest (*e.g.*, a constitutive expression construct and/or an inducible expression construct that comprises such nucleotide sequence. In embodiments, the immune cells are further engineered to express a DN TFG β R. In embodiments, the immune cells are further engineered to express an L-15-IL-15R α sushi-domain chimeric receptor. In some embodiments, the present disclosure provides methods of treating a subject having a tumor, such as a multiple myeloma, comprising administering to the subject a dual TACI-BCMA binding agent therapy described herein and/or a protein therapeutic described herein. In some embodiments, methods further comprise administration of one or more additional therapies (*e.g.*, a second binding agent (*e.g.*, CAR T cell, CAR-NK cell, TCR-T cell, TIL cell, allogeneic NK cell, and autologous NK cell), an

antibody-drug conjugate, an antibody, a bispecific antibody, a T cell-engaging bispecific antibody, an engineered antibody, and/or a polypeptide described herein).

[0147] A dual TACI-BCMA binding domain of the present disclosure may comprise antigen-binding sequences as found in an antibody described herein. In some instances, a dual TACI-BCMA binding domain of the present disclosure comprises a dual TACI-BCMA binding domain described herein, such as an scFv. Unless otherwise indicated, it is to be appreciated the references to TACI and BCMA in the present disclosure relate to human TACI and human BCMA. In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises at least one heavy chain CDR (HCDR) provided herein, *e.g.*, at least one HCDR disclosed in any one of Tables 4-12. In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises two HCDRs provided herein, *e.g.*, at least two HCDRs disclosed in any one of Tables 4-12. In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises three HCDRs provided herein, *e.g.*, three HCDRs disclosed in any one of Tables 4-12. In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises at least one light chain CDR (LCDR) provided herein, *e.g.*, at least one LCDR disclosed in any one of Tables 4-12. In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises two LCDRs provided herein, *e.g.*, at least two LCDRs disclosed in any one of Tables 4-12. In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises three LCDRs provided herein, *e.g.*, three LCDRs disclosed in any one of Tables 4-12.

[0148] In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises at least one HCDR provided herein, *e.g.*, at least one HCDR disclosed in any one of Tables 4-12, and at least one LCDR provided herein, *e.g.*, at least one LCDR disclosed in any one of Tables 4-12. In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises one HCDR provided herein, *e.g.*, at least one HCDR disclosed in any one of Tables 4-12, and one LCDR provided herein, *e.g.*, derived from the same Table of Tables 4-12 as the HCDR(s). In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises two HCDRs provided herein, *e.g.*, at least two HCDRs disclosed in any one of Tables 4-12, and two LCDRs provided herein, *e.g.*, at least two LCDRs disclosed in any one of Tables 4-12. In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises two HCDRs provided herein, *e.g.*, at least two HCDRs disclosed in any one of Tables 4-12, and two LCDRs provided herein, *e.g.*, derived from the same Table of Tables 4-12 as the HCDR(s). In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises three HCDRs provided herein, *e.g.*, three HCDRs disclosed in any one of

Tables 4-15, and three LCDRs provided herein, *e.g.*, three LCDRs disclosed in any one of Tables 4-15. In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises three HCDRs provided herein, *e.g.*, three HCDRs disclosed in any one of Tables 4-15, and three LCDRs derived from the same Table of Tables 4-15 as the HCDR(s).

[0149] In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises at least one heavy chain framework region (heavy chain FR) of a heavy chain variable domain disclosed herein, *e.g.*, at least one heavy chain FR of a heavy chain variable domain disclosed in any one of Tables 4-12. In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises two heavy chain FRs of a heavy chain variable domain disclosed herein, *e.g.*, at least two heavy chain FRs of a heavy chain variable domain disclosed in any one of Tables 4-12. In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises three heavy chain FRs of a heavy chain variable domain disclosed herein, *e.g.*, three heavy chain FRs of a heavy chain variable domain disclosed in any one of Tables 4-12.

[0150] In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises at least one light chain FR of a light chain variable domain disclosed herein, *e.g.*, at least one light chain FR of a light chain variable domain disclosed in any one of Tables 4-12. In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises two light chain FRs of a light chain variable domain disclosed herein, *e.g.*, at least two light chain FRs of a light chain variable domain disclosed in any one of Tables 4-12. In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises three light chain FRs of a light chain variable domain disclosed herein, *e.g.*, three light chain FRs of a light chain variable domain disclosed in any one of Tables 4-12.

[0151] In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises at least one heavy chain FR of a heavy chain variable domain disclosed herein, *e.g.*, at least one heavy chain FR of a heavy chain variable domain disclosed in any one of Tables 4-12, and at least one light chain FR of a light chain variable domain disclosed herein, *e.g.*, at least one light chain FR of a light chain variable domain disclosed in any one of Tables 4-12. In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises one heavy chain FR of a heavy chain variable domain disclosed herein, *e.g.*, at least one heavy chain FR of a heavy chain variable domain disclosed in any one of Tables 4-12, and one light chain FR of a light chain variable domain disclosed herein, *e.g.*, derived from the same Table of Tables 4-12 as the heavy chain FR(s). In various embodiments, a dual TACI-BCMA binding domain of the

present disclosure comprises two heavy chain FRs of a heavy chain variable domain disclosed herein, *e.g.*, at least two heavy chain FRs of a heavy chain variable domain disclosed in any one of Tables 4-12, and two light chain FRs of a light chain variable domain disclosed herein, *e.g.*, at least two light chain FRs of a light chain variable domain disclosed in any one of Tables 4-12. In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises two heavy chain FRs of a heavy chain variable domain disclosed herein, *e.g.*, at least two heavy chain FRs of a heavy chain variable domain disclosed in any one of Tables 4-12, and two light chain FRs of a light chain variable domain disclosed herein, *e.g.*, derived from the same Table of Tables 4-12 as the heavy chain FR(s). In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises three heavy chain FRs of a heavy chain variable domain disclosed herein, *e.g.*, three heavy chain FRs of a heavy chain variable domain disclosed in any one of Tables 4-12, and three light chain FRs of a light chain variable domain disclosed herein, *e.g.*, three light chain FRs of a light chain variable domain disclosed in any one of Tables 4-12. In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises three heavy chain FRs of a heavy chain variable domain disclosed herein, *e.g.*, three light chain FRs of a light chain variable domain disclosed in any one of Tables 4-12, and three light chain FRs derived from the same Table of Tables 4-12 as the heavy chain FR(s).

[0152] Exemplary antibody sequences provided in Tables 4-12 are suitable for use in any antibody format, comprising, *e.g.*, a tetrameric antibody, a monospecific antibody, a bispecific antibody, an antigen binding fragment, or a binding domain. Heavy chain variable domains and light chain variable domains and portions thereof provided in Tables 4-12 may be comprised in a dual TACI-BCMA binding domain.

[0153] In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises one, two, or three FRs that together or each individually have at least 75% identity (*e.g.*, at least 75%, at least 80%, at least 90%, at least 95%, or 100%, *e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%) to corresponding FR(s) of a heavy chain variable domain of a heavy chain variable domain disclosed in in any one of Tables 4-12. In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises one, two, or three FRs that together or each individually have at least 75% identity (*e.g.*, at least 75%, at least 80%, at least 90%, at least 95%, or 100%) to corresponding FR(s) of a light chain variable domain of a light chain variable domain disclosed in any one of Tables 4-12.

[0154] In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises at least one heavy chain variable domain having at least 75% sequence identity to a

heavy chain variable domain disclosed in any one of Tables 4-12 (*e.g.*, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%). In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises two heavy chain variable domains each having at least 75% sequence identity to a heavy chain variable domain disclosed in Tables 4-12 (*e.g.*, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%), which heavy chain variable domains may be same or different.

[0155] In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises at least one light chain variable domain having at least 75% sequence identity to a light chain variable domain disclosed in any one of Tables 4-12 (*e.g.*, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%). In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises two light chain variable domains each having at least 75% sequence identity to a light chain variable domain disclosed in any one of Tables 4-12 (*e.g.*, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%), which light chain variable domains may be same or different.

[0156] In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises at least one heavy chain variable domain having at least 75% sequence identity to a heavy chain variable domain disclosed in any one of Tables 4-12 (*e.g.*, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%) and at least one light chain variable domain having at least 75% sequence identity to a light chain variable domain disclosed in any one of Tables 4-12 (*e.g.*, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%). In certain embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises one heavy chain variable domain having at least 75% sequence identity to a heavy chain variable domain disclosed in any one of Tables 4-12 (*e.g.*, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%) and one light chain variable domain having at least 75% sequence identity to a light chain variable domain disclosed in any one of Tables 4-12 (*e.g.*, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%), where the heavy chain variable domain and light chain variable domain are optionally derived from the same Table of Tables 4-12.

[0157] In various embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises two heavy chain variable domains each having at least 75% sequence identity to a heavy chain variable domain disclosed in Tables 4-12 (*e.g.*, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%) and two light chain variable domains each having at least 75% sequence identity to a light chain variable domain disclosed in Tables 4-12 (*e.g.*, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%), where, in various embodiments, (i) each of the heavy chain variable domains may be same or different; (ii) each of the light chain variable domains may be same or different; (iii) at least one heavy chain variable domain and at least one light chain variable domain may be derived from the same Table of Tables 4-12; or (iv) the two heavy chain variable domains and the two light chain variable domains are all derived from the same Table of Tables 4-12.

[0158] Each of Tables 4-12 represents the heavy chain variable domain and light chain variable domain sequences of an exemplary antibody, comprising (i) the heavy chain variable domain of the exemplary antibody; (ii) a DNA sequence encoding the heavy chain variable domain (iii) three heavy chain variable domain CDRs of the heavy chain variable domain, according to IMGT, Kabat, and Chothia numbering; (iv) the light chain variable domain of the exemplary antibody; (v) a DNA sequence encoding the light chain variable domain; and (vi) three light chain variable domain CDRs of the light chain variable domain, according to IMGT, Kabat, and Chothia numbering. Information provided in each table provides framework amino acid sequences, as well as nucleotide sequences encoding each CDR amino acid sequence and nucleotide sequences encoding corresponding FR amino acid sequence.

[0159] In various embodiments, a dual TACI-BCMA binding domain may comprise a heavy chain variable domain of the present disclosure (*e.g.*, having at least 75% sequence identity to a heavy chain variable domain of any one of Tables 4-12, *e.g.*, at least 80%, 85%, 90%, 95%, or 100% identity; *e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%), a light chain variable domain of the present disclosure (*e.g.*, having at least 75% sequence identity to a light chain variable domain of any one of Tables 4-12, *e.g.*, at least 80%, 85%, 90%, 95%, or 100% identity; *e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%), and a linker (*e.g.*, a linker according to SEQ ID NO: 219). In various embodiments a dual TACI-BCMA binding domain may comprise a leader sequence, a heavy chain variable domain of the present disclosure (*e.g.*, having at least 75% sequence identity to a heavy chain variable domain of any one of Tables 4-12, *e.g.*, at least 80%, 85%, 90%, 95%, or 100% identity; *e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%), a light chain variable domain of the present disclosure (*e.g.*, having

at least 75% sequence identity to a light chain variable domain of any one of Tables 4-12, *e.g.*, at least 80%, 85%, 90%, 95%, or 100% identity; *e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%), and a linker. If provided with an amino acid or nucleotide sequence of a dual TACI-BCMA binding domain comprising a heavy chain variable domain of the present disclosure and a light chain variable domain of the present disclosure, the linker joining the two variable domains will be apparent from the sequence in view of the present disclosure. If provided with an amino acid or nucleotide sequence of a dual TACI-BCMA binding domain comprising a heavy chain variable domain of the present disclosure and a light chain variable domain of the present disclosure, the leader sequence will be apparent in view of the present disclosure. For the avoidance of doubt, a heavy chain variable domain and a light chain variable domain of the present disclosure may be present in any orientation, *e.g.*, an orientation in which the heavy chain variable domain is C terminal of the light chain variable domain or in which the heavy chain variable domain is N terminal of the light chain variable domain. In various embodiments a dual TACI-BCMA binding domain may comprise a linker according to SEQ ID NO: 219.

[0160] In certain embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises an a dual TACI-BCMA binding domain that comprises a heavy chain variable domain of the present disclosure, a light chain variable domain of the present disclosure, and a linker having at least 75% sequence identity to SEQ ID NO: 219 (*e.g.*, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%). In certain embodiments, an TACI-BCMA binding domain of the present disclosure comprises a dual TACI-BCMA binding domain that comprises a linker according to SEQ ID NO: 219. In certain embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises a dual TACI-BCMA binding domain that comprises a heavy chain variable domain of the present disclosure, a light chain variable domain of the present disclosure, and a leader sequence having at least 75% sequence identity to SEQ ID NO: 221 (*e.g.*, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%). In certain embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises a dual TACI-BCMA binding domain that comprises a CSF2RA leader sequence according to SEQ ID NO: 221 (MLLLVTSLLLCELPHPAFLIP; SEQ ID NO: 221). In embodiments, a leader sequence may be encoded by nucleic acid sequence at least 75% sequence identity to:

ATGCTTCTCCTGGTGACAAGCCTTCTGCTCTGTGAGTTACCACACCCAGCATTCCTC
CTGATTCT (SEQ ID NO: 222) (*e.g.*, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%). In certain

embodiments, a dual TACI-BCMA binding domain of the present disclosure comprises a dual TACI-BCMA binding domain that comprises a heavy chain variable domain of the present disclosure, a light chain variable domain of the present disclosure, a linker of the present disclosure, and a leader sequence of the present disclosure.

[0161] A binding agent of the present disclosure that is based on an exemplary antibody provided herein, such as for example Abs 1-9, may be provided in any fragment or format, comprising a heavy chain variable domain according to the indicated exemplary antibody and a light chain variable domain according to the indicated exemplary antibody.

Table 4: Exemplary Antibody Sequences 1 (Ab1)

SEQ ID NO:	Description	Sequence
1	Heavy Chain Variable Domain	QVQLVQSGAEVKKPGSSVKVSCKASGGTFADYAIISWVRQAPGQGLEWMG GIIPILGRANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCAR DRDSTSLPYNHYMDVWGKTTTVTVSS
2	VH (DNA)	caggtgcagctggtgcagctctgggctgaggtgaagaagcctgggtcct cgggtgaaggtctcctgcaaggtctctggaggcaccttcgcagactatgc tatcagctgggtgacagagccctggacaagggttgagtggatggga gggatcatccctatatattgggcagagcaaactacgcacagaagtccagg gcagagttacgattaccgcggacgaatccacgagcacagcctacatgga gctgagcagcctgagatctgaggacacggcggtgtactactgcgccaga gacagagacagcacaagcctgccgtacaaccactactacatggacgtat ggggcaagggtacaactgtcactgtctcctca
3	CDRH1 IMGT (Prot)	GGTFADYA
4	CDRH1 Kabat (Prot)	DYAIIS
5	CDRH1 Chothia (Prot)	GGTFADY
6	CDRH2 IMGT (Prot)	IIPILGRA
7	CDRH2 Kabat (Prot)	GIIPILGRANYAQKFQG
8	CDRH2 Chothia (Prot)	IPILGR
9	CDRH3 IMGT (Prot)	ARDRDSTSLPYNHYMDV
10	CDRH3 Kabat (Prot)	DRDSTSLPYNHYMDV
11	CDRH3 Chothia (Prot)	DRDSTSLPYNHYMDV
12	Light Chain Variable Domain	DIQMTQSPSSLSASVGRVTITCRASQSISSYLNWYQQKPGKAPKLLIY AASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSHIAPWTF GGGTKVEIK
13	VL (DNA)	gacatccagatgacccagctctccatcctcctgtctgcaagcggttgag atagagtcactatcacttgccgggcaagtcagagcatttagcagctat aaattggtatcagcagaaaccagggaagccctaaagtcctgatctat gctgcatccagtttgcaagtggggtcccatcaaggttcagtggcagtg

		gatccgggacagatttcactctcaccatcagcagctctgcaacctgaaga ttttgcaacttactactgtcagcaaagccacatcgcccccttggaactttt ggcggaggggaccaaggttgagatcaaa
14	CDRL1 IMGT (Prot)	QSISSY
15	CDRL1 Kabat (Prot)	RASQSISSYLN
16	CDRL1 Chothia (Prot)	RASQSISSYLN
17	CDRL2 IMGT (Prot)	AAS
18	CDRL2 Kabat (Prot)	AASSLQS
19	CDRL2 Chothia (Prot)	AASSLQS
20	CDRL3 IMGT (Prot)	QQSHIAPWT
21	CDRL3 Kabat (Prot)	QQSHIAPWT
22	CDRL3 Chothia (Prot)	QQSHIAPWT
23	ScFv	DIQMTQSPSSLSASVGDRTITCRASQSISSYLNWYQQKPGKAPKLLIY AASSLQSGVPSRFSGSGSGTDFLTITSSLPEDFATYYCQQSHIAPWTF GGGTKVEIKGSTSGSGKPGSGEGSTKGQVQLVQSGAEVKKPGSSSVKVS KASGGTFADYAIWVRQAPGGGLEWMGGIIPILGRANYAQKFQGRVTIT ADESTSTAYMELSSLRSEDTAVYYCARDRTSLPYNHYMDVWGKGT TVTVSS
24	ScFv	gacatccagatgacccagctctccatcctccctgtctgcaagcgttgag atagagtcactatcacttgccgggcaagtgcagagcattagcagctat aaattgggtatcagcagaaaccagggaagccctaagctcctgatctat gctgcatccagtttgcaaagtgggtcccatcaaggttcagtggcagtg gatccgggacagatttcactctcaccatcagcagctctgcaacctgaaga ttttgcaacttactactgtcagcaaagccacatcgcccccttggaacttt ggcggaggggaccaaggttgagatcaaaggagcactagcggctctggca aacctggatctggcgagggatctaccaaggggccaggtgcagctggtgca gtctggggctgaggtgaagaagcctgggtcctcgggtgaaggtctcctgc aaggcttctggaggcaccttcgcagactatgctatcagctgggtgcgac aggcccttgacaagggttgagtggatgggagggatcatccctatatt gggcagagcaaaactacgcacagaagttccagggcagagttacgattacc gcggacgaatccacgagcacagcctacatggagctgagcagcctgagat ctgaggacacggcggtgtactactgcgccagagacagagacagcacaag cctgccgtacaaccactactacatggacgtatggggcaagggtacaact gtcactgtctcctca

Table 5: Exemplary Antibody Sequences 2 (Ab2)

SEQ ID NO:	Description	Sequence
25	Heavy Chain Variable Domain	QVQLVQSGAEVKKPGSSSVKVSCKASGGTFADYAIWVRQAPGGGLEWM GGIIPILGRANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC ARDRTSLPYNHYMDVWGKGTITVTVSS
26	VH (DNA)	caggtgcagctggtgcagctctggggctgaggtgaagaagcctgggtcc tcgggtgaaggtctcctgcaaggcttctggaggcaccttcgcagactat

		gctatcagctgggtgcgacaggccctggacaagggcttgagtggatg ggagggatcatccctatatattgggcagagcaaaactacgcacagaagttc cagggcagagttacgattaccgcggacgaatccacgagcacagcctac atggagctgagcagcctgagatctgaggacacggcggtgtactactgc gccagagacagagaccgtacaagcctgccgtacaaccactactacatg gacgtatggggcaaagggaccacgggtcaccggtttcctca
27	CDRH1 IMGT (Prot)	GGTFADYA
28	CDRH1 Kabat (Prot)	DYAIS
29	CDRH1 Chothia (Prot)	GGTFADY
30	CDRH2 IMGT (Prot)	IIPILGRA
31	CDRH2 Kabat (Prot)	GIIPILGRANYAQKFQG
32	CDRH2 Chothia (Prot)	IPILGR
33	CDRH3 IMGT (Prot)	ARDRDRTSLPNHYMDV
34	CDRH3 Kabat (Prot)	DRDRTSLPNHYMDV
35	CDRH3 Chothia (Prot)	DRDRTSLPNHYMDV
36	Light Chain Variable Domain	DIQLTQSPSSLSASVGDRTITCRASQSILSYLNWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSSIAPW TFGGGTKVEIK
37	VL (DNA)	gacatccagttgaccagtcctccatccctcctgtctgcaagcgttgga gatagagtcactatcacttgccgggcaagtcagagcattctcagctat ttaaattggtatcagcagaaaccagggaaagccctaaagctcctgac tatgctgcatccagtttgcaaagtggggtcccatcaaggttcagtggc agtggatccgggacagatttcactctcaccatcagcagtcgtgcaacct gaagattttgcaacttactactgtcagcaaagctcgatcgcccttg actttcggcggagggaaccaaggttgagatcaaa
38	CDRL1 IMGT (Prot)	QSILSY
39	CDRL1 Kabat (Prot)	RASQSILSYLN
40	CDRL1 Chothia (Prot)	RASQSILSYLN
41	CDRL2 IMGT (Prot)	AAS
42	CDRL2 Kabat (Prot)	AASSLQS
43	CDRL2 Chothia (Prot)	AASSLQS
44	CDRL3 IMGT (Prot)	QQSSIAPWT
45	CDRL3 Kabat (Prot)	QQSSIAPWT
46	CDRL3 Chothia (Prot)	QQSSIAPWT
47	SeFv	DIQLTQSPSSLSASVGDRTITCRASQSILSYLNWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSSIAPW

		TFGGGTTKVEIKGSTSGSKPGSGEGSTKGQVQLVQSGAEVKKPGSSVK VSKASGGTFADYAIISWVRQAPQGQLEWMGGIIPILGRANYAQKFQGR VTITADESTSTAYMELSSLRSEDTAVYYCARDRDRTSLPYNHYMDVW GKGTTTVTVSS
48	ScFv	gacatccagttgacccagttctccatcctccctgtctgcaagcgttgga gatagagtcactatcacttgccgggcaagtcagagcattctcagctat ttaaattggtatcagcagaaaccagggaagccctaaagctcctgac tatgctgcatccagtttgcaaagtgggtcccatcaaggttcagtggc agtggatccgggacagatttcactctcaccatcagcagctctgcaacct gaagattttgcaacttactactgtcagcaaagctcgatcgccccttg actttcgggcggaggaccaaggttgagatcaaaggagcacaagcggc tctggcaaacctggatctggcgagggatctaccaagggccaggtgcag ctggtgcagctctggggtgaggtgaagaagcctgggtcctcgggtgaag gtctcctgcaaggcttctggaggcaccttcgcagactatgctatcagc tggtgacagaggccctggacaagggttgagtgatgggagggatc atccctatatgggcagagcaaactacgcacagaagttccagggcaga gttacgattaccgcgacgaatccacgagcacagcctacatggagctg agcagcctgagatctgaggacacggcggtgtactactgcgccagagac agagaccgtacaagcctgccgtacaaccactactacatggacgtatgg gcaaagggaccacggtcaccggtttctca

Table 6: Exemplary Antibody Sequences 3 (Ab3)

SEQ ID NO:	Description	Sequence
49	Heavy Chain Variable Domain	QVQLVQSGAEVKKPGSSVKVSKASGGTFEDYAIISWVRQAPQGQLEWM GGIIPILGRANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC ARDRLTSLPYNHYMDVWVGKGTTTVTVSS
50	VH (DNA)	caggtgcagctgggtgcagctctggggtgaggtgaagaagcctgggtcc tcggtgaaggtctcctgcaaggcttctggaggcaccttcgaagactat gctatcagctgggtgcgacaggccctggacaagggttgagtggtg ggagggatcatccctatatattgggcgagcaaaactacgcacagaagttc cagggcagagttacgattaccgcgacgaatccacgagcacagcctac atggagctgagcagcctgagatctgaggacacggcggtgtactactgc gccagagacagagacttgacaagcctgccgtacaaccactactacatg gacgtatggggcaaagggaccacggtcaccggtttctca
51	CDRH1 IMGT (Prot)	GGTFEDYA
52	CDRH1 Kabat (Prot)	DYAIIS
53	CDRH1 Chothia (Prot)	GGTFEDY
54	CDRH2 IMGT (Prot)	IIPILGRA
55	CDRH2 Kabat (Prot)	GIIPILGRANYAQKFQG
56	CDRH2 Chothia (Prot)	IPILGR
57	CDRH3 IMGT (Prot)	ARDRLTSLPYNHYMDV
58	CDRH3 Kabat (Prot)	DRDLTSLPYNHYMDV

59	CDRH3 Chothia (Prot)	DRDLTSLPYNHYMDV
60	Light Chain Variable Domain	DIQLTQSPSSLSASVGDRTITCRASQSISSYLNWYQQKPGKAPKLLI YAASQLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQSAIAPW TFGGGTKVEIK
61	VL (DNA)	gacatccagttgaccagtcctccatcctccctgtctgcaagcgttgga gatagagtcactatcacttgccgggcaagtcagagcattagcagctat ttaaattggtatcagcagaaaccagggaagcccctaagctcctgac tatgctgcatcccaattgcaaagtgggtcccatcaaggttcagtggc agtggatccgggacagatttcactctcaccatcagcagtcctgcaacct gaagattttgcaacttactactgtcagcaaagcgctatcgccccttg actttcggcggagggaaccaaggttgagatcaaa
62	CDRL1 IMGT (Prot)	QSISSY
63	CDRL1 Kabat (Prot)	RASQSISSYLN
64	CDRL1 Chothia (Prot)	RASQSISSYLN
65	CDRL2 IMGT (Prot)	AAS
66	CDRL2 Kabat (Prot)	AASQLQS
67	CDRL2 Chothia (Prot)	AASQLQS
68	CDRL3 IMGT (Prot)	QSAIAPWT
69	CDRL3 Kabat (Prot)	QSAIAPWT
70	CDRL3 Chothia (Prot)	QSAIAPWT
71	ScFv	DIQLTQSPSSLSASVGDRTITCRASQSISSYLNWYQQKPGKAPKLLI YAASQLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQSAIAPW TFGGGTKVEIKSGTSGSGKPGSGEGSTKGQVQLVQSGAEVKKPGSSVK VSKKASGGTFEDYAIISWVRQAPQGGLWMMGGIIPILGRANYAQKFQGR VTITADESTSTAYMELSSLRSEDTAVYYCARDRLTSLPYNHYMDVW GKGTITVTVSS
72	ScFv	gacatccagttgaccagtcctccatcctccctgtctgcaagcgttgga gatagagtcactatcacttgccgggcaagtcagagcattagcagctat ttaaattggtatcagcagaaaccagggaagcccctaagctcctgac tatgctgcatcccaattgcaaagtgggtcccatcaaggttcagtggc agtggatccgggacagatttcactctcaccatcagcagtcctgcaacct gaagattttgcaacttactactgtcagcaaagcgctatcgccccttg actttcggcggagggaaccaaggttgagatcaaaggagcacaagcggc tctggcaaacctggatctggcgagggatctaccaagggccaggtgcag ctggtgcagtcctggggtgaggtgaagaagcctgggtcctcggtgaag gtctcctgcaaggcttctggaggcaccttcgaagactatgctatcagc tgggtgcgacaggcccctggacaagggttgagtggtgggagggatc atccctatatattgggcccagcaaaactacgcacagaagttccagggcaga gttacgattaccgcgacgaatccacgagcacagcctacatggagctg agcagcctgagatctgaggacacggcggtgtactactgcgccagagac agagacttgacaagcctgccgtacaaccactactacatggacgtatgg ggcaaagggaaccacggtcaccgttttctca

Table 7: Exemplary Antibody Sequences 4 (Ab4)

SEQ ID NO:	Description	Sequence
73	Heavy Chain Variable Domain	QVQLVQSGAEVKKPGSSSVKVSCKASGGTFSHYAI SWVRQAPGQGLEWM GGIIPILGRANYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYC ARDRTWEGSPYYYYGMDVWGQGTMTVTVSS
74	VH (DNA)	caggtgcagctgggtgcagctctggggctgaagtgaagaagcctgggtcc tcggtgaaggtctcctgcaaggtctctggaggcaccttcagccactat gctatcagctgggtgcgacaggccctggacaagggcttgagtggatg ggagggatcatccctatatattgggcccagagcaaaactacgcacagaagttc cagggcagagtcacgattaccgcggacgaatccacgagcacagcctac atggagctgagcagcctgagatctgaggacacggcggtgtactactgc gccagagacagaacttgggaaggatctccctattattactacggaatg gacgtttggggccaagggacaatgggtcacggtttcctca
75	CDRH1 IMGT (Prot)	GGTFSHYA
76	CDRH1 Kabat (Prot)	HYAIS
77	CDRH1 Chothia (Prot)	GGTFSHY
78	CDRH2 IMGT (Prot)	IIPILGRA
79	CDRH2 Kabat (Prot)	GIIPILGRANYAQKFQG
80	CDRH2 Chothia (Prot)	IPILGR
81	CDRH3 IMGT (Prot)	ARDRTWEGSPYYYYGMDV
82	CDRH3 Kabat (Prot)	DRTWEGSPYYYYGMDV
83	CDRH3 Chothia (Prot)	DRTWEGSPYYYYGMDV
84	Light Chain Variable Domain	DIQLTQSPSSLSASVGDRTITCRASTSISSYLNWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSADAPW TFGGGTKVEIK
85	VL (DNA)	gacatccagttgacccagtcctccatcctcctgtctgcaagcgttgga gacagggtcactatcacttgccgggcaagtaccagcattagcagctat ttaaattggtatcagcagaaaccagggaagccctaaagctcctgac tatgctgcatccagtttgcaagtggggtcccatcaaggttcagtggc agtggatctgggacagatttcactctcaccatcagcagctctgcaacct gaagattttgcaacttactactgtcagcaaaagcgcgatgcccttgg actttcggcggaggggaccaaggttgagatcaaa
86	CDRL1 IMGT (Prot)	TSISSY
87	CDRL1 Kabat (Prot)	RASTSISSYLN
88	CDRL1 Chothia (Prot)	RASTSISSYLN
89	CDRL2 IMGT (Prot)	AAS
90	CDRL2 Kabat (Prot)	AASSLQS

91	CDRL2 Chothia (Prot)	AASSLQS
92	CDRL3 IMGT (Prot)	QQSADAPWT
93	CDRL3 Kabat (Prot)	QQSADAPWT
94	CDRL3 Chothia (Prot)	QQSADAPWT
95	ScFv	DIQLTQSPSSLSASVGDRTITCRASTSISSYLNWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSADAPW TFGGGTKEIKGSTSGSGKPGSGEGSTKGQVQLVQSGAEVKKPGSSVK VSKASGGTFSHYAISWVRQAPGQGLEWMGGIIPILGRANYAQKFQGR VTITADESTSTAYMELSSLRSEDTAVYYCARDRTWEGSPYYYYGMDVW GQGTMTVTVSS
96	ScFv	gacatccagttgacccagttctccatcctcctgtctgcaagcgttggga gacagggtcactatcacttgccgggcaagtaccagcattagcagctat ttaaattggtatcagcagaaaccagggaaagcccctaagctcctgac tatgctgcatccagtttgcaaagtgggtgccatcaaggttcagtggc agtggatctgggacagatttcactctcaccatcagcagctctgcaacct gaagattttgcaacttactactgtcagcaaagcgccgatgccccttg actttcggcggagggaaccaaggttgagatcaaaggagcacaagcggc tctggcaaacctggatccggcgagggatctaccaagggccaggtgcag ctggtgcagctctggggtgaagtgaagaagcctgggtcctcggtgaag gtctcctgcaagcctctggaggcaccttcagccactatgctatcagc tgggtgcgacaggccccctggacaagggttgagtgatgggagggatc atccctatatgggcccagcaaaactacgcacagaagttccagggcaga gtcacgattaccgcggacgaatccacgagcacagcctacatggagctg agcagcctgagatctgaggacacggcggtgtactactgcgccagagac agaacttgggaaggatctccctattattactacggaatggacgtttgg ggccaagggacaatggtcaccgtttcctca

Table 8: Exemplary Antibody Sequences 5 (Ab5)

SEQ ID NO:	Description	Sequence
97	Heavy Chain Variable Domain	QVQLVQSGAEVKKPGSSVKVSKASGGTFDDYAIISWVRQAPGQGLEWM GGIIPILGRANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC ARDRVWEGSPYYYYGMDVWGQGTMTVTVSS
98	VH (DNA)	caggtgcagctggtgcagttctggggtgaggtgaagaagcctgggtcc tcggtgaaggtctcctgcaaggcttctggaggcaccttcgacgactat gctatcagctgggttcgacaggccccctggacaagggttgagtgatg ggaggatcatccctatatattgggcagagcaaaactacgcacagaagttc cagggcagagtcacgattaccgcggacgaatccacgagcacagcctac atggagctgagcagcctgagatctgaggacacggcggtgtactactgc gccagagacagagtggtgggaaggatctccctattattactacggaatg gacgtttgggccaagggacaatggtcaccgtttcctca
99	CDRH1 IMGT (Prot)	GGTFDDYA
100	CDRH1 Kabat (Prot)	DYAIIS
101	CDRH1 Chothia (Prot)	GGTFDDY
102	CDRH2 IMGT (Prot)	IIPILGRA

103	CDRH2 Kabat (Prot)	GIIPILGRANYAQKFQG
104	CDRH2 Chothia (Prot)	IPILGR
105	CDRH3 IMGT (Prot)	ARDRVWEGSPYYYYGMDV
106	CDRH3 Kabat (Prot)	DRVWEGSPYYYYGMDV
107	CDRH3 Chothia (Prot)	DRVWEGSPYYYYGMDV
108	Light Chain Variable Domain	DIQLTQSPSSLSASVGDRTITCRASQSIASYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSAGAPWTFGGGTKVEIK
109	VL (DNA)	gacatccagttgacccagttctccatcctcctgtctgcaagcgttgga gatagagtcactatcacttgccgggcaagtcagagcattgccagctat ttaaatttggtatcagcagaaaccagggaagcccctaagctcctgac tatgctgcatccagtttgcaaagtggggtcccatcaaggttcagtggc agtggatccgggacagatttcactctcaccatcagcagctctgcaacct gaagattttgcaacttactactgtcagcaaagcgccggtgcaccttg actttcgcgaggaggaccaaggttgagatcaaa
110	CDRL1 IMGT (Prot)	QSIASY
111	CDRL1 Kabat (Prot)	RASQSIASYLN
112	CDRL1 Chothia (Prot)	RASQSIASYLN
113	CDRL2 IMGT (Prot)	AAS
114	CDRL2 Kabat (Prot)	AASSLQS
115	CDRL2 Chothia (Prot)	AASSLQS
116	CDRL3 IMGT (Prot)	QQSAGAPWT
117	CDRL3 Kabat (Prot)	QQSAGAPWT
118	CDRL3 Chothia (Prot)	QQSAGAPWT
119	ScFv	DIQLTQSPSSLSASVGDRTITCRASQSIASYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSAGAPWTFGGGTKVEIKGSTSGSGKPGSGEGSTKQVQLVQSGAEVKKPGSSVKVSKASGGTFDDYAIISWVRQAPQGQLEWMGGIIPILGRANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDRVWEGSPYYYYGMDVWGQGMVTVSS
120	ScFv	gacatccagttgacccagttctccatcctcctgtctgcaagcgttgga gatagagtcactatcacttgccgggcaagtcagagcattgccagctat ttaaatttggtatcagcagaaaccagggaagcccctaagctcctgac tatgctgcatccagtttgcaaagtggggtcccatcaaggttcagtggc agtggatccgggacagatttcactctcaccatcagcagctctgcaacct gaagattttgcaacttactactgtcagcaaagcgccggtgcaccttg actttcgcgaggaggaccaaggttgagatcaaaggaggacacaagcggc tctggcaaacctggatctggcgaggatctaccaagggccaggtgcag ctgggtgcagctctggggtgaggtgaagaagcctgggtcctcggtgaag gtctcctgcaaggcttctggaggcaccttcgacgactatgctatcagc

		tgggttcgacaggccccctggacaagggcttgagtggatgggagggatc atccctatatattgggcagagcaaaactacgcacagaagttccagggcaga gtcacgattaccgcggacgaatccacgagcacagcctacatggagctg agcagcctgagatctgaggacacggcggtgtactactgcgccagagac agagtgtgggaaggatctccctattattactacggaatggacgtttgg ggccaagggacaatggtcaccgtttctca
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Table 9: Exemplary Antibody Sequences 6 (Ab6)

SEQ ID NO:	Description	Sequence
121	Heavy Chain Variable Domain	QVQLVQSGAEVKKPGSSVKVSKASGGTFEHYAISWVRQAPGQGLEWM GGIIPILGRANYAQKFQGRVTITADESTSTAYMELSSLRSEDVAVYYC ARDRSWEGSPYMYGMDVWGQGTMTVSS
122	VH (DNA)	caggtgcagctggtgcagtctgggctgaggtgaagaagcctgggtcc tcggtgaaggtctcctgcaaggcttctggaggcaccttcgaacactat gctatcagctgggtgcgacaggccccctggacaggggcttgagtggatg ggagggatcatcccatattgggcccagagcaaaactacgcacagaagttc cagggcagagtcacgattaccgcggacgaatccacgagcacagcctac atggagctgagcagcctgagatctgaggacacggcggtgtactactgc gccagagacagaagctgggaaggatctccctatatgtactacggaatg gacgtttggggccaagggacaatggtcaccgtttctca
123	CDRH1 IMGT (Prot)	GGTFEHYA
124	CDRH1 Kabat (Prot)	HYAIS
125	CDRH1 Chothia (Prot)	GGTFEHY
126	CDRH2 IMGT (Prot)	IIPILGRA
127	CDRH2 Kabat (Prot)	GIIPILGRANYAQKFQG
128	CDRH2 Chothia (Prot)	IPILGR
129	CDRH3 IMGT (Prot)	ARDRSWEGSPYMYGMDV
130	CDRH3 Kabat (Prot)	DRSWEGSPYMYGMDV
131	CDRH3 Chothia (Prot)	DRSWEGSPYMYGMDV
132	Light Chain Variable Domain	DIQLTQSPSSLSASVGRVTITCRASQSIISLYLNWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQVAVAPW TFGGGTKVEIK
133	VL (DNA)	gacatccagttgaccagctctccatcctccctgtctgcaagcgttgga gacagagttactatcacttgccgggcaagtcagagcattagcctatat ttaaattggtatcagcagaaaccagggaaagccccctaagctcctgatc tatgctgcatccagtttgcaaagtggggtcccatcaaggttcagtggc agtggatccgggacagatttcaactctcaccatcagcagctctgcaacct gaagattttgcaacttactactgtcagcaagtggcgtcgcccccttgg actttcggcggagggaccaaggttgagatcaaa
134	CDRL1 IMGT (Prot)	QSIISLY

135	CDRL1 Kabat (Prot)	RASQSSISLYLN
136	CDRL1 Chothia (Prot)	RASQSSISLYLN
137	CDRL2 IMGT (Prot)	AAS
138	CDRL2 Kabat (Prot)	AASSLQS
139	CDRL2 Chothia (Prot)	AASSLQS
140	CDRL3 IMGT (Prot)	QQVAVAPWT
141	CDRL3 Kabat (Prot)	QQVAVAPWT
142	CDRL3 Chothia (Prot)	QQVAVAPWT
143	ScFv	DIQLTQSPSSLSASVGDRTITCRASQSSISLYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQVAVAPWTFGGGKVEIKGSTSGSGKPGSGEGSTKGQVQLVQSGAEVKKPGSSVKVSCASGGTFEYHAISWVRQAPQGLEWMGGIIPILGRANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDRSWEGSPYMYGMDVWGQGTMTVTVSS
144	ScFv	gacatccagttgacccagttctccatcctcctgtctgcaagcgttggagacagagttactatcacttgccgggcaagtcagagcattagcctatatataaattggtatcagcagaaaccagggaaagcccctaagctcctgactatgctgcatccagtttgcaaagtggtgcccataaggttcagtggtcagtggtacagagatttactctcaccatcagcagctctgcaacctgaagattttgcaacttactactgtcagcaagtggtcgccctggaactttcgccggagggaaccaaggttgagatcaaagggagcacaagcggctctggcaaacctggatctggcgagggtctaccaagggccaggtgcagctggtgcagctctgggctgaggtgaagaagcctgggtcctcggtgaaggtctcctgcaaggcttctggaggcaccttcgaacactatgctatcagctgggtgcgacaggcccctggacaggggttgagtggtggaggagatcatccccatattgggcccagcaaaactacgcacagaagttccagggcagagtcacgattaccgcgagcaatccacgagcacagcctacatggagctgagcagcctgagatctgaggacacggcggtgtactactgcgccagagacagaagctgggaaggtatctccctatatgtactacggaatggacgtttgggccaagggacaatggtcaccgtttctca

Table 10: Exemplary Antibody Sequences 7 (Ab7)

SEQ ID NO:	Description	Sequence
145	Heavy Chain Variable Domain	QVQLVESGGGVVQPGSRSLRLSCAASGFTFASEGMDHWVRQAPGKLEWV ASIYYEGVNKYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYC AKDVSYYDSSRLVYHGMDVWGQGTITVTVSS
146	VH (DNA)	caggtgcagctggtggagctctgggggaggcgtggtccagcctgggagg tccctgagactctcctgcgctgcatctggattcaccttcgccagcgaa ggcatgcactgggtccgccaggtccaggcaaggggctggagtggtg gcatccatatactatgagggagtcataaatactatgcagactccgtg aagggccgattcaccatctctagagacaattccaagaacacgctgtat ctgcaaatgaatagcctgagagccgaggacacggcggtgtactactgc

		gccaaggacgtgtcctactacgacagcagcagactagtttatcacgga atggacgtatgggggcaagggaaccaagggtcacggtttcctca
147	CDRH1 IMGT (Prot)	GFTFASEG
148	CDRH1 Kabat (Prot)	SEGMH
149	CDRH1 Chothia (Prot)	GFTFASE
150	CDRH2 IMGT (Prot)	IYYEGVNK
151	CDRH2 Kabat (Prot)	SIYYEGVNKYYADSVKG
152	CDRH2 Chothia (Prot)	YYEGVN
153	CDRH3 IMGT (Prot)	AKDVSYYDSSRLVYHGMDV
154	CDRH3 Kabat (Prot)	DVSYYDSSRLVYHGMDV
155	CDRH3 Chothia (Prot)	DVSYYDSSRLVYHGMDV
156	Light Chain Variable Domain	DIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLI YAAGSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQVHDFPL TFGGGTKVEIK
157	VL (DNA)	gacatccagttgacccagtcctccatcctccctgtctgcaagcgttga gatagagtcactatcacttgccgggcaagtcagagcattagcagctat ttaaattggtatcagcagaaaccagggaaagccccctaagctcctgac tatgcagccgggagtttgcaaagtgggtcccacaggttcagtggc agtggatccgggacagatttcactctcaccatcagcagctctgcaacct gaagattttgcaacttactactgtcagcaagtgacgacttcctctc actttcggcggaggggaccaaggttgagatcaaa
158	CDRL1 IMGT (Prot)	QSISSY
159	CDRL1 Kabat (Prot)	RASQSISSYLN
160	CDRL1 Chothia (Prot)	RASQSISSYLN
161	CDRL2 IMGT (Prot)	AAG
162	CDRL2 Kabat (Prot)	AAGSLQS
163	CDRL2 Chothia (Prot)	AAGSLQS
164	CDRL3 IMGT (Prot)	QQVHDFPLT
165	CDRL3 Kabat (Prot)	QQVHDFPLT
166	CDRL3 Chothia (Prot)	QQVHDFPLT
167	ScFv	DIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLI YAAGSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQVHDFPL TFGGGTKVEIKGSTSGSGKPGSGEGSTKGQVQLVESGGGVVQPGRSLR LSCAASGFTFASEGMHWRQAPGKGLEWVASIYYEGVNKYYADSVKGR

		FTISRDN SKNTLYLQMNSLRAEDTAVYYCAKDVSYDSSRLVYHGMDV WGQGT TVTVSS
168	ScFv	gacatccagttgaccaggtctccatcctcctgtctgcaagcgttgga gatagagtcactatcacttgccgggcaagtcagagcattagcagctat ttaaatgggtatcagcagaaaccagggaaagcccctaagctcctgac tatgcagccgggagtttgcaaagtgggtcccatcaagggtcagtgga agtggatccgggacagatttcaactctcaccatcagcagtcgcaacct gaagattttgcaacttactactgtcagcaagtgacgacttcctctc actttcggcggagggaacaggttgagatcaaaggagcacaagcggc tctggcaaacctggatctggcgagggtatctaccaagggccaggtgcag ctgggtggagtctgggggagggcgtgggtccagcctgggaggtccctgaga ctctcctgcgctgcatctggattcaccttcgccagcgaaggcatgcac tgggtccgccaggtccaggcaaggggctggagtgggtggcatccata tactatgagggagtcataaataactatgcagactcgtgaagggccga ttcaccatctctagagacaattccaagaacacgctgtatctgcaaatg aatagcctgagagccgaggacacggcggtgtactactgcgccaaggac gtgtcctactacgacagcagcagactagtttatcacggaatggacgta tgggggcaagggaccacgggtcacggtttcctca

Table 11: Exemplary Antibody Sequences 8 (Ab8)

SEQ ID NO:	Description	Sequence
169	Heavy Chain Variable Domain	QVQLVESGGGVVQPGSRSLRLSCAASGFTFASEGMHWVRQAPGKLEWV ASIYYEGVNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYC AKDRSYDSSGLVYHGMDVWGQGT TVTVSS
170	VH (DNA)	caggtgcagctggtggagtctgggggagggcgtgggtccagcctgggagg tccctgagactctcctgcgctgcatctggattcaccttcgccagcgaa ggcatgcaactgggtccgccaggtccaggcaaggggctggagtgggtg gcatccatatactatgagggagtcataaataactatgcagactcgtg aagggccgattcaccatctccagagacaattccaagaacacgctgtat ctgcaaatgaacagcctgagagccgaggacacggcggtgtactactgc gccaaggacagatcctactacgacagcagcgggctagtttatcacgga atggacgtatgggggcaagggaccacgggtcacggtttcctca
171	CDRH1 IMGT (Prot)	GFTFASEG
172	CDRH1 Kabat (Prot)	SEGMH
173	CDRH1 Chothia (Prot)	GFTFASE
174	CDRH2 IMGT (Prot)	IYYEGVNK
175	CDRH2 Kabat (Prot)	SIYYEGVNKYYADSVKG
176	CDRH2 Chothia (Prot)	YYEGVN
177	CDRH3 IMGT (Prot)	AKDRSYDSSGLVYHGMDV
178	CDRH3 Kabat (Prot)	DRSYDSSGLVYHGMDV
179	CDRH3 Chothia (Prot)	DRSYDSSGLVYHGMDV

180	Light Chain Variable Domain	DIQLTQSPSSLSASVGDRTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSGQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQVHDFPLTFGGGTKVEIK
181	VL (DNA)	gacatccagttgaccagtcctccatcctcctgtctgcaagcgttgga gacagagtcactatcacttgccgggcaagtcagagcatttagcagctat ttaaattggtatcagcagaaaccagggaaagcccctaagctcctgac tatgctgcatccagtggaacaaagtggggtcccatcaaggttcagtggc agtggatccgggacagatttcactctcaccatcagcagtcctgcaacct gaagattttgcaacttactactgtcagcaagtgacagacttcctctc actttcggcggagggaaccaaggttgagatcaaa
182	CDRL1 IMGT (Prot)	QSISSY
183	CDRL1 Kabat (Prot)	RASQSISSYLN
184	CDRL1 Chothia (Prot)	RASQSISSYLN
185	CDRL2 IMGT (Prot)	AAS
186	CDRL2 Kabat (Prot)	AASSGQS
187	CDRL2 Chothia (Prot)	AASSGQS
188	CDRL3 IMGT (Prot)	QQVHDFPLT
189	CDRL3 Kabat (Prot)	QQVHDFPLT
190	CDRL3 Chothia (Prot)	QQVHDFPLT
191	ScFv	DIQLTQSPSSLSASVGDRTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSGQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQVHDFPLTFGGGTKVEIKSGSTSGSGKPGSGEGSTKGQVQLVESGGGVVQPRSLRLSCAASGFTFASEGHWVRQAPGKGLEWVASIYYEGVNKYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKDRSYDDSSGLVYHGMDVWGQGTTTVTVSS
192	ScFv	gacatccagttgaccagtcctccatcctcctgtctgcaagcgttgga gacagagtcactatcacttgccgggcaagtcagagcatttagcagctat ttaaattggtatcagcagaaaccagggaaagcccctaagctcctgac tatgctgcatccagtggaacaaagtggggtcccatcaaggttcagtggc agtggatccgggacagatttcactctcaccatcagcagtcctgcaacct gaagattttgcaacttactactgtcagcaagtgacagacttcctctc actttcggcggagggaaccaaggttgagatcaaagggagcacaagcggc tctggcaaacctggatctggcgagggatctaccaagggccaggtgcag ctgggtggagtctgggggagggcgtgggtccagcctgggaggtccctgaga ctctcctgctgcatctggattcaccttcgccagcgaaggcatgcac tggtccgccaggtccaggcaaggggctggagtgggtggcatccata tactatgagggagtcaataaatactatgcagactcctgaagggccga ttcaccatctccagagacaattccaagaacacgctgtatctgcaaatg aacagcctgagagccgaggacacggcggtgtactactgcgccaaggac agatcctactacgacagcagcgggctagtttatcacggaatggacgta tgggggcaagggaccacgggtcacggtttcctca

Table 12: Exemplary Antibody Sequences 9 (Ab9)

SEQ ID NO:	Description	Sequence
193	Heavy Chain Variable Domain	QVQLVESGGGVVQPGRSRLRLSCAASGFTFSSEGMYWVRQAPGKGLEWV AAIWYEGSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYC AKDRSYDSSQLVYHGMDVWGQGTITVTVSS
194	VH (DNA)	caagttcagctggtggagtctgggggagggcgtggtccagcctgggagg tccctgagactctcctgcgctgcatctggattcaccttcagtagcgag ggaatgtactgggtccgccaggctccaggcaaggggctggagtgggtg gcagccatattggtatgaggggaagtaataaatactatgccgactccgtg aagggccgattcaccatctctcgcgacaattccaaaaatacgtgtat ctgcaaatgaatagccttagagccgaggacacggcggtgtactactgc gccaaaggacagatcctactacgacagcagccagctagtttatcacgga atggacgtatgggggcaaggggaccacggtcaccgtttcctca
195	CDRH1 IMGT (Prot)	GFTFSSEG
196	CDRH1 Kabat (Prot)	SEGMY
197	CDRH1 Chothia (Prot)	GFTFSSE
198	CDRH2 IMGT (Prot)	IWYEGSNK
199	CDRH2 Kabat (Prot)	AIWYEGSNKYYADSVKG
200	CDRH2 Chothia (Prot)	WYEGSN
201	CDRH3 IMGT (Prot)	AKDRSYDSSQLVYHGMDV
202	CDRH3 Kabat (Prot)	DRSYDSSQLVYHGMDV
203	CDRH3 Chothia (Prot)	DRSYDSSQLVYHGMDV
204	Light Chain Variable Domain	DIQLTQSPSSLSASVGRVTITCRASQSISSYLNWYQQKPGKAPKLLI YAASSLQGGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQIHDFPL TFGGGTKVEIK
205	VL (DNA)	gacatccagttgacccagctctccatcctccctgtctgcaagcgttgga gacagagtcactatcacttgccgggcaagtcagagcatttagcagctat ttaaattggtatcagcagaaaccagggaaagcccctaagctcctgac tatgctgcatccagtttgcaaggaggggtcccatcaaggttcagtggc agtggctctgggacagatttcactctcaccatcagcagctctgcaacct gaagattttgcaacttactactgtcagcaaatccagacttcctctc actttcggcggaggggaccaaggttgagatcaaa
206	CDRL1 IMGT (Prot)	QSISSY
207	CDRL1 Kabat (Prot)	RASQSISSYLN
208	CDRL1 Chothia (Prot)	RASQSISSYLN
209	CDRL2 IMGT (Prot)	AAS
210	CDRL2 Kabat (Prot)	AASSLQG

211	CDRL2 Chothia (Prot)	AASSLQG
212	CDRL3 IMGT (Prot)	QQIHDFPLT
213	CDRL3 Kabat (Prot)	QQIHDFPLT
214	CDRL3 Chothia (Prot)	QQIHDFPLT
215	ScFv	DIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLI YAASSLQGGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQIHDFPL TFGGGTKVEIKGSTSGSGKPGSGEGSTKGQVQLVESGGGVVQGRSLR LSCAASGFTFSSEGMVWVRQAPGKGLEWVAIIWYEGSNKYYADSVKGR FTISRDNKNTLYLQMNSLRAEDTAVYYCAKDRSYDSSQLVYHGMDV WGQGTITVTVSS
216	ScFv	gacatccagttgacccagttctccatccctccctgtctgcaagcgttgga gacagagtcactatcacttgccgggcaagtcagagcatttagcagctat ttaaattggtatcagcagaaaccagggaaagcccctaagctcctgatc tatgctgcatccagtttgcaaggaggggtcccatcaaggttcagtggc agtggctctgggacagatttcactctcaccatcagcagctctgcaacct gaagattttgcaacttactactgtcagcaaattcacgacttccctctc actttcggcggagggaaccaaggttgagatcaaaggagcacaagcggc tctggcaaacctggatctggcgagggatctaccaagggccaaagttcag ctggtggagtctggggaggcgtggtccagcctgggaggtccctgaga ctctcctgcgctgcatctggattcaccttcagttagcaggggaatgtac tgggtccgcccaggctccaggcaaggggctggagtgggtggcagccata tggtatgaggaagtaataaataactatgccgactccgtgaagggccga ttcaccatctctcgcgacaattccaaaaatacgtgtatctgcaaatg aatagccttagagccgaggacacggcgggtgtactactgcgccaaggac agatcctactacgacagcagccagctagtttatcacggaatggacgta tgggggcaagggaaccacgggtcaccggttctcctca

[0162] Chimeric antigen receptors (CARs) are engineered receptors that may direct or redirect T cells or NK cells (*e.g.*, patient or donor T or NK cells) to target a selected antigen. A CAR may be engineered to recognize an antigen and, when bound to that antigen, activate the immune cell to attack and destroy the cell bearing that antigen. When these antigens exist on tumor cells, an immune cell that expresses the CAR may target and kill the tumor cell. CARs generally comprise an extracellular binding domain that mediates antigen binding (*e.g.*, a dual TACI-BCMA binding domain), a transmembrane domain that spans, or is understood to span, the cell membrane when the CAR is present at a cell surface or cell membrane, and an intracellular (or cytoplasmic) signaling domain.

[0163] According to at least one non-limiting view, there have been at least three “generations” of CAR compositions. In a first generation of CARs, a binding domain (*e.g.*, a single chain fragment variable, binding domain) is linked or connected to a signaling domain (*e.g.*, CD3ζ) via a transmembrane domain, optionally comprising a hinge domain and one or more spacers. In a second generation of CARs, a costimulatory domain (CM1, such as CD28, 4-1BB, or OX-40) is

introduced with the signaling domain (*e.g.*, CD3 ζ). In a third generation of CARs, a second costimulatory domain (CM2) is comprised.

[0164] TCRs are heterodimers composed of an α -chain and a β -chain. TCR signaling requires recruitment of signaling proteins that generate an immune synapse. In addition, TCR localization at the plasma membrane depends on CD3 complex, which is expressed in T cells. Engineered single chain TCRs may be generated, *e.g.*, using transmembrane and signaling domains of CAR constructs, methods and constructs for which are known (*e.g.*, sTCR and TCR-CAR molecules, *e.g.*, fusion of a TCR β chain with CD28 TM and CD28 and CD3 ζ signaling modules).

[0165] A dual TACI-BCMA binding system of the present disclosure may comprise one or more antigen binding domains that bind TACI and BCMA. In some embodiments, an antigen binding system further comprises a costimulatory domain, and/or an extracellular domain (*e.g.*, a “hinge” or “spacer” region), and/or a transmembrane domain, and/or an intracellular (signaling) domain, and/or a CD3-zeta or CD3-epsilon activation domain. In some embodiments, a dual TACI-BCMA binding system of the present disclosure comprises at least a binding domain that binds human TACI and BCMA, a costimulatory domain, an extracellular domain, a transmembrane domain, and a CD3-zeta or CD3-epsilon activating domain.

[0166] In some embodiments, a dual TACI-BCMA binding CAR of the present disclosure may comprise an antigen binding system that comprises one or more, or all, of a leader peptide (P), dual TACI-BCMA binding (B), a costimulatory protein's extracellular domain (E), a transmembrane domain (T), a costimulatory domain (C), a second costimulatory domain (C'), and an activation domain (A). In some instances, a dual TACI-BCMA binding CAR is configured according to the following: B E T A. In some instances, a dual TACI-BCMA binding CAR is configured according to the following: P B E T A. In some instances, a dual TACI-BCMA binding CAR is configured according to the following: B E T C A. In some instances a dual TACI-BCMA binding CAR is configured according to the following: P B E T C A. In some instances, a dual TACI-BCMA binding CAR is configured according to the following: B E T C C' A. In some instances, a dual TACI-BCMA binding CAR is configured according to the following: P B E T C C' A. In some embodiments, a dual TACI-BCMA binding CAR comprises a VH and a VL, optionally wherein the CAR is configured according to the following: P-VH-VL-E-T-C-A or P-VL-VH-E-T-C-A. In some embodiments, the VH and the VL are connected by a linker (L), optionally wherein the CAR is configured according to the following, from N-terminus to C-terminus: P-VH-L-VL-E-T-C-A or P-VH-L-VL-E-T-C-A.

[0167] One or more antigen binding domains determine the target(s) of an antigen binding system. A binding domain of an antigen binding system may comprise any dual TACI-BCMA binding domain, *e.g.*, an antibody provided by the present disclosure, *e.g.*, a binding domain of the present disclosure. Binding domain are used in chimeric antigen receptors at least in part because they may be engineered to be expressed as part of a single chain along with the other CAR components. See, for example, U.S. Pat. Nos. 7,741,465, and 6,319,494 as well as Eshhar et al., *Cancer Immunol Immunotherapy* (1997) 45: 131-136, Krause et al., *J. Exp. Med.*, Volume 188, No. 4, 1998 (619-626); Finney et al., *Journal of Immunology*, 1998, 161: 2791-2797, each of which is incorporated herein by reference with respect to binding domains in CARs. A binding domain or scFv, is a single chain antigen binding fragment comprising a heavy chain variable domain and a light chain variable domain, which heavy chain variable domain and light chain variable domain are linked or connected together. See, for example, U.S. Pat. Nos. 7,741,465, and 6,319,494 as well as Eshhar et al., *Cancer Immunol Immunotherapy* (1997) 45: 131-136, each of which is incorporated herein by reference with respect to binding domain domains. When derived from a parent antibody, a binding domain may retain some of, retain all of, or essentially retain the parent antibody's binding of a target antigen. In some embodiments, a CAR contemplated herein comprises antigen-specific binding domain that may be a scFv (a murine, human or humanized scFv) that binds an antigen expressed on a cancer cell. In a certain embodiment, the scFv binds TACI and BCMA.

[0168] In certain embodiments, the CARs contemplated herein may comprise linker residues between the various domains, *e.g.*, between VH and VL domains, added for appropriate spacing conformation of the molecule. CARs contemplated herein, may comprise one, two, three, four, or five or more linkers. In some embodiments, the length of a linker is about 1 to about 25 amino acids, about 5 to about 20 amino acids, or about 10 to about 20 amino acids, or any intervening length of amino acids. In some embodiments, the linker is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or more amino acids long.

[0169] Illustrative examples of linkers include glycine polymers (G)_n; glycine-serine polymers (G₁₋₅S₁₋₅)_n, where n is an integer of at least one, two, three, four, or five; glycine-alanine polymers; alanine-serine polymers; and other flexible linkers known in the art. Glycine and glycine-serine polymers are relatively unstructured, and therefore may be able to serve as a neutral tether between domains of fusion proteins such as the CARs described herein. Glycine accesses more phi-psi space than even alanine, and is much less restricted than residues with longer side chains (see Scheraga, *Rev. Computational Chem.* 11173-142 (1992)). Other linkers contemplated herein include Whitlow linkers (see Whitlow, *Protein Eng.* 6(8): 989-95 (1993)). The ordinarily

skilled artisan will recognize that design of a CAR in some embodiments may include linkers that are all or partially flexible, such that the linker may include a flexible linker as well as one or more portions that confer less flexible structure to provide for a desired CAR structure. In one embodiment, any of the constructs described herein may comprise a “GS” linker. In another embodiment, any of the constructs described herein comprise a “GSG” linker. In an example a glycine-serine linker comprises or consists of the amino acid sequence GS (SEQ ID NO: 223), which may be encoded by the nucleic acid sequence according to ggatcc (SEQ ID NO: 224) or ggggtcc (SEQ ID NO: 225). In an example a glycine-serine linker comprises or consists of the amino acid sequence GGGSGGGS (SEQ ID NO: 226), which may be encoded by the nucleic acid sequence according to ggcggtggaagcggaggaggtcc (SEQ ID NO: 227). In another embodiment, the CARs described herein comprise the amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) of SEQ ID NO: 219 (GSTSGSGKPGSGEGSTKG (SEQ ID NO: 219). In an embodiment, a linker is encoded by a nucleic acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) to the nucleic acid sequence according to gggagcactagcggctctggcaaacctggatctggcgagggatctaccaagggc (SEQ ID NO: 220), gggagcacaagcggctctggcaaacctggatctggcgagggatctaccaagggc (SEQ ID NO: 228), or gggagcacaagcggctctggcaaacctggatccggcgagggatctaccaagggc (SEQ ID NO: 229).

[0170] In embodiments, a CAR comprises a scFv that further comprises a variable region linking sequence. A “variable region linking sequence,” is an amino acid sequence that connects a heavy chain variable region to a light chain variable region and provides a spacer function compatible with interaction of the two sub-binding domains so that the resulting polypeptide retains a specific binding affinity to the same target molecule as an antibody that comprises the same light and heavy chain variable regions. In one embodiment, the variable region linking sequence is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or more amino acids long.

[0171] In embodiments, the binding domain of the CAR is followed by one or more “spacer domains,” which refers to the region that moves the antigen binding domain away from the effector cell surface to enable proper cell/cell contact, antigen binding and activation (Patel *et al.*, *Gene Therapy*, 1999; 6: 412–419). The spacer domain may be derived either from a natural, synthetic, semi-synthetic, or recombinant source. In certain embodiments, a spacer domain is a portion of an immunoglobulin, including, but not limited to, one or more heavy chain constant

regions, *e.g.*, CH2 and CH3. The spacer domain may include the amino acid sequence of a naturally occurring immunoglobulin hinge region or an altered immunoglobulin hinge region.

[0172] The binding domain of the CAR may generally be followed by one or more “hinge domains,” which plays a role in positioning the antigen binding domain away from the effector cell surface to enable proper cell/cell contact, antigen binding and activation. A CAR generally comprises one or more hinge domains between the binding domain and the transmembrane domain. The hinge domain may be derived either from a natural, synthetic, semi-synthetic, or recombinant source. The hinge domain may include the amino acid sequence of a naturally occurring immunoglobulin hinge region or an altered immunoglobulin hinge region.

[0173] In some embodiments, an Antigen binding system of the present disclosure may comprise a hinge that is, is from, or is derived from (*e.g.*, comprises all or a fragment of) an immunoglobulin-like hinge domain. In some embodiments, a hinge domain is from or derived from an immunoglobulin. In some embodiments, a hinge domain is selected from the hinge of IgG1, IgG2, IgG3, IgG4, IgA, IgD, IgE, or IgM, or a fragment thereof. A hinge may be derived from a natural source or from a synthetic source. Hinge domains suitable for use in the CARs described herein include the hinge region derived from the extracellular regions of type 1 membrane proteins such as CD8 α , CD4, CD28 and CD7, which may be wild-type hinge regions from these molecules or may be altered, for example a truncated CD28 hinge domain. A hinge may be derived from a natural source or from a synthetic source. In some embodiments, an Antigen binding system of the present disclosure may comprise a hinge that is, is from, or is derived from (*e.g.*, comprises all or a fragment of) CD2, CD3 delta, CD3 epsilon, CD3 gamma, CD4, CD7, CD8 α , CD8 β , CD11a (ITGAL), CD11b (ITGAM), CD11c (ITGAX), CD11d (ITGAD), CD18 (ITGB2), CD19 (B4), CD27 (TNFRSF7), CD28, CD28T, CD29 (ITGB1), CD30 (TNFRSF8), CD40 (TNFRSF5), CD48 (SLAMF2), CD49a (ITGA1), CD49d (ITGA4), CD49f (ITGA6), CD66a (CEACAM1), CD66b (CEACAM8), CD66c (CEACAM6), CD66d (CEACAM3), CD66e (CEACAM5), CD69 (CLEC2), CD79A (B-cell antigen receptor complex-associated alpha chain), CD79B (B-cell antigen receptor complex-associated beta chain), CD84 (SLAMF5), CD96 (Tactile), CD100 (SEMA4D), CD103 (ITGAE), CD134 (OX40), CD137 (4-1BB), CD150 (SLAMF1), CD158A (KIR2DL1), CD158B1 (KIR2DL2), CD158B2 (KIR2DL3), CD158C (KIR3DP1), CD158D (KIRDL4), CD158F1 (KIR2DL5A), CD158F2 (KIR2DL5B), CD158K (KIR3DL2), CD160 (BY55), CD162 (SELPLG), CD226 (DNAM1), CD229 (SLAMF3), CD244 (SLAMF4), CD247 (CD3-zeta), CD258 (LIGHT), CD268 (BAFFR), CD270 (TNFSF14), CD272 (BTLA), CD276 (B7-H3), CD279 (PD-1), CD314 (NKG2D), CD319 (SLAMF7), CD335 (NK-p46), CD336 (NK-p44), CD337 (NK-p30), CD352 (SLAMF6), CD353

(SLAMF8), CD355 (CRTAM), CD357 (TNFRSF18), inducible T cell co-stimulator (ICOS), LFA-1 (CD11a/CD18), NKG2C, DAP-10, ICAM-1, NKp80 (KLRF1), IL-2R beta, IL-2R gamma, IL-7R alpha, LFA1-1, SLAMF9, LAT, GADS (GrpL), SLP-76 (LCP2), PAG1/CBP, a CD83 ligand, Fc gamma receptor, MHC class 1 molecule, MHC class 2 molecule, a TNF receptor protein, an immunoglobulin protein, a cytokine receptor, an integrin, activating NK cell receptors, or Toll ligand receptor, or which is a fragment or combination thereof.

[0174] In embodiments, the hinge domain comprises a truncated CD28 hinge region (CD28T) hinge region, such as disclosed in International Patent Application No: PCT/US2017/025351, filed March 31, 2017, which is incorporated herein by reference in its entirety. In embodiments the CARs described herein comprise a CD28T hinge domain having the amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) SEQ ID NO: 230 (LDNEKSNGTIIHVKGKHLCPSP LFPGPSKP (SEQ ID NO: 230)). In embodiments, a CD28T hinge domain is encoded by a nucleic acid having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) the nucleic acid having the sequence according to ctagacaatgagaagagcaatggaaccattatccatgtgaaagggaacaccttgtccaagtcacctatttcccgaccttctaagccc (SEQ ID NO: 231).

[0175] In embodiments, the hinge domain comprises a CD8 α hinge region. In embodiments the CARs described herein comprise a hinge domain from CD8 α having the amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) SEQ ID NO: 232 (TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD (SEQ ID NO: 232)). In embodiments, hinge domain from CD8 α is encoded by a nucleic acid having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) to the nucleic acid having the sequence according to accacgacgccagcgccgcgaccaccaacaccggcgccccaccatcgcgtcgcaaccctgtccctgcgccccgaggcgtgccggcc agcggcgggggggcgagtcgacacgagggggctggacttcgcctgtgat (SEQ ID NO: 233).

[0176] Polynucleotide and polypeptide sequences of these hinge domains are known. In some embodiments, the polynucleotide encoding a hinge domain comprises a nucleotide sequence at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at

least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% (e.g., 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%) identical to a nucleotide sequence known. In some embodiments, the polypeptide sequence of a hinge domain comprises a polypeptide sequence at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% (e.g., 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%) identical to a known polypeptide sequence.

[0177] In general, a “transmembrane domain” (e.g., of an antigen binding system) refers to a domain having an attribute of being present in the membrane when present in a molecule at a cell surface or cell membrane (e.g., spanning a portion or all of a cellular membrane). A costimulatory domain for an antigen binding system of the present disclosure may further comprise a transmembrane domain and/or an intracellular signaling domain. It is not required that every amino acid in a transmembrane domain be present in the membrane. For example, in some embodiments, a transmembrane domain is characterized in that a designated stretch or portion of a protein is substantially located in the membrane. Amino acid or nucleic acid sequences may be analyzed using a variety of algorithms to predict protein subcellular localization (e.g., transmembrane localization). The programs psort (PSORT.org) and Prosite (prosite.expasy.org) are exemplary of such programs.

[0178] The type of transmembrane domain comprised in an antigen binding system described herein is not limited to any type. In some embodiments, a transmembrane domain is selected that is naturally associated with a binding domain and/or intracellular domain. In some instances, a transmembrane domain comprises a modification of one or more amino acids (e.g., deletion, insertion, and/or substitution), e.g., to avoid binding of such domains to a transmembrane domain of the same or different surface membrane proteins to minimize interactions with other members of the receptor complex.

[0179] A transmembrane domain may be derived either from a natural or from a synthetic source. Where the source is natural, a domain may be derived from any membrane-bound or transmembrane protein. Exemplary transmembrane domains may be derived from (e.g., may comprise at least a transmembrane domain of) an alpha, beta or zeta chain of a T-cell receptor, 2B4, CD28, CD3 epsilon, CD3 delta, CD3 gamma, CD45, CD4, CD5, CD7, CD8, CD8 alpha, CD8beta, CD9, CD11a, CD11b, CD11c, CD11d, CD16, CD22, CD27, CD33, CD37, CD64, CD80, CD86, CD134, CD137, TNFSFR25, CD154, 4-1BB/CD137, activating NK cell receptors,

an Immunoglobulin protein, B7-H3, BAFFR, BLAME (SLAMF8), BTLA, CD100 (SEMA4D), CD103, CD160 (BY55), CD18, CD19, CD19a, CD2, CD247, CD276 (B7-H3), CD29, CD30, CD40, CD49a, CD49D, CD49f, CD69, CD84, CD96 (Tactile), CDS, CEACAM1, CRT AM, cytokine receptor, DAP-10, DAP-12, DNAM1 (CD226), Fc gamma receptor, GADS, GTR, HVEM (LIGHTR), IA4, ICAM-1, ICAM-1, Ig alpha (CD79a), IL-2R beta, IL-2R gamma, IL-7R alpha, inducible T cell costimulator (ICOS), integrins, ITGA4, ITGA4, ITGA6, ITGAD, ITGAE, ITGAL, ITGAM, ITGAX, ITGB2, ITGB7, ITGB1, KIRDS2, LAT, LFA-1, LFA-1, a ligand that binds with CD83, LIGHT, LIGHT, LTBR, Ly9 (CD229), lymphocyte function-associated antigen-1 (LFA-1; CD1-1a/CD18), MHC class 1 molecule, NKG2C, NKG2D, NKp30, NKp44, NKp46, NKp80 (KLRF1), OX-40, PAG/Cbp, programmed death-1 (PD-1), PSGL1, SELPLG (CD162), Signaling Lymphocytic Activation Molecules (SLAM proteins), SLAM (SLAMF1; CD150; IPO-3), SLAMF4 (CD244; 2B4), SLAMF6 (NTB-A; Ly108), SLAMF7, SLP-76, TNF receptor proteins, TNFR2, TNFSF14, a Toll ligand receptor, TRANCE/RANKL, VLA1, or VLA-6, or a fragment, truncation, or a combination thereof. In some embodiments, a transmembrane domain may be synthetic (and can, *e.g.*, comprise predominantly hydrophobic residues such as leucine and valine). In some embodiments, a triplet of phenylalanine, tryptophan and valine are comprised at each end of a synthetic transmembrane domain. In some embodiments, a transmembrane domain is directly linked or connected to a cytoplasmic domain. In some embodiments, a short oligo- or polypeptide linker (*e.g.*, between 2 and 10 amino acids in length) may form a linkage between a transmembrane domain and an intracellular domain. In some embodiments, a linker is a glycine-serine doublet.

[0180] In embodiments, the CARs described herein comprise a TM domain from CD28 having the amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) SEQ ID NO: 234 (FWVLVVVGVLACYSLLVTVAFIIFWV (SEQ ID NO: 234)). In embodiments, a TM domain from CD28 is encoded by a nucleic acid having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) the nucleic acid having the sequence according to ttttgggtgctggtggtggtggtggagtcctggcttgctatagcttgctagtaacagtggcctttattttctgggtg (SEQ ID NO: 235).

[0181] In embodiments, the CARs described herein comprise a TM domain from CD8 α having the amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%,

90–100%, or 95–100%) SEQ ID NO: 236 (IYIWAPLAGTCGVLLLSLVITLYC (SEQ ID NO: 236)). In embodiments, the TM domain from CD8 α is encoded by a nucleic acid having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) the nucleic acid having the sequence according to atctacatctgggcgcacctggccgggactgtggggctctctctgtcactggttatcacctttattgc (SEQ ID NO: 237).

[0182] Polynucleotide and polypeptide sequences of transmembrane domains provided herein are known. In some embodiments, the polynucleotide encoding a transmembrane domain comprises a nucleotide sequence at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% (*e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) identical to a nucleotide sequence known. In some embodiments, the polypeptide sequence of a transmembrane domain comprises a polypeptide sequence at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% (*e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) identical to a polypeptide sequence known. Optionally, short spacers may form linkages between any or some of the extracellular, transmembrane, and intracellular domains of the CAR.

[0183] Intracellular signaling domains that may transduce a signal upon binding of an antigen to an immune cell are known, any of which may be comprised in an antigen binding system of the present disclosure. For example, cytoplasmic sequences of a T cell receptor (TCR) are known to initiate signal transduction following TCR binding to an antigen (see, *e.g.*, Brownlie et al., Nature Rev. Immunol. 13:257–269 (2013)).

[0184] In some embodiments, CARs contemplated herein comprise an intracellular signaling domain. An “intracellular signaling domain,” refers to the part of a CAR that participates in transducing the message of effective CAR binding to a target antigen into the interior of the immune effector cell to elicit effector cell function, *e.g.*, activation, cytokine production, proliferation and cytotoxic activity, including the release of cytotoxic factors to the CAR-bound target cell, or other cellular responses elicited with antigen binding to the extracellular CAR domain. In some embodiments, a signaling domain and/or activation domain comprises an immunoreceptor tyrosine-based activation domain (ITAM). Examples of ITAM containing cytoplasmic signaling sequences comprise those derived from TCR zeta, FcR gamma, FcR beta,

CD3 zeta, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d (see, e.g., Love et al., Cold Spring Harb. Perspect. Biol. 2:a002485 (2010); Smith-Garvin et al., Annu. Rev. Immunol. 27:591-619 (2009)). In certain embodiments, suitable signaling domains comprise, without limitation, 4-1BB/CD137, activating NK cell receptors, an Immunoglobulin protein, B7-H3, BAFFR, BLAME (SLAMF8), BTLA, CD100 (SEMA4D), CD103, CD160 (BY55), CD18, CD19, CD19a, CD2, CD247, CD27, CD276 (B7-H3), CD28, CD29, CD3 delta, CD3 epsilon, CD3 gamma, CD30, CD4, CD40, CD49a, CD49D, CD49f, CD69, CD7, CD84, CD8alpha, CD8beta, CD96 (Tactile), CD11a, CD11b, CD11c, CD11d, CDS, CEACAM1, CRT AM, cytokine receptor, DAP-10, DNAM1 (CD226), Fc gamma receptor, GADS, GITR, HVEM (LIGHTR), IA4, ICAM-1, ICAM-1, Ig alpha (CD79a), IL-2R beta, IL-2R gamma, IL-7R alpha, inducible T cell costimulator (ICOS), integrins, ITGA4, ITGA4, ITGA6, ITGAD, ITGAE, ITGAL, ITGAM, ITGAX, ITGB2, ITGB7, ITGB1, KIRDS2, LAT, LFA-1, LFA-1, ligand that binds with CD83, LIGHT, LIGHT, LTBR, Ly9 (CD229), Ly108), lymphocyte function-associated antigen-1 (LFA-1; CD1-1a/CD18), MHC class 1 molecule, NKG2C, NKG2D, NKp30, NKp44, NKp46, NKp80 (KLRF1), OX-40, PAG/Cbp, programmed death-1 (PD-1), PSGL1, SELPLG (CD162), Signaling Lymphocytic Activation Molecules (SLAM proteins), SLAM (SLAMF1; CD150; IPO-3), SLAMF4 (CD244; 2B4), SLAMF6 (NTB-A, SLAMF7, SLP-76, TNF receptor proteins, TNFR2, TNFSF14, a Toll ligand receptor, TRANCE/RANKL, VLA1, or VLA-6, or a fragment, truncation, or a combination thereof.

[0185] The term “effector function” refers to a specialized function of the cell. Effector function of the T cell, for example, may be cytolytic activity or help or activity including the secretion of a cytokine. Thus, the term “intracellular signaling domain” refers to the portion of a protein which transduces the effector function signal and that directs the cell to perform a specialized function. While usually the entire intracellular signaling domain may be employed, in many cases it is not necessary to use the entire domain. To the extent that a truncated portion of an intracellular signaling domain is used, such truncated portion may be used in place of the entire domain as long as it transduces the effector function signal. The term intracellular signaling domain is meant to include any truncated portion of the intracellular signaling domain sufficient to transducing effector function signal.

[0186] It is known that signals generated through the TCR alone are insufficient for full activation of the T cell and that a secondary or costimulatory signal may also be required. Thus, T cell activation may be said to be mediated by two distinct classes of intracellular signaling domains: primary signaling domains that initiate antigen-dependent primary activation through the TCR (e.g., a TCR/CD3 complex) and costimulatory signaling domains that act in an antigen

independent manner to provide a secondary or costimulatory signal. In some embodiments, a CAR contemplated herein comprises an intracellular signaling domain that comprises one or more “costimulatory signaling domain” and a “primary signaling domain.”

[0187] Illustrative examples of ITAM containing primary signaling domains that are useful in the present disclosure include those derived from TCR ζ , FcR γ , FcR β , DAP12, CD3 γ , CD3 δ , CD3 ϵ , CD3 ζ , CD22, CD79a, CD79b, and CD66d. In some embodiments, a CAR comprises a CD3 ζ primary signaling domain and one or more costimulatory signaling domains. The intracellular primary signaling and costimulatory signaling domains may be linked in any order in tandem to the carboxyl terminus of the transmembrane domain. In one embodiment, the CARs have a CD3 ζ domain having the amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) SEQ ID NO: 238. LRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQE GLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 238). In embodiments, a CD3 ζ domain is encoded by a nucleic acid having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) the nucleic acid having the sequence according to ctgagagtgaagttcagcaggagcgcagacgccccgcgtaccagcagggccagaaccagctctataacgagctcaatctaggacgaa gagaggagtacgatgttttgacaagaggcgtggccgggaccctgagatgggggaaagccgagaaggagaaccctcaggaaggc ctgtacaatgaactgcagaaaataagatggcggaggcctacagtgagattgggatgaaaggcgagcgccggaggggcaaggggcac gatggcctftaccagggtctcagtacagccaccaaggacacctacgacgcccttcacatgcaggccctgccccctcgc (SEQ ID NO: 239).

[0188] CARs contemplated herein comprise one or more costimulatory signaling domains to enhance the efficacy and expansion of T cells expressing CAR receptors. As used herein, the term, “costimulatory signaling domain,” or “costimulatory domain”, refers to an intracellular signaling domain of a costimulatory molecule. In some embodiments, costimulatory molecules may include DAP-10, DAP-12, CD27, CD28, CD137(4-1BB), OX40 (CD134), CD30, CD40, PD-1, ICOS (CD278), CTLA4, LFA-1, CD2, CD7, LIGHT, TRIM, LCK3, SLAM, DAPIO, LAG3, HVEM, B7-H3, NKD2C, GITR, CD5, ICAM-1, CD11a, Lck, TNFR-I, TNFR-II, FasR, NKG2C, and B7-H3, and CD83.

[0189] In embodiments, the CARs comprise a CD28 costimulatory domain having the amino acid sequence of having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least

90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) SEQ ID NO: 240. RSKRSRLHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRS (SEQ ID NO: 240). In embodiments, a CD28 costimulatory domain is encoded by a nucleic acid having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) the nucleic acid having the sequence according to aggagtaagaggagcaggctcctgcacagtgactacatgaacatgactccccgccgccccgggccccaccgcaagcattaccagccct atgccccaccacgcgacttcgcagcctatcgctcc (SEQ ID NO: 241).

[0190] In embodiments, the CARs comprise a 4–IBB costimulatory domain having the amino acid sequence of having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) SEQ ID NO: 242. KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCE (SEQ ID NO: 242). In embodiments, a 4–IBB costimulatory domain is encoded by a nucleic acid having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) to the nucleic acid having the sequence according to aaacggggcagaagaagaactcctgtatatattcaacaaccatttatgagaccagtacaaactactcaagaggaagatggctgtagctgcc gatttcagaagaagaagaaggaggtgtgaa (SEQ ID NO: 243).

[0191] The engineered CARs described herein may also comprise an N-terminal signal peptide or tag at the N-terminus of the scFv or antigen binding domain. In one embodiment, a heterologous signal peptide may be used. The antigen binding domain or scFV may be fused to a leader or a signal peptide that directs the nascent protein into the endoplasmic reticulum and subsequent translocation to the cell surface. It is understood that, once a polypeptide containing a signal peptide is expressed at the cell surface, the signal peptide is generally proteolytically removed during processing of the polypeptide in the endoplasmic reticulum and translocation to the cell surface. Thus, a polypeptide such as the CAR constructs described herein, are generally expressed at the cell surface as a mature protein lacking the signal peptide, whereas the precursor form of the polypeptide includes the signal peptide. Any suitable signal sequence known in the art may be used. Similarly any known tag sequence known in the art may also be used. In one embodiment a signal sequence is a CSF2RA signal sequence. In embodiments, the CARs described herein comprise a CSF2RA signal sequence having the amino acid sequence of having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) to SEQ ID NO: 221;

MLLLVTSLLLCELPHPAFLIP (SEQ ID NO: 221) SEQ ID MEWTWVFLFLSVTAGVHS (SEQ ID NO: 244), or MALPVTALLPLALLLHAARP (SEQ ID NO: 245).

[0192] Components of a CAR may be exchanged or “swapped” using routine techniques of biotechnology for equivalent components. To provide just a few non-limiting and partial examples, a CAR of the present disclosure may comprise a binding domain as provided herein in combination with a hinge provided herein and a costimulatory domain provided herein. In certain examples, a CAR of the present disclosure may comprise a leader sequence as provided herein together with a binding domain as provided herein in combination with a hinge provided herein and a costimulatory domain provided herein.

[0193] The present disclosure comprises conjugates in which an antibody of the present disclosure is associated with a therapeutic agent or a detectable moiety. In various embodiments, the therapeutic agent is an anti-cancer agent as provided herein. In certain embodiments, the conjugate comprises one or more detectable moieties, i.e., is “labeled” with one or more such moieties. In some such embodiments, a conjugate of the present disclosure is useful in diagnostic or imaging applications, *e.g.*, diagnosing or imaging cancer. Any of a wide variety of detectable moieties may be used in labeled antibody conjugates described herein. Suitable detectable moieties comprise, without limitation: various ligands, radionuclides; fluorescent dyes; chemiluminescent agents (such as, for example, acridinium esters, stabilized dioxetanes, and the like); bioluminescent agents; spectrally resolvable inorganic fluorescent semiconductors nanocrystals (i.e., quantum dots); microparticles; metal nanoparticles (*e.g.*, gold, silver, copper, platinum, etc.); nanoclusters; paramagnetic metal ions; enzymes; colorimetric labels (such as, for example, dyes, colloidal gold, and the like); biotin; dioxigenin; haptens; and proteins for which antisera or monoclonal antibodies are available.

[0194] The present disclosure comprises nucleic acids encoding dual TACI-BCMA binding domains provided herein. The present disclosure comprises nucleic acids encoding antibodies of the provided herein, comprising, without limitation, nucleic acids encoding dual TACI-BCMA binding domains. The present disclosure comprises nucleic acids encoding antigen binding systems provided herein, comprising without limitation nucleic acids encoding dual TACI-BCMA binding chimeric antigen receptors. The nucleic acid sequence of SEQ ID NO: 2 comprises and provides exemplary nucleic acid sequences corresponding to and encoding each of SEQ ID NOs: 1 and 3-11. The nucleic acid sequence of SEQ ID NO: 13 comprises and provides exemplary nucleic acid sequences corresponding to and encoding each of SEQ ID NOs: 12 and 14-22. The

nucleic acid sequence of SEQ ID NO: 24 comprises and provides exemplary nucleic acid sequence corresponding to and encoding SEQ ID NO: 23.

[0195] The nucleic acid sequence of SEQ ID NO: 26 comprises and provides exemplary nucleic acid sequences corresponding to and encoding each of SEQ ID NOs: 25 and 27-35. The nucleic acid sequence of SEQ ID NO: 37 comprises and provides exemplary nucleic acid sequences corresponding to and encoding each of SEQ ID NOs: 36 and 38-46. The nucleic acid sequence of SEQ ID NO: 48 comprises and provides an exemplary nucleic acid sequence corresponding to and encoding SEQ ID NO: 47.

[0196] The nucleic acid sequence of SEQ ID NO: 50 comprises and provides exemplary nucleic acid sequences corresponding to and encoding each of SEQ ID NOs: 49 and 51-59. The nucleic acid sequence of SEQ ID NO: 61 comprises and provides exemplary nucleic acid sequences corresponding to and encoding each of SEQ ID NOs: 60 and 62-70. The nucleic acid sequence of SEQ ID NO: 72 comprises and provides an exemplary nucleic acid sequence corresponding to and encoding SEQ ID NO: 71.

[0197] The nucleic acid sequence of SEQ ID NO: 74 comprises and provides exemplary nucleic acid sequences corresponding to and encoding each of SEQ ID NOs: 73 and 75-83. The nucleic acid sequence of SEQ ID NO: 85 comprises and provides exemplary nucleic acid sequences corresponding to and encoding each of SEQ ID NOs: 84 and 86-94. The nucleic acid sequence of SEQ ID NO: 76 comprises and provides an exemplary nucleic acid sequence corresponding to and encoding SEQ ID NO: 95.

[0198] The nucleic acid sequence of SEQ ID NO: 98 comprises and provides exemplary nucleic acid sequences corresponding to and encoding each of SEQ ID NOs: 97 and 99-107. The nucleic acid sequence of SEQ ID NO: 109 comprises and provides exemplary nucleic acid sequences corresponding to and encoding each of SEQ ID NOs: 108 and 110-118. The nucleic acid sequence of SEQ ID NO: 120 comprises and provides an exemplary nucleic acid sequence corresponding to and encoding SEQ ID NO: 119.

[0199] The nucleic acid sequence of SEQ ID NO: 122 comprises and provides exemplary nucleic acid sequences corresponding to and encoding each of SEQ ID NOs: 121 and 123-131. The nucleic acid sequence of SEQ ID NO: 133 comprises and provides exemplary nucleic acid sequences corresponding to and encoding each of SEQ ID NOs: 132 and 134-142. The nucleic acid sequence of SEQ ID NO: 144 comprises and provides an exemplary nucleic acid sequence corresponding to and encoding SEQ ID NO: 143.

[0200] The nucleic acid sequence of SEQ ID NO: 146 comprises and provides exemplary nucleic acid sequences corresponding to and encoding each of SEQ ID NOs: 145 and 147-155. The nucleic acid sequence of SEQ ID NO: 157 comprises and provides exemplary nucleic acid sequences corresponding to and encoding each of SEQ ID NOs: 156 and 158-166. The nucleic acid sequence of SEQ ID NO: 168 comprises and provides an exemplary nucleic acid sequence corresponding to and encoding SEQ ID NO: 167.

[0201] The nucleic acid sequence of SEQ ID NO: 170 comprises and provides exemplary nucleic acid sequences corresponding to and encoding each of SEQ ID NOs: 169 and 171-179. The nucleic acid sequence of SEQ ID NO: 181 comprises and provides exemplary nucleic acid sequences corresponding to and encoding each of SEQ ID NOs: 180 and 182-190. The nucleic acid sequence of SEQ ID NO: 192 comprises and provides an exemplary nucleic acid sequence corresponding to and encoding SEQ ID NO: 191.

[0202] The nucleic acid sequence of SEQ ID NO: 194 comprises and provides exemplary nucleic acid sequences corresponding to and encoding each of SEQ ID NOs: 193 and 195-203. The nucleic acid sequence of SEQ ID NO: 205 comprises and provides exemplary nucleic acid sequences corresponding to and encoding each of SEQ ID NOs: 204 and 206-214. The nucleic acid sequence of SEQ ID NO: 216 comprises and provides an exemplary nucleic acid sequence corresponding to and encoding SEQ ID NO: 215.

[0203] In an embodiment, a dual TACI-BCMA binding CAR construct has an amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%)

SEQ	ID	NO:	246.
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DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPS
 RFSGSGSGTDFLTISLQPEDFATYYCQQSHIAPWTFGGGTKVEIKGSTSGSGKPGSGE
 GSTKGQVQLVQSGAEVKKPGSSVKVSKASGGTFADYAIWVRQAPGQGLEWMGGIIP
 ILGRANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDRDSTSLPYNHYY
 MDVWGKGTITVTVSSGSLDNEKSNGTIIHVKGKHLCPSPFPGPSKPFWLVVVGGVLA
 CYSLLVTVAFIIFWVRSKRSRLHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRSLRV
 KFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLY
 NELQKDKMAEAYSEIGMKGERRRGKGDGLYQGLSTATKDTYDALHMQALPPR (SEQ
 ID NO: 246). In embodiments, a dual TACI-BCMA binding CAR is encoded by a nucleic acid
 having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least
 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) to

the nucleic acid having the sequence according to:
gacatccagatgacccagtcctccatccctgtctgcaagcgttgagatagagtcactatcacttgccgggcaagtgcagagcattagcag
ctatttaaattggtatcagcagaaccagggaagcccctaagctcctgatctatgctgcatccagttgcaaagtgggtcccatcaagggt
cagtggcagtgatccgggacagatttactctcaccatcagcagctctgcaacctgaagatttgcacttactactgtcagcaaagccacat
cgccccttgacttttggcggagggaaccaagggtgagatcaaggaggagcactagcggctctggcaaacctggatctggcgagggatcta
ccaagggccaggtgcagctggtgagctggtgaggtgaagaagcctgggtcctcgggtgaagggtcctgcaaggcttctggaggc
accttcgcagactatgctatcagctgggtgcgacaggcccctggacaagggtgagtgatgggagggatcatccctatttgggcaga
gcaaactacgcacagaagttccagggcagagttacgattaccgcggacgaatccacgagcacagcctacatggagctgagcagcctga
gatctgaggacacggcgggtgtactactgcgccagagacagagacagcacaagcctgccgtacaaccactactacatggacgtatggggc
aagggtacaactgtcactgtctcctcagggtccctagacaatgagaagagcaatggaaccattatccatgtgaaagggaacacctttgtcc
aagtccttatttcccgaccttctaagccctttgggtgctggtggtggtggtggtgagtcctggcttctatagcttctagtaacagtggcct
ttatttttctgggtgaggagtaagaggagcaggctcctgcacagtactacatgaacatgactccccgcccccggggccaccgcga
gcattaccagccctatgccccaccacgcgacttcgcagcctatcgtccctgagagtgaagttcagcaggagcgcagacgccccgcgt
accagcaggggccagaaccagctctataacgagctcaatctaggacgaagagaggagtacgatgttttgacaagaggcgtggccggga
ccctgagatggggggaagccgagaaggaagaaccctcaggaaggcctgtacaatgaactgcagaaagataagatggcggaggccta
cagtgagattgggatgaaggcgagcggcggagggggcaaggggcacgatggcctttaccagggtctcagtacagccaccaaggacac
ctacagcgccttcacatgcaggccctgccccctcgc (SEQ ID NO: 247).

[0204] In an embodiment, a dual TACI-BCMA binding CAR construct has an amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) SEQ ID NO: 248.
DIQLTQSPSSLSASVGDRVTITCRASQSILSYLNWYQQKPGKAPKLLIYAASSLQSGVPSR
FSGSGSGTDFTLTISLQPEDFATYYCQQSSIAPWTFGGGTKVEIKGSTSGSGKPGSGEGS
TKGQVQLVQSGAEVKKPGSSVKVSCASGGTFADYAIWVRQAPGQGLEWMGGIPIIL
GRANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDRTSLPYNHYMD
VWGKGTITVTVSSGSLDNEKSNGTIIHVKGKHLCPSPFLPGPSKPFVWLTVVGGVLACYS
LLVTVAFIIFWVRSKRSRLHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRSLRVKFS
RSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNEL
QKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID
NO: 248). In embodiments, a dual TACI-BCMA binding CAR is encoded by a nucleic acid having
at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%,
or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) to the
nucleic acid having the sequence according to:
gacatccagttgacccagtcctccatccctgtctgcaagcgttgagatagagtcactatcacttgccgggcaagtgcagagcatttctcagc

tatttaaattggtatcagcagaaaccagggaagccccaagctcctgatctatgctgcatccagtttgcaaagtgggtcccatcaaggttc
 agtggcagtggtatccgggacagatttcactctcaccatcagcagctctgcaacctgaagattttgcaacttactactgtcagcaaagctcgtac
 gccccttggaactttcggcggagggaaccaaggttgagatcaaagggaagcacaagcggctctggcaaacctggatctggcgagggatctac
 caagggccaggtgcagctgggtgcagctctggggctgaggtgaagaagcctgggtcctcgggtgaaggtctcctgcaaggcttctggaggca
 ccttcgcagactatgctatcagctgggtgcgacaggcccctggacaagggttgagtggatgggagggatcatccctatattgggcagag
 caaactacgcacagaagtccaggggcagagttacgattaccgcgacgaatccacgagcagacctacatggagctgagcagcctgag
 atctgaggacacggcgggtgactactgcgccagagacagagaccgtacaagcctgccgtacaaccactactacatggacgtatggggca
 aagggaccacgggtaccgtttcctcagggtccctagacaatgagaagagcaatggaaccattatccatgtgaaaggaaacacctttgtcc
 aagtcacctatttcccggaccttctaagccctttgggtgctgggtgggtgggtgggtgagtcctggcttgcctatagcttgcctagtaacagtggcct
 ttattttttctgggtgaggagtaagaggagcaggctcctgcacagtgcactacatgaacatgactccccgcccccggggccaccgcga
 gcattaccagccctatgccccaccacgcgacttcgcagcctatcgtccctgagagtgaagttcagcaggagcgcagacgccccgcgt
 accagcagggccagaaccagctctataacgagctcaatctaggacgaagagaggagtacgatgttttgacaagaggcgtggccggga
 ccctgagatggggggaagccgagaaggaagaaccctcaggaaggcctgtacaatgaactgcagaaagataagatggcggaggccta
 cagtgagattgggatgaaggcgagcggcggagggggcaaggggcacgatggcctttaccagggtctcagtacagccaccaaggacac
 ctacgagcccttcacatgcaggccctgccccctcgc (SEQ ID NO: 249).

[0205] In an embodiment, a dual TACI-BCMA binding CAR construct has an amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%)

SEQ

ID

NO:

250.

DIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASQLQSGVPS
 RFSGSGSGTDFTLTISSLQPEDFATYYCQSAIAPWTFGGGTKVEIKGSTSGSGKPGSGE
 GSTKGQVQLVQSGAEVKKPGSSVKVSCKASGGTFEDYAIWVRQAPGQGLEWMGGIIP
 ILGRANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDRLTSLPYNHYY
 MDVWGKGTITVTVSSGSLDNEKSNGTIIHVKGKHLCPSPFPGPSKPFVWLTVVGGVLA
 CYSLLVTVAFIIFWVRSKRSRLHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRSLRV
 KFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRGRDPEMGGKPRRKNPQEGLY
 NELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR (SEQ
 ID NO: 250). In embodiments, a dual TACI-BCMA binding CAR is encoded by a nucleic acid having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) to the nucleic acid having the sequence according to:
 gacatccagttgaccagctcctccctgtctgcaagcgttgagatagagtactatcacttgcgggcaagtcagagcattagcag
 ctatttaaattggtatcagcagaaaccagggaagccccaagctcctgatctatgctgcatcccaattgcaaagtgggtcccatcaaggtt
 cagtggcagtggtatccgggacagatttcactctcaccatcagcagctctgcaacctgaagattttgcaacttactactgtcagcaaagcgtat

cgcccttggactttcggcggagggaaccaagggtgagatcaaaggagcacaagcggctctggcaaacctggatctggcgagggatcta
 ccaagggccagggtgcagctggtgcagctctgggctgaggtgaagaagcctgggtcctcgggtgaaggctcctgcaaggcttctggaggc
 acctcgaagactatgctatcagctgggtgcgacaggccctggacaaggccttgagtgatgggagggatcatcctatattgggccga
 gcaaactacgcacagaagttccagggcaggttacgattaccgaggacgaatccacgagcacagcctacatggagctgagcagcctga
 gatctgaggacacggcgggtgtactactgcgccagagacagagacttgacaagcctgccgtacaaccactactacatggacgtatggggc
 aaaggaccacggtcaccgtttcctcagggtccctagacaatgagaaggaatggaaccattatccatgtgaaagggaacacctttgtc
 caagtccttatttccggaccttctaagcccttttgggtgctggtggtggtggtggtgagtcctggcttctatagcttctagtaacagtggcc
 ttattatttttctgggtgaggagtaagaggagcaggctcctgcacagtactacatgaacatgactccccgccccggggcccccgcga
 agcattaccagccctatgccccaccacgcgacttcgcagcctatcgtccctgagagtgaaagttcagcaggagcgcagacgccccgcg
 taccagcaggccagaaccagctctataacgagctcaatctaggacgaagagaggagtacgatgtttggacaaggcgtggccggga
 ccctgagatggggggaagccgagaaggaagaaccctcaggaaggcctgtacaatgaactgcagaaagataagatggcggaggccta
 cagtgagattgggatgaaggcgagcggcggagggggcaaggggcacgatggcctttaccagggtctcagtacagccaccaaggacac
 ctacgacgcccttcacatgcaggccctgccccctcgc (SEQ ID NO: 251).

[0206] In an embodiment, a dual TACI-BCMA binding CAR construct has an amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%)

SEQ ID NO: 252.

DIQLTQSPSSLSASVGDRVTITCRASTSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSR
 FSGSGSGTDFTLTISLQPEDFATYYCQQSADAPWTFGGGTKVEIKGSTSGSGKPGSGEG
 STKGQVQLVQSGAEVKKPGSSVKVSKASGGTFSHYAISWVRQAPGQGLEWMGGIIPIL
 GRANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDRTWEGSPYIIYGM
 DVWGQGTMTVTVSSGSLDNEKSNGTIIHVKGKHLCPSPFLPGPSKPFVWLTVVGGVLAC
 YSLLVTVAFIIFWVRSKRSRLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSLRVK
 FRSADAPAYQQGQNQLYNELNLGRREEYDVLDRGRDPEMGGKPRRKNPQEGLYN
 ELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR (SEQ

ID NO: 252). In embodiments, a dual TACI-BCMA binding CAR is encoded by a nucleic acid having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) to the nucleic acid having the sequence according to:

gacatccagttgaccagctcctcctcctgtctgcaagcgttgagacagggtcactatcacttgcgggcaagtaccagcattagcag
 ctatttaaattggtatcagcagaaccagggaagccctaaagctcctgatctatgctgcatccagtttgcgaagtgggtcccatcaagggtt
 cagtggcagtgagatgggacagatttactctcaccatcagcagcttgcacctgaagattttgcaacttactactgtcagcaaagcgccga
 tgccttggactttcggcggagggaaccaagggtgagatcaaaggagcacaagcggctctggcaaacctggatccggcgagggatcta
 ccaagggccagggtgcagctggtgcagctctgggctgaagtgagaagcctgggtcctcgggtgaaggctcctgcaaggcttctggaggc

accttcagccactatgctatcagctgggtgcgacagggccctggacaagggcttgagtggatgggaggatcatccctatatattgggccga
gcaaactacgcacagaagttccagggcagagtcacgattaccgcggacgaatccacgagcacagcctacatggagctgagcagcctga
gatctgaggacacggcggtgtactactgcgccagagacagaacttgggaaggatctccctattattactacggaatggacgtttggggcca
agggacaatggtcaccgtttcctcagggtccctagacaatgagaaggaatggaaccattatccatgtgaaagggaaacacctttgccca
agtccccattttcccgaccttctaagcccttttgggtgctgggtgggtgggtgggtgagtcctggcttgctatagcttgctagtaacagtggccttt
attattttctgggtgaggagtaagaggagcaggtcctgcacagtactacatgaacatgactccccgccggcccgccaccgcgaag
cattaccagccctatgccccaccacgcgacttcgcagcctatcgctccctgagagtgaagttcagcaggagcgcagacgccccgcgtac
cagcaggggcagaaccagctctataacgagctcaatctaggacgaagagaggagtacgatgtttggacaagaggcgtggccgggacc
ctgagatgggggaaagccgagaaggaagaaccctcaggaaggcctgtacaatgaactgcagaagataagatggcggaggcctaca
gtgagattgggatgaaaggcgagcgccggagggggcaaggggcacgatggcctttaccagggtctcagtacgccaccaaggacacct
acgacgcccctcatcagcagccctgccccctcgc (SEQ ID NO: 253).

[0207] In an embodiment, a dual TACI-BCMA binding CAR construct has an amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%)

SEQ

ID

NO:

254.

DIQLTQSPSSLSASVGDRVITTCRASQSIASYNWYQQKPGKAPKLLIYAASSLQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQQSAGAPWTFGGGTKVEIKGSTSGSGKPGSGE
GSTKGQVQLVQSGAEVKKPGSSVKVSKKASGGTFDDYAISWVRQAPGQGLEWMGGIIP
ILGRANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDRVWEGSPYIYYG
MDVWGQGTMTVTVSSGSLDNEKSNGTIIHVKGKHLCPSPFLPGPSKPFVVLVVGGLA
CYSLLVTVAFIIFWVRSKRSRLHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRSLRV
KFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPEMGGKPRRKNPQEGLY
NELQKDKMAEAYSEIGMKGERRRGKGGHDGLYQGLSTATKDTYDALHMQALPPR (SEQ
ID NO: 254). In embodiments, a dual TACI-BCMA binding CAR is encoded by a nucleic acid having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) to the nucleic acid having the sequence according to:

gacatccagttgaccagctcctccctgtctgcaagcgttgagatagagtcactatcacttgccgggcaagtgcagcattgccag
ctatttaaattggtatcagcagaaaccagggaagcccctaagctcctgatctatgctgcatccagttgcaaagtgggtcccatcaaggtt
cagtgccagttgagtcgggacagatttactctaccatcagcagctctgcaacctgaagattttgcaacttactactgtcagcaagcgccg
gtgcaccttgactttcgccggagggaagggtgagatcaaaggagcacaagcggtctggcaaacctggatctggcgagggatct
accaaggggcaggtgcagctgggtgcagctctggggtgaggtgaagaagcctgggtcctcggtaaggctcctgcaaggcttctggagg
caccttcagcactatgctatcagctgggttcacagggccctggacaagggcttgagtggatgggaggatcatccctatatattgggcaga
gcaaactacgcacagaagttccagggcagagtcacgattaccgcggacgaatccacgagcacagcctacatggagctgagcagcctga

gatctgaggacacggcgggtgtactactgcgccagagacagagtgtgggaaggatctccctatttactacggaatggacgtttggggcca
 agggacaatggtcaccgtttcctcagggtccctagacaatgagaagagcaatggaaccattatccatgtgaaagggaaacacctttgtcca
 agtccccatttcccgaccttctaagcccttttgggtgctgggtgggtgggtggagtcctggcttgctatagcttgctagtaacagtggccttt
 attatttctgggtgaggagtaagaggagcaggctcctgcacagtactacatgaacatgactccccgccgccccggccccaccgcaag
 cattaccagccctatgccccaccacgcgacttcgcagcctatcgctccctgagagtgaagttcagcaggagcgcagacgccccgcgtac
 cagcaggggcagaaccagctctataacgagctcaatctaggacgaagagaggagtacgatgtttggacaagaggcgtggccgggacc
 ctgagatggggggaaagccgagaaggaagaaccctcaggaaggcctgtacaatgaactgcagaaagataagatggcggaggcctaca
 gtgagattgggatgaaagcgagcgcggagggggcaaggggcacgatggcctttaccagggtctcagtacagccaccaaggacacct
 acgacgcccctcacatgcaggccttccccctcgc (SEQ ID NO: 255).

[0208] In an embodiment, a dual TACI-BCMA binding CAR construct has an amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%)

SEQ ID NO: 256.

DIQLTQSPSSLSASVGDRVTITCRASQSIISLYLNWYQQKPGKAPKLLIYAASSLQSGVPSR
 FSGSGSGTDFTLTISLQPEDFATYYCQQVAVAPWTFGGGTKVEIKGSTSGSGKPGSGEG
 STKGQVQLVQSGAEVKKPGSSVKVSCKASGGTFEHYAISWVRQAPGQGLEWMGGIPI
 LGRANYAQKFQGRVTITADESTSTAYMELSSLRSEDNAVYYCARDRSWEGSPYMYYG
 MDVWGQGTMTVTVSSGSLDNEKSNGTIIHVKGKHLCPSPFPGPSKPFVVLVVGGLA
 CYSLLVTVAFIIFWVRSKRSRLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSLRV
 KFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPEMGGKPRRKNPQEGLY
 NELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR (SEQ
 ID NO: 256). In embodiments, a dual TACI-BCMA binding CAR is encoded by a nucleic acid having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) to the nucleic acid having the sequence according to:

gacatccagttgaccagctctccatcctcctgtctgcaagcgttgagacagagtactatcacttgccgggcaagtcagagcattagccta
 tatttaattggtatcagcagaaaccagggaagccccctaagctcctgatctatgctgcatccagtttgcaaagtggtgccatcaagggtc
 agtggcagtggtacgggacagatttactctcaccatcagcagctctgcaacctgaagattttgcaacttactactgtcagcaagtgccgctc
 gcccccttgactttggcggaggggaccaaggtgagatcaaagggagcacaagcggctctggcaaacctggatctggcgagggatctac
 caaggggccaggtgcagctggtgcagctctgggctgaggtgaagaagcctgggtcctcggtgaaggtctcctgcaaggcttctggaggca
 ccttgaacactatgctatcagctgggtgcgacaggccccctggacaggggcttgagtggatgggagggatcatcccatattggccgag
 caaactacgcacagaagttccagggcagagtcacgattaccgggacgaatccacgagcacagcctacatggagctgagcagcctgag
 atctgaggacacggcgggtgtactactgcgccagagacagaagctgggaaggatctccctatatgtactacggaatggacgtttggggcca
 agggacaatggtcaccgtttcctcagggtccctagacaatgagaagagcaatggaaccattatccatgtgaaagggaaacacctttgtcca

agtcacctattccccggaccttcaaaccccttttgggtgctgggtgggttgggtggagtcctggcttgctatagcttgctagtaacagtggcccttt
attattttctgggtgaggagtaagaggagcaggtcctgcacagtgactacatgaacatgactccccgccgccccggggccaccgcgaag
cattaccagccctatgccccaccacgcgacttcgcagcctatcgtccctgagagtgaagttcagcaggagcgcagacgccccgcgtac
cagcaggggccagaaccagctctataacgagctcaatctaggacgaagagaggagtlacgatgttttgacaagaggcgtggccgggacc
ctgagatggggggaaagccgagaaggaagaaccctcaggaaggcctgtacaatgaactgcagaagataaatggcggaggcctaca
gtgagattgggatgaaagcgagcggcgaggggcaaggggcacgatggcctttaccagggtctcagtlacgccaccaaggacacct
acgacgccccttcacatgcaggccctgccccctcgc (SEQ ID NO: 257).

[0209] In an embodiment, a dual TACI-BCMA binding CAR construct has an amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%)

SEQ	ID	NO:	258:

DIQLTQSPSSLSASVGDVRTITCRASQSISSYLNWYQQKPGKAPKLLIYAAGSLQSGVPS
RFSGSGSGTDFLTITSSLQPEDFATYYCQQVHDFPLTFGGGKTKVEIKGSTSGSGKPGSGE
GSTKGQVQLVESGGGVVQPGRSLRLSCAASGFTFASEGMHWVRQAPGKGLEWVASIY
YEGVNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKDVSYDYSSRLV
YHGMDVWVGQGT TVTVSSGSLDNEKSNGTIIHVKGKHLCPSP LFPGPSKPFWLVVVGG
VLACYSLLVTVAFIIFWVRSKRSRL LHS DYMNMTPRRPGPTRKH YQPYAPPRDFAAYRS
LRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVL DKRRGRDP EMGGKPRRKNPQE
GLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
(SEQ ID NO: 258). In embodiments, a dual TACI-BCMA binding CAR is encoded by a nucleic
acid having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at
least 95%, or 100% identity; e.g., 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%)
to the nucleic acid having the sequence according to:
gacatccagttgaccagctgccatcctcctgtctgcaagcgttgagatagagtcactatcacttgcgggcaagtcagagcattagcag
ctattttaaattggtatcagcagaaaccagggaagccccaagctcctgatctatgcagccgggagtttgcaagtgggggtcccatcaaggt
tcagtggcagtggtatccgggacagatttcactctcaccatcagcagctctgcaacctgaagatttgcacttactactgtcagcaagtcacg
acttccctctcactttcggcggagggaaccaaggttgagatcaaaggggagcacaagcggctctggcacaacctggatctggcgagggatcta
ccaaggggccagggtgcagctgggtggagtctgggggaggcgtggtccagcctgggaggtccctgagactctcctgcgctgcatctggattc
accttcgccagcgaaggcatgcactgggtccgccagggtccaggcaaggggctggagtgggtggcatccatatactatgaggggagtc aa
taatactatgcagactccgtgaagggccgattcaccatctctagagacaattccaagaacacgctgtatctgcaaatgaatagcctgagag
ccgaggacacggcggtgtactactgcgccaaggacgtgtcctactacgacagcagcagactagtttatcacggaatggacgtatggggg
caaggggaccacgggtcaccgtttcctcagggtccctagacaatgagaagagcaatggaaccattatccatgtgaaagggaacacctttgtc
caagtcccctattttcccgaccttctaagcccttttgggtgctgtgtgtgtgtgtgtggagtcttggttgcctatagcttgctagtaacagtggcc
tttattattttctgggtgaggagtaagaggagcagggtcctgcacagtgactacatgaacatgactccccgccggccggggcccccacccgca

agcattaccagccctatgccccaccacgcgacttcgcagcctatcgctccctgagagtgaagttcagcaggagcgcagacgccccgcg
taccagcaggggcagaaccagctctataacgagctcaatctaggacgaagagaggagtacgatgtttggacaagaggcggtggccggga
ccctgagatgggggaaagccgagaaggaagaacctcaggaaggcctgtacaatgaactgcagaaagataagatggcggaggccta
cagtgagattgggatgaagggcagcggcgaggggcaaggggcacgatggcctttaccagggctcagtagcagccaccaaggacac
ctacgacgcccttcacatgcaggccctgccccctcgc (SEQ ID NO: 259).

[0210] In an embodiment, a dual TACI-BCMA binding CAR construct has an amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%)

SEQ ID NO: 260.

DIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSGQSGVPSR
FSGSGSGTDFTLTISSLQPEDFATYYCQQVHDFPLTFGGGTKVEIKGSTSGSGKPGSGEGS
TKGQVQLVESGGGVVQPGRSLRLSCAASGFTFASEGMHWVRQAPGKGLEWVASIYYE
GVNKEYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKDRSYDSSGLVYH
GMDVWGQGTITVTVSSGSLDNEKSNGTIIHVKGKHLCPSPLPFGPSKPFVWLVVVGGVL
ACYSLLVTVAFIIFWVRSKRSRLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSLR
VKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPEMGGKPRRKNPQEGL
YNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQUALPPR

(SEQ ID NO: 260). In embodiments, a dual TACI-BCMA binding CAR is encoded by a nucleic acid having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) to the nucleic acid having the sequence according to:

gacatccagttgaccagctctccatcctcctgtctgcaagcgttgagacagagtcactatcacttgcgggcaagtcagagcattagcag
ctatttaaattggtatcagcagaaccagggaagcccctaagctcctgatctatgctgcatccagtgacaaagtgggtcccatcaaggt
tcagtggcagtgatccgggacagattcactctcaccatcagcagctctgcaacctgaagattttgcaacttactactgtcagaagtgcacg
actccctctcactttcggcggagggaaccaaggttgagatcaaaggagcacaagcggctctggcaaacctggatctggcagggatcta
ccaagggccaggtgcagctggtggagtctgggggagggcgtggtccagcctgggaggtccctgagactctctgcgctgcatctggattc
accttcgcagcgaaggcatgactgggtccgccaggtccaggcaaggggctggagtgggtggcatccatatactatgaggagtgcaa
taaatactatgcagactccgtgaaggccgattcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgaga
gccgaggacacggcgtgtactactgcgccaaggacagatcctactacgacagcagcgggctagtattacacggaatggacgtatgggg
gcaagggaaccacggtcaccgtttcctcagggtccctagacaatgagaagagcaatggaaccattatccatgtgaaagggaacacctttgt
ccaagtccctatttcccggacattctaagcccttttgggtgctggtggtggtggtggtgagtcctggcttgctatagcttgcagtaacagtggc
ctttattattttctgggtgaggagtaagaggagcaggctcctgcacagtactacatgaacatgactccccggccccggccccaccgc
aagcattaccagccctatgccccaccacgcgacttcgcagcctatcgctccctgagagtgaagttcagcaggagcgcagacgccccgc
gtaccagcaggggcagaaccagctctataacgagctcaatctaggacgaagagaggagtacgatgtttggacaagaggcggtggccgg

gaccctgagatgggggaaagccgagaaggaagaaccctcaggaaggcctgtacaatgaactgcagaaagataagatggcggagggc
ctacagtgagattgggatgaaaggcgagcgccggaggggcaaggggcacgatggcctttaccagggtctcagtacagccaccaagga
cacctacgacgcccttcacatgcaggccctgccccctcgc (SEQ ID NO: 261).

[0211] In an embodiment, a dual TACI-BCMA binding CAR construct has an amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%)

SEQ ID NO: 262.

DIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQGGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQIHDFPLTFGGGKVEIKGSTSGSGKPGSGEG
STKGQVQLVESGGGVVQPGRSLRLSCAASGFTFSSEGMWVRQAPGKGLEWVAIIWY
EGSNKYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKDRSYDSSQLVY
HGMDVWGQGTITVTVSSGSLDNEKSNGTIIHVKGKHLCPSPFPGPSKPFVVLVVVGGV
LACYSLLVTVAFIIFWVRSKRSRLHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRSL
RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPGMPRRKPNPQEG
LYNELQKDKMAEAYSEIGMKGERRRGKGHDLGLYQGLSTATKDTYDALHMQALPPR

(SEQ ID NO: 262). In embodiments, a dual TACI-BCMA binding CAR is encoded by a nucleic acid having at least 75% sequence identity (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) to the nucleic acid having the sequence according to:

gacatccagttgaccagctcctccctgtctgcaagcgttgagacagagtcactatcacttgcggggaagtcagagcattagcag
ctatttaaattggtatcagcagaaccagggaagccctaaagctcctgatctatgctgcatccagttgcaaggagggtcccatcaagggt
cagtgccagtggtctgggacagattcactctcaccatcagcagctctgcaacctgaagatttgcacttactactgtcagcaattcagac
ttccctctcactttcggcggagggaaggtgagatcaaaggagcacaagcggctctggcaaacctggatctggcgaggatctacc
aaggccaagttcagctggtggagtctggggaggcgtggtccagcctgggaggtccctgagactctctgcgtgcatctggattcacc
ttcagtagcgagggaatgtactgggtccgccaggctccaggcaaggggctggagtgggtggcagccatatggtatgagggaagtaataa
atactatgccgactccgtgaaggccgattcaccatctctcgcgacaattccaaaatacgtgtatctgcaaatgaatagccttagagccga
ggacacggcgtgtactactgcgccaaggacagatcctactacgacagcagccagctagttatcacggaatggacgtatgggggcaag
ggaccacggtcaccgttctcaggtccctagacaatgagaagagcaatggaaccattatccatgtgaaagggaacaccttgcctcaag
tcccctatttcccgaccttctaagcccttttgggtgctggtggtggtggtggagtctggttgcctatagcttgcctagtaaacagtggccttatt
atttctgggtgaggagtaagaggagcaggtcctgcacagtgtactacatgaacatgactccccgccgccccgggccaccgcaagca
ttaccagccctatgccccaccacgcgacttcgcagcctatcgtcctcctgagagtgaagttcagcaggagcgcagacgcccccggtacca
gcagggccagaaccagctctataacgagctcaatctaggacgaagagaggagtacgatgtttggacaagaggcgtggccgggacacct
gagatggggggaaagccgagaaggaagaaccctcaggaaggcctgtacaatgaactgcagaaagataagatggcggaggcctacagt

gagattgggatgaaaggcgagcgccggaggggcaaggggcacgatggcctttaccagggtctcagtacagccaccaaggacacctac
gacgcccttcacatgcaggccctgccccctgc (SEQ ID NO: 263).

[0212] In embodiments, a dual TACI-BCMA binding CAR is encoded by a nucleic acid having at least 75% sequence identity (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; e.g., 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) to the nucleic acid having the sequence according to:

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAAGCGTTGGAGAtAGAGTC
ACtATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCAGCAG
AAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGG
GGTCCCATCAAGGTTCAAGTGGCAGTGGATCcGGGACAGATTTCACTCTCACCATCAG
CAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCTCAGCAAAGCCACATCGCCCC
TTGGACTTTTGGCGGAGGGACCAAGGTTGAGATCAAAGGGAGCAtAGCGGCTCTG
GCAAACCTGGATCTGGCGAGGGATCTACCAAGGGCCAGGTGCAGCTGGTGCAGTCT
GGGGCTGAGGTGAAGAAGCCTGGGTCTCGGTGAAGGTCTCCTGCAAGGCTTCTGG
AGGCACCTTCGCAGACTATGCTATCAGCTGGGTGCGACAGGCCCTGGACAAGGGC
TTGAGTGGATGGGAGGGATCATCCCTATATTGGGCAGAGCAAACCTACGCACAGAAG
TTCCAGGGCAGAGTiACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGGA
GCTGAGCAGCCTGAGATCTGAGGACACGGCGGTGTACTACTGCGCCAGAGACAGAG
ACAGCACAAGCCTGCCGTACAACCACTACTACATGGACGTATGGGGCAAGGGTACA
ACTGTCACTgtCTCCTCtggGtctCTAGACAATGAGAAGAGCAATGGAACCATTATCCAT
GTGAAAGGGAAACACCTTTGTCCAAGTCCCCTATTTCCCGGACCTTCTAAGCCCTTT
TGGGTGCTGGTGGTGGTTGGTGGAGTCCTGGCTTGCTATAGCTTGCTAGTAACAGTG
GCCTTTATTATTTTCTGGGTGAGGAGTAAGAGGAGCAGGCTCCTGCACAGTGACTAC
ATGAACATGACTCCCCGCCGCCCGGGCCACCCGCAAGCATTACCAGCCCTATGC
CCCACCACGCGACTTCGCAGCCTATCGCTCCCTGAGAGTGAAGTTCAGCAGGAGCG
CAGACGCCCCCGCGTACCAGCAGGGCCAGAACCAGCTCTATAACGAGCTCAATCTA
GGACGAAGAGAGGAGTACGATGTTTTGGACAAGAGgCGTGGCCGGGACCCTGAGAT
GGGGGGAAAGCCGAGAAGGAAGAACCCTCAGGAAGGCCTGTACAATGAACTGCAG
AAAGATAAGATGGCGGAGGCCTACAGTGAGATTGGGATGAAAGGCGAGCGCCGGA
GGGGCAAGGGGCACGATGGCCTTTACCAGGGTCTCAGTACAGCCACCAAGGACACC
TACGACGCCCTTCACATGCAGGCCCTGCCCCCTCGC (SEQ ID NO: 293).

[0213] In embodiments, a dual TACI-BCMA binding CAR is encoded by a nucleic acid having at least 75% sequence identity (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; e.g., 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) to the nucleic

acid having the sequence according to:

GACATCCAGTTGACCCAGTCTCCATCCTCCCTGTCTGCAAGCGTTGGAGACAGAGTt
 ACtATCACTTGCCGGGCAAGTCAGAGCATTAGCCTATATTTAAATTGGTATCAGCAG
 AAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGG
 GGTCCCATCAAGGTTTCAGTGGCAGTGGATCcGGGACAGATTTCACTCTCACCATCAG
 CAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTGTCAGCAAGTGGCCGTGCGCCC
 TTGGACTTTTCGGCGGAGGGACCAAGGTTGAGATCAAAGGGAGCACAAGCGGCTCTG
 GCAAACCTGGATCTGGCGAGGGATCTACCAAGGGCCAGGTGCAGCTGGTGCAGTCT
 GGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGG
 AGGCACCTTCGAACACTATGCTATCAGCTGGGTGCGACAGGCCCTGGACAGGGGC
 TTGAGTGGATGGGAGGGATCATCCCcATATTGGGCCGAGCAAACCTACGCACAGAAG
 TTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGGA
 GCTGAGCAGCCTGAGATCTGAGGACACGGCGGTGTACTACTGCGCCAGAGACAGAA
 GCTGGGAAGGATCTCCCTATATGTACTACGGAATGGACGTTTGGGGCCAAGGGACA
 ATGGTCACCGTtTCCTCAggGtctCTAGACAATGAGAAGAGCAATGGAACCATTATCCA
 TGTGAAAGGGAAACACCTTTGTCCAAGTCCCCTATTTCCCGGACCTTCTAAGCCCTT
 TTGGGTGCTGGTGGTGGTTGGTGGAGTCCTGGCTTGCTATAGCTTGCTAGTAACAGT
 GGCCTTTATTATTTTCTGGGTGAGGAGTAAGAGGAGCAGGCTCCTGCACAGTGACT
 ACATGAACATGACTCCCCGCGCCCCGGGCCACCCGCAAGCATTACCAGCCCTAT
 GCCCCACCACGCGACTTCGCAGCCTATCGCTCCCTGAGAGTGAAGTTCAGCAGGAG
 CGCAGACGCCCCCGCGTACCAGCAGGGCCAGAACCAGCTCTATAACGAGCTCAATC
 TAGGACGAAGAGAGGAGTACGATGTTTTGGACAAGAGgCGTGGCCGGGACCCTGAG
 ATGGGGGGAAAGCCGAGAAGGAAGAACCCTCAGGAAGGCCTGTACAATGAACTGC
 AGAAAGATAAGATGGCGGAGGCCTACAGTGAGATTGGGATGAAAGGCGAGCGCCG
 GAGGGGCAAGGGGCACGATGGCCTTTACCAGGGTCTCAGTACAGCCACCAAGGAC
 ACCTACGACGCCCTTCACATGCAGGCCCTGCCCCCTCGC (SEQ ID NO: 294).

[0214] In embodiments, a codon optimized dual TACI-BCMA binding CAR (e.g. Dual binder #1 (CAR only) Version 2) is encoded by a nucleic acid having at least 75% sequence identity (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; e.g., 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) to the nucleic acid having the sequence according to:
 ATGCTTCTCCTGGTGACAAGCCTTCTGCTCTGTGAATTACCACACCCAGCATTCTC
 CTGATTCTGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAAGCGTTGGA
 GATAGAGTCACTATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTG
 GTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTT

TGCAAAGTGGGGTCCCATCAAGGTTTCAGTGGCAGTGGATCCGGGACAGATTTCACT
CTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGCAAAGC
CACATCGCCCCCTTGACTTTTGGCGGAGGGACCAAGGTTGAGATCAAAGGGAGCAC
TAGCGGCTCTGGCAAACCTGGATCTGGCGAGGGATCTACCAAGGGCCAGGTGCAGC
TGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTCTCCTGC
AAGGCTTCTGGAGGCACCTTCGCAGACTATGCTATCAGCTGGGTGCGACAGGCCCC
TGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTATATTGGGCAGAGCAAACCT
ACGCACAGAAGTTCCAGGGCAGAGTTACGATTACCGCGGACGAATCCACGAGCACA
GCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCGGTGTACTACTGCGC
CAGAGACAGAGACAGCACAAGCCTGCCGTACAACCACTACTACATGGACGTATGGG
GCAAGGGTACAACCTGTCACTGTCTCCTCTGGGTCTCTAGACAATGAGAAGAGCAAT
GGAACCATTATCCATGTGAAAGGGAAACACCTTTGTCCAAGTCCCCTATTTCCCGGA
CCTTCTAAGCCCTTTTGGGTGCTGGTGGTGGTTGGTGGAGTCCTGGCTTGCTATAGC
TTGCTAGTAACAGTGGCCTTTATTATTTTCTGGGTGAGGAGTAAGAGGAGCAGGCTC
CTGCACAGTGACTACATGAACATGACTCCCCGCCGCCCGGGCCACCCGCAAGCA
TTACCAGCCCTATGCCCCACCACGCGACTTCGCAGCCTATCGCTCCCTGAGAGTGAA
GTTTCAGCAGGAGCGCAGACGCCCCCGCGTACCAGCAGGGCCAGAACCAGCTCTATA
ACGAGCTCAATCTAGGACGAAGAGAGGAGTACGATGTTTTGGACAAGAGGCGTG
CCGGGACCCTGAGATGGGGGGAAAGCCGAGAAGGAAGAACCCTCAGGAAGGCCTG
TACAATGAACTGCAGAAAGATAAGATGGCGGAGGCCTACAGTGAGATTGGGATGA
AAGGCGAGCGCCGGAGGGGCAAGGGGCACGATGGCCTTTACCAGGGTCTCAGTAC
AGCCACCAAGGACACCTACGACGCCCTTCACATGCAGGCCCTGCCCCCTCGCTGA
(SEQ ID NO: 302).

[0215] In embodiments, a codon optimized dual TACI-BCMA binding CAR (e.g. Dual binder # 3 (CAR only) Version 2) is encoded by a nucleic acid having at least 75% sequence identity (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; e.g., 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) to the nucleic acid having the sequence according to: ATGCTTCTCCTGGTGACAAGCCTTCTGCTCTGTGAATTACCACACCCAGCATTCCCTC CTGATTCCCTGACATCCAGTTGACCCAGTCTCCATCCTCCCTGTCTGCAAGCGTTGGA GACAGAGTTACTATCACTTGCCGGGCAAGTCAGAGCATTAGCCTATATTTAAATTGG TATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTT GCAAAGTGGGGTCCCATCAAGGTTTCAGTGGCAGTGGATCCGGGACAGATTTCACTC TCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGCAAGTGG CCGTCGCCCCCTTGACTTTTCGGCGGAGGGACCAAGGTTGAGATCAAAGGGAGCACA

AGCGGCTCTGGCAAACCTGGATCTGGCGAGGGATCTACCAAGGGCCAGGTGCAGCT
 GGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTCTCCTGCA
 AGGCTTCTGGAGGCACCTTCGAACACTATGCTATCAGCTGGGTGCGACAGGCCCT
 GGACAGGGGCTTGAGTGGATGGGAGGGATCATCCCCATATTGGGGCCGAGCAAATA
 CGCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCACGAGCACA
 GCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCGGTGTACTACTGCGC
 CAGAGACAGAAGCTGGGAAGGATCTCCCTATATGTACTACGGAATGGACGTTTGGG
 GCCAAGGGACAATGGTCACCGTTTCCTCAGGGTCTCTAGACAATGAGAAGAGCAAT
 GGAACCATTATCCATGTGAAAGGGAAACACCTTTGTCCAAGTCCCCTATTTCCCGGA
 CCTTCTAAGCCCTTTTGGGTGCTGGTGGTGGTGGTGGAGTCCTGGCTTGCTATAGC
 TTGCTAGTAACAGTGGCCTTTATTATTTCTGGGTGAGGAGTAAGAGGAGCAGGCTC
 CTGCACAGTGACTACATGAACATGACTCCCCGCCGCCCGGGCCACCCGCAAGCA
 TTACCAGCCCTATGCCCCACCACGCGACTTCGCAGCCTATCGCTCCCTGAGAGTGAA
 GTTCAGCAGGAGCGCAGACGCCCCCGCGTACCAGCAGGGCCAGAACCAGCTCTATA
 ACGAGCTCAATCTAGGACGAAGAGAGGAGTACGATGTTTTGGACAAGAGGCGTGG
 CCGGGACCCTGAGATGGGGGGAAAGCCGAGAAGGAAGAACCCTCAGGAAGGCCTG
 TACAATGAACTGCAGAAAGATAAGATGGCGGAGGCCTACAGTGAGATTGGGATGA
 AAGGCGAGCGCCGGAGGGGCAAGGGGCACGATGGCCTTTACCAGGGTCTCAGTAC
 AGCCACCAAGGACACCTACGACGCCCTTCACATGCAGGCCCTGCCCCCTCGCTGA
 (SEQ ID NO: 303).

[0216] Both engineered T cell receptors (TCR) and chimeric antigen receptor (CAR) therapies harness the specificity and immunotherapeutic effect of T cells for the treatment of a wide variety of malignancies. Some studies suggest that these therapies may be susceptible to the suppressive factors in the TME that result from T cell suppression by TGF- β (Bendle et al., J Immunol, 191:3232–3239 (2013) and Vong et al., Blood, 130:1791 (2017)). The present disclosure contemplates the use of the dominant negative (DN) TGF- β Receptors described herein in combination with either TCR or CAR therapies as a way to maintain, or in some cases, restore TCR and/or CAR expansion in the presence of TGF- β suppression.

[0217] Chimeric antigen receptor (CAR) T cell therapy provides another therapeutic approach against tumor progression. Clinically, investigators have demonstrated that CAR expansion and persistence is correlated with therapeutic efficacy. Without being bound by any theory, it is believed that TGF- β repressed T cell populations found in the TME may be limiting CAR T cell expansion and persistence in patients who do not respond to CAR therapy. The resulting inhibitory

cytokines in the TME are believed to limit CAR cell function and expansion. Thus, TGF- β could limit the efficacy of therapeutic engineered T cells or NK cells.

[0218] Combining any CAR constructs or TCRs as described herein with a DN TGF- β receptors may restore, maintain or enhance the therapeutic effect of CAR T therapy challenged by TGF- β suppression. Thus, in embodiments, the DN TGF- β receptors, for example DN TGF- β RI or RII, are co-expressed in a T cell or an NK cell with a dual TACI-BCMA binding CAR, as described herein. In some embodiments, the DN TGF- β receptors, for example DN TGF- β RI or RII, are co-expressed in a T cell or NK cell with a dual TACI-BCMA binding CAR, such as described herein. In some embodiments the the DN TGF- β receptors, for example DN TGF- β RI or RII, are co-expressed in a T cell or NK cell with a dual TACI-BCMA binding TCR. Exemplary DN TGF- β receptors are described in International Patent Application No. PCT/US2020/070157, which is hereby incorporated herein by reference in its entirety.

[0219] The engineered TGF- β receptors may comprise an N-terminal signal peptide at the N-terminus, for example at the N-terminus of the extracellular ligand binding domain of DN TGF- β RI. In one embodiment, a heterologous signal peptide may be used. The extracellular domain of a DN TGF- β RI may be fused to a leader or a signal peptide that directs the nascent protein into the endoplasmic reticulum and subsequent translocation to the cell surface. It is understood that, once a polypeptide containing a signal peptide is expressed at the cell surface, the signal peptide is generally proteolytically removed during processing of the polypeptide in the endoplasmic reticulum and translocation to the cell surface. Thus, a polypeptide such as a DN TGF- β RI is generally expressed at the cell surface as a mature protein lacking the signal peptide, whereas the precursor form of the polypeptide includes the signal peptide. Any suitable signal sequence may be used. In one embodiment described herein, the DN TGF- β RI comprises the amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) of SEQ ID NO: 264 or a portion thereof. MEAAVAAPRPRLLLLVLAAAAAAAALLPGATA (SEQ ID NO: 264).

[0220] In the present disclosure, the signal peptide is joined to the N-terminus of the extracellular antigen-binding domain of the DN TGF- β RI as a fusion protein. In one embodiment, the DN TGF- β RI comprises an extracellular ligand binding domain having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) the wild-type TGF- β RI and a signal peptide at the N-terminus of the extracellular domain TGF- β RI, having at least 75% sequence

identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) the amino acid sequence of SEQ ID NO: 265.

[0221] MEAAVAAPRPRLLLLVLAAAAAAAAAALLPGATALQCFCHLCTKDNFTCVTDGL
CFVSVTETTDKVIHNSMCIAEIDLIPDRPFVFCAPSSKTGVSVTTTYCCNQDHCNKIELPTT
VKSSPGLGPVEL (SEQ ID NO: 265).

[0222] The engineered DN TGF- β RII constructs may also comprise an N-terminal signal peptide at the N-terminus of the extracellular ligand binding domain of TGF- β RII. In one embodiment, a heterologous signal peptide may be used. The extracellular domain of a DN TGF- β RII may be fused to a leader or a signal peptide that directs the nascent protein into the endoplasmic reticulum and subsequent translocation to the cell surface. It is understood that, once a polypeptide containing a signal peptide is expressed at the cell surface, the signal peptide is generally proteolytically removed during processing of the polypeptide in the endoplasmic reticulum and translocation to the cell surface. Thus, a polypeptide such as a DN TGF- β RII is generally found at the cell surface as a mature protein lacking the signal peptide, whereas the precursor form of the polypeptide includes the signal peptide. Any suitable signal sequence may be used. In one embodiment described herein, the DN TGF- β RII constructs described herein comprise a signal sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) the amino acid sequence of SEQ ID NO: 266 or a portion thereof. MGRGLLRGLWPLHIVLWTRIAS (SEQ ID NO: 266). In another embodiment, the signal sequence is derived from Colony Stimulating Factor 2 Receptor Alpha subunit (CSF2R α) comprising the amino acid sequence at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) of SEQ ID NO: 221 or a portion thereof. MLLLVTSLLLCELPHPAFLIP (SEQ ID NO: 221). The signal sequences described herein may also be optionally used with any suitable protein tag, including but not limited to: V5-tag, myc-tag, HA-tag, Spot-tag, NE-tag. In one embodiment described herein, the signal sequence and tag comprise the amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) SEQ ID NO: 267. MLLLVTSLLLCELPHPAFLIPEQKLISEEDL (SEQ ID NO: 267). In embodiments, the signal sequence and tag may be encoded by nucleic acid sequence at least 75% sequence identity to atgcttctcctggtgacaagccttctgctctgtgagttaccacaccagcattcctcctgattcctgaacagaagctgataagtgaggaggact

tg (SEQ ID NO: 268) (*e.g.*, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%) .

[0223] It is understood that use of this signal peptide is exemplary. Any suitable signal peptide, as are well known in the art, may be applied to the DN TGF- β RI or RII to provide cell surface expression in an immune cell. Useful signal peptides may be derived from cell surface proteins naturally expressed in the T cell NK cell or precursor cell thereof, including any of the signal peptides of the polypeptides disclosed herein. Thus, any suitable signal peptide may be utilized to direct the DN TGF- β RI RII to be expressed at the cell surface of a T cell or NK cell.

[0224] In embodiments, a DN TGF- β RI comprises an amino acid sequence at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%) the amino acid sequence of SEQ ID NO: 269.

[0225] MEAAVAAPRPRLLLLVLAAAAAAAAAALLPGATALQCFCHLCTKDNFTCVTDGL
CFVSVTETTDKVIHNSMCIAEIDLIPDRPFVCPASSKTGSVTTTYCCNQDHCNKIELPTT
VKSSPGLGPVELAAVIAGPVCFVCISLMLMVYIRVNRQ (SEQ ID NO: 269).

[0226] In one embodiment a DN TGF- β RII comprises an amino acid sequence at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%) the amino acid sequence of SEQ ID NO: 270:

[0227] MGRGLLRGLWPLHIVLWTRIASTIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFC
DVRFSTCDNQKSCMSNCSITSICEKPQEVCAVWRKNDENITLETVCHDPKLPYHDFILE
DAASPKCIMKEKKKPGETFFMCSSDECNDNIIFSEEYNTSNPDLLLVIQVTGISLLPPL
GVAISVIIIIFYCYRVNRQ (SEQ ID NO: 270).

[0228] In an embodiment a DN TGF- β RII comprises an amino acid sequence at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85-90%, 85-95%, 85-100%, 90-95%, 90-100%, or 95-100%) the amino acid sequence of SEQ ID NO: 271.

[0229] TIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSIC
EKPQEVCAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMC
SCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 271).

[0230] In one embodiment described herein, the DN TGF- β RII comprises an amino acid sequence at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) the wild-type TGF- β RII as shown in the amino acid sequence of SEQ ID NO: 272.

[0231] TIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSIC
EKPQEVCAVWRKNDENTLETVCHDPKLPYHDFILEDAAAPKCMKEKKKPGETFFMC
SCSSDECNDNIIFSEEYNTSNPDLLLVIQVGTGISLLPPLGVAISVIIIIFYCY (SEQ ID NO:
272).

[0232] In one embodiment described herein, the DN TGF- β RII comprises an amino acid sequence at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) the amino acid sequence of SEQ ID NO: 273.

[0233] TIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSIC
EKPQEVCAVWRKNDENTLETVCHDPKLPYHDFILEDAAAPKCMKEKKKPGETFFMC
SCSSDECNDNIIFSEEYNTSNPDSPILLTISILSFFSVALLVIL (SEQ ID NO: 273).

[0234] In one embodiment described herein, the DN TGF- β RII comprises an amino acid sequence at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) as shown in the amino acid sequence of SEQ ID NO: 274.

[0235] TIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSIC
EKPQEVCAVWRKNDENTLETVCHDPKLPYHDFILEDAAAPKCMKEKKKPGETFFMC
SCSSDECNDNIIFSEEYNTSNPDSPILLTCPTISILSFFSVALLVIL (SEQ ID NO: 274).

[0236] T In one embodiment described herein, the DN TGF- β RII comprises an amino acid sequence at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) SEQ ID NO: 275.

[0237] ACVLWKKRIKPIVWPSLPDHKKTLEHLCKKPRKNLNVSFNPESFLDCQIHRVDDI
QARDEVEGFLQDTPPQLEESEKQRLGGDVQSPNCPSEDVVITPESFGRDSSLTCLAGN
VSACDAPILSSSRSLDCRESGKNGPHVYQDLLLSLGTNSTLPPPSLQSGILTLNPVAQG
QPILTSLGSNQEEAYVTMSSFYQNNQ (SEQ ID NO: 275).

[0238] In one embodiment described herein, the DN TGF- β RII comprises an amino acid sequence at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) the amino acid sequence of SEQ ID NO: 276.

[0239] TIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSIC
EKPQEVCAVWRKNDENITLETVCHDPKLPYHDFILEDAAASPKCIMKEKKKPGETFFMC
SCSSDECNDNIIFSEEYNTSNPDSPGILLTISILSFFSVALLVILACVLWKKRIKPIVWPSLP
DHKKTLEHLCKKPRKLNVSFNPESFLDCQIHRVDDIQARDEVEGFLQDTFPQQLEESE
KQRLGGDVQSPNCPSEDVVITPESFGRDSSLTCLAGNVSACDAPILSSSRSLDCRESGKN
GPHVYQDLLLLSLGTTNSTLPPPSLQSGILTLNPVAQGGQPILTSLSNQEAYVTMSSFYQ
NQ (SEQ ID NO: 276).

[0240] In one embodiment described herein, the DN TGF- β RII comprises an amino acid sequence at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) to the amino acid sequence of SEQ ID NO: 277.

[0241] TIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSIC
EKPQEVCAVWRKNDENITLETVCHDPKLPYHDFILEDAAASPKCIMKEKKKPGETFFMC
SCSSDECNDNIIFSEEYNTSNPDSPGILLTCPTISILSFFSVALLVILACVLWKKRIKPIVWP
SLPDHKKTLEHLCKKPRKLNVSFNPESFLDCQIHRVDDIQARDEVEGFLQDTFPQQLEE
SEKQRLGGDVQSPNCPSEDVVITPESFGRDSSLTCLAGNVSACDAPILSSSRSLDCRESGK
NGPHVYQDLLLLSLGTTNSTLPPPSLQSGILTLNPVAQGGQPILTSLSNQEAYVTMSSFY
QNQ (SEQ ID NO: 277).

[0242] In an embodiment, an engineered DN TGF- β RII comprises an amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) the amino acid sequence of SEQ ID NO: 278.

[0243] MLLLVTSLLLCELPHPAFLLIPTIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCD
VRFSTCDNQKSCMSNCSITSICEKPQEVCAVWRKNDENITLETVCHDPKLPYHDFILED
AASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 278).

[0244] In an embodiment, an engineered DN TGF- β RII comprises an amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least

95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) SEQ ID NO: 279.

[0245] MLLLVTSLLLCELPHPAFLLIPEQKLISEEDLTIPPHVQKSVNNDMIVTDNNGAVK
FPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCAVWRKNDENITLETVCHDPK
LPYHDFILEDAAAPKCMKEKKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID
NO: 279).

[0246] In an embodiment, an engineered DN TGF- β RII comprises an amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) SEQ ID: 280.

[0247] MLLLVTSLLLCELPHPAFLLIPTIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCD
VRFSTCDNQKSCMSNCSITSICEKPQEVCAVWRKNDENITLETVCHDPKLPYHDFILED
AAPKCMKEKKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPDSPILLTISILSFFSVALL
VILACVLWKKRIKPIVWPSLPDHKKKTLEHLCKKPRKLNVSFNPESFLDCQIHRVDDIQA
RDEVEGFLQDTFPQQLEESEKQRLGGDVQSPNCPSEDVVITPESFGRDSSLTCLAGNVSA
CDAPILSSSRSLDCRESGKNGPHVYQDLLLLSLGTTNSTLPPFSLQSGILTLNPVAQGQPIL
TSLGSNQEEAYVTMSSFYQNNQ (SEQ ID NO: 280).

[0248] In an embodiment, an engineered DN TGF- β RII comprises an amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) SEQ ID: 281.

[0249] MLLLVTSLLLCELPHPAFLLIPEQKLISEEDLTIPPHVQKSVNNDMIVTDNNGAVK
FPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCAVWRKNDENITLETVCHDPK
LPYHDFILEDAAAPKCMKEKKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPDSPILLTI
SILSFFSVALLVILACVLWKKRIKPIVWPSLPDHKKKTLEHLCKKPRKLNVSFNPESFLDC
QIHRVDDIQA RDEVEGFLQDTFPQQLEESEKQRLGGDVQSPNCPSEDVVITPESFGRDSS
LTCLAGNVSA CDAPILSSSRSLDCRESGKNGPHVYQDLLLLSLGTTNSTLPPFSLQSGILT
LNPVAQGQPILTSLGSNQEEAYVTMSSFYQNNQ (SEQ ID NO: 281).

[0250] In an embodiment, an engineered DN TGF- β RII comprises an amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least

95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) SEQ ID: 282.

[0251] MLLLVTSLLLCELPHPAFLLIPTIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCD VRFSTCDNQKSCMSNCSITSICEKPQEVCAVWRKNDENITLETVCHDPKLPYHDFILED AASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPDSPILLTISILSFFSVALL VILACVLWKKRIKPIVWPSLPDHKKTLEHLCKKPRKNLNVSFNPESFLDCQIHRVDDIQA RDEVEGFLQDTPPQQLLEESEKQRLGGDVQSPNCPSEDVVITPESFGRDSSLTCLAGNVSA CDAPILSSSRSLDCRESGKNGPHVYQDLLLLSLGTTNSTLPPPSLQSGILTLNPVAQGQPIL TSLGSNQEEAYVTMSSFYQNN (SEQ ID NO: 282).

[0252] In an embodiment, an engineered DN TGF- β RII comprises an amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) SEQ ID: 283.

[0253] MLLLVTSLLLCELPHPAFLLIPEQKLISEEDLTIPPHVQKSVNNDMIVTDNNGAVK FPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCAVWRKNDENITLETVCHDPK LPYHDFILED AASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPDSPILLTC PTISILSFFSVALLVILACVLWKKRIKPIVWPSLPDHKKTLEHLCKKPRKNLNVSFNPESF LDCQIHRVDDIQA RDEVEGFLQDTPPQQLLEESEKQRLGGDVQSPNCPSEDVVITPESFGR DSSLTCLAGNVSACDAPILSSSRSLDCRESGKNGPHVYQDLLLLSLGTTNSTLPPPSLQSG ILTLNPVAQGQPILTSLGSNQEEAYVTMSSFYQNN (SEQ ID NO: 283).

[0254] In an embodiment, an engineered DN TGF- β RII comprises an amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) SEQ ID: 284.

[0255] MLLLVTSLLLCELPHPAFLLIPTIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCD VRFSTCDNQKSCMSNCSITSICEKPQEVCAVWRKNDENITLETVCHDPKLPYHDFILED AASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPDSPILLTCPTISILSFFSV ALLVILACVLWKKRIKPIVWPSLPDHKKTLEHLCKKPRKNLNVSFNPESFLDCQIHRVD DIQARDEVEGFLQDTPPQQLLEESEKQRLGGDVQSPNCPSEDVVITPESFGRDSSLTCLAG NVSACDAPILSSSRSLDCRESGKNGPHVYQDLLLLSLGTTNSTLPPPSLQSGILTLNPVAQ GQPILTSLGSNQEEAYVTMSSFYQNN (SEQ ID NO: 284).

[0256] In an embodiment, an engineered DN TGF- β RII comprises an amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) SEQ ID: 297.

[0257] QLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVAVWRKNDENITLETVCH
DPKLPYHDFILEDAAAPKCMKEKKKPGETFFMCSCSSDECNDNIIFSEE (SEQ ID NO:
297).

[0258] In an embodiment, an engineered DN TGF- β RII comprises an amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) SEQ ID: 298.

[0259] QLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVAVWRKNDENITLETVCH
DPKLPYHDFILEDAAAPKCMKEKKKPGETFFMCSCSSDECNDNIIFSEELLVIFQVTGIS
LLPPLGVAISVIIIIFYCY (SEQ ID NO: 298).

[0260] In an embodiment, an engineered DN TGF- β RII comprises an amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) SEQ ID: 299.

[0261] MGRGLLRGLWPLHIVLWTRIASQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQ
EVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAAAPKCMKEKKKPGETFFMCSCSS
DECNDNIIFSEELLVIFQVTGISLLPPLGVAISVIIIIFYCY (SEQ ID NO: 299).

[0262] The present disclosure contemplates, the expression of polynucleotides encoding the a dual TACI-BCMA CARs, and TCRs disclosed herein and the co-expression of polynucleotides comprising the engineered DN TGF- β Receptors with a dual TACI-BCMA binding CARs, TCRs and fragments thereof, cells and compositions comprising the same, and vectors that express polypeptides.

[0263] In one embodiment described herein, a dual TACI-BCMA binding CAR linked to a DN TGF- β Receptor has an amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) SEQ ID NO: 285.
DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPS

RFSGSGSGTDFTLTISSLQPEDFATYYCQQSHIAPWTFGGGTKVEIKGSTSGSGKPGSGE
GSTKGQVQLVQSGAEVKKPGSSVKVSCKASGGTFADYAIWVRQAPGQGLEWMGGIIP
ILGRANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARDRDSTSLPYNHYY
MDVWGKGTITVTVSSGSLDNEKSNGTIIHVKGKHLCPSPFPGPSKPFVWLTVVVGGLA
CYSLLVTVAFIIFWVRSKRSRLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSLRV
KFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPEMGGKPRRKNPQEGLY
NELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRSGE
GRGSLTTCGDVEENPGPMGRGLLRGLWPLHIVLWTRIASTIPPHVQKSVNNDMIVTDNN
GAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCAVWRKNDENITLETVC
HDPKLPYHDFILEDAAAPKCMKEKKKPGETFFMCSSECDNDNIIFSEYNTSNPDLLL
VIFQVTGISLLPPLGVAISVIIIIFYCYRVNRQ (SEQ ID NO: 285). In embodiments, a dual
TACI-BCMA binding CAR is encoded by a nucleic acid having at least 75% sequence identity to
(such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; e.g., 85–90%,
85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) the nucleic acid having the sequence
according to:

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAAGCGTTGGAGATAGAGTC
ACTATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCAGCA
GAAACCAGGGAAAGCCCCTAAGCTCCTCATCTATGCTGCATCCAGTTTGCAAAGTG
GGGTCCCATCAAGGTTTAGTGGCAGTGGATCCGGGACAGATTTCACTCTCACCATCT
CGAGCCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGCAAAGCCACATCGCCC
CTTGGACTTTTGGCGGAGGGACCAAGGTTGAGATCAAAGGGAGCACTAGCGGCTCT
GGAAAACCGGGATCTGGCGAGGGATCTACCAAGGGCCAGGTGCAGCTGGTGCAGT
CTGGGGCTGAAGTCAAAAAGCCTGGGTCTCGGTGAAGGTCTCCTGCAAGGCTTCT
GGAGGCACCTTCGCAGACTATGCTATCAGCTGGGTGCGACAGGCCCCCGGACAAGG
GCTTGAGTGGATGGGAGGAATAATCCCTATATTGGGCAGAGCAAACCTACGCACAGA
AGTTCCAGGGACGCGTTACGATTACCGCGGACGAATCTACGAGCACAGCCTACATG
GAGCTGAGCAGCCTGAGATCTGAGGACACGGCGGTGTATTACTGCGCCAGAGACAG
AGACAGCACaTCTCTGCCGTACAACCACTATTATATGGACGTATGGGGCAAGGGTAC
AACTGTCACTGTCTCCTCTGGGAGTCTGGACAACGAGAAGAGCAACGGAACTATCA
TCCACGTAAAGGGCAAGCATTTATGCCCTAGCCCTCTGTTTCCCGGACCCAGCAAGC
CGTTTTGGGTACTGGTGGTGGTGGGAGGAGTGCTGGCTTGTTACTCTTTACTGGTCA
CCGTGGCCTTCATCATCTTCTGGGTTTGAAGCAAGAGGTCTAGACTGCTGCACAGCG
ACTACATGAACATGACCCCCAGAAGACCCGGCCCCACCAGAAAGCACTACCAGCCT
TACGCCCCCTCCCCGCGACTTCGCCGCCTATCGTAGCCTGCGCGTAAAGTTTTTCGAGG
TCTGCTGATGCCCCAGCTTACCAACAAGGCCAAAATCAGCTTTATAATGAGTTGAAT

CTAGGCAGGCGTGGAAGAATACGACGTATTAGATAAGAGGCGGGGACGGGACCCTG
 AAATGGGCGGCAAACCCAGACGGAAGAATCCACAAGAGGGATTATATAACGA
 ACTTCAGAAGGACAAAATGGCTGAAGCTTACAGCGAAATCGGAATGAAGGGGGAGAGG
 CGCAGAGGAAAAGGACATGATGGACTATATCAGGGCCTGTCCACCGCTACAAAAG
 ATACCTATGACGCACTGCATATGCAGGCCTTGCCTCCAAGAGGTTTCAGGAGAAGGC
 AGGGGCTCTCTCCTGACCTGCGGCGACGTGGAAGAGAACCCTGGCCCCATGGGACG
 CGGTTTATTGAGAGGACTGTGGCCCTTACACATCGTTCTGTGGACTCGTATCGCCTC
 TACCATCCCCCCCCATGTCCAAAAGAGCGTAAACAACGATATGATCGTGACCGACA
 ACAATGGCGCTGTCAAGTTCCACAGCTGTGCAAGTTTTGTGACGTGCGCTTCAGCA
 CTTGTGACAATCAGAAAAGCTGCATGAGCAACTGCTCCATCACCTCCATCTGTGAG
 AAACCCCAAGAAGTGTGCGTCGCCGTCTGGCGTAAGAACGACGAGAACATCACTTT
 AGAGACTGTTTGCCACGATCCCAAAGTCCCTACCATGACTTCATATTGGAAGATGC
 AGCCTCTCCCAAGTGTATCATGAAAGAAAAGAAAAAACCTGGAGAGACCTTCTTCA
 TGTGTTCTTGTTCGTCTGATGAGTGCAATGATAATATAATCTTCAGCGAAGAGTACA
 ATACCTCGAACCCCGATCTGTTGCTCGTGATCTTCCAAGTTACCGGCATTTCTTCT
 GCCTCCGTTGGGTGTGGCAATCAGCGTGATCATTTTTCTACTGCTATCGTGTTAA
 CCGTCAGT (SEQ ID NO: 286).

[0264] In one embodiment described herein, a dual TACI-BCMA binding CAR linked to a DN TGF- β Receptor has an amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) SEQ ID NO: 287. DIQLTQSPSSLSASVGDRVTITCRASQISLYLNWYQQKPGKAPKLLIYAASSLQSGVPSR FSGSGSGTDFLTITSLQPEDFATYYCQQVAVAPWTFGGGTKVEIKGSTSGSGKPGSGEG STKGQVQLVQSGAEVKKPGSSVKVSKASGGTFEHYAIWVRQAPGQGLEWMGGIPI LGRANYAQKFQGRVTITADESTSTAYMELSSLRSEDYVYYCARDRSWEGSPYMYG MDVWGQGTMTVTVSSGSLDNEKSNGTIIHVKGKHLCPSPFPGPSKPFVVLVVVGGVLA CYSLLVTVAFIIFWVRSKRSRLHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRSLRV KFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPEMGGKPRRKNPQEGLY NELQKDKMAEAYSEIGMKGERRRGKGGHDGLYQGLSTATKDTYDALHMQALPPRSGE GRGSLTCDGVEENPGPMGRGLLRGLWPLHIVLWTRIASTIPPHVQKSVNNDMIVTDNN GAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCAVVRKNDENITLETVC HDPKLPYHDFILEDAAAPKCMKEKKKPGETFFMCSSDECNDNIIFSEEYNTSNPDLLL VIFQVTGISLLPPLGVAISVIIIIFYCYRVNRQ (SEQ ID NO: 287). In embodiments a dual TACI-BCMA binding CAR is encoded by a nucleic acid having at least 75% sequence identity to

(such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; e.g., 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) the nucleic acid having the sequence according to:

GACATCCAGTTGACCCAGTCTCCATCCTCCCTGTCTGCAAGCGTTGGAGACAGAGTT
ACTATCACTTGCCGGGCAAGTCAGAGCATTAGCCTATATTTAAATTGGTATCAGCAG
AAACCAGGGAAAGCCCCTAAGTTGCTGATCTATGCTGCATCTAGTTTGCAAAGTGG
GGTCCCATCACGATTCAGTGGCAGTGGATCCGGGACAGATTTCACTCTCACCATCTC
gAGTCTACAACCTGAAGATTTTGCAACTTACTACTGTCAGCAAGTGGCCGTCGCCCC
TTGGACTTTCGGCGGAGGGACCAAGGTTGAGATCAAAGGGAGCACAAGCGGCTCTG
GGAAACCGGGATCTGGCGAGGGATCTACCAAGGGCCAGGTGCAGCTGGTGCAGTCT
GGGGCTGAGGTGAAAAAGCCTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGG
AGGCACCTTCGAACACTATGCTATCAGCTGGGTGCGACAGGCCCTGGACAGGGAC
TTGAGTGGATGGGGGGGATCATCCCCATACTAGGCCGAGCAAACCTACGCACAGAAG
TTCCAGGGCAGAGTCACTATTACCGCGGACGAATCGACGAGCACAGCCTACATGGA
GCTGAGCAGCCTGAGATCTGAGGACACGGCGGTGTATTACTGCGCCCGTGACAGAA
GCTGGGAAGGATCTCCCTATATGTACTACGGAATGGACGTTTGGGGCCAAGGGACA
ATGGTTACCGTTAGCAGTGGGAGTCTGGACAACGAGAAGAGCAACGGAACCTATCAT
CCACGTTAAGGGCAAGCATTTATGCCCTAGCCCTCTGTTTCCCGGACCCAGCAAGCC
GTTTTGGGTACTGGTGGTGGTGGGAGGAGTGCTGGCTTGTTACTCTTTACTGGTCAC
CGTGGCCTTCATCATCTTCTGGGTTCGAAGCAAGAGGTCTAGACTGCTGCACAGCGA
CTACATGAACATGACCCCCAGAAGACCCGGCCCCACCAGAAAGCACTACCAGCCTT
ACGCCCCCTCCCCGCGACTTCGCCGCTATCGTAGCCTGCGCGTAAAGTTTTTCGAGGT
CTGCTGATGCCCCAGCTTACCAACAAGGCCAAAATCAGCTTTATAATGAGTTGAATC
TAGGCAGGCGTGAAGAATACGACGTATTAGATAAGAGGCGGGGCAGGGACCCTGA
AATGGGCGGCAAACCCAGACGGAAGAATCCACAAGAGGGATTATATAACGAACTT
CAGAAGGACAAAATGGCTGAAGCTTACAGCGAAATCGGAATGAAGGGGGAGAGGC
GCAGAGGAAAAGGACATGATGGACTATATCAGGGCCTGTCCACCGCTACAAAAGAT
ACCTATGACGCACTGCATATGCAGGCCTTGCCTCCAAGAGGTTTCAGGAGAAGGCAG
GGGCTCTCTCCTGACCTGCGGCGACGTGGAAGAGAACCTGGCCCCATGGGACGCG
GTTTATTGAGAGGACTGTGGCCCTTACACATCGTTCTGTGGACTCGTATCGCCTCTA
CCATCCCCCCCCATGTCCAAAAGAGCGTAAACAACGATATGATCGTGACCGACAAC
AATGGCGCTGTCAAGTTCCACAGCTGTGCAAGTTTTGTGACGTGCGCTTCAGCACT
TGTGACAATCAGAAAAGCTGCATGAGCAACTGCTCCATCACCTCCATCTGTGAGAA
ACCCCAAGAAGTGTGCGTCGCCGTCTGGCGTAAGAACGACGAGAACATCACTTTAG
AGACTGTTTGCCACGATCCCAAACCTGCCCTACCATGACTTCATATTGGAAGATGCAG

CCTCTCCCAAGTGTATCATGAAAGAAAAGAAAAACCTGGAGAGACCTTCTTCATG
TGTTCTTGTTCTGCTGATGAGTGCAATGATAATATAATCTTCAGCGAAGAGTACAAT
ACCTCGAACCCCGATCTGTTGCTCGTGATCTTCCAAGTTACCGGCATTTCTCTTCTGC
CTCCGTTGGGTGTGGCAATCAGCGTGATCATCATTTTCTACTGCTATCGTGTTAACC
GTCAGT (SEQ ID NO: 288).

[0265] In embodiments a codon optimized dual TACI-BCMA binding CAR linked to a DN TGF- β Receptor (e.g. Dual binder #1 + DNR Version 2) is encoded by a nucleic acid having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; e.g., 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) the nucleic acid having the sequence according to:

ATGCTTCTCCTGGTGACAAGCCTTCTGCTCTGTGAATTACCACACCCAGCATTCTC
CTGATTCTGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAAGCGTTGGA
GATAGAGTCACTATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTG
GTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTT
TGCAAAGTGGGGTCCCATCAAGGTTTCAGTGGCAGTGGATCCGGGACAGATTTCACT
CTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGCAAAGC
CACATCGCCCCTTGACTTTTGGCGGAGGGACCAAGGTTGAGATCAAAGGGAGCAC
TAGCGGCTCTGGCAAACCTGGATCTGGCGAGGGATCTACCAAGGGCCAGGTGCAGC
TGGTGCACTCTGGGGCTGAGGTGAAGAAGCCTGGGTCTCGGTGAAGGTCTCCTGC
AAGGCTTCTGGAGGCACCTTCGCAGACTATGCTATCAGCTGGGTGCGACAGGCCCC
TGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTATATTGGGCAGAGCAAACCT
ACGCACAGAAGTTCCAGGGCAGAGTTACGATTACCGCGGACGAATCCACGAGCACA
GCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCGGTGTACTACTGCGC
CAGAGACAGAGACAGCACAAGCCTGCCGTACAACCACTACTACATGGACGTATGGG
GCAAGGGTACAACCTGTCACTGTCTCCTCTGGGTCTCTAGACAATGAGAAGAGCAAT
GGAACCATTATCCATGTGAAAGGGAAACACCTTTGTCCAAGTCCCCTATTTCCCGGA
CCTTCTAAGCCCTTTTGGGTGCTGGTGGTGGTTGGTGGAGTCCTGGCTTGCTATAGC
TTGCTAGTAACAGTGGCCTTTATTATTTTCTGGGTGAGGAGTAAGAGGAGCAGGCTC
CTGCACAGTGACTACATGAACATGACTCCCCGCCGCCCGGGCCACCCGCAAGCA
TTACCAGCCCTATGCCCCACCACGCGACTTCGCAGCCTATCGCTCCCTGAGAGTGAA
GTTTCAGCAGGAGCGCAGACGCCCCCGCGTACCAGCAGGGCCAGAACCAGCTCTATA
ACGAGCTCAATCTAGGACGAAGAGAGGAGTACGATGTTTTGGACAAGAGGCGTGG
CCGGGACCCTGAGATGGGGGGAAAGCCGAGAAGGAAGAACCCTCAGGAAGGCCTG
TACAATGAACTGCAGAAAGATAAGATGGCGGAGGCCTACAGTGAGATTGGGATGA

AAGGCGAGCGCCGGAGGGGCAAGGGGCACGATGGCCTTTACCAGGGTCTCAGTAC
 AGCCACCAAGGACACCTACGACGCCCTTCACATGCAGGCCCTGCCCCCTCGCGGCT
 CTGGAGAAGGCAGGGGCTCTCTGCTGACCTGCGGGGACGTGGAAGAGAACCCAGG
 CCCCATGGGAAGAGGTTTATTGAGAGGACTGTGGCCCTTACACATCGTTCTGTGGAC
 TCGTATCGCCTCTACCATCCCCCCCCCATGTCCAAAAGAGCGTAAACAACGACATGAT
 CGTGACCGACAACAATGGCGCTGTCAAGTTCCCCCAGCTGTGCAAGTTTTGTGACGT
 GCGCTTCAGCACTTGTGACAATCAGAAGAGCTGCATGAGCAACTGCTCCATCACCT
 CCATCTGTGAGAAACCCCAAGAAGTGTGCGTCGCCGTCTGGCGTAAGAACGACGAG
 AACATCACTTTAGAGACAGTGTGCCACGATCCCAAAGTGCCTACCATGACTTCATT
 TTAGAAGATGCAGCCTCTCCCAAGTGTATCATGAAGGAAAAGAAAAAGCCTGGCGA
 GACCTTCTTCATGTGTTCTTGTTCGTCTGATGAGTGCAACGATAACATCATCTTCAGC
 GAAGAGTACAATACCTCGAACCCCGATTTATTACTGGTGATCTTCCAAGTTACCGGC
 ATTTCTCTTCTGCCTCCGTTGGGTGTGGCTATCAGCGTGATCATCATTTTCTACTGCT
 ATCGTGTTAACCGTCAGTGA (SEQ ID NO: 300).

[0266] In embodiments a codon optimized dual TACI-BCMA binding CAR linked to a DN TGF- β Receptor (e.g. Dual binder #3 + DNR Version 2) is encoded by a nucleic acid having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; e.g., 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) the nucleic acid having the sequence according to:

ATGCTTCTCCTGGTGACAAGCCTTCTGCTCTGTGAATTACCACACCCAGCATTCCTC
 CTGATTCTGACATCCAGTTGACCCAGTCTCCATCCTCCCTGTCTGCAAGCGTTGGA
 GACAGAGTTACTATCACTTGCCGGGCAAGTCAGAGCATTAGCCTATATTTAAATTGG
 TATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTT
 GCAAAGTGGGGTCCCATCAAGGTTCAAGTGGCAGTGGATCCGGGACAGATTTCACTC
 TCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGCAAGTGG
 CCGTCGCCCCCTTGGACTTTCGGCGGAGGGACCAAGGTTGAGATCAAAGGGAGCACA
 AGCGGCTCTGGCAAACCTGGATCTGGCGAGGGATCTACCAAGGGCCAGGTGCAGCT
 GGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTCTCCTGCA
 AGGCTTCTGGAGGCACCTTCGAACACTATGCTATCAGCTGGGTGCGACAGGCCCT
 GGACAGGGGCTTGAAGTGGATGGGAGGGATCATCCCCATATTGGGCCGAGCAAATA
 CGCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCACGAGCACA
 GCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCGGTGTACTACTGCGC
 CAGAGACAGAAGCTGGGAAGGATCTCCCTATATGTACTACGGAATGGACGTTTGGG
 GCCAAGGGACAATGGTCACCGTTTCCTCAGGGTCTCTAGACAATGAGAAGAGCAAT

GGAACCATTATCCATGTGAAAGGGAAACACCTTTGTCCAAGTCCCCTATTTCCCGGA
CCTTCTAAGCCCTTTTGGGTGCTGGTGGTGGTGGTGGAGTCCTGGCTTGCTATAGC
TTGCTAGTAACAGTGGCCTTTATTATTTTCTGGGTGAGGAGTAAGAGGAGCAGGCTC
CTGCACAGTGACTACATGAACATGACTCCCCGCCGCCCGGGCCACCCGCAAGCA
TTACCAGCCCTATGCCCCACCACGCGACTTCGCAGCCTATCGCTCCCTGAGAGTGAA
GTTACAGCAGGAGCGCAGACGCCCCCGCGTACCAGCAGGGCCAGAACCAGCTCTATA
ACGAGCTCAATCTAGGACGAAGAGAGGAGTACGATGTTTTGGACAAGAGGCGTGG
CCGGGACCCTGAGATGGGGGGAAAGCCGAGAAGGAAGAACCCTCAGGAAGGCCTG
TACAATGAACTGCAGAAAGATAAGATGGCGGAGGCCTACAGTGAGATTGGGATGA
AAGGCGAGCGCCGGAGGGGCAAGGGGCACGATGGCCTTTACCAGGGTCTCAGTAC
AGCCACCAAGGACACCTACGACGCCCTTCACATGCAGGCCCTGCCCCCTCGCGGCT
CTGGAGAAGGCAGGGGCTCTCTGCTGACCTGCGGCGACGTGGAAGAGAACCCAGG
CCCCATGGGAAGAGGTTTATTGAGAGGACTGTGGCCCTTACACATCGTTCTGTGGAC
TCGTATCGCCTCTACCATCCCCCCCCATGTCCAAAAGAGCGTAAACAACGACATGAT
CGTGACCGACAACAATGGCGCTGTCAAGTTCCCCCAGCTGTGCAAGTTTTGTGACGT
GCGCTTCAGCACTTGTGACAATCAGAAGAGCTGCATGAGCAACTGCTCCATCACCT
CCATCTGTGAGAAACCCCAAGAAGTGTGCGTCGCCGTCTGGCGTAAGAACGACGAG
AACATCACTTTAGAGACAGTGTGCCACGATCCCCAACTGCCCTACCATGACTTCATT
TTAGAAGATGCAGCCTCTCCCAAGTGTATCATGAAGGAAAAGAAAAAGCCTGGCGA
GACCTTCTTCATGTGTTCTTGTTTCGTCTGATGAGTGCAACGATAACATCATCTTCAGC
GAAGAGTACAATACCTCGAACCCCGATTTATTACTGGTGATCTTCCAAGTTACCGGC
ATTTCTCTTCTGCCTCCGTTGGGTGTGGCTATCAGCGTGATCATCTTTTCTACTGCT
ATCGTGTTAACCGTCAGTG (SEQ ID NO: 301).

[0267] “Polypeptide,” “polypeptide fragment,” “peptide” and “protein” are, unless specified to the contrary, and according to conventional meaning, i.e., as a sequence of amino acids. Polypeptides are not limited to a specific length, e.g., they may comprise a full length protein sequence or a fragment of a full length protein, and may include post-translational modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations and the like, as well as other modifications known in the art, both naturally occurring and non-naturally occurring. In various embodiments, the polypeptides contemplated herein comprise a signal (or leader) sequence at the N-terminal end of the protein, which co-translationally or post-translationally directs transfer of the protein.

[0268] Polypeptides include “polypeptide variants.” Polypeptide variants may differ from a naturally occurring polypeptide in one or more substitutions, deletions, additions and/or insertions.

Such variants may be naturally occurring or may be synthetically generated, for example, by modifying one or more of the above polypeptide sequences. For example, in some embodiments, it may be desirable to improve the binding affinity and/or other biological properties of the engineered DN TGF- β Receptors and engineered dual TACI-BCMA binding CAR and TCRs. Receptors by introducing one or more substitutions, deletions, additions and/or insertions. Preferably, polypeptides of the disclosure include polypeptides having at least about 50%, 60%, 65%, 70%, 75%, 85%, 90%, 95%, 98%, or 99% amino acid identity thereto. Polypeptides of the disclosure include variants having at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to any of the reference sequences described herein (see, e.g., Sequence Listing), typically where the variant maintains at least one biological activity of the reference sequence. Polypeptides include “polypeptide fragments.” Polypeptide fragments refer to a polypeptide, which may be monomeric or multi-meric that has an amino-terminal deletion, a carboxyl-terminal deletion, and/or an internal deletion or substitution of a naturally-occurring or recombinantly-produced polypeptide. In certain embodiments, a polypeptide fragment may comprise an amino acid chain at least 5 to about 500 amino acids long. It will be appreciated that in certain embodiments, fragments are at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 150, 200, 250, 300, 350, 400, or 450 amino acids long.

[0269] The polypeptide may also be fused in-frame or conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. As noted above, polypeptides of the present disclosure may be altered in various ways including amino acid substitutions, deletions, truncations, and insertions. Methods for such manipulations are generally known in the art. For example, amino acid sequence variants of a reference polypeptide may be prepared by mutations in the DNA. Methods for mutagenesis and nucleotide sequence alterations are well known in the art. See, for example, Kunkel (1985, *Proc. Natl. Acad. Sci. USA.* 82: 488–492), Kunkel *et al.*, (1987, *Methods in Enzymol.* 154: 367–382), U.S. Pat. No. 4,873,192, Watson, J. D. *et al.*, (*Molecular Biology of the Gene*, Fourth Edition, Benjamin/Cummings, Menlo Park, Calif., 1987) and the references cited therein. Guidance as to appropriate amino acid substitutions that do not affect biological activity of the protein of interest may be found in the model of Dayhoff *et al.*, (1978) Atlas of Protein Sequence and Structure (Natl. Biomed. Res. Found., Washington, D.C.).

[0270] In certain embodiments, a variant will contain conservative substitutions. A “conservative substitution” is one in which an amino acid is substituted for another amino acid that has similar

properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydrophobic nature of the polypeptide to be substantially unchanged. Modifications may be made in the structure of the polynucleotides and polypeptides of the present disclosure and still obtain a functional molecule that encodes a variant or derivative polypeptide with desirable characteristics.

[0271] Polypeptide variants further include glycosylated forms, aggregative conjugates with other molecules, and covalent conjugates with unrelated chemical moieties (e.g., pegylated molecules). Covalent variants may be prepared by linking functionalities to groups which are found in the amino acid chain or at the N- or C-terminal residue, as is known in the art. Variants also include allelic variants, species variants, and muteins. Truncations or deletions of regions which do not affect functional activity of the proteins are also variants.

[0272] Where expression of two or more polypeptides is desired, the polynucleotide sequences encoding them may be separated by an IRES sequence. In another embodiment, two or more polypeptides may be expressed as a fusion protein that comprises one or more self-cleaving polypeptide sequences, such as a T2A polypeptide. In other embodiments, they are expressed from different promoters and can be in two or more vectors. In some embodiments, a dual TACI-BCMA binding CAR or TCR is encoded in the same vector as an engineered DN TGF- β Receptor and is operably linked to the same promoter as the engineered DN TGF- β Receptor where the sequences are separated by an IRES sequence. In some embodiments, a dual TACI-BCMA binding CAR or TCR is encoded in the same vector as an engineered DN TGF- β Receptor is operably linked to a different promoter than the promoter the engineered DN TGF- β Receptor. In an embodiment, a DN TGF- β Receptor is expressed with an anti-BCMA CAR, such as described in International Patent Application Nos: PCT/US2018/039917 and PCT/2018/038549, both of which are specifically incorporated herein by reference in their entirety. In certain embodiments, the dual TACI-BCMA binding CAR or TCR is expressed on a cell that has also been engineered to express an engineered membrane bound IL-15-IL-15R α sushi domain chimeric receptor, such as disclosed in US Provisional Patent No. 63/159,610, filed on March 11, 2021 which is specifically incorporated herein by reference in its entirety. In some embodiments, a dual TACI-BCMA binding CAR or TCR is encoded in the same vector as an engineered membrane bound IL-15-IL-15R α sushi domain chimeric receptor and is operably linked to the same promoter as the an engineered membrane bound IL-15-IL-15R α sushi domain chimeric receptor where the sequences are separated by an IRES sequence or a cleavable linker. In some embodiments, a dual TACI-BCMA binding CAR or TCR is encoded in the same vector as an engineered membrane bound IL-15-IL-15R α sushi domain chimeric receptor is operably linked to a different promoter than the

promotor the an engineered membrane bound IL-15-IL-15R α sushi domain chimeric receptor. In some embodiments, a dual TACI-BCMA binding CAR is encoded in a different vector as an engineered membrane bound IL-15-IL-15R α sushi domain chimeric receptor.

[0273] In an embodiment an anti-BCMA CAR has an amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) SEQ ID NO: 289. EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSISGSGDYIY YADSVKGRFTISRDISKNTLYLQMNSLRAEDTAVYYCAKEGTGANSSLADYRGQGTLV TVSSFVPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCGVLLLSLVITLYCNHRNKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPE EEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPGEMGGKP RRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALH MQALPPR (SEQ ID NO: 289). In embodiments, an anti-BCMA CAR is encoded by a nucleic acid having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) the nucleic acid having the sequence according to: GAGGTGCAGCTGTTGGAGTCCGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAG ACTCTCCTGCGCTGCATCTGGATTACCTTTTCGTCTTATGCCATGAGCTGGGTCCGC CAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCATCTATTAGTGGTAGTGGTGATTA CATATATTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAGACATATCCA AGAACACGCTGTATCTGCAAATGAACAGTCTGAGAGCCGAGGACACGGCCGTCTAT TACTGTGCGAAGGAAGGAACAGGTGCCAACAGCAGCTTGGCAGACTACAGAGGCC AGGGCACCTTGGTAACCGTTCCTCATTCGTGCCCCGTGTTCTGCCCCGCAAGCCTAC AACAAACCCTGCTCCCCGTCCTCCTACGCCTGCACCTACAATCGCCAGCCAGCCTCT GTCTCTGAGGCCGGAAGCTTGTAGACCTGCGGCTGGCGGAGCCGTGCATACCAGAG GACTGGATTTTCGCTGCGACATCTACATTTGGGCCCCTTTGGCTGGAACATGTGGCG TTCTGCTGCTGAGCCTCGTGATCACCTGTACTGCAACCACCGGAACAAGCGGGGC CGAAAGAAGCTGCTGTACATCTTCAAGCAGCCCTTCATGCGGCCCGTCCAAACTAC CCAGGAAGAGGACGGCTGCTCCTGTCGTTTTCCCGAGGAAGAAGAAGGCGGCTGCG AGCTGAGAGTGAAGTTCAGCAGAAGCGCCGACGCGCCTGCCTATCAGCAAGGGCA GAACCAGCTGTATAACGAGTTAAACCTGGGCAGACGGGAAGAGTACGATGTGTTGG ATAAAAGACGTGGCCGGGATCCTGAGATGGGGGGAAGCCGCGCCGAAAAAACCC TCAGGAAGGCCTGTACAATGAACTGCAAAAGGATAAGATGGCCGAGGCCTACAGT GAGATTGGGATGAAAGGCGAGCGCCGAGGGGCAAGGGGCACGATGGCCTTTACC

AGGGTTTGAGTACCGCCACCAAGGACACCTACGACGCTCTTCACATGCAAGCCCTG
CCCCCTCGC (SEQ ID NO: 290).

[0274] In an embodiment an anti-BCMA CAR linked to a DN TGF- β Receptor has an amino acid sequence having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%)

SEQ	ID	NO:	289.
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EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSISGSDYIY
YADSVKGRFTISRDISKNTLYLQMNSLRAEDTAVYYCAKEGTGANSSLADYRGQGTLV
TVSSFPVFLPAKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI
WAPLAGTCGVLLLSLVITLYCNHRNKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRPE
EEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKP
RRKNPQEGLYNELQDKMAEAYSEIGMKGERRRGKGGHDGLYQGLSTATKDTYDALH
MQALPPRSGEGRGSLLTCGDVEENPGPMGRGLLRGLWPLHIVLWTRIASTIPPHVQKS
VNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCAVVR
KNDENITLETVCHDPKLPYHDFILEDASPCKIMKEKKKPGETFFMCSCSSDECNDNIIFS
EEYNTSNPDLLLVIQVTGISLLPPLGVAISVIIIIFYCYRVNRQ (SEQ ID NO: 291). In

embodiments, an anti-BCMA CAR linked to a DN TGF- β Receptor is encoded by a nucleic acid having at least 75% sequence identity to (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; *e.g.*, 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) the nucleic acid having the sequence according to:

GAGGTGCAGCTGTTGGAGTCCGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAG
ACTCTCCTGCGCTGCATCTGGATTACCTTTTCGTCTTATGCCATGAGCTGGGTCCGC
CAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCATCTATTAGTGGTAGTGGTGATTA
CATATATTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAGACATATCCA
AGAACACGCTGTATCTGCAAATGAACAGTCTGAGAGCCGAGGACACGGCCGTCTAT
TACTGTGCGAAGGAAGGAACAGGTGCCAACAGCAGCTTGGCAGACTACAGAGGCC
AGGGCACCTTGGTAACCGTTCCTCATTCGTGCCCCGTGTTCCCTGCCCCCAAGCCTAC
AACAAACCCTGCTCCCCGTCCTACGCCTGCACCTACAATCGCCAGCCAGCCTCT
GTCTCTGAGGCCGGAAGCTTGTAGACCTGCGGCTGGCGGAGCCGTGCATACCAGAG
GACTGGATTTGCTGCGACATCTACATTTGGGCCCTTTGGCTGGAACATGTGGCG
TTCTGCTGCTGAGCCTCGTGATCACCTGTACTGCAACCACCGGAACAAGCGGGGC
CGAAAGAAGCTGCTGTACATCTTCAAGCAGCCCTTCATGCGGCCCGTCCAAACTAC
CCAGGAAGAGGACGGCTGCTCCTGTCGTTTTCCCGAGGAAGAAGAAGGCGGCTGCG
AGCTGAGAGTGAAGTTCAGCAGAAGCGCCGACGCGCCTGCCTATCAGCAAGGGCA

GAACCAGCTGTATAACGAGTTAAACCTGGGCAGACGGGAAGAGTACGATGTGTTGG
 ATAAAAGACGTGGCCGGGATCCTGAGATGGGGGGAAAGCCGCGCCGAAAAAACCC
 TCAGGAAGGCCTGTACAATGAACTGCAAAAGGATAAGATGGCCGAGGCCTACAGT
 GAGATTGGGATGAAAGGCGAGCGCCGGAGGGGCAAGGGGCACGATGGCCTTTACC
 AGGGTTTGAGTACCGCCACCAAGGACACCTACGACGCTCTTCACATGCAAGCCCTG
 CCCCCTCGCGGCTCTGGAGAAGGCAGGGGCTCTCTGCTGACCTGCGGCGACGTGGA
 AGAGAACCCAGGCCCCATGGGAAGAGGTTTATTGAGAGGACTGTGGCCCTTACACA
 TCGTTCTGTGGACTCGTATCGCCTCTACCATCCCCCCCCATGTCCAAAAGAGCGTAA
 ACAACGACATGATCGTGACCGACAACAATGGCGCTGTCAAGTTCCCCCAGCTGTGC
 AAGTTTTGTGACGTGCGCTTCAGCACTTGTGACAATCAGAAGAGCTGCATGAGCAA
 CTGCTCCATCACCTCCATCTGTGAGAAACCCCAAGAAGTGTGCGTCGCCGTCTGGCG
 TAAGAACGACGAGAACATCACTTTAGAGACAGTGTGCCACGATCCCAAAGTGCCT
 ACCATGACTTCATTTTAGAAGATGCAGCCTCTCCCAAGTGTATCATGAAGGAAAAG
 AAAAAGCCTGGCGAGACCTTCTTCATGTGTTCTTGTTCGTCTGATGAGTGCAACGAT
 AACATCATCTTCAGCGAAGAGTACAATACCTCGAACCCCGATTATTACTGGTGATC
 TTCCAAGTTACCGGCATTTCTCTCTGCCTCCGTGGGTGTGGCTATCAGCGTGATCA
 TCATTTTCTACTGCTATCGTGTTAACCGTCAGT (SEQ ID NO: 292).

[0275] In embodiments a dual TACI-BCMA binding CAR linked to a DN TGF- β Receptor is encoded by a nucleic acid having at least 75% sequence identity (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; e.g., 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) the nucleic acid having the sequence according to:
 GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAAGCGTTGGAGAtAGAGTC
 ACtATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCAGCAG
 AAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGG
 GGTCCCATCAAGGTTCAAGTGGCAGTGGATC_cGGGACAGATTTCACTCTCACCATCAG
 CAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGCAAAGCCACATCGCCCC
 TTGGACTTTTGGCGGAGGGACCAAGGTTGAGATCAAAGGGAGCAtAGCGGCTCTG
 GCAAACCTGGATCTGGCGAGGGATCTACCAAGGGCCAGGTGCAGCTGGTGCAGTCT
 GGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGG
 AGGCACCTTCGCAGACTATGCTATCAGCTGGGTGCGACAGGCCCTGGACAAGGGC
 TTGAGTGGATGGGAGGGATCATCCCTATATTGGGCAGAGCAAACCTACGCACAGAAG
 TTCCAGGGCAGAGTtACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGGA
 GCTGAGCAGCCTGAGATCTGAGGACACGGCGGTGTACTACTGCGCCAGAGACAGAG
 ACAGCACAAGCCTGCCGTACAACCACTACTACATGGACGTATGGGGCAAGGGTACA

ACTGTCACtGTCTCCTCtggGtctCTAGACAATGAGAAGAGCAATGGAACCATTATCCAT
 GTGAAAGGGAAACACCTTTGTCCAAGTCCCCTATTTCCCGGACCTTCTAAGCCCTTT
 TGGGTGCTGGTGGTGGTTGGTGGAGTCCTGGCTTGCTATAGCTTGCTAGTAACAGTG
 GCCTTTATTATTTTCTGGGTGAGGAGTAAGAGGAGCAGGCTCCTGCACAGTGACTAC
 ATGAACATGACTCCCCGCCGCCCGGGCCCAACCGCAAGCATTACCAGCCCTATGC
 CCCACCACGCGACTTCGCAGCCTATCGCTCCCTGAGAGTGAAGTTCAGCAGGAGCG
 CAGACGCCCCCGCGTACCAGCAGGGCCAGAACCAGCTCTATAACGAGCTCAATCTA
 GGACGAAGAGAGGAGTACGATGTTTTGGACAAGAGgCGTGGCCGGGACCCTGAGAT
 GGGGGGAAAGCCGAGAAGGAAGAACCCTCAGGAAGGCCTGTACAATGAACTGCAG
 AAAGATAAGATGGCGGAGGCCTACAGTGAGATTGGGATGAAAGGCGAGCGCCGGA
 GGGGCAAGGGGCACGATGGCCTTTACCAGGGTCTCAGTACAGCCACCAAGGACACC
 TACGACGCCCTTCACATGCAGGCCCTGCCCCCTCGCgGCTCTGGAGAAGGCAGGGG
 CTCTCTGCTGACCTGCGGCGACGTGGAAGAGAACCCAGGCCCCATGGGAAGAGGTT
 TATTGAGAGGACTGTGGCCCTTACACATCGTTCTGTGGACTCGTATCGCCTCTACCA
 TCCCCCCCCATGTCCAAAAGAGCGTAAACAACGACATGATCGTGACCGACAACAAT
 GCGCTGTCAAGTTCCCCCAGCTGTGCAAGTTTTGTGACGTGCGCTTCAGCACTTGT
 GACAATCAGAAGAGCTGCATGAGCAACTGCTCCATCACCTCCATCTGTGAGAAACC
 CCAAGAAGTGTGCGTCGCCGTCTGGCGTAAGAACGACGAGAACATCACTTTAGAGA
 CAGTGTGCCACGATCCCAAAGTGCCTACCATGACTTCATTTTAGAAGATGCAGCCT
 CTCCCAAGTGTATCATGAAGGAAAAGAAAAAGCCTGGCGAGACCTTCTTCATGTGT
 TCTTGTTCGTCTGATGAGTGCAACGATAACATCATCTTCAGCGAAGAGTACAATACC
 TCGAACCCCGATTTATTACTGGTGATCTTCCAAGTTACCGGCATTTCTCTTCTGCCTC
 CGTTGGGTGTGGCTATCAGCGTGATCATTTTTCTACTGCTATCGTGTTAACCGTC
 AGT (SEQ ID NO: 295).

[0276] In embodiments a dual TACI-BCMA binding CAR linked to a DN TGF- β Receptor is encoded by a nucleic acid having at least 75% sequence identity (such as, at least 75%, at least 80%, at least 90%, at least 95%, or 100% identity; e.g., 85–90%, 85–95%, 85–100%, 90–95%, 90–100%, or 95–100%) the nucleic acid having the sequence according to:
 GACATCCAGTTGACCCAGTCTCCATCCTCCCTGTCTGCAAGCGTTGGAGACAGAGTt
 ACtATCACTTGCCGGGCAAGTCAGAGCATTAGCCTATATTTAAATTGGTATCAGCAG
 AAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGG
 GGTCCCATCAAGGTTCAAGTGGCAGTGGATCcGGGACAGATTTCACTCTCACCATCAG
 CAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGCAAGTGGCCGTCGCCCC
 TTGGACTTTTCGGCGGAGGGACCAAGGTTGAGATCAAAGGGAGCACAAAGCGGCTCTG

GCAAACCTGGATCTGGCGAGGGATCTACCAAGGGCCAGGTGCAGCTGGTGCAGTCT
GGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGG
AGGCACCTTCGAACACTATGCTATCAGCTGGGTGCGACAGGCCCTGGACAGGGGC
TTGAGTGGATGGGAGGGATCATCCCcATATTGGGCCGAGCAAACCTACGCACAGAAG
TTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGGA
GCTGAGCAGCCTGAGATCTGAGGACACGGCGGTGTACTACTGCGCCAGAGACAGAA
GCTGGGAAGGATCTCCCTATATGTACTACGGAATGGACGTTTGGGGCCAAGGGACA
ATGGTCACCGTtTCCTCAggGtctCTAGACAATGAGAAGAGCAATGGAACCATTATCCA
TGTGAAAGGGAAACACCTTTGTCCAAGTCCCCTATTTCCCGGACCTTCTAAGCCCTT
TTGGGTGCTGGTGGTGGTTGGTGGAGTCCTGGCTTGCTATAGCTTGCTAGTAACAGT
GGCCTTTATTATTTTCTGGGTGAGGAGTAAGAGGAGCAGGCTCCTGCACAGTGACT
ACATGAACATGACTCCCCGCCGCCCGGGCCCCACCCGCAAGCATTACCAGCCCTAT
GCCCCACCACGCGACTTCGCAGCCTATCGCTCCCTGAGAGTGAAGTTCAGCAGGAG
CGCAGACGCCCCCGCGTACCAGCAGGGCCAGAACCAGCTCTATAACGAGCTCAATC
TAGGACGAAGAGAGGAGTACGATGTTTTGGACAAGAGgCGTGGCCGGGACCCTGAG
ATGGGGGGAAAGCCGAGAAGGAAGAACCCTCAGGAAGGCCTGTACAATGAACTGC
AGAAAGATAAGATGGCGGAGGCCTACAGTGAGATTGGGATGAAAGGCGAGCGCCG
GAGGGGCAAGGGGCACGATGGCCTTTACCAGGGTCTCAGTACAGCCACCAAGGAC
ACCTACGACGCCCTTCACATGCAGGCCCTGCCCCCTCGCgGCTCTGGAGAAGGCAGG
GGCTCTCTGCTGACCTGCGGCGACGTGGAAGAGAACCCAGGCCCCATGGGAAGAGG
TTTATTGAGAGGACTGTGGCCCTTACACATCGTTCTGTGGACTCGTATCGCCTCTAC
CATCCCCCCCCATGTCCAAAAGAGCGTAAACAACGACATGATCGTGACCGACAACA
ATGGCGCTGTCAAGTTCCCCCAGCTGTGCAAGTTTTGTGACGTGCGCTTCAGCACTT
GTGACAATCAGAAGAGCTGCATGAGCAACTGCTCCATCACCTCCATCTGTGAGAAA
CCCCAAGAAGTGTGCGTCGCCGTCTGGCGTAAGAACGACGAGAACATCACTTTAGA
GACAGTGTGCCACGATCCCAAACCTGCCCTACCATGACTTCATTTTAGAAGATGCAGC
CTCTCCCAAGTGTATCATGAAGGAAAAGAAAAAGCCTGGCGAGACCTTCTTCATGT
GTTCTTGTTTCGTCTGATGAGTGCAACGATAACATCATCTTCAGCGAAGAGTACAATA
CCTCGAACCCCGATTTATTACTGGTGATCTTCCAAGTTACCGGCATTTCTCTTGCC
TCCGTTGGGTGTGGCTATCAGCGTGATCATTTTTCTACTGCTATCGTGTTAACCGT
CAGT (SEQ ID NO: 296).

[0277] Polypeptides of the present disclosure include fusion polypeptides. In some embodiments, fusion polypeptides and polynucleotides encoding fusion polypeptides are provided. Fusion polypeptides and fusion proteins refer to a polypeptide having at least two, three, four, five, six,

seven, eight, nine, or ten or more polypeptide segments. Fusion polypeptides are typically linked C-terminus to N-terminus, although they may also be linked C-terminus to C-terminus, N-terminus to N-terminus, or N-terminus to C-terminus. The polypeptides of the fusion protein may be in any order or a specified order. Fusion polypeptides or fusion proteins may also include conservatively modified variants, polymorphic variants, alleles, mutants, subsequences, and interspecies homologs, so long as the desired transcriptional activity of the fusion polypeptide is preserved. Fusion polypeptides may be produced by chemical synthetic methods or by chemical linkage between the two moieties or may generally be prepared using other common techniques. Ligated DNA sequences comprising the fusion polypeptide are operably linked to suitable transcriptional or translational control elements as discussed elsewhere herein.

[0278] In one embodiment, a fusion partner comprises a sequence that assists in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be targeted to desired intracellular compartments or to facilitate transport of the fusion protein through the cell membrane.

[0279] Fusion polypeptides may further comprise a polypeptide cleavage signal between each of the polypeptide domains described herein. In addition, polypeptide site may be put into any linker peptide sequence. Exemplary polypeptide cleavage signals include polypeptide cleavage recognition sites such as protease cleavage sites, nuclease cleavage sites (e.g., rare restriction enzyme recognition sites, self-cleaving ribozyme recognition sites), and self-cleaving viral oligopeptides (see deFelipe and Ryan, 2004. *Traffic*, 5(8); 616–26).

[0280] Suitable protease cleavages sites and self-cleaving peptides are known to the skilled person (see, e.g., in Ryan *et al.*, 1997. *J Gener. Viral.* 78, 699–722; Scymczak *et al.* (2004) *Nature Biotech.* 5, 589–594). Exemplary protease cleavage sites include, but are not limited to the cleavage sites of potyvirus Nia proteases (e.g., tobacco etch virus protease), potyvirus HC proteases, potyvirus PI (P35) proteases, byovirus Nia proteases, byovirus RNA-2-encoded proteases, aphthovirus L proteases, enterovirus 2A proteases, rhinovirus 2A proteases, picorna 3C proteases, comovirus 24K proteases, nepovirus 24K proteases, RTSV (rice tungro spherical virus) 3C-like protease, PYVF (parsnip yellow fleck virus) 3C-like protease, heparin, thrombin, factor Xa and enterokinase. Due to its high cleavage stringency, TEV (tobacco etch virus) protease cleavage sites may be used. In other embodiments, self-cleaving peptides may include those polypeptide sequences obtained from potyvirus and cardiovirus 2A peptides, FMDV (foot-and-mouth disease virus), equine rhinitis A virus, Thosea asigna virus and porcine teschovirus. In other

embodiments, the self-cleaving polypeptide site comprises a 2A or 2A-like site, sequence or domain (Donnelly *et al.*, 2001. *J Gen. Viral.* 82:1027–1041).

[0281] Generally, it is understood that any appropriate viral vector or vectors may be used for transduction of the engineered constructs described herein. In one embodiment described herein, a cell (e.g., T cell or NK cell) is transduced with a retroviral vector, e.g., a lentiviral vector. As used herein, the term “retrovirus” refers to an RNA virus that reverse transcribes its genomic RNA into a linear double-stranded DNA copy and subsequently covalently integrates its genomic DNA into a host genome. Illustrative retroviruses suitable for use in some embodiments, include, but are not limited to: Moloney murine leukemia virus (M-MuLV), Moloney murine sarcoma virus (MoMSV), Harvey murine sarcoma virus (HaMuSV), murine mammary tumor virus (MuMTV), gibbon ape leukemia virus (GaLV), feline leukemia virus (FLV), spumavirus, Friend murine leukemia virus, Murine Stem Cell Virus (MSCV) and Rous Sarcoma Virus (RSV) and lentivirus.

[0282] As used herein, the term “lentivirus” refers to a group (or genus) of complex retroviruses. Illustrative lentiviruses include, but are not limited to: HIV (human immunodeficiency virus; including HIV type 1, and HIV type 2); visna-maedi virus (VMV) virus; the caprine arthritis encephalitis virus (CAEV); equine infectious anemia virus (EIAV); feline immunodeficiency virus (FIV); bovine immune deficiency virus (BIV); and simian immunodeficiency virus (SIV).

[0283] The term “vector” is used herein to refer to a nucleic acid molecule capable transferring or transporting another nucleic acid molecule. The transferred nucleic acid is generally linked to, e.g., inserted into, the vector nucleic acid molecule. A vector may include sequences that direct autonomous replication in a cell, or may include sequences sufficient to allow integration into host cell DNA. Useful vectors include, for example, plasmids (e.g., DNA plasmids or RNA plasmids), transposons, cosmids, bacterial artificial chromosomes, and viral vectors. Useful viral vectors include, e.g., replication defective retroviruses and lentiviruses.

[0284] As will be evident to one of skill in the art, the term “viral vector” is widely used to refer either to a nucleic acid molecule (e.g., a transfer plasmid) that includes virus-derived nucleic acid elements that typically facilitate transfer of the nucleic acid molecule or integration into the genome of a cell or to a viral particle that mediates nucleic acid transfer. Viral particles will typically include various viral components and sometimes also host cell components in addition to nucleic acid(s).

[0285] The term viral vector may refer either to a virus or viral particle capable of transferring a nucleic acid into a cell or to the transferred nucleic acid itself. Viral vectors and transfer plasmids

contain structural and/or functional genetic elements that are primarily derived from a virus. The term “retroviral vector” refers to a viral vector or plasmid containing structural and functional genetic elements, or portions thereof, that are primarily derived from a retrovirus. The term “lentiviral vector” refers to a viral vector or plasmid containing structural and functional genetic elements, or portions thereof, including LTRs that are primarily derived from a lentivirus. The term “hybrid vector” refers to a vector, LTR or other nucleic acid containing both retroviral, e.g., lentiviral, sequences and non-retroviral viral sequences. In one embodiment, a hybrid vector refers to a vector or transfer plasmid comprising retroviral e.g., lentiviral, sequences for reverse transcription, replication, integration and/or packaging.

[0286] In some embodiments, the terms “lentiviral vector,” “lentiviral expression vector” may be used to refer to lentiviral transfer plasmids and/or infectious lentiviral particles. Where reference is made herein to elements such as cloning sites, promoters, regulatory elements, heterologous nucleic acids, etc., it is to be understood that the sequences of these elements are present in RNA form in the lentiviral particles of the disclosure and are present in DNA form in the DNA plasmids of the disclosure. In one embodiment described herein, the expression vector is a lentivirus expression vector.

[0287] At each end of the provirus are structures called “long terminal repeats” or “LTRs.” The term “long terminal repeat (LTR)” refers to domains of base pairs located at the ends of retroviral DNAs which, in their natural sequence context, are direct repeats and contain U3, R and U5 regions. LTRs generally provide functions fundamental to the expression of retroviral genes (e.g., promotion, initiation and polyadenylation of gene transcripts) and to viral replication. The LTR contains numerous regulatory signals including transcriptional control elements, polyadenylation signals and sequences needed for replication and integration of the viral genome. The viral LTR is divided into three regions called U3, R, and U5. The U3 region contains the enhancer and promoter elements. The U5 region is the sequence between the primer binding site and the R region and contains the polyadenylation sequence. The R (repeat) region is flanked by the U3 and U5 regions. The LTR is composed of U3, R and U5 regions and appears at both the 5’ and 3’ ends of the viral genome. Adjacent to the 5’ LTR are sequences necessary for reverse transcription of the genome (the tRNA primer binding site) and for efficient packaging of viral RNA into particles (the Psi site).

[0288] As used herein, the term “packaging signal” or “packaging sequence” refers to sequences located within the retroviral genome which are required for insertion of the viral RNA into the viral capsid or particle, see e.g., Clever et al., 1995. J of Virology, Vol. 69, No. 4; pp. 2101–2109.

Several retroviral vectors use the minimal packaging signal (also referred to as the psi [Ψ] sequence) needed for encapsidation of the viral genome. Thus, as used herein, the terms “packaging sequence,” “packaging signal,” “psi” and the symbol “ Ψ ,” are used in reference to the non-coding sequence required for encapsidation of retroviral RNA strands during viral particle formation.

[0289] In various embodiments, vectors comprise modified 5' LTR and/or 3' LTRs. Either or both of the LTR may comprise one or more modifications including, but not limited to, one or more deletions, insertions, or substitutions. Modifications of the 3' LTR are often made to improve the safety of lentiviral or retroviral systems by rendering viruses replication-defective. As used herein, the term “replication-defective” refers to virus that is not capable of complete, effective replication such that infective virions are not produced (e.g., replication-defective lentiviral progeny). The term “replication-competent” refers to wild-type virus or mutant virus that is capable of replication, such that viral replication of the virus is capable of producing infective virions (e.g., replication-competent lentiviral progeny).

[0290] “Self-inactivating” (SIN) vectors refers to replication-defective vectors, e.g., retroviral or lentiviral vectors, in which the right (3') LTR enhancer-promoter region, known as the U3 region, has been modified (e.g., by deletion or substitution) to prevent viral transcription beyond the first round of viral replication. This is because the right (3') LTR U3 region is used as a template for the left (5') LTR U3 region during viral replication and, thus, the viral transcript cannot be made without the U3 enhancer-promoter. In a further embodiment of the disclosure, the 3'LTR is modified such that the U5 region is replaced, for example, with an ideal poly(A) sequence. It should be noted that modifications to the LTRs such as modifications to the 3'LTR, the 5'LTR, or both 3' and 5'LTRs, are also contemplated herein.

[0291] An additional safety enhancement is provided by replacing the U3 region of the 5'LTR with a heterologous promoter to drive transcription of the viral genome during production of viral particles. Examples of heterologous promoters which may be used include, for example, viral simian virus 40 (SV40) (e.g., early or late), cytomegalovirus (CMV) (e.g., immediate early), Moloney murine leukemia virus (MoMLV), Rous sarcoma virus (RSV), and herpes simplex virus (HSV) (thymidine kinase) promoters. Typical promoters are able to drive high levels of transcription in a Tat-independent manner. This replacement reduces the possibility of recombination to generate replication-competent virus because there is no complete U3 sequence in the virus production system. In certain embodiments, the heterologous promoter has additional advantages in controlling the manner in which the viral genome is transcribed. For example, the

heterologous promoter may be inducible, such that transcription of all or part of the viral genome will occur only when the induction factors are present. Induction factors include, but are not limited to, one or more chemical compounds or the physiological conditions such as temperature or pH, in which the host cells are cultured.

[0292] In some embodiments, viral vectors comprise a TAR element. The term “TAR” refers to the “trans-activation response” genetic element located in the R region of lentiviral (e.g., HIV) LTRs. This element interacts with the lentiviral trans-activator (tat) genetic element to enhance viral replication.

[0293] The “R region” refers to the region within retroviral LTRs beginning at the start of the capping group (i.e., the start of transcription) and ending immediately prior to the start of the poly A tract. The R region is also defined as being flanked by the U3 and U5 regions. The R region plays a role during reverse transcription in permitting the transfer of nascent DNA from one end of the genome to the other.

[0294] As used herein, the term “FLAP element” refers to a nucleic acid whose sequence includes the central polypurine tract and central termination sequences (cPPT and CTS) of a includes the central polypurine tract and central termination sequences (cPPT and CTS) of a retrovirus, e.g., HIV-I or HIV-2. Suitable FLAP elements are described in U.S. Pat. No. 6,682,907 and in Zennou, et al., 2000, Cell, 101: 173. During HIV-I reverse transcription, central initiation of the plus-strand DNA at the central polypurine tract (cPPT) and central termination at the central termination sequence (CTS) lead to the formation of a three-stranded DNA structure: the HIV-I central DNA flap. While not wishing to be bound by any theory, the DNA flap may act as a cis-active determinant of lentiviral genome nuclear import and/or may increase the titer of the virus.

[0295] In one embodiment, retroviral or lentiviral transfer vectors comprise one or more export elements. The term “export element” refers to a cis-acting post-transcriptional regulatory element which regulates the transport of an RNA transcript from the nucleus to the cytoplasm of a cell. Examples of RNA export elements include, but are not limited to, the human immunodeficiency virus (HIV) rev response element (RRE) (see e.g., Cullen et al., 1991. J Virol. 65: 1053; and Cullen et al., 1991. Cell 58: 423), and the hepatitis B virus post-transcriptional regulatory element (HPRE). Generally, the RNA export element is placed within the 3' UTR of a gene, and may be inserted as one or multiple copies.

[0296] In other embodiments, expression of heterologous sequences in viral vectors is increased by incorporating post-transcriptional regulatory elements, efficient polyadenylation sites, and

optionally, transcription termination signals into the vectors. A variety of posttranscriptional regulatory elements may increase expression of a heterologous nucleic acid at the protein, e.g., woodchuck hepatitis virus post-transcriptional regulatory element (WPRE; Zufferey et al., 1999, *J Virol.*, 73:2886); the post-transcriptional regulatory element present in hepatitis B virus (HPRE) (Huang et al., *Mol. Cell. Biol.*, 5:3864); and the like (Liu et al., 1995, *Genes Dev.*, 9:1766).

[0297] In some embodiments, vectors may include regulatory oligonucleotides having transcriptional or translational regulatory activity. Such an oligonucleotide can be used in a variety of gene expression configurations for regulating control of expression. A transcriptional regulatory oligonucleotide, can increase (enhance) or decrease (silence) the level of expression of a recombinant expression construct. Regulatory oligonucleotides may selectively regulate expression in a context specific manner, including, for example, for conferring tissue specific, developmental stage specific, or the like expression of the polynucleotide, including constitutive or inducible expression. A regulatory oligonucleotide of the disclosure also can be a component of an expression vector or of a recombinant nucleic acid molecule comprising the regulatory oligonucleotide operatively linked to an expressible polynucleotide. A regulatory element can be of various lengths from a few nucleotides to several hundred nucleotides.

[0298] Elements directing the efficient termination and polyadenylation of the heterologous nucleic acid transcripts increases heterologous gene expression. Transcription termination signals are generally found downstream of the polyadenylation signal. In some embodiments, vectors comprise a polyadenylation sequence 3' of a polynucleotide encoding a polypeptide to be expressed. The term "poly A site" or "poly A sequence" as used herein denotes a DNA sequence which directs both the termination and polyadenylation of the nascent RNA transcript by RNA polymerase II. Polyadenylation sequences may promote mRNA stability by addition of a poly A tail to the 3' end of the coding sequence and thus, contribute to increased translational efficiency. Efficient polyadenylation of the recombinant transcript is desirable as transcripts lacking a poly A tail are unstable and are rapidly degraded. Illustrative examples of poly A signals that may be used in a vector of the disclosure, includes an ideal poly A sequence (e.g., AATAAA, ATTAAA, AGTAAA), a bovine growth hormone poly A sequence (BGHpA), a rabbit β -globin poly A sequence (r β gpA), or another suitable heterologous or endogenous poly A sequence known in the art.

[0299] Also described herein are "codon-optimized" nucleic acids. A "codon-optimized" nucleic acid refers to a nucleic acid sequence that has been altered such that the codons are optimal for expression in a particular system (such as a particular species or group of species). For example,

a nucleic acid sequence can be optimized for expression in mammalian cells or in a particular mammalian species (such as human cells) by replacing at least one, more than one, or a significant number, of codons of the native sequence with codons that are more frequently or most frequently used in the genes of that species. Codon optimization does not alter the amino acid sequence of the encoded protein.

[0300] The codon-optimized nucleotide sequences can present improved properties related to expression efficacy. In some embodiments, the DNA sequence to be transcribed may be optimized to facilitate more efficient transcription and/or translation. In some embodiments, the DNA sequence may be optimized regarding cis-regulatory elements (e.g., TATA box, termination signals, and protein binding sites), artificial recombination sites, chi sites, CpG dinucleotide content, negative CpG islands, GC content, polymerase slippage sites, and/or other elements relevant to transcription; the DNA sequence may be optimized regarding cryptic splice sites, mRNA secondary structure, stable free energy of mRNA, repetitive sequences, RNA instability domain, and/or other elements relevant to mRNA processing and stability; the DNA sequence may be optimized regarding codon usage bias, codon adaptability, internal chi sites, ribosomal binding sites (e.g., IRES), premature polyA sites, Shine-Dalgarno (SD) sequences, and/or other elements relevant to translation; and/or the DNA sequence may be optimized regarding codon context, codon-anticodon interaction, translational pause sites, and/or other elements relevant to protein folding.

[0301] The vectors may have one or more LTRs, wherein any LTR comprises one or more modifications, such as one or more nucleotide substitutions, additions, or deletions. The vectors may further comprise one or more accessory elements to increase transduction efficiency (e.g., a cPPT /FLAP), viral packaging (e.g., a Psi (Ψ) packaging signal, RRE), and/or other elements that increase therapeutic gene expression (e.g., poly (A) sequences), and may optionally comprise a WPRE or HPRE. The skilled artisan would appreciate that many other different embodiments may be fashioned from the existing embodiments of the disclosure.

[0302] A “host cell” includes cells transfected, infected, or transduced in vivo, ex vivo, or in vitro with a recombinant vector or a polynucleotide of the disclosure. Host cells may include packaging cells, producer cells, and cells infected with viral vectors. In some embodiments, host cells infected with viral vector of the disclosure are administered to a subject in need of therapy. In certain embodiments, the term “target cell” is used interchangeably with host cell and refers to transfected, infected, or transduced cells of a desired cell type. In some embodiments, the target cell is a T cell.

[0303] Large scale viral particle production is often necessary to achieve a reasonable viral titer. Viral particles are produced by transfecting a transfer vector into a packaging cell line that comprises viral structural and/or accessory genes, e.g., gag, pol, env, tat, rev, vif, vpr, vpu, vpx, or nef genes or other retroviral genes.

[0304] As used herein, the term “packaging vector” refers to an expression vector or viral vector that lacks a packaging signal and comprises a polynucleotide encoding one, two, three, four or more viral structural and/or accessory genes. Typically, the packaging vectors are included in a packaging cell, and are introduced into the cell via transfection, transduction or infection. Methods for transfection, transduction or infection are well known by those of skill in the art. A retroviral/lentiviral transfer vector of the present disclosure may be introduced into a packaging cell line, via transfection, transduction or infection, to generate a producer cell or cell line. The packaging vectors of the present disclosure may be introduced into human cells or cell lines by common methods including, e.g., calcium phosphate transfection, lipofection or electroporation. In some embodiments, the packaging vectors are introduced into the cells together with a dominant selectable marker, such as neomycin, hygromycin, puromycin, blastocidin, zeocin, thymidine kinase, DHFR, Gln synthetase or ADA, followed by selection in the presence of the appropriate drug and isolation of clones. A selectable marker gene may be linked physically to genes encoding by the packaging vector, e.g., by IRES or self-cleaving viral peptides.

[0305] Viral envelope proteins (env) determine the range of host cells which may ultimately be infected and transformed by recombinant retroviruses generated from the cell lines. In the case of lentiviruses, such as HIV-1, HIV-2, SIV, FIV and EIV, the env proteins include gp41 and gp120. In some embodiments, the viral env proteins expressed by packaging cells of the disclosure are encoded on a separate vector from the viral gag and pol genes, as has been previously described.

[0306] Illustrative examples of retroviral-derived env genes which may be employed in the embodiments described herein include, but are not limited to: MLV envelopes, IOAI envelope, BAEV, FeLV-B, RDI 14, SSAV, Ebola, Sendai, FPV (Fowl plague virus), and influenza virus envelopes. Similarly, genes encoding envelopes from RNA viruses (e.g., RNA virus families of Picomaviridae, Calciviridae, Astroviridae, Togaviridae, Flaviviridae, Coronaviridae, Paramyxoviridae, Rhabdoviridae, Filoviridae, Orthomyxoviridae, Bunyaviridae, Arenaviridae, Reoviridae, Bimaviridae, Retroviridae) as well as from the DNA viruses (families of Hepadnaviridae, Circoviridae, Parvoviridae, Papovaviridae, Adenoviridae, Herpesviridae, Poxviridae, and Iridoviridae) may be utilized. Representative examples include, FeLV, VEE,

HFVW, WDSV, SFV, Rabies, ALV, BIV, BL V, EBV, CAEV, SNV, ChTL V, STLV, MPMV, SMRV, RAV, FuSV, MH2, AEV, AMV, CTIO, and EIAV.

[0307] In other embodiments, envelope proteins for pseudotyping a virus of present disclosure include, but are not limited to any of the following virus: Influenza A such as H1N1, H1N2, H3N2 and H5N1 (bird flu), Influenza B, Influenza C virus, Hepatitis A virus, Hepatitis B virus, Hepatitis C virus, Hepatitis D virus, Hepatitis E virus, Rotavirus, any virus of the Norwalk virus group, enteric adenoviruses, parvovirus, Dengue fever virus, Monkey pox, Mononegavirales, Lyssavirus such as rabies virus, Lagos bat virus, Mokola virus, Duvenhage virus, European bat virus 1 & 2 and Australian bat virus, Ephemero virus, Vesiculovirus, Vesicular Stomatitis Virus (VSV), Herpes viruses such as Herpes simplex virus types 1 and 2, varicella zoster, cytomegalovirus, Epstein–Barr virus (EBV), human herpesviruses (HHV), human herpesvirus type 6 and 8, Human immunodeficiency virus (HIV), papilloma virus, murine gamma herpes virus, Arenaviruses such as Argentine hemorrhagic fever virus, Bolivian hemorrhagic fever virus, Sabia–associated hemorrhagic fever virus, Venezuelan hemorrhagic fever virus, Lassa fever virus, Machupo virus, Lymphocytic choriomeningitis virus (LCMV), Bunyaviridae such as Crimean–Congo hemorrhagic fever virus, Hantavirus, hemorrhagic fever with renal syndrome causing virus, Rift Valley fever virus, Filoviridae (filovirus) including Ebola hemorrhagic fever and Marburg hemorrhagic fever, Flaviviridae including Kaysanur Forest disease virus, Omsk hemorrhagic fever virus, Tick–borne encephalitis causing virus and Paramyxoviridae such as Hendra virus and Nipah virus, variola major and variola minor (smallpox), alphaviruses such as Venezuelan equine encephalitis virus, eastern equine encephalitis virus, western equine encephalitis virus, SARS–associated coronavirus (SARS–Co V), West Nile virus, or any encephalitis causing virus.

[0308] The terms “pseudotype” or “pseudotyping” as used herein, refer to a virus whose viral envelope proteins have been substituted with those of another virus possessing other characteristics. For example, HIV may be pseudotyped with vesicular stomatitis virus G–protein (VSV–G) envelope proteins, which allows HIV to infect a wider range of cells because HIV envelope proteins (encoded by the env gene) normally target the virus to CD4+ presenting cells.

[0309] As used herein, the term “packaging cell lines” is used in reference to cell lines that do not contain a packaging signal, but do stably or transiently express viral structural proteins and replication enzymes (e.g., gag, pol and env) which are necessary for the correct packaging of viral particles. Any suitable cell line may be employed to prepare packaging cells of the disclosure. Generally, the cells are mammalian cells. In another embodiment, the cells used to produce the packaging cell line are human cells. Suitable cell lines which may be used to produce the

packaging cell line include, for example, CHO cells, BHK cells, MDCK cells, C3H 10T1/2 cells, FLY cells, Psi-2 cells, BOSC 23 cells, P A317 cells, WEHI cells, COS cells, BSC 1 cells, BSC 40 cells, BMT 10 cells, VERO cells, W138 cells, MRC5 cells, A549 cells, HTI080 cells, 293 cells, 293T cells, B-50 cells, 3T3 cells, NIH3T3 cells, HepG2 cells, Saos-2 cells, Huh7 cells, HeLa cells, W163 cells, 211 cells, and 211A cells.

[0310] As used herein, the term “producer cell line” refers to a cell line which is capable of producing recombinant retroviral particles, comprising a packaging cell line and a transfer vector construct comprising a packaging signal. The production of infectious viral particles and viral stock solutions may be carried out using conventional techniques. Methods of preparing viral stock solutions are known in the art and are illustrated by, e.g., Y. Soneoka et al. (1995) *Nucl. Acids Res.* 23:628–633, and N. R. Landau et al. (1992) *J Virol.* 66:5110–5113. Infectious virus particles may be collected from the packaging cells using conventional techniques. For example, the infectious particles may be collected by cell lysis, or collection of the supernatant of the cell culture, as is known in the art. Optionally, the collected virus particles may be purified if desired. Suitable purification techniques are well known to those skilled in the art.

[0311] The delivery of a gene(s) or other polynucleotide sequence using a retroviral or lentiviral vector by means of viral infection rather than by transfection is referred to as “transduction.” In one embodiment, retroviral vectors are transduced into a cell through infection and provirus integration. In certain embodiments, a target cell, e.g., a T cell or NK cell, is “transduced” if it comprises a gene or other polynucleotide sequence delivered to the cell by infection using a viral or retroviral vector. In some embodiments, a transduced cell comprises one or more genes or other polynucleotide sequences delivered by a retroviral or lentiviral vector in its cellular genome.

[0312] Disclosed are host cells expressing one or more of the constructs of the disclosure. The host cells may be transduced with one or more viral vectors comprising nucleic acid sequences encoding one or more polypeptides expressing an engineered TCR and/or a CAR. Other methods relating to the use of viral vectors in gene therapy, which may be utilized according to certain embodiments of the present disclosure, may be found in, e.g., Kay, M.A. (1997) *Chest* 111(6 Supp.): 138S–142S; Ferry, N. and Heard, J.M. (1998) *Hum. Gene Ther.* 9:1975–81; Shiratory, Y. et al., (1999) *Liver* 19:265–74; Oka, K. et al., (2000) *Curr. Opin. Lipidol.* 11:179–86; Thule, P. M. and Liu, J.M. (2000) *Gene Ther.* 7:1744–52; Yang, N. S. (1992) *Crit. Rev. Biotechnol.* 12:335–56; Alt, M. (1995) *J Hepatol.* 23:746–58; Brody, S. L. and Crystal, R.G. (1994) *Ann. NY Acad. Sci.* 716:90–101; Strayer, D.S. (1999) *Expert Opin. Investig. Drugs* 8:2159–2172; Smith–Arica,

J. R. and Bartlett, J. S. (2001) *Curr. Cardiol. Rep.* 3:43–49; and Lee, H. C. et al., (2000) *Nature* 408:483–8.

[0313] The compositions described herein may comprise one or more polynucleotides, polypeptides, vectors comprising same, and T cell composition and NK compositions, as contemplated herein. One embodiment described herein is a composition comprising a modified T cell that expresses a dual TACI-BCMA binding TCR and/or CAR. Another embodiment described herein is a composition comprising a modified NK cell that expresses a dual TACI-BCMA binding TCR and/or CAR. Compositions include, but are not limited to pharmaceutical compositions. A “pharmaceutical composition” refers to a composition formulated in pharmaceutically-acceptable or physiologically-acceptable solutions for administration to a cell or an animal, either alone, or in combination with one or more other modalities of therapy. It will also be understood that, if desired, the compositions of the present disclosure may be administered in combination with other agents as well, such as, e.g., cytokines, growth factors, hormones, small molecules, chemotherapeutics, pro-drugs, drugs, antibodies, or other various pharmaceutically-active agents. There is virtually no limit to other components that may also be included in the compositions, provided that the additional agents do not adversely affect the ability of the composition to deliver the intended therapy.

[0314] The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0315] As used herein “pharmaceutically acceptable carrier, diluent or excipient” includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, surfactant, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals. Exemplary pharmaceutically acceptable carriers include, but are not limited to, to sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; tragacanth; malt; gelatin; talc; cocoa butter, waxes, animal and vegetable fats, paraffins, silicones, bentonites, silicic acid, zinc oxide; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol;

polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and any other compatible substances employed in pharmaceutical formulations.

[0316] In one embodiment described herein, compositions of the present disclosure comprise an amount of modified T cells or NK cells contemplated herein. It may generally be stated that a pharmaceutical composition comprising the T cells or NK cells contemplated herein may be administered at a dosage of 10^2 to 10^{10} cells/kg body weight, 10^5 to 10^9 cells/kg body weight, 10^5 to 10^8 cells/kg body weight, 10^5 to 10^7 cells/kg body weight, 10^7 to 10^9 cells/kg body weight, or 10^7 to 10^8 cells/kg body weight, including all integer values within those ranges. The number of cells will depend upon the ultimate use for which the composition is intended as will the type of cells included therein. T cells or NK cells modified to express an engineered TCR or CAR may be administered multiple times at dosages within these ranges. The cells may be allogeneic, syngeneic, xenogeneic, or autologous to the patient undergoing therapy. If desired, the treatment may also include administration of mitogens (e.g., PHA) or lymphokines, cytokines, and/or chemokines (e.g., IFN- γ , IL-2, IL-7, IL-15, IL-12, TNF-alpha, IL-18, and TNF-beta, GM-CSF, IL-4, IL-13, Flt3-L, RANTES, MIP1 α , etc.) as described herein to enhance engraftment and function of infused T cells.

[0317] Generally, compositions comprising 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 or immunosuppressed. In some, compositions comprising the modified T cells or NK cells contemplated herein are used in the treatment of cancers. The modified T cells or NK cells described herein may be administered either alone, or as a pharmaceutical composition in combination with carriers, diluents, excipients, and/or with other components such as IL-2, IL-7, and/or IL-15 or other cytokines or cell populations. In some embodiments, pharmaceutical compositions contemplated herein comprise an amount of genetically modified T cells or NK cells, in combination with one or more pharmaceutically or physiologically acceptable carriers, diluents or excipients.

[0318] Pharmaceutical compositions comprising modified T cells or NK cells contemplated herein may further 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

disclosure may be formulated for parenteral administration, e.g., intravascular (intravenous or intra-arterial), intraperitoneal or intramuscular administration.

[0319] The liquid pharmaceutical compositions, whether they be solutions, suspensions or other like form, may include one or more of the following: sterile diluents such as water for injection, saline solution, such as physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils such as synthetic mono or diglycerides which may serve as the solvent or suspending medium, polyethylene glycols, glycerin, propylene glycol or other solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation may be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. Sterile injectable pharmaceutical composition are also included.

[0320] In some embodiments, compositions contemplated herein comprise an effective amount of an expanded modified T cell or NK cell composition, alone or in combination with one or more therapeutic agents. Thus, the T cell or NK cell compositions may be administered alone or in combination with other known cancer treatments, such as radiation therapy, chemotherapy, transplantation, immunotherapy, hormone therapy, photodynamic therapy, etc. The compositions may also be administered in combination with antibiotics and anti-viral agents. Such therapeutic agents may be accepted in the art as a treatment for a disease state as described herein, such as a cancer. In one embodiment the compositions contemplated herein may also be administered with inhibitors of TGF- β , for example the small molecule inhibitor LY55299. Exemplary therapeutic agents contemplated include cytokines, growth factors, steroids, NSAIDs, DMARDs, anti-inflammatories, chemotherapeutics, radiotherapeutics, therapeutic antibodies, or other active and ancillary agents.

[0321] In certain embodiments, compositions comprising T cells or NK cells contemplated herein may be administered in conjunction with any number of chemotherapeutic agents. Illustrative examples of chemotherapeutic agents include but are not limited to alkylating agents such as thiotepa and cyclophosphamide (CYTOXAN™); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylolomelamine resins; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin,

phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabycin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, 5-FU; androgens such as calusterone, dromostanolone propionate, epitioestanol, mepitioestane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK®; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2, 2', 2''trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g. paclitaxel (TAXOL®, Bristol-Myers Squibb Oncology, Princeton, N.J.) and doxetaxel (TAXOTERE®, Rhone-Poulenc Rorer, Antony, France); chlorambucil; gemcitabine; 6- thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; CPT-11; topoisomerase inhibitor RPS 2000; difluoromethylomithine (DMFO); retinoic acid derivatives such as Targretin™ (bexarotene), Panretin™ (alitretinoin); ONTAK™ (denileukin diftitox); esperamicins; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included in this definition are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

[0322] A variety of other therapeutic agents may be used in conjunction with the compositions described herein. In one embodiment, the composition comprising T cells is administered with an anti-inflammatory agent. Anti-inflammatory agents or drugs include, but are not limited to, steroids and glucocorticoids (including betamethasone, budesonide, dexamethasone, hydrocortisone acetate, hydrocortisone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone), nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin, ibuprofen, naproxen, methotrexate, sulfasalazine, leflunomide, anti-TNF medications, cyclophosphamide and mycophenolate.

[0323] In some embodiments, NSAIDs are chosen from the group consisting of ibuprofen, naproxen, naproxen sodium, Cox-2 inhibitors such as VIOXX® (rofecoxib) and CELEBREX® (celecoxib), and sialylates. Exemplary analgesics are chosen from the group consisting of acetaminophen, oxycodone, tramadol or propoxyphene hydrochloride. Exemplary glucocorticoids are chosen from the group consisting of cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, or prednisone. Exemplary biological response modifiers include molecules directed against cell surface markers (e.g., CD4, CD5, etc.), cytokine inhibitors, such as the TNF antagonists (e.g., etanercept (ENBREL®), adalimumab (HUMIRA®) and infliximab (REMICADE®), chemokine inhibitors and adhesion molecule inhibitors. The biological response modifiers include monoclonal antibodies as well as recombinant forms of molecules. Exemplary disease-modifying anti-rheumatic drugs (DMARDs) include azathioprine, cyclophosphamide, cyclosporine, methotrexate, penicillamine, leflunomide, sulfasalazine, hydroxychloroquine, Gold (oral (auranofin) and intramuscular) and minocycline.

[0324] In other embodiments, the therapeutic antibodies suitable for combination with the CAR or TCR modified T cells or NK cells contemplated herein, include but are not limited to, abagovomab, adecatumumab, afutuzumab, alemtuzumab, altumomab, amatuximab, anatumomab, arcitumomab, bavituximab, bectumomab, bevacizumab, bivatumumab, blinatumomab, brentuximab, cantuzumab, catumaxomab, cetuximab, citatuzumab, cixutumumab, clivatuzumab, conatumumab, daratumumab, drozitumab, duligotumab, dusigitumab, detumomab, dacetuzumab, dalotuzumab, ecomeximab, elotuzumab, ensituximab, ertumaxomab, etaracizumab, farietuzumab, ficlatuzumab, figitumumab, flavotumab, futuximab, ganitumab, gemtuzumab, girentuximab, glembatumumab, ibritumomab, igovomab, imgatuzumab, indatuximab, inotuzumab, intetumumab, ipilimumab, iratumumab, labetuzumab, lexatumumab, lintuzumab, lorvotuzumab, lucatumumab, mapatumumab, matuzumab, milatuzumab, minretumomab, mitumomab, moxetumomab, namatumab, naptumomab, necitumumab, nimotuzumab, nofetumomab, ocaratuzumab, ofatumumab, olaratumab, onartuzumab, oportuzumab,

oregovomab, panitumumab, parsatuzumab, patritumab, pentumomab, pertuzumab, pintumomab, pritumumab, racotumomab, radretumab, rilotumumab, rituximab, robatumumab, satumomab, sibrotuzumab, siltuximab, simtuzumab, solitomab, tacatuzumab, taplitumomab, tenatumomab, teprotumumab, tigatuzumab, tositumomab, trastuzumab, tucotuzumab, ublituximab, veltuzumab, vorsetuzumab, votumumab, zalutumumab, CC49 and 3F8.

[0325] In some embodiments, the compositions described herein are administered in conjunction with a cytokine. By “cytokine” as used herein is meant a generic term for proteins released by one cell population that act on another cell as intercellular mediators. Examples of such cytokines are lymphokines, monokines, chemokines, and traditional polypeptide hormones. Included among the cytokines are growth hormones such as human growth hormone, N-methionyl human growth hormone, and bovine growth hormone; parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prolaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH); hepatic growth factor; fibroblast growth factor; prolactin; placental lactogen; tumor necrosis factor- α and - β ; mullerian-inhibiting substance; mouse gonadotropin-associated peptide; inhibin; activin; vascular endothelial growth factor; integrin; thrombopoietin (TPO); nerve growth factors such as NGF- β ; platelet-growth factor; transforming growth factors (TGFs) such as TGF- α and TGF- β ; insulin-like growth factor-I and -II; erythropoietin (EPO); osteoinductive factors; interferons such as interferon- α , - β , and - γ ; colony stimulating factors (CSFs) such as macrophage-CSF (M-CSF); granulocyte-macrophage-CSF (GM-CSF); and granulocyte-CSF (G-CSF); interleukins (ILs) such as IL-1, IL-1 α , IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12; IL-15, a tumor necrosis factor such as TNF- α or TNF- β ; and other polypeptide factors including LIF and kit ligand (KL). As used herein, the term cytokine includes proteins from natural sources or from recombinant cell culture, and biologically active equivalents of the native sequence cytokines.

[0326] Any cell may be used as a host cell for the polynucleotides, the vectors, or the polypeptides of the present disclosure. In some embodiments, the cell can be a prokaryotic cell, fungal cell, yeast cell, or higher eukaryotic cells such as a mammalian cell. Suitable prokaryotic cells include, without limitation, eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacterales such as Escherichia, e.g., E. coli; Enterobacter; Erwinia; Klebsiella; Proteus; Salmonella, e.g., Salmonella typhimurium; Serratia, e.g., Serratia marcescens, and Shigella; Bacilli such as B. subtilis and B. licheniformis; Pseudomonas such as P. aeruginosa; and Streptomyces. In some embodiments, the cell is a human cell. In some embodiments, the cell is an immune cell. In some embodiments, the immune cell is selected from the group consisting of

a T cell, a B cell, a tumor infiltrating lymphocyte (TIL), a TCR expressing cell, a natural killer (NK) cell, a dendritic cell, a granulocyte, an innate lymphoid cell, a megakaryocyte, a monocyte, a macrophage, a platelet, a thymocyte, and a myeloid cell. In one embodiment, the immune cell is a T cell. In another embodiment, the immune cell is an NK cell. In certain embodiments, the T cell is a tumor-infiltrating lymphocyte (TIL), autologous T cell, engineered autologous T cell (eACT™), an allogeneic T cell, a heterologous T cell, or any combination thereof. Unlike antibody therapies or standalone TCR or CAR modified T cells, T cells (or any cells as described above)

[0327] Another embodiment described herein is a method of treating a cancer in a subject in need thereof comprising administering an effective amount, e.g., therapeutically effective amount of a composition comprising T cells or NK cells expressing TCR or CAR as described herein. 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.

[0328] In other embodiments, methods comprising administering a therapeutically effective amount of modified T cells contemplated herein or a composition comprising the same, to a patient in need thereof, alone or in combination with one or more therapeutic agents, are provided. In certain embodiments, the cells of the disclosure are used in the treatment of patients at risk for developing a cancer. Thus, the present disclosure provides methods for the treatment or prevention of a cancer comprising administering to a subject in need thereof, a therapeutically effective amount of the modified T cells of the disclosure.

[0329] One of ordinary skill in the art would recognize that multiple administrations of the compositions of the disclosure may be required to affect the desired therapy. For example a composition may be administered 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more times over a span of 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 1 year, 2 years, 5, years, 10 years, or more.

[0330] In certain embodiments, it may be desirable 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 disclosure, and reinfuse the patient with these activated and expanded T cells. This process may be carried out multiple times every few weeks. In certain embodiments, T cells may be activated from blood draws of from 10cc to 400cc. Not to be bound by theory, using this multiple blood draw/multiple reinfusion protocol may serve to select out certain populations of T cells.

[0331] The administration of the compositions contemplated herein may be carried out in any convenient manner, including by aerosol inhalation, injection, ingestion, transfusion, implantation or transplantation. In some embodiments, compositions are administered parenterally. The phrases “parenteral administration” and “administered parenterally” as used herein refers to modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravascular, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intratumoral, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion. In one embodiment, the compositions contemplated herein are administered to a subject by direct injection into a tumor, lymph node, or site of infection.

[0332] In one embodiment, a subject in need thereof is administered an effective amount of a composition to increase a cellular immune response to a cancer in the subject. The immune response may include cellular immune responses mediated by cytotoxic T cells capable of killing infected cells, regulatory T cells, and helper T cell responses. Humoral immune responses, mediated primarily by helper T cells capable of activating B cells thus leading to antibody production, may also be induced. A variety of techniques may be used for analyzing the type of immune responses induced by the compositions of the present disclosure, which are well described in the art; e.g., *Current Protocols in Immunology*, Edited by: John E. Coligan, Ada M. Kruisbeek, David H. Margulies, Ethan M. Shevach, Warren Strober (2001) John Wiley & Sons, NY, N.Y.

[0333] In the case of T cell-mediated killing, CAR-ligand binding initiates CAR signaling to the T cell, resulting in activation of a variety of T cell signaling pathways that induce the T cell to produce or release proteins capable of inducing target cell apoptosis by various mechanisms. These T cell-mediated mechanisms include (but are not limited to) the transfer of intracellular cytotoxic granules from the T cell into the target cell, T cell secretion of proinflammatory cytokines that may induce target cell killing directly (or indirectly via recruitment of other killer effector cells), and up regulation of death receptor ligands (e.g. FasL) on the T cell surface that induce target cell apoptosis following binding to their cognate death receptor (e.g. Fas) on the target cell.

[0334] In embodiments described herein is a method of treating a subject diagnosed with a cancer, comprising removing T cells from the subject, genetically modifying said T cells with a vector comprising a nucleic acid encoding a dual TACI-BCMA binding CAR as contemplated herein, thereby producing a population of modified T cells, and administering the population of modified T cells to the same subject.

[0335] In certain embodiments, the present disclosure also provides methods for stimulating an effector cell mediated immune modulator response to a target cell population in a subject comprising the steps of administering to the subject an immune effector cell population expressing a nucleic acid construct encoding a dual TACI-BCMA binding CAR molecule.

[0336] The methods for administering the cell compositions described herein includes any method which is effective to result in reintroduction of ex vivo genetically modified immune effector cells that either directly express an engineered CAR in the subject or on reintroduction of the genetically modified progenitors of immune effector cells that on introduction into a subject differentiate into mature immune effector cells that express the dual TACI-BCMA binding CAR molecule,. One method comprises transducing peripheral blood T cells ex vivo with a nucleic acid construct in accordance with the present disclosure and returning the transduced cells into the subject.

[0337] Although the foregoing disclosure has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to one of ordinary skill in the art in light of the teachings of this disclosure that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims. The following examples are provided by way of illustration only and not by way of limitation. Those skilled in the art will readily recognize a variety of noncritical parameters that could be changed or modified to yield essentially similar results.

EXAMPLES

Example 1. T cell transduction

[0338] The dual TACI-BCMA binding CARs (mAb1-mAb9) used in the following examples included a CSF2RA signal sequence, a myc tag to detect expression, a dual TACI-BCMA binding scFv, a truncated CD28 hinge, a CD28 transmembrane domain, an CD28 co-stimulatory domain, and a CD3zeta signaling domain. CAR expressing vectors included an EF1a promoter to drive constitutive expression of the dual TACI-BCMA binding CAR.

[0339] CD3⁺ cells obtained from ALLCells® (Alameda, California) were isolated from peripheral blood mononuclear cells obtained from healthy donors and frozen down in CryoStor® cell cryopreservation media (Sigma Aldrich®). Pan CD3⁺ T cells were isolated from leukopaks containing peripheral blood mononuclear cells (PBMCs) by negative selection using a commercially available kit from STEMCELL Technologies™ (Vancouver, Canada) according to manufacturer's directions and then frozen in liquid nitrogen. Chimeric antigen receptor (CAR) T cells were generated from frozen human Pan CD3⁺ T cells. Before lentivirus transduction, the

CD3+ pan T cells were thawed, and activated *ex vivo* using anti-CD3/CD28 Dynabeads[®], (ThermoFisher Scientific) and 100 IU/ml exogenous interleukin-2 (IL-2) according to manufacturer recommendations. The activated cells were rested overnight. One day after anti-CD3/CD28 bead activation, T cells were plated and transduced with a lentiviral vector (with a dual TACI-BCMA binding CAR). The CARs were transduced with a multiplicity of infection (MOI) of 5. T cells were de-beaded 3 days after transduction and evaluated for expression and cytotoxicity assays between days 8 and 11 following transduction. All flow cytometry data was collected on BD LSRFortessa[™] (BD and Company) with BD FACSDiva[™] software (BD and Company) and data was analyzed using FlowJo (BD and Company). All antibody staining was performed at 4°C in PBS containing 1% BSA.

Example 2. Assessment of T cell transduction

[0340] Seven days after transduction, T cells transduced as described in example 1 were harvested to determine transduction efficiencies. 1.5×10^5 T cells were plated in 96 well plates in duplicate. The T cells were cultured overnight in hTCM (human T cell media), that included of x-vivo 15 (Lonza (Basel, Switzerland)), 5% human serum (Valley Biomedical (Winchester, Virginia)), and 1% Glutamax (Gibco). After overnight culture, CAR expression was measured using an antibody to the myc tag, which was included on the test constructs solely to aid in detection of expression. The cells were stained with the anti-myc antibody and the stained cells were detected via flow cytometry. The transduction rates of CARs in the T cells, varied from 57-85 %. See table 13.

Table 13: Percent transduction of T cells.

CAR	mAb1	mAb2	mAb3	mAb4	mAb5	mAb6	mAb7	mAb8	mAb9
Expression	84.9%	80.6%	82.3%	83.5%	69.7%	77.5%	77.4%	57.2%	69.5%

Example 3. T cell-dependent cytotoxicity of the CAR T cells

[0341] For T cell-dependent cytotoxicity assays, the cytotoxicity of dual TACI-BCMA binding CART cells transduced as described in example 1 was measured at an effector (T cell)-to-target cell ratio of (E:T) of 1-3. T cells were cocultured with target cells for 24 h in X-VIVO 15 without Gentamicin, L-Gln, and Phenol Red (Lonza 04-744Q), and supplemented with 5% Human Serum (Valley Biomedical, HP1022), 10mL per liter 100X Glutamax (Gibco, 3050-061), 1mL per liter Gentamicin 50mg/mL (Lonza, 14-518L). The number of CAR T cells per well in a 96 well plate was normalized for transduction efficiency (see Example 2). To facilitate tracking of T cells in culture, the dual TACI-BCMA binding CAR T cells were labeled with CellTrace[™] Violet (CTV)

reagent according to the manufacturer's instructions and subsequently washed. To facilitate tracking of cells expressing CAR T target antigens ("target cells"), target cells were engineered to express luciferase. Target cells were added to each well as shown in Table 14.

[0342] Luciferase-expressing target cells used for this example comprised K562 cells or K562 cells that were transduced with either TACI or BCMA or with TACI and BCMA. After 24 hours a luciferase assay was performed and the % lysis was calculated by quantifying the target cells that were remaining after 24 h of co-culture. Briefly, D-luciferin substrate was added to the co-culture wells and plates were incubated at 37°C in the dark. Controls comprised un-transduced (UNTR) T cells (i.e., T cells not expressing a CAR) as a negative control. The results are described in Table 14.

Table 14: Average % lysis of tumor cells after co-culturing them with Anti-TACI + Anti-BCMA CAR T cells at E:T-1-3 for 24 h

% Killing	mAb 1	mAb 2	mAb 3	mAb 4	mAb 5	mAb 6	mAb 7	mAb 8	mAb 9	UNT R
K562-Parent	24.5	45.7	24	7.33	0.76	11.2	49.3	52.8	41.5	8.5
K562-BCMA	53.8	73.3	61	46.9	38	47.9	61.3	71.7	52.5	6.4
K562-TACI	71.7	85	76.3	66	60.37	69.6	75	81.9	73.3	8.6
K562-TACI+BCMA	76.9	90	82	74	61.8	77.5	81.7	89	83	13.9

Example 4. Cytokine release of the CAR T cells

[0343] Cytokine release (IL-2) in pg/ml of dual TACI-BCMA binding CAR T cells transduced as described in example 1 was measured at an effector (T cell)-to-target cell ratio of (E:T) of 1-3. T cells were cocultured with target cells for 24 h After 24 h. IL-2 release from CAR T cells was measured after co-culture with either K562 cells or K562 cells that were transduced with either TACI or BCMA or with TACI and BCMA at an E:T-1-3. Supernatants were then harvested and cytokine release (IL-2) was determined via MSD 384-Well Multi-array And Multi-spot Human Cytokine Assay using the manufacturer's directions. Supernatants from the co-cultures of T-cell products plated at the 13 E:T ratio with antigen-expressing target cells were analyzed for levels of IL-2, secretion mediated by antigen engagement. All samples were diluted to be within the range of detection. The level of IL-2 is reported as pg/ml. Controls comprised un-transduced (UNTR) T cells (i.e., T cells not expressing a CAR) as a negative control. Shown in table 15 are

the average values of IL-2 in pg/ml, released by the CAR T cells after co-culturing them with target cells at an E: T-1-3 for 24h.

Table 15: Average IL-2 release

IL-2 pg/ml	mAb 1	mAb 2	mAb 3	mAb 4	mAb 5	mAb 6	mAb 7	mAb 8	mAb 9	UNT R
K562-Parent	28	241	32.3	54	49.2	7.5	327	88	225.3	80.5
K562-BCMA	68154	77328	76091	74804	67015	91081	77578	87313	90700	154.9
K562-TACI	8430	15217	23201	28398	20307	38930	24075	20719	24840	77.68
K562-TACI+BCMA	49571	48890	46290	60684	50541	74411	50209	59339	36318	89.5

Example 5. Tumor cell killing by the CAR T cells

[0344] Killing assays were performed with different multiple myeloma cell lines to demonstrate the ability of the dual TACI-BCMA CAR T cells to kill multiple myeloma cells. The selected cell-lines, Rec-1 (ATCC® Ref No. CRL-3004), MM1.S (ATCC® Ref. No. CRL-2974), RPMI-8226 (ATCC® Ref. No. CCL-155), and JJN3 (DSMZ Ref. No. ACC 541) express one or more of TACI and BCMA. For T cell-dependent cytotoxicity assays, the cytotoxicity of T cells transduced as described in example 1 was measured at an effector (T cell)-to-target cell ratio of (E:T) of 1-3 after 24 h of coculture. Table 16 shows the results of killing assays performed where CAR T cells were co-cultured with either K562 cells, Rec-1, MM1.S, RPMI-8226 or JJN3 cells at an E:T-1-3, for 24 h. After 24 hours a luciferase assay was performed and the % lysis was calculated by quantifying the target cells that were remaining after 24 h of co-culture. Briefly, D-luciferin substrate was added to the co-culture wells and plates were incubated at 37°C in the dark. Luminescent signal was read immediately after in a microplate reader. Controls comprised untransduced (UNTR) T cells (i.e., T cells not expressing a CAR) as a negative control. The results are described in Table 16.

Table 16: Average % lysis of tumor cells after co-culturing with Anti-TACI + Anti-BCMA CAR T cells at E:T-1-3 for 24 h

% Killing	mAb 1	mAb 2	mAb 3	mAb 4	mAb 5	mAb 6	mAb 7	mAb 8	mAb 9	UNT R
K562-Parent	24.5	45.7	24	7.33	0.76	11.2	49.3	52.8	41.5	8.5
Rec-1	62.3	74.4	66.6	62.5	45.9	63.5	72.8	74.5	70.6	-4.9
MM1.S	76.8	90	78.9	69.5	50.7	78.6	90.2	96.7	95	2.9

RPMI-8226	83.8	89.3	82.6	79.3	76.6	87.2	92.2	90.8	91.2	33.8
JJN3	98.5	98.8	98.6	97.6	96.5	98.7	99	99	99.5	46.4

Example 6. Cytokine release in coculture with tumor cells

[0345] Cytokine release (IL-2) in pg/ml of dual TACI-BCMA binding CAR T cells transduced as described in example 1 was measured at an effector (T cell)-to-target cell ratio of (E:T) of 1-3 after coculture with selected multiple myeloma cell lines. Cytokine release was measured as described in Example 4. Table 17 shows results of cytokine release (IL-2) in pg/ml, by each of the CAR T cells after co-culture with either K562 cells or the multiple myeloma cells lines Rec-1, MM1.S, RPMI-8226 and JJN3 cells at an E:T-1-3, for 24 h. Supernatants were harvested and cytokine release (IL-2) was determined via MSD 384-Well Multi-array And Multi-spot Human Cytokine Assay using the manufacturer's directions. Supernatants from the co-cultures of T-cell products plated at the 13 E:T ratio with antigen-expressing target cells were analyzed for levels of IL-2, secretion mediated by antigen engagement. All samples were diluted to be within the range of detection. The level of each cytokine is reported as pg/mL and the lower limit of quantitation and upper limit of quantitation of each assay is reported. Controls comprised untransduced (UNTR) T cells (i.e., T cells not expressing a CAR) as a negative control. Shown in table 17 are the average values of IL-2 in pg/ml, released by the CAR T cells after co-culturing them with target cells at an E: T-1-3 for 24h.

Table 17: Average IL-2 released by the Anti-TACI + Anti-BCMA CAR T cells after co-culturing them tumor cells E:T-1-3 for 24 h

IL-2 pg/ml	mAb1	mAb2	mAb3	mAb4	mAb5	mAb6	mAb7	mAb8	mAb9	UNTR
K562-Parent	28	241	32.3	54	49.2	7.5	327	88	225.3	80.5
Rec-1	30445	52715	58756	30275	13443	54032	89499	86170	83976	277
MM1.S	86268	75512	78572	65657	67225	84258	45922	48077	45724	479
RPMI-8226	11019	12470	16356	4746	7605	13119	5708	6185	5280	180
JJN3	31510	31848	37325	19532	31387	36307	8687	8682	4144	497

Example 7. Phenotypes of the CAR T cells

[0346] The phenotype of dual TACI-BCMA binding CAR T cells transduced as described in example 1 was determined. Briefly, 2.0×10^5 per well were aliquoted to the wells of a 96 well plate. Media was removed and the cells washed with phospho-buffered saline (PBS). The cells

were then suspended in a 1:1000 dilution in L/D Near IR and stained in L.D for 15 mins. Cells were washed again with PBS and resuspend with the antibody cocktail shown in Table 19.

Table 19: Antibody cocktails

Fluorochrome	Antibody
BV421	CCR7
BV510	CD8
BV605	CD3
BV786	CD4
FITC	CD45RO
PE	aMyc
PE-Cy7	CD107a
APC-Cy7	Live Dead N/R
DL650	rBCMA

[0347] All antibodies were used at 1:100 dilution and cells were stained for 30 mins on ice. Cells were washed PBS or FACS buffer, and read on a flowcytometer. Table 20 Shows quantification of expression of CD4 and CD8 positive CAR T cells. A transduction check was done using day 9 cells, by staining with anti-Myc antibody and rBCMA protein. No significant difference in the CD4:CD8 ratio and the phenotype observed between CARs. Controls comprised un-transduced (UNTR) T cells (i.e., T cells not expressing a CAR) as a negative control.

Table 20: Quantification of CD4:CD8 ratio and the phenotype of Anti-TACI + Anti-BCMA CAR T cells

	CAR+/CD4+	CAR+/CD8+
mAb1	59.7 %	36.3 %
mAb5	55.2 %	40.6 %
mAb6	59.7 %	35.9 %
mAb7	52.3 %	44.1 %
UNTR	3.01 %	53.1 %

Table 21: Quantification of expression of markers of phenotype for CAR T cells

	CCR7- , CD45RO+	CCR7+ , CD45RO+	CCR7+ , CD45RO-	CCR7- , CD45RO-
	Effector Memory Cells	Central Memory Cells	Naïve Cells	Effector Cells
mAb1	59.6 %	2.00 %	0.059 %	38.3 %
mAb5	37.8 %	1.95 %	0.59 %	59.7 %
mAb6	47.1 %	1.89 %	0.28 %	50.7 %
mAb7	47.5 %	2.21 %	0.31 %	50.0 %
UNTR	43.5 %	9.00 %	4.84 %	42.7 %

Example 8. *In vivo* anti-tumor efficacy

[0348] The anti-tumor efficacy of CAR T cells comprising a dual TACI-BCMA binding CAR was tested against RPMI-8226 cell that express both BCMA and TACI. Dual TACI-BCMA binding CAR T cells were tested against disseminated luciferase-expressing RPMI-8226 multiple myeloma tumors in NSG mice. Response was evaluated based on bioluminescence imaging (BLI). BLI was performed on days 7, 9, 12, 14, 16, 19, 21, 23, 26, 28, 30, 33, 35, 37, 40, 42, 44, 47, 49, and 51 to monitor tumor reduction. The study was terminated on day 51. CAR T cells were administered at a dose, and to a number of mice, shown in Table 22. All CAR T cells were administered intravenously (QDx1).

Table 22: CAR T cell dosing schedule

Group	# of mice	# RPMI-8226	Staging/ Dosing Day	CAR scFv	Dose
1	6	1e7, s.c.		Vehicle	N/A
2	6	1e7, s.c.	D7	Un-transduced	1.5e6
3	6	1e7, s.c.	D7	Un-transduced	3e5
4	6	1e7, s.c.	D7	mAb1	1.5e6
5	6	1e7, s.c.	D7	mAb1	3e5
6	6	1e7, s.c.	D7	mAb5	1.5e6
7	6	1e7, s.c.	D7	mAb5	3e5
8	6	1e7, s.c.	D7	mAb6	1.5e6
9	6	1e7, s.c.	D7	mAb6	3e5
10	6	1e7, s.c.	D7	mAb7	1.5e6
11	6	1e7, s.c.	D7	mAb7	3e5
12	6	1e7, s.c.	D7	mAb9	1.5e6
13	6	1e7, s.c.	D7	mAb9	3e5

[0349] Results are shown in Table 23 below. Anti-tumor efficacy was observed for Dual TACI-BCMA binding CAR T cells.

Table 23: *In vivo* anti-tumor efficacy

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7		
Day	Mean tumor volume (mm ³) +/- Standard error	Mean tumor volume (mm ³) +/- Standard error	Mean tumor volume (mm ³) +/- Standard error	Mean tumor volume (mm ³) +/- Standard error	Mean tumor volume (mm ³) +/- Standard error	Mean tumor volume (mm ³) +/- Standard error	Mean tumor volume (mm ³) +/- Standard error		
7	100+/-6	96+/-6	101+/-5	99+/-5	94+/-7	100+/-6	98+/-9		
9	122+/-11	119+/-11	120+/-9	122+/-5	112+/-6	115+/-7	107+/-11		
12	166+/-17	173+/-12	155+/-13	227+/-23	207+/-13	191+/-17	203+/-17		
14	220+/-22	212+/-18	179+/-15	241+/-26	279+/-25	266+/-29	252+/-24		
16	308+/-24	265+/-20	231+/-24	245+/-24	330+/-34	268+/-29	311+/-18		
19	430+/-23	374+/-29	340+/-40	99+/-15	175+/-20	175+/-23	383+/-21		
21	451+/-28	404+/-29	365+/-41	46+/-21	155+/-14	157+/-23	407+/-21		
23	503+/-31	356+/-29	380+/-44	25+/-16	66+/-22	111+/-23	417+/-25		
26	582+/-34	417+/-58	490+/-73		28+/-18	81+/-18	497+/-40		
28	663+/-42	466+/-74	539+/-70		24+/-15	50+/-23	566+/-66		
30	859+/-58	593+/-115	697+/-96			27+/-17	720+/-88		
33	1193+/-77	776+/-196	877+/-134			11+/-11	884+/-124		
35		888+/-227	1060+/-181					1125+/-203	
37		1032+/-268	1310+/-197					1358+/-260	
40		1315+/-392	1840+/-297					1698+/-358	
42		1021+/-394							
44		1056+/-408							
47		1302+/-544							
49									
51									
	Group 8	Group 9	Group 10	Group 11	Group 12	Group 13			
Day	Mean tumor volume (mm ³) +/- Standard error	Mean tumor volume (mm ³) +/- Standard error	Mean tumor volume (mm ³) +/- Standard error	Mean tumor volume (mm ³) +/- Standard error	Mean tumor volume (mm ³) +/- Standard error	Mean tumor volume (mm ³) +/- Standard error			
7	99+/-6	97+/-5	97+/-7	97+/-5	96+/-4	96+/-7			
9	113+/-10	112+/-6	114+/-9	112+/-6	110+/-6	109+/-8			
12	135+/-17	178+/-18	163+/-13	145+/-13	152+/-11	120+/-11			
14	148+/-18	248+/-21	201+/-21	249+/-19	209+/-28	181+/-12			
16	170+/-15	304+/-19	206+/-23	348+/-23	238+/-28	239+/-28			
19	115+/-13	144+/-19	118+/-18	289+/-15		289+/-31			
21	85+/-20	91+/-19	72+/-26	262+/-17		248+/-36			
23	50+/-23	62+/-20	14+/-14	286+/-26		196+/-35			
26	15+/-15	29+/-19		271+/-41		134+/-23			
28		25+/-16		290+/-67					

30		12+/-12		356+/-112			
33				394+/-150			
35				464+/-191			
37				588+/-241			
40				695+/-284			
42				850+/-363			
44				679+/-336			
47				802+/-403			
49				518+/-315			
51				735+/-459			

Example 9. TGF β RII DNR Enhancement in BCMA/TACI Dual Binder CARs *in vivo*

[0350] This example tested the use of a dominant negative (DN) TGF- β receptor in combination with the CAR T in a myeloma mouse model with RPMI8226 cells.

[0351] Each test group included 6 animals, and received T cells transduced with a corresponding CAR. The numbers of animals and their received treatments are listed in Table 24. The volume of each tumor in the animal was about 150-250 mm³. A BCMA scFv and two dual binders were used, each tested with or without expression of the dominant negative (DN) TGF- β receptor (DNR). Dual Binder #1 includes the scFv sequence (SEQ ID NO:23) of Table 4. Dual Binder #3 includes the scFv sequence (SEQ ID NO:143) of Table 9. The DNR includes the sequence of SEQ ID NO: 297.

Table 24. Test groups and treatments

Group	# of mice	scFv	Dose
1	6	Vehicle	N/A
3	6	NTD (untransduced)	Low Dose Match
9	6	BCMA CAR	2 x 10 ⁵ cells
11	6	BCMA CAR + DNR	2 x 10 ⁵ cells
13	6	Dual Binder #1	2 x 10 ⁵ cells
15	6	Dual Binder #1 + DNR	2 x 10 ⁵ cells
17	6	Dual Binder #3	2 x 10 ⁵ cells
19	6	Dual Binder #3 + DNR	2 x 10 ⁵ cells

[0352] The tumor volumes were measured after the treatments, and the results are presented in **FIG. 1**. Without the DNR, the single BCMA-targeting CAR T cells did not exhibit observable efficacy; in combination with the DNR, by contrast, tumor growth slowed down on about day 24 and the tumor started to shrink on day 55 (**FIG. 1A**). Both dual CARs, with Binders #1 and #3, exhibited significant antitumor effects starting on day 40 (**FIG. 1B** and **1C**, middle curves). When used in combination with DNR, the efficacy was remarkably enhanced. For dual Binder #1, the

tumors started to shrink on day 20, and essentially disappeared on day 50 (**FIG. 1B**). For dual Binder #3, the tumors were gone even on day 30 (**FIG. 1C**).

[0353] This example, therefore, demonstrates significantly enhanced efficacy for low dose CAR-T cell treatments with TGF β RII dominant-negative receptors.

**Example 10. TGF β RII DNR Enhancement in Codon Optimized
BCMA/TACI Dual Binder CARs *in vivo***

[0354] This example tested the expression of codon optimized BCMA/TACI dual binder CARs with co-expression of a dominant negative (DN) TGF- β receptor. Further tested were *in vitro* cytotoxicity as well as cytokine assays. Also, tested was *in vivo* efficacy using a model of disseminated the OPM2 multiple myeloma cell line labeled with luciferase. BCMA/TACI dual binders were tested with or without expression of the dominant negative (DN) TGF- β receptor (DNR). Dual Binder #1 includes the scFv sequence (SEQ ID NO:23) of Table 4. Dual Binder #3 includes the scFv sequence (SEQ ID NO:143) of Table 9. The DNR includes the sequence of SEQ ID NO: 297. The codon optimized sequence for Dual Binder #1 Version 2 (CAR only) is SEQ ID NO: 302. The codon optimized sequence for Dual Binder #3 Version 2 (CAR only) is SEQ ID NO: 303.

[0355] As shown in Figures 2A and 2B, CAR T cells were manufactured and stained with Dylight-650 labelled recombinant BCMA to detect CAR. Codon optimization of dual binder #1 (indicated as dual binder #1 version 2) as well as codon optimization of dual binder #3 (indicated as dual binder #3 version 2) improved expression (as indicated by mean fluorescence intensity (MFI)) of both CARs.

[0356] As shown in Figures 3A and 3B, CAR T cells were manufactured to express both CAR and TGF β RII DNR and stained with Dylight-650 labelled recombinant BCMA to detect CAR and anti-TGF β RII-FITC to detect TGF β RII DNR. Codon optimization of dual binder #1 (indicated as dual binder #1 version 2) as well as codon optimization of dual binder #3 (indicated as dual binder #3 version 2) improved expression (as indicated by MFI) of both CARs and the TGF β RII DNR.

[0357] As shown in Figures 4A and 4B, similar cytotoxicity and cytokine secretion is seen in coculture assays of the CAR and TGF β RII DNR (with and without codon optimization) with OPM2 and RPMI 8226 multiple myeloma target cells.

[0358] CAR-T cell *in vivo* efficacy was assessed using a model of disseminated OPM2 multiple myeloma cell line labeled with luciferase. The OPM2 *in vivo* study was designed to compare version 1 and codon optimized, version 2 dual binders + TGFβRII DNR as shown in Table 25.

Table 25. Test groups and treatments

Group	# of mice	CAR construct	CAR+ Dose
1	5	Vehicle	N/A
2	5	NTD (untransduced)	2 x 10 ⁶ cells match
3	5	DB#1 + DNR Version 1	2 x 10 ⁶ cells
5	5	DB#1 + DNR Version 2	2 x 10 ⁶ cells
7	5	DB#3 + DNR Version 1	2 x 10 ⁶ cells
9	5	DB#3 + DNR Version 2	2 x 10 ⁶ cells

[0359] Mice were treated with 2E6 CAR-T cells on Day 9, and tumor growth was monitored by bioluminescent imaging to detect luciferase-labeled tumor cells. As shown in Figures 5A and 5B, the codon optimized versions (version 2) of the dual binders were better able to control tumors than their non-codon optimized variants as seen by the lower BLI signal in mice treated with the codon optimized (version 2) CARs compared to the non-codon optimized (version 1) counterparts.

[0360] In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification and the claims, but should be construed to include all possible embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

CLAIMS

1. An antibody, or antigen binding fragment thereof comprising a dual TACI-BCMA binding domain, wherein the dual TACI-BCMA binding domain comprises sequences of three heavy chain complementarity determining regions (HCDRs) of any one of the heavy chain variable region (HCVR) selected from the group consisting of SEQ ID NOs: 1, 25, 49, 73, 97, 121, 145, 169, and 193 and sequences of three light chain CDRs (LCDRs) of the light chain variable region (LCVR) selected from the group consisting of SEQ ID NOs: 12, 36, 60, 84, 108, 132, 156, 180, and 204.

2. The antibody, or antigen binding fragment thereof of claim 1, wherein the dual TACI-BCMA binding domain comprises a first domain comprising three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) and a second domain comprising three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3), wherein

- (i) the HCDR1 has a sequence according to any one of SEQ ID NOs: 3-5, 27-29, 51-53, and 75-77, 99-101, 123-125, 147-149, 171-173, and 195-197;
- (ii) the HCDR2 has a sequence according to any one of SEQ ID NOs: 6-8, 30-32, 54-56, and 78-80, 102-104, 126-128, 150-152, 174-176, and 198-200;
- (iii) the HCDR3 has a sequence according to any one of SEQ ID NOs: 9-11, 33-35, 57-59, and 81-83, 105-107, 129-131, 153-155, 177-179, and 201-203;
- (iv) the LCDR1 has a sequence according to any one of SEQ ID NOs: 14-16, 38-40, 62-64, and 86-88, 110-112, 134-136, 158-160, 182-184, and 206-208;
- (v) the LCDR2 has a sequence according to any one of SEQ ID NOs: 17-19, 41-43, 65-67, and 89-91, 113-115, 137-139, 161-163, 185-187, and 209-211; and
- (vi) the LCDR3 has a sequence according to any one of SEQ ID NOs: 20-22, 44-46, 68-70, and 92-94, 116-118, 140-142, 164-166, 188-190, and 212-214.

3. The antibody, or antigen binding fragment thereof of claim 1 or 2 wherein the HCDRs comprise:

- (i) an HCDR1 according to any of SEQ ID NOs: 3-5; an HCDR2 according to any of SEQ ID NOs: 6-8; an HCDR3 according to any one of SEQ ID NOs: 9-11;
- (ii) an HCDR1 according to any of SEQ ID NOs: 27-29; an HCDR2 according to any of SEQ ID NOs: 30-32; an HCDR3 according to any one of SEQ ID NOs: 33-35;

- (iii) an HCDR1 according to any of SEQ ID NOs: 51-53; an HCDR2 according to any of SEQ ID NOs: 54-56; an HCDR3 according to any one of SEQ ID NOs: 57-59;
 - (iv) an HCDR1 according to any of SEQ ID NOs: 75-77; an HCDR2 according to any of SEQ ID NOs: 78-80; an HCDR3 according to any one of SEQ ID NOs: 81-83;
 - (v) an HCDR1 according to any of SEQ ID NOs: 99-101; an HCDR2 according to any of SEQ ID NOs: 102-104; an HCDR3 according to any one of SEQ ID NOs: 105-107;
 - (vi) an HCDR1 according to any of SEQ ID NOs: 123-125; an HCDR2 according to any of SEQ ID NOs: 126-128; an HCDR3 according to any one of SEQ ID NOs: 129-131;
 - (vii) an HCDR1 according to any of SEQ ID NOs: 147-149; an HCDR2 according to any of SEQ ID NOs: 150-152; an HCDR3 according to any one of SEQ ID NOs: 153-155;
 - (viii) an HCDR1 according to any of SEQ ID NOs: 171-173; an HCDR2 according to any of SEQ ID NOs: 174-176; an HCDR3 according to any one of SEQ ID NOs: 177-179; or
 - (ix) an HCDR1 according to any of SEQ ID NOs: 195-197; an HCDR2 according to any of SEQ ID NOs: 198-200; an HCDR3 according to any one of SEQ ID NOs: 201-203;
- and

the LCDRs comprise:

- (i) an LCDR1 according to any of SEQ ID NOs: 14-16; an LCDR2 according to any of SEQ ID NOs: 17-19; an LCDR3 according to any one of SEQ ID NOs: 20-22;
- (ii) an LCDR1 according to any of SEQ ID NOs: 38-40; an LCDR2 according to any of SEQ ID NOs: 41-43; an LCDR3 according to any one of SEQ ID NOs: 44-46;
- (iii) an LCDR1 according to any of SEQ ID NOs: 62-64; an LCDR2 according to any of SEQ ID NOs: 65-67; an LCDR3 according to any one of SEQ ID NOs: 68-70;
- (iv) an LCDR1 according to any of SEQ ID NOs: 86-88; an LCDR2 according to any of SEQ ID NOs: 89-91; an LCDR3 according to any one of SEQ ID NOs: 92-94;
- (v) an LCDR1 according to any of SEQ ID NOs: 110-112; an LCDR2 according to any of SEQ ID NOs: 113-115; an LCDR3 according to any one of SEQ ID NOs: 116-118;
- (vi) an LCDR1 according to any of SEQ ID NOs: 134-136; an LCDR2 according to any of SEQ ID NOs: 137-139; an LCDR3 according to any one of SEQ ID NOs: 140-142;
- (vii) an LCDR1 according to any of SEQ ID NOs: 158-160; an LCDR2 according to any of SEQ ID NOs: 161-163; an LCDR3 according to any one of SEQ ID NOs: 164-166;
- (viii) an LCDR1 according to any of SEQ ID NOs: 182-184; an LCDR2 according to any of SEQ ID NOs: 185-187; an LCDR3 according to any one of SEQ ID NOs: 188-190; or
- (ix) an LCDR1 according to any of SEQ ID NOs: 206-208; an LCDR2 according to any of SEQ ID NOs: 209-211; an LCDR3 according to any one of SEQ ID NOs: 212-214.

4. The antibody, or antigen binding fragment thereof of any one of claims 1-3, wherein the antibody, or antigen binding fragment thereof comprises a first domain comprising three heavy chain complementarity determining regions (HCDRs) and a second domain comprising three light chain complementarity determining regions (LCDRs), wherein:

the HCDRs and LCDRs comprise:

(i) an HCDR1 according to any of SEQ ID NOs: 3-5; an HCDR2 according to any of SEQ ID NOs: 6-8; an HCDR3 according to any one of SEQ ID NOs: 9-11; an LCDR1 according to any of SEQ ID NOs: 14-16; an LCDR2 according to any of SEQ ID NOs: 17-19; an LCDR3 according to any one of SEQ ID NOs: 20-22;

(ii) an HCDR1 according to any of SEQ ID NOs: 27-29; an HCDR2 according to any of SEQ ID NOs: 30-32; an HCDR3 according to any one of SEQ ID NOs: 33-35; an LCDR1 according to any of SEQ ID NOs: 38-40; an LCDR2 according to any of SEQ ID NOs: 41-43; an LCDR3 according to any one of SEQ ID NOs: 44-46;

(iii) an HCDR1 according to any of SEQ ID NOs: 51-53; an HCDR2 according to any of SEQ ID NOs: 54-56; an HCDR3 according to any one of SEQ ID NOs: 57-59; an LCDR1 according to any of SEQ ID NOs: 62-64; an LCDR2 according to any of SEQ ID NOs: 65-67; an LCDR3 according to any one of SEQ ID NOs: 68-70;

(iv) an HCDR1 according to any of SEQ ID NOs: 75-77; an HCDR2 according to any of SEQ ID NOs: 78-80; an HCDR3 according to any one of SEQ ID NOs: 81-83; an LCDR1 according to any of SEQ ID NOs: 86-88; an LCDR2 according to any of SEQ ID NOs: 89-91; an LCDR3 according to any one of SEQ ID NOs: 92-94;

(v) an HCDR1 according to any of SEQ ID NOs: 99-101; an HCDR2 according to any of SEQ ID NOs: 102-104; an HCDR3 according to any one of SEQ ID NOs: 105-107; an LCDR1 according to any of SEQ ID NOs: 110-112; an LCDR2 according to any of SEQ ID NOs: 113-115; an LCDR3 according to any one of SEQ ID NOs: 116-118;

(vi) an HCDR1 according to any of SEQ ID NOs: 123-125; an HCDR2 according to any of SEQ ID NOs: 126-128; an HCDR3 according to any one of SEQ ID NOs: 129-131; an LCDR1 according to any of SEQ ID NOs: 134-136; an LCDR2 according to any of SEQ ID NOs: 137-139; an LCDR3 according to any one of SEQ ID NOs: 140-142;

(vii) an HCDR1 according to any of SEQ ID NOs: 147-149; an HCDR2 according to any of SEQ ID NOs: 150-152; an HCDR3 according to any one of SEQ ID NOs: 153-155; an LCDR1 according to any of SEQ ID NOs: 158-160; an LCDR2 according to any of SEQ ID NOs: 161-163; an LCDR3 according to any one of SEQ ID NOs: 164-166;

(viii) an HCDR1 according to any of SEQ ID NOs: 171-173; an HCDR2 according to any of SEQ ID NOs: 174-176; an HCDR3 according to any one of SEQ ID NOs: 177-179; an

LCDR1 according to any of SEQ ID NOs: 182-184; an LCDR2 according to any of SEQ ID NOs: 185-187; an LCDR3 according to any one of SEQ ID NOs: 188-190; or

(ix) an HCDR1 according to any of SEQ ID NOs: 195-197; an HCDR2 according to any of SEQ ID NOs: 198-200; an HCDR3 according to any one of SEQ ID NOs: 201-203; an LCDR1 according to any of SEQ ID NOs: 206-208; an LCDR2 according to any of SEQ ID NOs: 209-211; an LCDR3 according to any one of SEQ ID NOs: 212-214.

5. The antibody, or antigen binding fragment thereof of any one of claims 1-4, wherein the antibody, or antigen binding fragment thereof comprises a first heavy chain variable domain comprising the three HCDRs and a light chain variable domain comprising the three LCDRs, wherein:

(i) the heavy chain variable domain is at least 80% identical to SEQ ID NO: 1 SEQ ID NO: 25, SEQ ID NO: 49, SEQ ID NO: 73, SEQ ID NO: 97, SEQ ID NO: 121, SEQ ID NO: 145, SEQ ID NO: 169, or SEQ ID NO: 193; and

(ii) the light chain variable domain is at least 80% identical to SEQ ID NO: 12, SEQ ID NO: 36, SEQ ID NO: 60, SEQ ID NO: 84, SEQ ID NO: 108, SEQ ID NO: 132, SEQ ID NO: 156, SEQ ID NO: 180, or SEQ ID NO: 204.

6. The antibody, or antigen binding fragment thereof of claim 5, wherein the antibody, or antigen binding fragment thereof comprises a first heavy chain variable domain comprising the three HCDRs and a light chain variable domain comprising the three LCDRs, wherein:

(i) the heavy chain variable domain is at least 80% identical to SEQ ID NO: 1 and the light chain variable domain is at least 80% identical to SEQ ID NO: 12;

(ii) the heavy chain variable domain is at least 80% identical to SEQ ID NO: 25 and the light chain variable domain is at least 80% identical to SEQ ID NO: 36;

(iii) the heavy chain variable domain is at least 80% identical to SEQ ID NO: 49 and the light chain variable domain is at least 80% identical to SEQ ID NO: 60;

(iv) the heavy chain variable domain is at least 80% identical to SEQ ID NO: 73 and the light chain variable domain is at least 80% identical to SEQ ID NO: 84;

(v) the heavy chain variable domain is at least 80% identical to SEQ ID NO: 97 and the light chain variable domain is at least 80% identical to SEQ ID NO: 108;

(vi) the heavy chain variable domain is at least 80% identical to SEQ ID NO: 121 and the light chain variable domain is at least 80% identical to SEQ ID NO: 132;

(vii) the heavy chain variable domain is at least 80% identical to SEQ ID NO: 145 and the light chain variable domain is at least 80% identical to SEQ ID NO: 156;

(viii) the heavy chain variable domain is at least 80% identical to SEQ ID NO: 169 and the light chain variable domain is at least 80% identical to SEQ ID NO: 180; or

(ix) the heavy chain variable domain is at least 80% identical to SEQ ID NO: 193 and the light chain variable domain is at least 80% identical to SEQ ID NO: 204.

7. The antibody, or antigen binding fragment thereof of any one of claims 1-6, wherein the three HCDRs and the three LCDRs are comprised by a single polypeptide.

8. The antibody, or antigen binding fragment thereof of any one of claims 1-7, wherein the antigen binding fragment thereof comprises an scFv.

9. A nucleic acid encoding the antibody, or antigen binding fragment thereof of any one of claims 1-8.

10. A chimeric antigen receptor, comprised by the antibody, or antigen binding fragment thereof of any one of claims 1-9.

11. The chimeric antigen receptor of claim 10, further comprising a transmembrane domain of 4-1BB/CD137, an alpha chain of a T cell receptor, a beta chain of a T cell receptor, 2B4, CD3 epsilon, CD4, CD5, CD8 alpha, CD9, CD16, CD19, CD22, CD28, CD33, CD37, CD45, CD64, CD80, CD86, CD134, CD137, CD154, NKG2D, or a zeta chain of a T cell receptor, or any combination thereof.

12. A nucleic acid comprising the chimeric antigen receptor of claim 10 or 11.

13. A recombinant vector comprising the nucleic acid of claim 9 or 12.

14. The recombinant vector or nucleic acid of claim 12 or 13, wherein the recombinant vector further comprises a nucleic acid encoding a dominant negative TGF β receptor (DN TGF β R), comprising:

an extracellular domain (ECD) from a TGF- β receptor

and a transmembrane domain (TMD), wherein the recombinant polypeptide lacks amino acid residues responsible for signaling and phosphorylation present in a wild-type TGF- β receptor.

15. The recombinant vector according to claim 14, wherein the ECD is selected from TGF- β RI or TGF- β RII.

16. The recombinant vector according to claim 14 or 15, wherein the TMD is selected from TGF- β RI, TGF- β RII, PDGFR, CD4, CD8, CD28, CD127, CD132, CD3 ζ , 4-1BB, OX40, ICOS, CTLA-4, PD-1, LAG-3, 2B4, IL-5, IL-7, IL-7R α , BTLA or mutants of any of the foregoing.

17. The recombinant vector according to any one of claims 14–16, wherein the DN TGF β R further comprises a heterologous intracellular domain (ICD) which lacks amino acid residues responsible for signaling and phosphorylation present in wild-type TGF- β receptor.

18. A host cell transformed with the nucleic acid of any one of claims 9, 12 or the recombinant vector of any one of claims 13-17.

19. A host cell transformed with:
the nucleic acid of any one of claims 9, 12, and
a nucleic acid encoding a dominant negative TGF β receptor (DN TGF β R).

20. The host cell of claim 19, wherein the host cell is transformed with a nucleic acid encoding a membrane bound IL-15-IL-15R α sushi domain chimeric receptor.

21. The host cell of any one of claims 18-20, where the host cell comprises an iPSC, a T cell or a NK cell.

22. A pharmaceutical composition comprising the T cell and/or an NK cell of claim 21.

23. A method of treating disease in a patient in need of thereof, comprising administering the T cell and/or an NK cell of claim 21 or the pharmaceutical composition of claim 22 to the patient.

24. The method of claim 23, where the disease is multiple myeloma.

25. A method of inducing an immune response in a subject or immunizing a subject against a multiple myeloma, the method comprising administering to the subject the T cell and/or an NK cell of claim 21 or the pharmaceutical composition of claim 22 to the patient.

26. The method of any one of claims 23-25, wherein the T cell and/or an NK cell s allogeneic to the patient.