BISPECIFIC ANTIBODY CAR CELL IMMUNOTHERAPY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 62/898,503, filed September 10, 2019, the contents of which is incorporated by reference in its entireties into the present application.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on September 4, 2020, is named 113086-0112_SL.txt and is 134,417 bytes in size.

TECHNICAL FIELD

[0003] The present disclosure relates generally to the field of human immunology, specifically cancer immunotherapy.

BACKGROUND

[0004] The following discussion of the background of the invention is merely provided to aid art to the present invention.

[0005] Current cancer treatment regimens including chemotherapies, immunomodulatory drugs[14], monoclonal antibodies[15], and autologous or allogeneic transplantation. These therapies often lead to remission, but nearly all patients eventually relapse and succumb to death due to return of the disease. Thus, there is an unmet need for new therapies, including new combination immunotherapies for relapsed and/or refractory disease. This disclosure addresses these limitations and provides related advantages as well.

SUMMARY ~~OF THE DISCLOSURE~~

[0006] Chimeric antigen receptor (CAR) T cells have been used successfully in the clinic for the treatment of both hematological malignancies and solid tumors, and have recently been approved by the U.S. FDA[1-4]. Bispecific antibodies (BsAb) have also been approved by the FDA for cancer treatment and are being used as an alternative immunotherapeutic approach to CAR T cell therapy[5]. However, CAR- and BsAb-based cancer immunotherapies still need improvement for five important reasons. First, in some cases, CAR T cells cannot be expanded in vivo and cannot survive for a sufficient period of time

to initiate tumor lysis in patients[6]. It has been reported that the efficacy of CAR T cells correlates with the quantity and duration of CAR T cell presence in vivo [6-8]. Second, tumor cells can shed targeted antigens to evade therapy, especially when only a single antigen is targeted. Third, in addition to being costly and time-consuming to manufacture, BsAb have a short half-life and to date have not been shown to be curative[9,10]. Fourth, combination therapy of CAR T cells with BsAb targeting two distinct tumor associated antigens could be a good approach; however, producing each individually ex vivo would be labor intensive and costly; engineering T cells to express both a CAR and a BsAb (such as, a bispecific T cell engager, i.e., BiTE, or a bispecific natural killer cell engager, i.e., BiKE) within a single construct, of which the BsAb engages all cytolytic effector cells has not yet been reported or shown to be additive or synergistic, or to enhance T cell survival in vivo. Finally, current approaches to CAR immunotherapy mainly focus on one immune cell type, i.e., T cells, excluding all other cytolytic effector cells in the innate and adaptive arms of the immune system. NKG2D is a c-lectin type of receptor that is expressed on virtually all cytolytic effector cells in both the innate and adaptive arms of the immune system[11,12].

[0007] This disclosure provides a platform to resolve these issues, in part or in full, by engineering T cells and/or Natural killer (NK) cells infected with a single vector delivering these two modes of therapy, i.e., producing a T cell or an NK cell whose CAR is targeting one specific tumor-associated antigen and which expresses and/or secretes BsAb targeting another specific tumor-associated antigen.

[0008] In one aspect, the present disclosure provides a polypeptide comprising: (a) (i) an amino acid sequence of a chimeric antigen receptor (CAR) comprising: (1) an antigen binding domain that recognizes and binds a first tumor associated antigen (TAA) on a cancer cell (first anti-TAA antigen binding domain) with the proviso that the first TAA is not a B-cell maturation antigen (BCMA); (2) a hinge domain; (3) a transmembrane domain; and (4) an intracellular domain; and (ii) a bispecific antibody comprising (1) an antigen binding domain that recognizes and binds a second TAA on the cancer cell (second anti-TAA antigen binding domain); and (2) an antigen binding domain that recognizes and binds NKG2D (anti-NKG2D antigen binding domain); or (b) (i) an amino acid sequence of a CAR comprising: (1) an antigen binding domain that recognizes and binds BCMA (anti-BCMA antigen binding domain); (2) a hinge domain; (3) a transmembrane domain; and (4) an intracellular domain; and (ii) a bispecific antibody comprising (1) an antigen binding domain that recognizes and binds NKG2D (anti-NKG2D antigen binding domain) and

(2) an antigen binding domain that recognizes and binds CS1 (anti-CS1 antigen binding domain).

[0008a] In another aspect, the present disclosure provides a polynucleotide encoding one or more of: a polypeptide as described herein, a CAR of the polypeptide as described herein, or a bispecific antibody of the polypeptide as described herein. In another aspect, the present disclosure provides a vector comprising a polynucleotide as described herein. In another aspect, the present disclosure provides an isolated or engineered cell comprising one or more of the following: a polypeptide as described herein, a polynucleotide as described herein, or a vector as described herein.

[0008b] In a further aspect, the present disclosure provides a cell population comprising a cell as described herein. In a further aspect, the present disclosure provides a composition comprising a carrier and one or more of the following: a polypeptide as described herein, a polynucleotide as described herein, a vector as described herein; an isolated or engineered cell as described herein, and/or a cell population as described herein. In a further aspect, the present disclosure provides an isolated complex comprising either or both of the following: an isolated or engineered cell as described herein bound to a cancer cell, wherein the cancer cell is bound to the isolated cell by the first anti-TAA antigen binding domain as described herein or the anti-BCMA antigen binding domain as described herein; or a polypeptide as described herein bound to a cancer cell, wherein the cancer cell is bound to the polypeptide by either or both of: the first anti-TAA antigen binding domain as described herein or the anti-BCMA antigen binding domain as described herein, and/or the second anti-TAA antigen binding domain as described herein or the anti-CS1 antigen binding domain as described herein.

[0008c] In a further aspect, the present disclosure provides a method of producing a cell expressing a CAR and secreting a bispecific antibody comprising transducing or transfecting a cell or a cell population with a polynucleotide as described herein and/or a vector as described herein. In a further aspect, the present disclosure provides an *in vitro* method of inhibiting the growth of a cancer cell expressing a tumor associated antigen (TAA) or a tissue comprising the cancer cell, comprising contacting the cancer cell or the tissue with the isolated or engineered cell as described herein or a cell population as described herein.

[0008d] In a further aspect, the present disclosure provides a use of an isolated or

engineered cell as described herein or a cell population as described herein in the manufacture of a medicament for one or more of: inhibiting the growth of a cancer, inhibiting metastasis of a cancer, or treating a cancer, in a subject in a subject in need thereof. In a further aspect, the present disclosure provides a use of an isolated or engineered cell as described herein or a cell population as described herein in the manufacture of a medicament for treating a cancer in a subject selected for the treatment.

[0008e] Thus, in one ~~aspect~~example, provided herein are bispecific antibody-chimeric antigen receptors (BsAb-CAR, referred to herein as a BsAb-CAR construct or a CAR construct) comprising, or alternatively consisting essentially of, or yet further consisting of: (1) a chimeric antigen receptor (CAR) comprising, or alternatively consisting essentially of, or yet further consisting of: (a) an antigen binding domain of a cancer or tumor targeting antibody; (b) a hinge domain, (c) a transmembrane domain, and (d) an intracellular domain; and (2) a bispecific antibody comprising, or alternatively consisting essentially of, or yet further consisting of an antigen binding domain of an antibody directed to a cancer or tumor antigen expressed on the same cancer or tumor cell to which the CAR binds, and an anti-NKG2D antigen binding domain. In one ~~aspect~~example, the intracellular domain comprises one or more, or two or more costimulatory regions that can comprise or consisting essentially of a CD28 costimulatory signaling region and/or a 4-1BB costimulatory domain.

The bispecific antibody portion of the CAR can further comprise, or consist essentially of, or yet further consist of a signaling domain located prior to the anti-NKG2D antigen binding domain. Polynucleotides and vectors encoding these constructs are further provided herein as well as the polypeptides encoded by them. In one ~~aspect~~example, the CAR and the BsAb are expressed from a single contiguous polynucleotide and the cancer or tumor targeting antibody is expressed on the cell surface of the host cell and the BsAb component is secreted by the cell expressing the CAR. Polynucleotides encoding these constructs are further provided herein as well as the polypeptides encoded by them in vitro or in vivo.

[0009] In certain ~~embodiment~~examples, the antigen binding domain of the tumor targeting antibody comprises, or alternatively consists essentially of, or further consists of one or more of: a heavy chain variable region and a light chain variable region, an scFv fragment, and/or an Fc fragment that are optionally linked by a linker peptide. In some ~~embodiment~~examples, the heavy and/or light chain variable region comprises, or alternatively consists essentially of, or further consists of the relevant CDR regions of an antibody directed to any one of B-cell maturation antigen (BCMA) and/or SLAMF7 (also known as CS1 or CD319), and/or an equivalent of each thereof. In one ~~aspect~~example, the tumor targeting antibody targets BCMA and the BsAb comprises an antigen binding fragment of an anti-CS1 antibody. In some ~~embodiment~~examples, the heavy chain and/or light chain variable region comprises, or alternatively consists essentially of, or further consists of the amino acid sequence of an antibody any one of B-cell maturation antigen (BCMA) and/or SLAMF7 (also known as CS1 or CD319), and/or an equivalent of each thereof. In one ~~aspect~~example, this construct further comprises, or alternatively consists essentially of, or yet further consists of a signaling domain. Polynucleotides and vector encoding these constructs are further provided herein as well as the polypeptides encoded by them in vitro or in vivo.

[0010] In certain ~~embodiment~~examples, the CAR, further comprises, or alternatively further consists essentially of, or yet further consists of, a linker polypeptide located between the heavy chain variable region and the light chain variable region and/or the ScFv and Fc regions and/or the antigen binding domains. In one ~~aspect~~example, the linker polypeptide is located between the antibody fragments of anti-NKG2D and anti-CS1. In certain ~~embodiment~~examples, the linker is a glycine-serine linker. In further ~~embodiment~~examples, the linker polypeptide comprises, or alternatively consists essentially of, or further consists of the sequence (glycine-serine)n wherein n is an integer from 1 to 6 (SEQ ID NO: 110), e.g. wherein n is 4. In another

~~aspect~~example, the polynucleotide comprises a sequence encoding a self-cleaving peptide such as a T2A peptide located between the CAR and the bispecific antibody, e.g., between the anti-BCMA CAR and the anti-NKG2D antigen binding domain. In one ~~aspect~~example, the BsAb-CAR further comprises a self-cleaving peptide such as for example a T2A peptide located between the anti-NKG2D and the second antigen binding domain that binds the cancer or tumor antigen, e.g., CS1, both of which are linked to a Fc fragment. In this case, a "knobs-into-holes" system can be added so that homodimer of the NKG2D-Fc or CS1-Fc will not happen while the heterodimer of the two will occur using the method described in Protein Engineering, Vol. 9(6):617-621 (1996). In one ~~aspect~~example, this CAR further comprises, or alternatively consisting essentially of, or yet further consisting of a signaling domain. In one ~~aspect~~example, the signaling domain, e.g., an IgG1 signal peptide, is located at the beginning of the NKG2D-tumor antigen portion of the BsAb-CAR. Other signal peptides are known in the art. Polynucleotides and vectors encoding these constructs are further provided herein as well as the polypeptides encoded by them in vitro or in vivo.

[0011] In one ~~aspect~~example, the BsAb-CAR comprises the structure shown in part in **FIG. 1E**, i.e., a single BsAb-CAR comprising or consisting essentially of (a) a BCMA antigen binding polypeptide, a self-cleaving peptide such as T2A, anti-NKG2D scFv and Fc polypeptides, a second self-cleaving peptide such as T2A, and anti-CS1 scFv and Fc polypeptides. In this case, a "knobs-into-holes" system can be added so that homodimer of the NKG2D-Fc or CS1-Fc will not happen while the heterodimer of the two will occur using the method described in Protein Engineering, Vol. 9(6):617-621 (1996). The CAR, such as an anti-BCMA CAR can further comprise a hinge domain, a transmembrane domain, and an intracellular domain. In one ~~aspect~~example, this Bs-Ab CAR construct further comprises, or alternatively consists essentially of, or yet further consists of a signaling domain. In one ~~aspect~~example, this Bs-Ab CAR construct further comprises, or alternatively consists essentially of, or yet further consists of signal peptide, e.g., an IgG1 signal peptide, optionally located at the beginning of the anti-NKG2D-anti-tumor-antigen portion of the BsAb-CAR construct. Other signal peptides are known in the art. Further provided are polynucleotides and vectors encoding these BsAb-CAR constructs as well as the polypeptides encoded by them in vitro or in vivo.

[0012] In one ~~aspect~~example, the BsAb-CAR comprises the structure shown in part in **FIG. 1F**, i.e., a single CAR comprising or consisting essentially of (a) a BCMA antigen binding

polypeptide, a self-cleaving peptide such as T2A, anti-NKG2D scFv and Fc polypeptides, an HMA polypeptide, and anti-CS1 scFv and Fc polypeptides. The BCMA CAR can further comprise a hinge domain, a transmembrane domain, and an intracellular domain. In one ~~aspect~~example, this polypeptide further comprises, or alternatively consists essentially of, or yet further consists of a signaling domain. In one ~~aspect~~example, this construct further comprises, or alternatively consists essentially of, or yet further consists of a signal peptide, e.g., an IgG1 signal peptide, is located at the beginning of the NKG2D-tumor antigen portion of the BsAb-CAR. Other signal peptides are known in the art. Further provided are polynucleotides and vectors encoding these BsAb-CAR constructs as well as the polypeptides encoded by them in vitro or in vivo.

[0013] In one ~~aspect~~example, the BsAb-CAR comprises the structure shown in part in **FIG. 1G**, i.e., a single Bs-Ab CAR comprising or consisting essentially of (a) a BCMA antigen binding polypeptide, a self-cleaving peptide such as T2A, anti-NKG2D scFv and Fc polypeptides, a linker such as G4S polypeptide (SEQ ID NO: 134), and anti-CS1 scFv and Fc polypeptides. The BCMA CAR can further comprise a hinge domain, a transmembrane domain, and an intracellular domain. In one ~~aspect~~example, this polypeptide further comprises, or alternatively consists essentially of, or yet further consists of a signaling domain. In one ~~aspect~~example, this construct further comprises, or alternatively consists essentially of, or yet further consists of a signaling domain, e.g., an IgG1 signal peptide, is located at the beginning of the NKG2D-tumor antigen portion of the BsAb-CAR. Other signal peptides are known in the art. Further provided are polynucleotides and vectors encoding these BsAb-CAR constructs as well as the polypeptides encoded by them in vitro or in vivo.

[0014] In one ~~aspect~~example, provided herein is: (a) a CAR comprising, or alternatively consisting essentially of, or yet further consisting of: (i) an antigen binding domain of a cancer or tumor targeting antibody that binds a cancer or tumor cell with the optional proviso that the cancer or tumor targeting antibody does not target a B-cell maturation antigen (BCMA), (ii) a hinge domain, (iii) a transmembrane domain, and (iv) an intracellular domain; and (b) a bispecific antibody comprising, or alternatively consisting essentially of, or yet further consisting of an antigen binding domain that recognizes and binds a NKG2D and an antigen binding domain of an antibody that binds a different antigen expressed by the cancer or tumor cell of the CAR. The CAR combined with the secreted BsAb are designed to reduce the chance of clonal resistance to one modality (e.g., the CAR). In addition, by using

NKG2D, it brings to the tumor microenvironment a variety of cytolytic effects (in addition to the CAR), to the tumor bed (e.g., NK cells) and Applicant shows herein that this significantly adds to the tumor cell killing. This is unexpected from the knowledge of one of skill in the art. Tumor-specific combinations have been reported (Townsend et al. (2018), J. Exper. & Clin. Cancer Res. 37:163, and references cited therein) but heretofore, they have not been combined with an NKG2D element.

[0015] In one ~~aspect~~example, the hinge domain comprises, or alternatively consists essentially of, or yet further consists of, a CD8 α hinge domain. In one ~~aspect~~example, this polynucleotide further comprises, or alternatively consists essentially of, or yet further consists of a polynucleotide encoding a signaling domain. In one ~~aspect~~example, the signaling domain, e.g., an IgG1 signal peptide, is located at the beginning of the NKG2D-tumor antigen portion of the BsAb-CAR. Other signal peptides are known in the art.

[0016] In one ~~aspect~~example, the transmembrane domain of the CAR comprises, or consists essentially of, or yet further consists of, a CD8 α transmembrane domain. In another ~~aspect~~example, the intracellular domain comprises, or alternatively consists essentially of, or yet further consists of, one or more, or two or more costimulatory regions selected from a CD28 costimulatory signaling region, a 4-1BB costimulatory signaling region, an ICOS costimulatory signaling region, or an OX40 costimulatory region. In another ~~aspect~~example, the transmembrane domain comprises, or consists essentially of or yet further consists of a CD28 costimulatory signaling region and/or a 4-1BB costimulatory signaling region. In another ~~aspect~~example, the signaling domain comprises, or alternatively consists essentially of, or yet further consists of, a CD3 zeta signaling domain.

[0017] In some ~~aspect~~examples, the bispecific antibody comprises, or consists essentially of, or yet further consists of a ligand of NKG2D, oran anti-NKG2D scFv, and/or an equivalent each thereof. In some ~~aspect~~examples, the ligand of NKG2D, an anti-NKG2D scFv, CDR regions of an antibody that binds to NKG2D, and/or an equivalent of each thereof. In some ~~aspect~~examples, the bispecific antibody comprises, or consists essentially of, or yet further consists of the heavy chain and light chain variable region of an antibody to NKG2D, and/or an equivalent of each thereof. In some ~~aspect~~examples, the bispecific antibody comprises, or consists essentially of, or yet further consists of a single chain variable fragment (scFv) derived from an antibody to NKG2D, and/or an equivalent each thereof.

[0018] Non-limiting examples of antigens targeted by the CAR or cancer or tumor targeting antibody are selected from antibodies that bind to a target of the group: CD19, mesothelin, human epidermal growth factor receptor 2 (HER2), prostate stem cell antigen (PSCA), carcinoembryonic antigen (CEA), CD33, GTPase-activating protein (GAP), ganglioside G2 (GD2), CD5, prostate specific membrane antigen (PSMA), receptor tyrosine kinase-like orphan receptor 1 (ROR1), CD123, CD70, CD38, mucin 1, (Muc1), ephrin type-A receptor 2 precursor (EphA2), epidermal growth factor receptor variant III (EGFRVIII), interleukin 13 receptor alpha 2 (IL13Ra2), CD133, glypican 3 (GPC3), epithelial cell adhesion molecule precursor (EpCam), fibroblast activation protein alpha (FAP), vascular endothelial growth factor receptor 2 (VEGFR2), cancer/testis (CT), guanylyl cyclase C (GUCY2C), tumor-associated glycoprotein-72 (TAG-72), thymidine kinase 1 (TK1), and hypoxanthine guanine phosphoribosyltransferase (HPRT1). Additional tumor targeting antibodies are known in the art.

[0019] In one ~~aspect~~example, the CAR recognizes and binds FLT3 and the bispecific antibody binds CD123, and is useful to treat AML. In another ~~aspect~~example, the CAR recognizes and binds EGFR and the bispecific antibody binds IL13Ra2 and is used to treat glioblastoma (GBM).

[0020] Further provided are polynucleotides encoding the above noted CAR constructs as well as the polypeptides encoded by them in vitro or in vivo. In one ~~aspect~~example, the polynucleotide encodes: (a) a CAR comprising, or alternatively consisting essentially of, or yet further consisting of: (i) an antigen binding domain of a cancer or tumor targeting antibody with the proviso that the cancer or tumor targeting antibody does not target a B-cell maturation antigen (BCMA); (ii) a hinge domain; (iii) a transmembrane domain; (iv) and an intracellular domain; and (b) a polynucleotide encoding a bispecific antibody comprising, or alternatively consisting essentially of, or yet further consisting of an antigen binding domain that recognizes and binds a NKG2D and polynucleotide that recognizes and binds an antigen on the tumor or cancer cell that is a different target than the CAR. In one ~~aspect~~example, the polynucleotide encodes a CD8 α hinge domain. In one ~~aspect~~example, this polynucleotide further comprises, or alternatively consisting essentially of, or yet further consisting of a polynucleotide encoding a signaling domain.

[0021] In one ~~aspect~~example, the polynucleotide further encodes a transmembrane domain that comprises, or consists essentially of, or yet further consists of, a CD8 α transmembrane domain. In another ~~aspect~~example, the polynucleotide further encodes an intracellular domain that

comprises, or alternatively consists essentially of, or yet further consists of, a CD28 costimulatory signaling region and/or a 4-1BB costimulatory signaling region. In a further ~~aspect~~example, the polynucleotide further comprises a polynucleotide that encodes a CD3 zeta signaling domain.

[0022] In some ~~aspect~~examples, the polynucleotide encodes a bispecific antibody that comprises, or consists essentially of, or yet further consists of a ligand of NKG2D, or an anti-NKG2D scFv, and/or an equivalent each thereof. In some ~~aspect~~examples, the ligand of NKG2D or an anti-NKG2D scFv that comprises, or consists essentially of, or yet further consists of, CDR regions of an antibody that binds to NKG2D, and/or an equivalent of each thereof. In some ~~aspect~~examples, the polynucleotide encodes a bispecific antibody that comprises, or alternatively consists essentially of, or yet further consists of, a heavy chain variable region and a light chain variable region of an antibody directed to (such as recognizing and binding) NKG2D, and/or an equivalent of each thereof. In some ~~aspect~~examples, the polynucleotide encodes a bispecific antibody that comprises, or consists essentially of, or yet further consists of, a single chain variable fragment (scFv) derived from an antibody directed to (such as recognizing and binding) NKG2D, and/or an equivalent thereof.

[0023] Non-limiting examples of antibodies or antigen binding domains encoded by the polynucleotides are selected from those that bind an antigen selected from the group: FLT3, EGFR, CD123, IL13Ra2, CD19, mesothelin, human epidermal growth factor receptor 2 (HER2), prostate stem cell antigen (PSCA), carcinoembryonic antigen (CEA), CD33, GTPase-activating protein (GAP), ganglioside G2 (GD2), CD5, prostate specific membrane antigen (PSMA), receptor tyrosine kinase-like orphan receptor 1 (ROR1), CD123, CD70, CD38, mucin 1, (Muc1), ephrin type-A receptor 2 precursor (EphA2), epidermal growth factor receptor variant III (EGFRVIII), interleukin 13 receptor alpha 2 (IL13Ra2), CD133, glypican 3 (GPC3), epithelial cell adhesion molecule precursor (EpCam), fibroblast activation protein alpha (FAP), vascular endothelial growth factor receptor 2 (VEGFR2), cancer/testis (CT), guanylyl cyclase C (GUCY2C), tumor-associated glycoprotein-72 (TAG-72), thymidine kinase 1 (TK1), and hypoxanthine guanine phosphoribosyltransferase (HPRT1). Additional tumor targeting antibodies are known in the art.

[0024] In some ~~aspect~~examples, the polynucleotide of (a) and (b) are contiguous. Non-limiting examples of such are shown in **FIGS. 1E-1G** and **FIG. 3A.**

[0025] This disclosure also provides a vector that comprises, or alternatively consists essentially of, or yet further consists of any one of the preceding polynucleotides. In some ~~aspect~~examples, the polynucleotide or vector further comprises, or consists essentially of, or yet further consists of, regulatory elements to drive expression of the polynucleotide and/or the CAR and/or bispecific antibodies, such as a promoter and/or an enhancer element. In some ~~aspect~~examples, the vector is a plasmid or a viral vector, non-limiting examples of such are selected from the group of a retroviral vector, a lentiviral vector, an adenoviral vector, and an adeno-associated viral vector.

[0026] Also provided herein is an isolated cell comprising, or alternatively consisting essentially of, or yet further consisting of, any one of the preceding vectors, CARs, and/or polynucleotides as described herein. The cell can be a prokaryotic cell (e.g., a bacterial cell) or a eukaryotic cell. Non-limiting examples of eukaryotic cells include, but are not limited to a yeast cell, an animal cell, a mammalian cell, a bovine cell, a feline cell, a canine cell, a murine cell, an equine cell, or a human cell. In some ~~aspect~~examples, the eukaryotic cell, mammalian or human cell is an immune cell, optionally a T-cell, a B cell, a NK cell, a dendritic cell, a myeloid cell, a monocyte, or a macrophage. In some ~~aspect~~examples, the isolated cell expresses the CAR and secretes the bispecific antibody.

[0027] Further provided herein are compositions comprising a carrier and any one of the preceding polynucleotides and/or any one of the preceding vectors and/or any one of the preceding isolated cells. In one ~~aspect~~example, the carrier is a pharmaceutically acceptable carrier.

[0028] In some ~~aspect~~examples, the disclosure is drawn to an isolated complex comprising any one of the preceding isolated cells bound to a cancer or tumor cell, wherein the cancer or tumor cell is bound to the isolated cell by the antigen binding domain of the antigen or tumor targeting antibody expressed by the CAR- or BsAb-encoding polynucleotide.

[0029] In some ~~aspect~~examples, the disclosure is drawn to a method of producing a CAR-expressing cell comprising transducing an isolated cell with any one of the preceding polynucleotides. In some ~~aspect~~examples, the CAR expressing cell is selected from a group consisting of T-cells, B cells, NK cells, dendritic cells, myeloid cells, monocytes, or macrophages.

[0030] In some ~~aspect~~examples, the disclosure is drawn to a method of inhibiting the growth of a cancer cell or tumor expressing a cancer or tumor antigen or tissue comprising the cancer or

tumor cell, comprising, or alternatively consisting essentially of, or yet further consisting of, contacting the cancer cell, tumor or tissue with any one of the preceding CARs and bispecific antibodies and/or isolated cells expressing the CARs and/or bispecific antibodies. In some ~~aspect~~examples, the contacting is in vitro or in vivo. In some ~~aspect~~examples, the contacting is in vivo and the isolated cells are autologous or allogeneic to a subject being treated. In some ~~aspect~~examples, the contacting is in vivo and the isolated cells are allogenic to a subject being treated. The contacting in vivo can be by administration of the cells to the subject in need of such treatment. As is apparent to the skilled artisan, the antigen binding domain of the tumor or cancer antigen is selected to bind to and treat or inhibit the growth of the cancer or tumor cell.

[0031] In some ~~aspect~~examples, this disclosure provides a method of inhibiting the growth of a cancer cell or tumor expressing a cancer or tumor antigen or tissue comprising the cancer or tumor cell by administering to a subject an effective amount of the CAR and bispecific antibody and/or host cell expressing the BsAb-CAR as described herein and a cytoreductive therapy or chemotherapy or therapy that upregulates the expression of a target antigen of the antigen binding domain of the CAR. In some ~~aspect~~examples, the cytoreductive therapy comprises, or alternatively consists essentially of, or yet further consists of one or more of a chemotherapy, cryotherapy, hyperthermia, targeted therapy, and/or radiation therapy.

[0032] In some ~~aspect~~examples, provided herein is a method for one or more of: inhibiting the growth of a cancer or tumor, inhibiting metastasis of a cancer or a tumor, or treating a cancer or a tumor, in a subject in need thereof, comprising, or consisting essentially of, or yet further consisting of administering any one of the preceding CARs and bispecific antibodies, or isolated cells expressing the CAR and bispecific antibodies to the subject. In some ~~aspect~~examples, the isolated cell is autologous or allogeneic to the subject in need. In some ~~aspect~~examples, the isolated cell is allogenic to the subject in need. As is apparent to the skilled artisan, the antigen binding domain of the tumor or cancer antigen of the CAR is selected to bind to and treat or inhibit the growth of the cancer or tumor cell.

[0033] In some ~~aspect~~examples, the above methods further comprise, or alternatively consist essentially of, or yet further consists of administering to the subject cytoreductive therapy or chemotherapy or therapy that upregulates the expression of a target antigen. In some ~~aspect~~examples, the cytoreductive therapy comprises, or consists essentially of, or consists of, one

or more of chemotherapy, cryotherapy, hyperthermia, targeted therapy, and/or radiation therapy.

[0034] Also provided herein is a kit comprises, or alternatively consists essentially of, or yet further consists of, one or more of a CAR, a BsAb-CAR, a polynucleotide, a cell, or a composition as disclosed herein and optionally, instructions for making or using the same. The kit optionally further comprises the compositions to assay a patient sample for the phenotype of the cancer or tumor in a patient sample such that the appropriate CAR or BsAb-CAR can be selected to treat the cancer or tumor.

[0035] In further ~~aspect~~examples, provided herein are isolated nucleic acids that encode, in one construct, the CAR and bispecific antibody as disclosed above ("BsAb-CAR construct"). In one ~~aspect~~example, the isolated nucleic acid encodes an antigen binding fragment that targets a cancer or tumor associated antigen other than BCMA and a bispecific antibody, e.g., one scFv targeting an antigen on an AML or GBM, (e.g., FLT-3, EGFR, CD123 or IL13Ra2) and one scFv from an anti-NKG2D antibody, joined together by a nucleic acid encoding a non-immunogenic protein linker such as from human muscle aldolase (HMA). An exemplary BsAb-CAR vector is shown in **FIG. 3**. The vectors optionally comprise regulatory sequences such as promoters, enhancers, and viral long terminal repeats (LTRs).

[0036] Some ~~aspect~~examples of the disclosure relate to a method of producing a CAR expressing cell or a CAR expressing cell that secretes BsAb, the method comprising, or alternatively consisting essentially of, or yet further consisting of transducing an isolated cell with the nucleic acid sequence encoding a CAR and BsAb or the isolated nucleic acid encoding the BsAb-CAR, as described herein.

[0037] In a further ~~aspect~~example, the method further comprises selecting and isolating the cell expressing the CAR or BsAb-CAR. In a further ~~aspect~~example, the cell is a eukaryotic cell such as a mammalian cell, e.g., a human cell such as a T-cell, a B cell, a NK cell, a dendritic cell, a myeloid cell, a monocyte, a macrophage, any subsets thereof, or any other immune cell. The cells can be transduced using the viral vectors as described herein or alternatively using technology described in Riet et al. (2013) Meth. Mol. Biol. 969:187-201 entitled "Nonviral RNA transfection to transiently modify T cell with chimeric antigen receptors for adoptive therapy."

[0038] In certain ~~embodiment~~examples, the method further comprises, or alternatively consists essentially of, or yet further consists of transducing the cell with an isolated polynucleotide comprising, or alternatively consisting essentially of, or yet further consisting of a polynucleotide encoding a bispecific antibody, which optionally recognizes and binds NKG2D. In some ~~embodiment~~examples, the bispecific antibody comprises, or alternatively consists essentially of, or further consists of an NKG2D ligand optionally codon optimized ligand. In certain ~~embodiment~~examples, the bispecific antibody comprises, or alternatively consists essentially of, or further consists of the relevant CDR regions of an antibody directed to NKG2D, optionally codon optimized, or an equivalent of each thereof. In some ~~embodiment~~examples, the bispecific antibody comprises, or alternatively consists essentially of, or further consists of the heavy chain and/or light chain variable region of an antibody directed to NKG2D, that are optionally codon optimized and/or an equivalent of each thereof. In some ~~embodiment~~examples, the bispecific antibody comprises a single chain variable fragment (scFv) derived from an antibody directed to NKG2D, that is optionally codon optimized, and/or an equivalent each thereof. The cells can be transduced using the viral vectors, e.g., lentiviral vectors, as described herein or alternatively using technology described in Riet et al. (2013) Meth. Mol. Biol. 969:187-201 entitled "Nonviral RNA transfection to transiently modify T cell with chimeric antigen receptors for adoptive therapy."

[0039] In certain ~~embodiment~~examples, the method of producing a CAR or BsAb-CAR expressing cell further comprises, or alternatively consists essentially of, or yet further consists of activating and expanding the population of CAR expressing cells. Certain ~~aspect~~examples of the present disclosure relate to an isolated, activated population of cells comprising, or alternatively consisting essentially of, or yet further consisting of a CAR or BsAb-CAR. In certain ~~embodiment~~examples, the cells are one or more of T-cells, B cells, NK cells, dendritic cells, myeloid cells, monocytes, macrophages, any subsets thereof, or any other immune cells.

[0040] ~~Aspect~~Examples of the disclosure relate to a method of inhibiting the growth of a tumor expressing a cancer or tumor antigen, by contacting the tumor with an effective amount of the isolated cells or compositions disclosed above. The contacting can be in vitro or in vivo. When the contacting is in vitro, the method can be used to test personalized therapy against a patient's tumor or to assay for combination therapies. When the contacting is in vivo, the method is useful to inhibit the growth of the tumor or cancer cell in a subject in need thereof, such as a human patient suffering from cancer and the patient receives an

effective amount of the cells. In certain ~~embodiment~~examples, the tumor is a solid tumor. An effective amount is administered alone or in combination with other therapies as described herein. In certain ~~embodiment~~examples, the cancer/tumor targeted is a solid tumor or a cancer affecting the blood and/or bone marrow, e.g., multiple myeloma (MM), acute myeloid leukemia (AML), or glioblastoma (GBM). In certain ~~embodiment~~examples, the isolated cells are autologous to the subject being treated. In another ~~aspect~~example, the cells are allogeneic to the subject being treated. In another ~~aspect~~example, the method further comprises, or consists essentially of, or yet further consists of, administering to the subject an effective amount of a cytoreductive therapy. In a further ~~aspect~~example, the method further comprises the steps of isolating the cells to be administered to the subject, transducing the cells with an effective amount of an isolated nucleic acid encoding a CAR or BsAb-CAR as described herein, culturing the cells to obtain a population of CAR or BsAb-CAR encoding cells, that are optionally expanded and activated and then administering the cells to the patient.

[0041] The above compositions and methods are unique and overcome the limitation of the state of the art in that they provide a CAR cell that simultaneously secretes a NKG2D-based BsAb targeting a second tumor-associated antigen, wherein the cancer or tumor targeting antibody of the CAR does not target a B-cell maturation antigen (BCMA). The disclosed CAR NKGD2D-based BsAb is exemplary only. This approach can be modified for any number of tumor antigens, as known in the art, e.g., EGFR, FLT-3, IL13Ra2, EGFRVIII; CD70, mesothelin, CD123, CD19, CEA, CD133, Her2, see Townsend et al. (2018) J. Exp. & Clinical Cancer Res. 37:163. In a further ~~aspect~~example, the cancer or tumor targeting antibody of the CAR does not target one or more of a B-cell maturation antigen (BCMA), EGFRVIII; CD70, mesothelin, CD123, CD19, CEA, CD133, Her2.

[0042] An exemplary construct was tested in a multiple myeloma model (MM). MM is a malignancy characterized by an accumulation of clonal plasma cells[13]. As noted above, current treatment regimens including chemotherapies, immunomodulatory drugs[14], monoclonal antibodies[15], and autologous or allogeneic transplantation often lead to remission, but nearly all patients eventually relapse and succumb to death due to return of the disease. Thus, there is an unmet need for new therapies, including new combination immunotherapies for relapsed and/or refractory MM, solid tumors and other cancers.

[0043] As a component of the innate immune system, natural killer (NK) cells play an important role in preventing tumor growth[16] , but NK cell anti-tumor activity has been

found to be dampened in many MM patients[17]. Adoptive transfer of activated or allogeneic NK cells produce effective anti-tumor responses in the treatment of a number of hematological malignancies, including MM[18,19], and solid tumors. However, in many cases, NK cell–mediated antitumor responses are weak, which may result from NK cell expression of inhibitory receptors, poor capacity for survival, or limited migration of effector cells into tumor sites [20-22]. Meanwhile, as a part of adaptive immunity, T cells can migrate efficiently into various tissues, and tend to proliferate well in response to antigen stimulation. However, T cells have strict specificities dictated by antigen-specific T-cell receptors (TCR). Thus, a method to engage both T cells and NK cells, and thus overcome their own limitations would be of great benefit for cancer immunotherapy. This disclosure provides this benefit.

BRIEF DESCRIPTION OF THE DRAWINGS

[0044] **FIGS. 1A-1G** show the results of engineering T cells to express BCMA CAR and anti-NKG2D-anti-CS1 bispecific fusion protein individually or in combination that is presented as an example of the disclosed technology. (**FIG. 1A**) Schematic representation of the BCMA CAR lentiviral constructs containing a scFv against BCMA linked to CD28 and CD3zeta(ζ) endodomains. The expression of the transgene was traced by GFP expression driven by an EF1alpha(α) promoter. LTR, long terminal repeats; SP, signal peptide; VH, variable H chain; L, linker; VL, variable L chain. MyC, MyC tag; Hinge, Hinge Chain; CD28, a T cell co-stimulatory molecule; CD3ζ, CD3 zeta chain. (**FIG. 1B**) Schematic diagram of lentiviral construct for mammalian expression of anti-NKG2D-anti-CS1 bispecific antibody (BsAb). The anti-NKG2D-anti-CS1 BsAb consisted of an anti-NKG2D scFv, which was composed of VH and VL linked together by a linker (L), and an anti-CS1 scFv. Expression of the BsAb is driven by a CMV promoter flanked by lentiviral LTR. (**FIG. 1C**) PBMC (peripheral blood mononuclear cells) from healthy donors were activated with CD3 and CD28 beads and transduced with the pCDH empty vector (EV), BCMA CAR, anti-NKG2D-anti-CS1 BsAb. The activated T cells were also sequentially transduced with BsAb and BCMA-CAR and these transduced cells were named “BsAb-BCMA seq. trans. T”. GFP-positive cells were sorted, and cells were stained with biotin labeled goat anti-mouse Fab specific or isotype-matched control antibody, followed by streptavidin and CD3 antibody staining. (**FIG. 1D**) Supernatant of unmodified T cells, BsAb T cells or BsAb-BCMA seq. trans. T cells were collected, and individual cell lysates

WHAT IS CLAIMED IS:

1. A polypeptide comprising:

(a) (i) an amino acid sequence of a chimeric antigen receptor (CAR) comprising:

(1) an antigen binding domain that recognizes and binds a first tumor associated antigen (TAA) on a cancer cell (first anti-TAA antigen binding domain) with the proviso that the first TAA is not a B-cell maturation antigen (BCMA);

(2) a hinge domain;

(3) a transmembrane domain; and

(4) an intracellular domain; and

(ii) a bispecific antibody comprising

(1) an antigen binding domain that recognizes and binds a second TAA on the cancer cell (second anti-TAA antigen binding domain); and

(2) an antigen binding domain that recognizes and binds NKG2D (anti-NKG2D antigen binding domain);

or

(b) (i) an amino acid sequence of a CAR comprising:

(1) an antigen binding domain that recognizes and binds BCMA (anti-BCMA antigen binding domain);

(2) a hinge domain;

(3) a transmembrane domain; and

(4) an intracellular domain; and

(ii) a bispecific antibody comprising

(1) an antigen binding domain that recognizes and binds NKG2D (anti-NKG2D antigen binding domain) and

(2) an antigen binding domain that recognizes and binds CS1 (anti-CS1 antigen binding domain).

2. The polypeptide of claim 1, wherein the hinge domain comprises a CD8 α hinge domain or an IgG1 hinge domain, optionally wherein the IgG1 hinge domain comprises LEPKSCDKTHTCPPCPDPKGT (SEQ ID NO: 1) or an equivalent thereof; and

optionally wherein the transmembrane domain comprises a CD8 α transmembrane domain or a CD28 transmembrane domain; and

optionally wherein the intracellular domain comprises one or more or two or more costimulatory regions selected from a CD28 costimulatory signaling region, a 4-1BB costimulatory signaling region, an ICOS costimulatory signaling region, or an OX40 costimulatory region.

~~3. The polypeptide of claim 2, wherein the IgG1 hinge domain comprises LEPKSCDKTHTCPPCPDPKGT (SEQ ID NO: 1) or an equivalent thereof.~~

~~4. The polypeptide of any one of claims 1 to 3, wherein the transmembrane domain comprises a CD8 α transmembrane domain or a CD28 transmembrane domain.~~

~~5. The polypeptide of any one of claims 1 to 4, wherein the intracellular domain comprises one or more or two or more costimulatory regions selected from a CD28 costimulatory signaling region, a 4-1BB costimulatory signaling region, an ICOS costimulatory signaling region, or an OX40 costimulatory region.~~

~~6~~3. The polypeptide of claim ~~4 or 5~~2, wherein the CAR comprises a CD28 transmembrane and cytoplasmic domain comprising FWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYA PPRDFAAYRS (SEQ ID NO: 2) or an equivalent thereof; and

optionally wherein the intracellular domain further comprises a CD3 zeta signaling domain, and

optionally wherein the CD3 zeta signaling domain comprises RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEG LYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 3) or an equivalent thereof; and

optionally wherein the intracellular domain further comprises an IL2Rβ or a fragment thereof comprising an JAK-STAT activation domain.

~~7. The polypeptide of any one of claims 1-6, wherein the intracellular domain further comprises a CD3 zeta signaling domain.~~

~~8. The polypeptide of claim 7, wherein the CD3 zeta signaling domain comprises RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEG LYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 3) or an equivalent thereof.~~

~~9. The polypeptide of any one of claims 1 to 8, wherein the intracellular domain further comprises an IL2Rβ or a fragment thereof comprising an JAK-STAT activation domain.~~

~~10~~4. The polypeptide of any one of claims 1 to ~~9~~3, further comprising a suicide gene product, optionally wherein the suicide gene product is selected from one or more of: HSV-TK (Herpes simplex virus thymidine kinase), cytosine deaminase, nitroreductase, carboxylesterase, cytochrome P450 or PNP (Purine nucleoside phosphorylase), truncated EGFR, or inducible caspase ("iCasp").

~~11. The polypeptide of claim 10, wherein the suicide gene product is selected from one or more of: HSV-TK (Herpes simplex virus thymidine kinase), cytosine deaminase, nitroreductase, carboxylesterase, cytochrome P450 or PNP (Purine nucleoside phosphorylase), truncated EGFR, or inducible caspase ("iCasp").~~

~~12~~5. The polypeptide of any one of claims 1 to ~~11~~4, wherein the CAR further comprises a signal peptide at its N terminus, optionally wherein the signal peptide comprises MGWSSIILFLVATATGVH (SEQ ID NO: 5), or an equivalent thereof.

~~13. The polypeptide of claim 12, wherein the signal peptide comprises MGWSSIILFLVATATGVH (SEQ ID NO: 5), or an equivalent thereof.~~

~~14. The polypeptide of any one of claims 1 to 13, wherein the CAR further comprises a detectable or purification marker.~~

~~15~~6. The polypeptide of any one of claims 1 to ~~14~~5, wherein the anti-NKG2D antigen binding domain comprises one or two or three or four or five or all six of the following complementarity-determining regions (CDRs):

a light chain complementarity-determining region 1 (CDRL1) comprising SGSSSNIGNNAVN (SEQ ID NO: 6) or an equivalent thereof;

a light chain complementarity-determining region 2 (CDRL2) comprising YDDLLPS (SEQ ID NO: 7) or an equivalent thereof;

a light chain complementarity-determining region 3 (CDRL3) comprising AAWDDSLNGPV (SEQ ID NO: 8) or an equivalent thereof;

a heavy chain complementarity-determining region 1 (CDRH1) comprising GFTFSSY (SEQ ID NO: 9) or an equivalent thereof;

a heavy chain complementarity-determining region 2 (CDRH2) comprising RYDGSN (SEQ ID NO: 10) or an equivalent thereof; and

a heavy chain complementarity-determining region 3 (CDRH3) comprising DRGLGDGTYFDY (SEQ ID NO: 11) or an equivalent thereof,

wherein the equivalents thereof recognize and bind NKG2D.

~~16~~7. The polypeptide of any one of claims 1 to ~~15~~6, wherein the anti-NKG2D antigen binding domain comprises:

a light chain variable region comprising QSALTQPASVSGSPGQSITISCSGSSSNIGNNAVNWYQQLPGKAPKLLIYYDDLLPSGVSD RFSGSKSGTSAFLAISGLQSEDEADYYCAAWDDSLNGPVFGGGTKLTVL (SEQ ID NO: 12), or an equivalent thereof; and/or

a heavy chain variable region comprising QVQLVESGGGLVKPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAFIRYDGSN KYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRGLGDGTYFDYWGQG TTVTVSS (SEQ ID NO: 13), or an equivalent thereof,

wherein the equivalent thereof recognizes and binds NKG2D; and

optionally wherein the equivalent of SEQ ID NO: 12 or 13 is at least 80%, or at least 85%, or at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99% identical to SEQ ID NO: 12 or 13, respectively; and

optionally wherein the equivalent of SEQ ID NOs: 6-13 comprises the amino acid domain of C terminus to N terminus of SEQ ID NO: 6-13, respectively.

~~17. The polypeptide of claim 16, wherein the equivalent of SEQ ID NO: 12 or 13 is at least 80%, or at least 85%, or at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99% identical to SEQ ID NO: 12 or 13, respectively.~~

~~18. The polypeptide of claim 16 or 17, wherein the equivalent of SEQ ID NOs: 6-13 comprises the amino acid domain of C terminus to N terminus of SEQ ID NO: 6-13, respectively.~~

~~19. The polypeptide of any one of claims 16 to 18, wherein the anti-NKG2D antigen binding domain further comprises a peptide linker between the light chain variable region or the equivalent thereof and the heavy chain variable region or the equivalent thereof.~~

~~20. The polypeptide of any one of claims 16 to 19, wherein the anti-NKG2D antigen binding domain further comprises a peptide linker comprising GGGGSGGGGSGGGGS (SEQ ID NO: 14) or an equivalent thereof between the light chain variable region or the equivalent thereof and the heavy chain variable region or the equivalent thereof.~~

~~21. The polypeptide of any one of claims 1 to 20, the first TAA is fms-like tyrosine kinase 3 (FLT3).~~

~~22. The polypeptide of claim 21, wherein the first anti-TAA antigen binding domain is an anti-FLT3 antigen binding domain comprising one or two or three or four or five or all six of the following CDRs:~~

~~a CDRL1 comprising RASQSISNNLH (SEQ ID NO: 15), KSSQSLLNSGNQKNYM (SEQ ID NO: 16), or an equivalent of each thereof;~~

~~a CDRL2 comprising YASQSIS (SEQ ID NO: 17), GASTRES (SEQ ID NO: 18), or an equivalent of each thereof;~~

~~a CDRL3 comprising QQSNTWPYT (SEQ ID NO: 19), QNDHSYPLT (SEQ ID NO: 20), or an equivalent of each thereof;~~

~~a CDRH1 comprising SYWMH (SEQ ID NO: 21), NYGLH (SEQ ID NO: 22), or an equivalent of each thereof;~~

a CDRH2 comprising EIDPSDSYKDYNQKFKD (SEQ ID NO: 23), VIWSGGSTDYNAAFIS (SEQ ID NO: 24), or an equivalent of each thereof; and

a CDRH3 comprising AITTTPFDF (SEQ ID NO: 25), GGIYYANHYYAMDY (SEQ ID NO: 26), or an equivalent of each thereof,

wherein the equivalents thereof recognize and bind FLT3.

23. The polypeptide of claim 21 or 22, wherein the anti-FLT3 antigen binding domain comprises

a light chain variable region comprising a sequence selected from DIVLTQSPATLSVTPGDSVSLSCRASQSISNNLHWYQQKSHESPRLLIKYASQSISGIPSRFSGSGSGTDFTLSINSVETEDFGVYFCQQSNTWPYTFGGGTKLEIKR (SEQ ID NO: 27), DIVMTQSPSSLSVSAGEKVTMSCKSSQSLLNSGNQKNYMAWYQQKPGQPPKLLIYGASTRESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCQNDHSYPLTFGAGTKLELKR (SEQ ID NO: 28), or an equivalent of each thereof; and/or

a heavy chain variable region comprising a sequence selected from QVQLQQPGAELVKPGASLKLSCKSSGYTFTSYWMHWVRQRPGHGLEWIGEIDPSDSYKDYNQKFKDKATLTVDRSSNTAYMHLSSLTSDDSAVYYCARAITTTPFDFWGQGTTLTVSS (SEQ ID NO: 29), QVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGLHWVRQSPGKGLEWLGVIWSGGSTDYNAAFISRLSISKDNSKSQVFFKMNSLQADDTAIYYCARKGGIYYANHYYAMDYWGQGTSVTVSS (SEQ ID NO: 30) or an equivalent of each thereof,

wherein the equivalent thereof recognizes and binds FLT3.

24. The polypeptide of claim 23, wherein the equivalent of SEQ ID NOs: 27-30 is at least 80%, or at least 85%, or at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99% identical to SEQ ID NOs: 27-30, respectively.

25. The polypeptide of any one of claims 22 to 24, wherein the equivalent of SEQ ID NOs: 15-30 comprises the amino acid sequence of C terminus to N terminus of SEQ ID NOs: 15-30, respectively.

26. The polypeptide of any one of claims 23 to 25, wherein the anti-FLT3 antigen binding domain further comprises a peptide linker between the light chain variable region or the equivalent thereof and the heavy chain variable region or the equivalent thereof.

27. The polypeptide of any one of claims 23 to 26, wherein the anti-FLT3 antigen binding domain further comprises a peptide linker comprising GGGGSGGGGSGGGGS (SEQ ID NO: 14) or an equivalent thereof between the light chain variable region or the equivalent thereof and the heavy chain variable region or the equivalent thereof.

28. The polypeptide of any one of claims 1 to 27, wherein the second TAA is CD123.

29. The polypeptide of any one of claims 1 to 20, wherein the first TAA is epidermal growth factor receptor (EGFR).

30. The polypeptide of claim 29, wherein the first anti-TAA antigen binding domain is an anti-EGFR antigen binding domain comprising one or two or three or four or five or six of the following CDRs:

a CDRL1 comprising RSSQNIVHNNGITYLE (SEQ ID NO: 31), RASQGIRNNLA (SEQ ID NO: 32), or an equivalent of each thereof;

a CDRL2 comprising KVSDRFS (SEQ ID NO: 33), AASNLQS (SEQ ID NO: 34), or an equivalent of each thereof;

a CDRL3 comprising FQGSHIPPT (SEQ ID NO: 35), LQHHSYPLT (SEQ ID NO: 36), or an equivalent of each thereof;

a CDRH1 comprising GDTFTSY (SEQ ID NO: 37), GFTFSSY (SEQ ID NO: 38), or an equivalent of each thereof;

a CDRH2 comprising YPGSGG (SEQ ID NO: 39), SGSGGS (SEQ ID NO: 40), or an equivalent of each thereof; and

a CDRH3 comprising SGGPYFFDY (SEQ ID NO: 41), SSGWSEY (SEQ ID NO: 42), or an equivalent of each thereof,

wherein the equivalents thereof recognize and bind EGFR.

31. The polynucleotide of claim 29 or 30, wherein the anti-EGFR antigen binding domain comprises

a light chain variable region comprising a sequence selected from DILMTQSPLSLPVSLGDQASISCRSSQNIVHNNGITYLEWYLQRPGQSPKLLIYKVSDRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGIYYCFQGSHIPPTFGGGTKLEIKRAA (SEQ ID NO: 43), DIQMTQSPSSLSASVGDRVTITCRASQGIRNNLAWYQQKPGKAPKRLIYAASNLQSGVPSRFTGSGSGTEFTLIVSSLQPEDFATYYCLQHHSYPLTSGGGTKVEIKYAHNS (SEQ ID NO: 44), or an equivalent of each thereof and/or

a heavy chain variable region comprising a sequence selected from QVQLQQSGSEMARPGASVKLPCKASGDTFTSYWMHWVKQRHGHGPEWIGNIYPGSGGTNYAEKFKNKVTLTVDRSSRTVYMHLSRLTSEDSAVYYCTRSGGPYFFDYWGQGTTLTVSS (SEQ ID NO: 45), EVQVLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTNYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAGSSGWSEYWGQGTLVTVSS (SEQ ID NO: 46), or an equivalent of each thereof,

wherein the equivalent thereof recognizes and binds EGFR.

32. The polypeptide of claim 31, wherein the equivalent of SEQ ID NOs: 43-46 is at least 80%, or at least 85%, or at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99% identical to SEQ ID NOs: 43-46, respectively.

33. The polypeptide of any one of claims 30 to 32, wherein the equivalent of SEQ ID NOs: 31-46 comprises the amino acid sequence of C terminus to N terminus of SEQ ID NOs: 31-46, respectively.

34. The polypeptide of any one of claims 31 to 33, wherein the anti-EGFR antigen binding domain further comprises a peptide linker between the light chain variable region or the equivalent thereof and the heavy chain variable region or the equivalent thereof.

35. The polypeptide of any one of claims 31 to 34, wherein the anti-EGFR antigen binding domain further comprises a peptide linker comprising GGGGSGGGGSGGGGS (SEQ ID NO: 14) or an equivalent thereof between the light chain variable region or the equivalent thereof and the heavy chain variable region or the equivalent thereof.

~~36. The polypeptide of any one of claims 1 to 27 and 29 to 35, wherein the second TAA is IL13Ra2.~~

~~37~~8. The ~~polynucleotide~~ polypeptide of any one of claims 1 to7~~20~~, wherein the anti-BCMA antigen binding domain comprises one or two or three or four or five or six of the following CDRs:

a CDRL1 comprising RASESVTILGSHLIH (SEQ ID NO: 47), SASQDISNYLN (SEQ ID NO: 48), RASESVTILGSHLIY (SEQ ID NO: 49), or an equivalent of each thereof;

a CDRL2 comprising LASNVQT (SEQ ID NO: 50), YTSNLHS (SEQ ID NO: 51), LASNVQT (SEQ ID NO: 52), or an equivalent of each thereof;

a CDRL3 comprising LQSRTIPRT (SEQ ID NO: 53), QQYRKLPWT (SEQ ID NO: 54), LQSRTIPRT (SEQ ID NO: 55), or an equivalent of each thereof;

a CDRH1 comprising GYTFTDY (SEQ ID NO: 56), GGTFSNY (SEQ ID NO: 57), GYTFRHY (SEQ ID NO: 58), or an equivalent of each thereof;

a CDRH2 comprising INTETRE (SEQ ID NO: 59), YRGHSD (SEQ ID NO: 60), NTESGV (SEQ ID NO: 61), or an equivalent of each thereof; and

a CDRH3 comprising DYSYAMDY (SEQ ID NO: 62), GAIYNGYDVLDN (SEQ ID NO: 63), DYLYSLDF (SEQ ID NO: 64), or an equivalent of each thereof,

wherein the equivalents thereof recognize and bind BCMA.

~~38~~9. The ~~polynucleotide~~polypeptide of claim ~~37~~1, wherein the anti-BCMA antigen binding domain comprises

a light chain variable region comprising a sequence selected from DIVLTQSPPSLAMSLGKRATISCRASESVTILGSHLIHWYQQKPGQPPTLLIQLASNVQTG VPARFSGSGSRTDFTLTIDPVEEDDVAVYYCLQSRTIPRTFGGGTKLEIK (SEQ ID NO: 65), DIQMTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQKPGKAPKLLIYYTSNLHSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQYRKLPWTFGQGTKLEIKR (SEQ ID NO: 66), DIVLTQSPPSLAMSLGKRATISCRASESVTILGSHLIYWYQQKPGQPPTLLIQLASNVQTG

VPARFSGSGSRTDFTLTIDPVEEDDVAVYYCLQSRTIPRTFGGGTKLEIK (SEQ ID NO: 67), or an equivalent of each thereof and/or

a heavy chain variable region comprising a sequence selected from QIQLVQSGPELKKPGETVKISCKASGYTFTDYSINWVKRAPGKGLKWMGWINTETREPA YAYDFRGRFAFSLETSASTAYLQINNLKYEDTATYFCALDYSYAMDYWGQGTSVTVSS (SEQ ID NO: 68),
QVQLVQSGAEVKKPGSSVKVSCKASGGTFSNYWMHWVRQAPGQGLEWMGATYRGHS DTYYNQKFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCARGAIYNGYDVLDNWGQ GTLVTVSS (SEQ ID NO: 69),

QIQLVQSGPELKKPGETVKISCKASGYTFRHYSMNWVKQAPGKGLKWMGRINTESGVP IYADDFKGRFAFSVETSASTAYLVINNLKDEDTASYFCSNDYLYSLDFWGQGTALTVSS (SEQ ID NO: 70), or an equivalent of each thereof,

wherein the equivalent thereof recognizes and bins BCMA; and

optionally wherein the equivalent of SEQ ID NOs: 65-70 is at least 80%, or at least 85%, or at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99% identical to SEQ ID NOs: 65-70, respectively; and

optionally wherein the equivalent of SEQ ID NOs: 47-70 comprises the amino acid sequence of C terminus to N terminus of SEQ ID NOs: 47-70, respectively.

~~39. The polypeptide of claim 38, wherein the equivalent of SEQ ID NOs: 65-70 is at least 80%, or at least 85%, or at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99% identical to SEQ ID NOs: 65-70, respectively.~~

~~40. The polypeptide of any one of claims 37 to 39, wherein the equivalent of SEQ ID NOs: 47-70 comprises the amino acid sequence of C terminus to N terminus of SEQ ID NOs: 47-70, respectively.~~

~~41. The polypeptide of any one of claims 38 to 40, wherein the anti-BCMA antigen binding domain further comprises a peptide linker between the light chain variable region or the equivalent thereof and the heavy chain variable region or the equivalent thereof.~~

~~42. The polypeptide of any one of claims 38 to 41, wherein the anti-BCMA antigen binding domain further comprises a peptide linker comprising GGGGSGGGGSGGGGS (SEQ ID NO:~~

~~14) or an equivalent thereof between the light chain variable region or the equivalent thereof and the heavy chain variable region or the equivalent thereof.~~

~~43. The polypeptide of any one of claims 1 to 27 and 29 to 35, wherein the second TAA is CS1 and the second anti-TAA antigen binding domain is an anti-CS1 antigen binding domain.~~

~~44~~10. The polypeptide of any one of claims 1 ~~and 37 to 43~~to 9, wherein the anti-CS1 antigen binding domain comprises one or two or three or four or five or six of the following CDRs:

a CDRL1 comprising KASQDVITGVA (SEQ ID NO: 71) or an equivalent thereof;

a CDRL2 comprising SASYRYT (SEQ ID NO: 72) or an equivalent thereof;

a CDRL3 comprising QQHYSTPLT (SEQ ID NO: 73) or an equivalent thereof;

a CDRH1 comprising GYSFTTY (SEQ ID NO: 74) or an equivalent thereof;

a CDRH2 comprising HPSDSE (SEQ ID NO: 75) or an equivalent thereof; and

a CDRH3 comprising STMIATRAMDY (SEQ ID NO: 76) or an equivalent thereof,

wherein the equivalents thereof recognizes and binds CS1.

~~45~~11. The polypeptide of claim ~~44~~1, wherein the anti-CS1 antigen binding domain comprises

a light chain variable region comprising a sequence selected from SDIVMTQSQKSMSTSVGDRVSITCKASQDVITGVAWYQQKPGQSPKLLIYSASYRYTGV PDRFTGSGSGTDFTFTISNVQAEDLAVYYCQQHYSTPLTFGAGTKLELK (SEQ ID NO: 77)

KLELKTGAGFTLPTSYHQQCYYVALDEAQVNSITFTFDTGSGSGTFRDPVGTYRY SASYILLKPSQGPKQQYWAVGTIVDQSAKCTISVRDGVSTSMSKQSQTMVIDS (SEQ ID NO: 154),
DIVMTQSQKSMSTSVGDRVSITCKASQDVITGVAWYQQKPGQSPKLLIYSASYRYTGVP DRFTGSGSGTDFTFTISNVQAEDLAVYYCQQHYSTPLTFGAGTKLELK (SEQ ID NO: 78), or an equivalent of each thereof and/or

a heavy chain variable region comprising a sequence selected from SVTVSTGQGWYDMARTAIMTSRACYYVASDESTPSSLQMYATSSSKDVTLTAKDKFKQ

NLRTESDSPHIMGIWELGQGPRQKVWNMWYTTFSYGSAKCSLKVSAGPRVLEAGPQQL QVQS (SEQ ID NO: 79),

SSVTVSTGQGWYDMARTAIMTSRACYYVASDESTPSSLQMYATSSSKDVTLTAKDKFK QNLRTESDSPHIMGIWELGQGPRQKVWNMWYTTFSYGSAKCSLKVSAGPRVLEAGPQQ LQVQ (SEQ ID NO: 149),

SQVQLQQPGAELVRPGASVKLSCKASGYSFTTYWMNWVKQRPGQGLEWIGMIHPSDSE TRLNQKFKDKATLTVDKSSSTAYMQLSSPTSEDSAVYYCARSTMIATRAMDYWGQGTS VTVS (SEQ ID NO: 80),

QVQLQQPGAELVRPGASVKLSCKASGYSFTTYWMNWVKQRPGQGLEWIGMIHPSDSE TRLNQKFKDKATLTVDKSSSTAYMQLSSPTSEDSAVYYCARSTMIATRAMDYWGQGTS VTVSS (SEQ ID NO: 150), or an equivalent of each thereof,

wherein the equivalent thereof recognizes and binds CS1; and

optionally wherein the equivalent of SEQ ID NOs: 77 to 80 is at least 80%, or at least 85%, or at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99% identical to SEQ ID NOs: 77 to 80, respectively; and

optionally wherein the equivalent of SEQ ID NOs: 71-80, 149-150 and 154 comprises the amino acid sequence of C terminus to N terminus of SEQ ID NOs: 71-80, 149-150 and 154, respectively.

~~46. The polypeptide of claim 45, wherein the equivalent of SEQ ID NOs: 77 to 80 is at least 80%, or at least 85%, or at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99% identical to SEQ ID NOs: 77 to 80, respectively.~~

~~47. The polypeptide of any one of claims 44 to 46, wherein the equivalent of SEQ ID NOs: 71-80, 149-150 and 154 comprises the amino acid sequence of C terminus to N terminus of SEQ ID NOs: 71-80, 149-150 and 154, respectively.~~

~~48. The polypeptide of any one of claims 45 to 47, wherein the anti-CS1 antigen binding domain further comprises a peptide linker between the light chain variable region or the equivalent thereof and the heavy chain variable region or the equivalent thereof.~~

~~49. The polypeptide of any one of claims 45 to 48, wherein the anti-CS1 antigen binding domain further comprises a peptide linker comprising GGGGSGGGGSGGGGS (SEQ ID NO: 14) or an equivalent thereof between the light chain variable region or the equivalent thereof and the heavy chain variable region or the equivalent thereof.~~

~~50~~12. The polypeptide of any one of claims 1 to ~~49~~11, wherein the bispecific antibody further comprises a fragment crystallizable (Fc) region of an immunoglobulin, a mutant thereof, or an equivalent thereof,

optionally wherein the Fc region comprises ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 81), or an equivalent thereof that binds an Fc receptor on an immune cell or on a platelet or that binds a complement protein; and

optionally wherein the Fc region comprises ESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY VDGVEVHNAKTKPREEQFQSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 82) or an Fc equivalent having mutations at a position corresponding to amino acid (aa) 16, aa 17 and aa 79 of SEQ ID NO: 81, and binding an Fc receptor on an immune cell or on a platelet or binding a complement protein..

~~51. The polypeptide of claim 50, wherein the Fc region or a mutant thereof is a human Fc region or a mutant thereof.~~

~~52. The polypeptide of claim 50 or 51, wherein the Fc region comprises ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID~~

~~NO: 81), or an equivalent thereof that binds an Fc receptor on an immune cell or on a platelet or that binds a complement protein.~~

~~53. The polypeptide of any one of claims 50 to 52, wherein the Fc region comprises ESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFQSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 82) or an Fc equivalent having mutations at a position corresponding to amino acid (aa) 16, aa 17 and aa 79 of SEQ ID NO: 81, and binding an Fc receptor on an immune cell or on a platelet or binding a complement protein.~~

~~54~~13. The polypeptide of any one of claims 1 to ~~53~~12, wherein the bispecific antibody further comprises a peptide linker between the two antigen binding domains; and

optionally wherein the peptide linker comprises PSGQAGAAASESLFVSNHAY (SEQ ID NO: 83); and

optionally wherein the bispecific antibody further comprises a signal peptide at its N terminus, optionally different from the signal peptide of the CAR, optionally wherein the signal peptide comprises a sequence selected from MYRMQLLSCIALSLALVTNS (SEQ ID NO: 4).

~~55. The polypeptide of claim 54, wherein the peptide linker comprises PSGQAGAAASESLFVSNHAY (SEQ ID NO: 83).~~

~~56. The polypeptide of any one of claims 1 to 55, wherein the bispecific antibody further comprises a signal peptide at its N terminus, optionally different from the signal peptide of the CAR.~~

~~57. The polypeptide of claim 56, wherein the signal peptide comprises a sequence selected from MYRMQLLSCIALSLALVTNS (SEQ ID NO: 4), or an equivalent thereof that facilitates secretion of the bispecific antibody, fragment or equivalent thereof. IL-2 signal peptide~~

~~58. The polypeptide of any one of claims 1 to 57, wherein the bispecific antibody further comprises a detectable or purification marker.~~

~~59. The polypeptide of claim 58, wherein the detectable marker comprises YPYDVPDYA (SEQ ID NO: 84).~~

~~60~~14. The polypeptide of any one of claims 1 to 13~~59~~, wherein the bispecific antibody and the CAR are contiguous sequences.

~~61~~15. The polypeptide of any one of claims 1 to ~~59~~14, further comprising a cleavable peptide located between any two of the following:

the CAR;

the bispecific antibody; and

an optional suicide gene product;

optionally wherein the cleavable peptide is a self-cleaving peptide; and

optionally the self-cleaving peptide is a T2A peptide; and

optionally wherein cleavable peptide or self-cleaving peptide or the T2A peptide comprises HVGSGEGRGSLLTCGDVEENPGP (SEQ ID NO: 85) or an equivalent thereof.

~~62. The polypeptide of claim 61, wherein the cleavable peptide is a self-cleaving peptide.~~

~~63. The polypeptide of claim 62, wherein the self-cleaving peptide is a T2A peptide.~~

~~64. The polypeptide of any one of claims 61 to 63, wherein cleavable peptide or self-cleaving peptide or the T2A peptide comprises HVGSGEGRGSLLTCGDVEENPGP (SEQ ID NO: 85) or an equivalent thereof.~~

~~65. The polypeptide of any one of claims 1 to 20 and 50 to 64, wherein either or both of the first TAA and the second TAA is or are selected from: FLT3, CD19, mesothelin, human epidermal growth factor receptor 2 (HER2), prostate stem cell antigen (PSCA), carcinoembryonic antigen (CEA), CD33, GTPase-activating protein (GAP), ganglioside G2 (GD2), CD5, prostate specific membrane antigen (PSMA), receptor tyrosine kinase-like orphan receptor 1 (ROR1), CD123, CD70, CD38, mucin 1, (Muc1), ephrin type-A receptor 2 precursor (EphA2), epidermal growth factor receptor variant III (EGFRVIII), interleukin 13 receptor alpha 2 (IL13Ra2), CD133, glypican 3 (GPC3), epithelial cell adhesion molecule precursor (EpCam), fibroblast activation protein alpha (FAP), vascular endothelial growth factor receptor 2 (VEGFR2), cancer/testis (CT), guanylyl cyclase C (GUCY2C), tumor-associated glycoprotein-72 (TAG-72), thymidine kinase 1 (TK1), and hypoxanthine guanine phosphoribosyltransferase (HPRT1).~~

~~66. The polypeptide of any one of claims 1 to 65, further comprises a detectable or purification marker.~~

~~67~~16. A polynucleotide encoding one or more of: a polypeptide of any one of claims 1 to ~~66~~15, a CAR of the polypeptide of any one of claims 1 to ~~66~~15, or a bispecific antibody of the polypeptide of any one of claims 1 to ~~66~~15.

~~68. The polynucleotide of claim 67, further comprising any one or any two or all three of the following:~~

~~a first regulatory sequence directing the expression of the polypeptide;~~

~~a second regulatory sequence directing the expression of the bispecific antibody; and~~

~~a third regulatory sequence directing the expression of the CAR.~~

~~69. The polynucleotide of claim 68, wherein each of the regulatory sequences comprises one or more of the following: a promoter, an intron, an enhancer, or a polyadenylation signal.~~

~~70. The polynucleotide of any one of claims 67 to 69, further comprising a suicide gene.~~

~~71. The polynucleotide of claim 70, wherein the suicide gene encodes a product selected from one or more of: HSV-TK (Herpes simplex virus thymidine kinase), cytosine deaminase, nitroreductase, carboxylesterase, cytochrome P450 or PNP (Purine nucleoside phosphorylase), truncated EGFR, or inducible caspase ("iCasp").~~

~~72. The polynucleotide of claim 70 or 71, further comprising an inducible regulatory sequence directing expression of the suicide gene.~~

~~73. The polynucleotide of any one of claims 67 to 72, comprising one or more of the following:~~

~~(I) a nucleotide sequence encoding a signal peptide, and wherein the nucleotide sequence comprises ATGGGGTGGTCAAGCATTATTCTGTTTCTGGTCGCTACCGCTACAGGCGTCCAT (SEQ ID NO: 86), ATGTACAGGATGCAACTCCTGTCTTGCATTGCACTAAGTCTTGCACTTGTCACAAACAGT (SEQ ID NO: 87), or an equivalent of each thereof;~~

(II) a nucleotide sequence encoding a linker peptide, and wherein the nucleotide sequence comprises GGTGGGGGCGGCTCTGGTGGCGGTGGCAGCGGCGGAGGTGGCAGT (SEQ ID NO: 88);

(III) a nucleotide sequence encoding a transmembrane and cytoplasmic domain, and wherein the nucleotide sequence comprises TTTTGGGTGCTGGTGGTGGTTGGTGGAGTCCTGGCTTGCTATAGCTTGCTAGTAACA GTGGCCTTTATTATTTTCTGGGTGAGGAGTAAGAGGAGCAGGCTCCTGCACAGTGAC TACATGAACATGACTCCCCGCCGCCCCGGGCCCACCCGCAAGCATTACCAGCCCTAT GCCCCACCACGCGACTTCGCAGCCTATCGCTCC (SEQ ID NO: 89) or an equivalent thereof;

(IV) a nucleotide sequence encoding a signaling domain, and wherein the nucleotide sequence comprises AGAGTGAAGTTCAGCAGGAGCGCAGACGCCCCCGCGTACCAGCAGGGCCAGAACC AGCTCTATAACGAGCTCAATCTAGGACGAAGAGAGGAGTACGATGTTTTGGACAAG AGACGTGGCCGGGACCCTGAGATGGGGGGAAAGCCGAGAAGGAAGAACCCTCAGG AAGGCCTGTACAATGAACTGCAGAAAGATAAGATGGCGGAGGCCTACAGTGAGATT GGGATGAAAGGCGAGCGCCGGAGGGGCAAGGGGCACGATGGCCTTTACCAGGGTCT CAGTACAGCCACCAAGGACACCTACGACGCCCTTCACATGCAGGCCCTGCCCCCTCG C (SEQ ID NO: 90) or an equivalent thereof;

(V) a nucleotide sequence encoding a cleavable peptide, and wherein the nucleotide sequence comprises CACGTGGGTTCTGGAGAAGGACGCGGTTCCTTGTTGACGTGTGGCGATGTAGAGGA AAATCCGGGTCCA (SEQ ID NO: 91) or an equivalent thereof;

(VI) a nucleotide sequence encoding a linker, such as a HMA linker also referred to herein as HMA a sequence, and wherein the nucleotide sequence comprises CCGAGCGGCCAGGCGGGCGCGGCGGCATCGGAGTCCCTGTTTGTGTCAAATCACGC CTAC (SEQ ID NO: 92) or an equivalent thereof;

(VII) a nucleotide sequence encoding an anti-BCMA light chain variable region, and wherein the nucleotide sequence is selected from:

GATATTGTTCTTACTCAATCACCCCCAAGCCTTGCGATGTCTCTTGGTAAACG AGCGACAATTAGTTGTAGAGCTTCTGAAAGCGTAACTATTCTTGGGTCACATCTTAT TCATTGGTATCAACAAAAGCCGGGACAACCGCCTACACTCTTGATTCAACTCGCGAG CAATGTTCAAACGGGTGTCCCTGCACGCTTTTCTGGGAGCGGTTCACGAACAGATTT TACTCTCACGATTGATCCAGTCGAAGAAGATGATGTCGCTGTATATTATTGTCTCCA AAGTAGGACAATACCAAGAACTTTTGGTGGTGGTACAAAATTGGAAATTAAA (SEQ ID NO: 93),

GACATCCAGATGACCCAGAGCCCTAGCTCACTGAGCGCCAGCGTGGGCGACA GGGTGACCATTACCTGCTCCGCCAGCCAGGACATCAGCAACTACCTGAACTGGTACC AGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACTACACCTCCAACCTGCAC TCCGGCGTGCCCAGCAGGTTCAGCGGAAGCGGCAGCGGCACCGATTTCACCCTGAC CATCTCCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGTACAGGAA GCTCCCCTGGACTTTCGGCCAGGGCACCAAACTGGAGATCAAGCGT (SEQ ID NO: 94),

GACATCGTGCTGACCCAGAGCCCCCCCAGCCTGGCCATGTCTCTGGGCAAGA GAGCCACCATCAGCTGCCGGGCCAGCGAGAGCGTGACCATCCTGGGCAGCCACCTG ATCTACTGGTATCAGCAGAAGCCTGGCCAGCCCCCCACCCTGCTGATCCAGCTGGCT AGCAATGTGCAGACCGGCGTGCCCGCCAGATTCAGCGGCAGCGGCAGCAGAACCGA CTTCACCCTGACCATCGACCCCGTGGAAGAGGACGACGTGGCCGTGTACTACTGCCT GCAGAGCCGGACCATCCCCCGGACCTTTGGCGGAGGAACAAAGCTGGAAATCAAG (SEQ ID NO: 95),

GACATCGTGCTGACCCAGAGCCCCCCCAGCCTGGCCATGTCTCTGGGCAAGA GAGCCACCATCAGCTGCCGGGCCAGCGAGAGCGTGACCATCCTGGGCAGCCACCTG ATCCACTGGTATCAGCAGAAGCCCGGCCAGCCCCCCACCCTGCTGATCCAGCTCGCC AGCAATGTGCAGACCGGCGTGCCCGCCAGATTCAGCGGCAGCGGCAGCAGAACCGA CTTCACCCTGACCATCGACCCCGTGGAAGAGGACGACGTGGCCGTGTACTACTGCCT GCAGAGCCGGACCATCCCCCGGACCTTTGGCGGAGGCACCAAACTGGAAATCAAG (SEQ ID NO: 96) or an equivalent of each thereof;

(VIII) a nucleotide sequence encoding an anti-BCMA heavy chain variable region, and wherein the nucleotide sequence is selected from:

CAGATCCAGCTGGTGCAGTCCGGCCCCGAGCTGAAGAAGCCCGGCGAGACC GTGAAGATCTCCTGCAAGGCCTCCGGCTACACCTTCACCGACTACTCCATCAACTGG GTGAAGCGGGCCCCCGGCAAGGGCCTGAAGTGGATGGGCTGGATCAACACCGAGAC CGGGAGCCCGCCTACGCCTACGACTTCCGGGGCCGGTTCGCCTTCTCCCTGGAGAC CTCCGCCTCCACCGCCTACCTGCAGATCAACAACCTGAAGTACGAGGACACCGCCA CCTACTTCTGCGCCCTGGACTACTCCTACGCCATGGACTACTGGGGCCAGGGCACCT CCGTGACCGTGTCCTCC (SEQ ID NO: 97),

CAGGTGCAGCTGGTCCAGAGCGGCGCCGAAGTGAAGAAGCCCGGCAGCTCC GTGAAAGTGAGCTGCAAGGCCAGCGGCGGCACCTTCAGCAACTACTGGATGCACTG GGTGAGGCAGGCCCCCGGACAGGGCCTGGAGTGGATGGGCGCCACCTACAGGGCCC ACAGCGACACCTACTACAACCAGAAGTTCAAGGGCCGGGTGACCATCACCGCCGAC AAGAGCACCAGCACCGCCTACATGGAACTGAGCAGCCTCAGGAGCGAGGACACCGC TGTGTATTACTGCGCCAGGGGCGCCATCTACAACGGCTACGACGTGCTGGACAACTG GGGCCAGGGCACACTAGTGACCGTGTCCAGC (SEQ ID NO: 98),

ATGGGATGGAGCTCTATCATCCTCTTCTTGGTAGCAACAGCTACAGGTGTCCA CCAGATTCAGCTGGTGCAGAGCGGCCCTGAGCTGAAGAAACCCGGCGAGACAGTGA AGATCAGCTGCAAGGCCTCCGGCTACACCTTCCGGCACTACAGCATGAACTGGGTG AAACAGGCCCCTGGCAAGGGCCTGAAGTGGATGGGCCGGATCAACACCGAGAGCG GCGTGCCCATCTACGCCGACGACTTCAAGGGCAGATTCGCCTTCAGCGTGGAAACC AGCGCCAGCACCGCCTACCTGGTGATCAACAACCTGAAGGACGAGGATACCGCCAG CTACTTCTGCAGCAACGACTACCTGTACAGCCTGGACTTCTGGGGCCAGGGCACCGC CCTGACCGTGTCCAGC (SEQ ID NO: 99), or

CAGATTCAGCTGGTGCAGAGCGGCCCTGAGCTGAAGAAACCCGGCGAGACA GTGAAGATCAGCTGCAAGGCCTCCGGCTACACCTTCACCGACTACAGCATCAACTG GGTGAAAAGAGCCCCTGGCAAGGGCCTGAAGTGGATGGGCTGGATCAACACCGAGA CAAGAGAGCCCGCCTACGCCTACGACTTCCGGGGCAGATTCGCCTTCAGCCTGGAA ACCAGCGCCAGCACCGCCTACCTGCAGATCAACAACCTGAAGTACGAGGACACCGC CACCTACTTTTGCGCCCTGGACTACAGCTACGCCATGGACTACTGGGGCCAGGGCAC CAGCGTGACCGTGTCCAGC (SEQ ID NO: 100) or an equivalent of each thereof;

(IX) a nucleotide sequence encoding an anti-NKG2D light chain variable region, and wherein the nucleotide sequence comprises CAGTCAGCGGCTTACGGCAGCCGGCGTCGGTGTCGGGTTCCCCGGGTCAGTCGATCACG ATCAGCTGTAGTGGGAGCAGCTCCAACATCGGTAACAACGCAGTGAACTGGTATCA GCAACTGCCCGGGAAAAGCGCCGAAACTGCTGATTTACTATGATGATTTGCTGCCAAG TGGAGTTAGTGACCGCTTTTCCGGCAGTAAATCGGGTACCTCGGCTTTTCTGGCTATT TCGGGTCTCCAGAGCGAGGATGAAGCTGATTATTATTGCGCCGCATGGGATGATAGC TTAAATGGCCCAGTTTTTGGCGGCGGTACTAAACTGACCGTGCTG (SEQ ID NO: 101) or an equivalent thereof;

(X) a nucleotide sequence encoding an anti-NKG2D heavy chain variable region, and wherein the nucleotide sequence comprises CAAGTGCAGCTGGTTGAATCCGGTGGCGGTCTGGTCAAGCCGGGCGGCTCTTTGCGT CTGAGCTGTGCCGCGTCGGGTTTTACCTTCAGCTCTTATGGTATGCATTGGGTGCGTC AGGCGCCTGGCAAAGGTCTGGAGTGGGTTGCGTTCATCCGCTACGATGGGTCTAACA AATATTATGCCGACTCAGTAAAAGGACGCTTCACTATTAGCCGCGACAATAGCAAA AATACCCTGTACCTGCAAATGAATAGCCTGCGCGCCGAAGATACCGCCGTTTACTAT TGCGCTAAAGATCGTGGCCTGGGTGATGGTACGTACTTCGATTACTGGGGTCAGGGC ACCACCGTTACCGTTAGTTCA (SEQ ID NO: 102) or an equivalent thereof;

(XI) a nucleotide sequence encoding an anti-FLT3 light chain variable region, and wherein the nucleotide sequence comprises GATATTGTGCTAACTCAGTCTCCAGCCACCCTGTCTGTGACTCCAGGAGATAGCGTC AGTCTTTCCTGCAGGGCCAGCCAGAGTATTAGCAACAACCTACACTGGTATCAACAA AAATCACATGAGTCTCCAAGGCTTCTCATCAAGTATGCTTCCCAGTCCATCTCTGGG ATCCCCTCCAGGTTCAGTGGCAGTGGATCAGGGACAGATTTCACTCTCAGTATCAAC AGTGTGGAGACTGAAGATTTTGGAGTGTATTTCTGTCAACAGAGTAACACCTGGCCG TACACGTTCGGAGGGGGGACCAAGCTGGAAATAAAACGG (SEQ ID NO: 103), GACATTGTGATGACACAGTCTCCATCCTCCCTGAGTGTGTCAGCAGGAGAGAAGGTC ACTATGAGCTGCAAGTCCAGTCAGAGTCTGTTAAACAGTGGAAATCAAAAGAACTA TATGGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCTAAACTGTTGATCTACGGGGC ATCCACTAGGGAATCTGGGGTCCCTGATCGCTTCACAGGCAGTGGATCTGGAACCGA TTTCACTCTTACCATCAGCAGTGTGCAGGCTGAAGACCTGGCAGTTTATTACTGTCA

~~GAATGATCATAGTTATCCGCTCACGTTCGGTGCTGGGACCAAGCTGGAGCTGAAACGG G (SEQ ID NO: 104) or an equivalent of each thereof;~~

~~(XII) a nucleotide sequence encoding an anti-FLT3 heavy chain variable region, and wherein the nucleotide sequence comprises CAGGTCCAACTGCAGCAGCCTGGGGCTGAGCTTGTGAAGCCTGGGGCTTCATTGAA GCTGTCCTGCAAGTCTTCCGGGTACACCTTCACCAGCTACTGGATGCACTGGGTGAG GCAGAGGCCTGGACATGGCCTTGAGTGGATCGGAGAGATTGATCCTTCTGACAGTTA TAAAGACTACAATCAGAAGTTCAAGGACAAGGCCACATTGACTGTGGACAGATCCT CCAACACAGCCTACATGCACCTCAGCAGCCTGACATCTGATGACTCTGCGGTCTATT ATTGTGCAAGACGGATTACGACGACCCCCTTTGACTTCTGGGGCCAAGGCACCACTC TCACAGTCTCCTCA (SEQ ID NO: 105), CAGGTGCAGCTGAAGCAGTCAGGACCTGGCCTAGTGCAGCCCTCACAGAGCCTGTC CATCACCTGCACAGTCTCTGGTTTCTCATTAACTAACTATGGTTTACACTGGGTTCGC CAGTCTCCAGGAAAGGGCCTGGAGTGGCTGGGAGTGATATGGAGTGGTGGAAGCAC AGACTATAATGCAGCTTTCATATCCAGACTGAGCATCAGCAAGGACAACTCCAAGA GCCAAGTTTTCTTTAAAATGAACAGTCTGCAGGCTGATGACACAGCCATATACTACT GTGCCAGAAAAGGAGGGATCTACTATGCTAACCATTACTATGCTATGGACTACTGGG GTCAAGGAACCTCAGTCACCGTCTCCTCA (SEQ ID NO: 106) or an equivalent of each thereof;~~

~~(XIII) a nucleotide sequence encoding an anti-CS1 light chain variable region, and wherein the nucleotide sequence comprises AAACTTGAGT TGAAGACCGG TGCCGGCTTC ACCTTACCGA CCAGTTATCA TCAACAATGC TATTACGTGG CCCTGGACGA AGCACAGGTG AATTCAATTA CGTTTACGTT TGATACCGGC TCTGGCAGCG GTACATTTCG TGATCCCGTG GGCACTTACC GCTATTCGGC GAGTTATATC TTGCTGAAAC CTTCCCAAGG TCCGAAACAG CAGTACTGGG CGGTTGGCAC CATTGTAGAC CAATCAGCCA AATGTACAAT CTCGGTTCGC GATGGTGTCA GTACGTCGAT GTCTAAGCAG TCACAGACAA TGGTTATCGA T (SEQ ID NO: 107) or an equivalent thereof;~~

~~(XIV) a nucleotide sequence encoding an anti-CS1 heavy chain variable region, and wherein the nucleotide sequence comprises AGCGTTACCG TGAGTACAGG CCAGGGCTGG~~

~~TATGACATGG CACGTACAGC CATCATGACC TCGCGCGCAT GTTACTACGT CGCGTCAGAT GAATCGACGC CTTCCTCGCT GCAAATGTAT GCAACCTCCA GCAGCAAAGA TGTTACCCTG ACCGCAAAGG ACAAGTTTAA ACAGAATTTG CGTACGGAGA GTGACTCCCC GCACATCATG GGAATCTGGG AGTTGGGTCA GGGGCCTCGT CAGAAGGTAT GGAACATGTG GTATACAACT TTTTCGTACG GCTCAGCAAA ATGCAGCTTG AAAGTGTCGG CAGGTCCGCG CGTGCTGGAC GCCGGTCCGC AGCAGCTGCA AGTCCAGTCT (SEQ ID NO: 108) or an equivalent thereof; and~~

~~(XV) a nucleotide sequence encoding a hinge domain, and wherein the nucleotide sequence comprises CTCGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCCGGATCCCAAA GGTACC (SEQ ID NO: 109) or an equivalent thereof.~~

~~74. A polynucleotide, which is reverse, complement, or reverse-complement to the polynucleotide of any one of claims 67 to 73.~~

~~75. The polynucleotide of any one of claims 67 to 74, further comprising detectable or purification marker.~~

~~76~~17. A vector comprising a polynucleotide of ~~any of claims 67 to 75~~claim 16.

~~77. The vector of claim 76, which is a non-viral vector or a viral vector.~~

~~78. The vector of claim 77, wherein the non-viral vector is a plasmid.~~

~~79. The vector of claim 77, wherein the viral vector is selected from the group of a retroviral vector, a lentiviral vector, an adenoviral vector, and an adeno-associated viral vector.~~

~~80. The vector of any one of claims 76 to 79, further comprising a regulatory sequence directing the replication or expression of the polynucleotide.~~

~~81. The vector of claim 80, wherein the regulatory sequence comprises one or more of the following: a promoter, an intron, an enhancer, or a polyadenylation signal.~~

~~82. The vector of any one of claims 76 to 81, further comprises a detectable or purification marker.~~

1883. An isolated or engineered cell comprising one or more of the following: a polypeptide of any one of claims 1 to 6615, a polynucleotide of ~~any one of claims 67 to 75~~claim 16, or a vector of ~~any one of claims 76 to 82~~claim 17.

~~84. The isolated or engineered cell of claim 83, wherein the cell is a prokaryotic cell or a eukaryotic cell.~~

~~85. The isolated or engineered cell of claim 83 or 84, wherein the cell is a eukaryotic cell.~~

~~86. The isolated or engineered cell of claim 84 or 85, wherein the eukaryotic cell is selected from an animal cell, a mammalian cell, a bovine cell, a feline cell, a canine cell, a murine cell, an equine cell, or a human cell.~~

8719. The isolated or engineered cell of ~~any one of claims 84 to 86~~claim 18, wherein the eukaryotic cell is an immune cell, optionally selected from a T-cell, a B cell, a NK cell, a NKT cell, a dendritic cell, a myeloid cell, a monocyte, or a macrophage.

~~88. The isolated or engineered cell of claim 87, wherein the immune cell is derived from hematopoietic stem cells (HSCs) and/or induced pluripotent stem cells (iPSCs).~~

8920. The isolated or engineered cell of any one of claims ~~83 to 88~~18 to 19, secreting the bispecific antibody of the polypeptide.

~~90. The isolated or engineered cell of any one of claims 83 to 89, further comprising a detectable or purification marker.~~

9121. A cell population comprising a cell of any one of claims ~~83~~18 to 20~~90~~.

~~92. The cell population of claim 91, which is substantially homogenous.~~

9322. A composition comprising a carrier and one or more of the following: a polypeptide of any one of claims 1 to 6615, a polynucleotide of ~~any one of~~ claim~~s 67 to 75~~16, a vector of ~~any one of~~ claim~~s 76 to 82~~17; an isolated or engineered cell of any one of claims ~~83~~18 to ~~90~~20, and/or a cell population of claim ~~91 or 92~~21.

~~94. The composition of claim 93, wherein the carrier is a pharmaceutically acceptable carrier.~~

9523. An isolated complex comprising either or both of the following:

an isolated or engineered cell of any one of claims ~~83~~18 to ~~90~~20 bound to a cancer cell, wherein the cancer cell is bound to the isolated cell by the first anti-TAA antigen binding domain of claim 1(a) or the anti-BCMA antigen binding domain of claim 1(b); or

a polypeptide of any one of claims 1 to ~~66~~15 bound to a cancer cell, wherein the cancer cell is bound to the polypeptide by either or both of: the first anti-TAA antigen binding domain of claim 1(a) or the anti-BCMA antigen binding domain of claim 1(b), and/or the second anti-TAA antigen binding domain of claim 1(a) or the anti-CS1 antigen binding domain of claim 1(b).

~~96~~24. A method of producing a cell expressing a CAR and secreting a bispecific antibody comprising transducing or transfecting a cell or a cell population with a polynucleotide of ~~any of claims 67 to 75~~claim 16 and/or a vector of ~~any one of claims 76 to 82~~claim 17.

~~97. The method of claim 96, wherein the cell is selected from a Hematopoietic stem cell (HSC), an induced pluripotent stem cell (iPSCs), or an immune cell.~~

~~98. The method of claim 96, wherein the cell population comprises a Hematopoietic stem cell (HSC), an induced pluripotent stem cell (iPSCs), or an immune cell.~~

~~99. The method of claim 97 or 98, wherein the immune cells is selected from a group consisting of T-cells, B-cells, NK-cells, NKT-cells, dendritic cells, myeloid cells, monocytes, or macrophages.~~

~~100. The method of any one of claims 97 to 99, wherein the immune cell is derived from HSCs and/or iPSCs.~~

~~101~~25. An *in vitro* method of inhibiting the growth of a cancer cell expressing a tumor associated antigen (TAA) or a tissue comprising the cancer cell, comprising contacting the cancer cell or the tissue with the isolated or engineered cell of any one of claims ~~87~~18 to ~~90~~20 or a cell population of claim ~~91 or 92~~21.

~~102. The method of claim 101, wherein the contacting is in vitro or in vivo.~~

~~103. The method of claim 101 or 102, wherein the contacting is in vivo and the isolated cells are autologous or allogeneic to a subject being treated.~~

~~104. The method of claim 101 or 102, wherein the contacting is in vivo and the isolated cells are allogenic to a subject being treated.~~

~~105. The method of any one of claims 101 to 104, further comprising contacting the cancer cell or the tissue with an effective amount of a cytoreductive therapy or a therapy that upregulates the expression of a TAA.~~

~~106. The method of claim 105, wherein the cytoreductive therapy comprises chemotherapy, cryotherapy, hyperthermia, targeted therapy, and/or radiation therapy.~~

~~107. The method of any one of claims 103 to 106, wherein the subject is a mammal, a canine, a feline, an equine, a murine, or a human patient.~~

~~108~~26. The method of any one of claims ~~101~~24 to ~~107~~25, wherein the cancer cell expresses the first TAA of claim 1(a) or BCMA of claim 1(b).

~~109. The method of any one of claims 101 to 108, wherein the cancer cell expresses the second TAA of claim 1(a) or CS1 of claim 1(b).~~

~~110~~27. ~~A method for one or more of: inhibiting the growth of a cancer, inhibiting metastasis of a cancer, or treating a cancer, in a subject in need thereof, comprising administering~~Use of an isolated or engineered cell of any one of claims ~~87~~18 to ~~90~~20 or a cell population of claim ~~91 or 92~~21 in the manufacture of a medicament for one or more of: inhibiting the growth of a cancer, inhibiting metastasis of a cancer, or treating a cancer, in a subject in ~~to the~~a subject in need thereof.

~~111. The method of claim 110, wherein the isolated or engineered cell is autologous to the subject in need.~~

~~112. The method of claim 110, wherein the isolated or engineered cell is allogenic to the subject in need.~~

~~113. The method of any one of claims 110 to 112, wherein the subject is selected for the therapy by determining expression of either or both of: the first TAA of claim 1(a) or BCMA of claim 1(b), and/or the second TAA of claim 1(a) or the CS1 of claim 1(b).~~

~~114. The method of claim 113, wherein the expression is determined by contacting a sample of the subject with an antigen binding domain recognizing and binding the TAA or BCMA or~~

~~CS1 in vitro or in vivo and detecting binding between the sample and the antigen binding domain.~~

~~115. The method of claim 114, wherein the antigen binding domain further comprises a detectable marker.~~

~~116. The method of any one of claims 110 to 115, further comprising administering to the subject an effective amount of a cytoreductive therapy or a therapy that upregulates the expression of a TAA.~~

~~117. The method of claim 116, wherein the cytoreductive therapy comprises chemotherapy, cryotherapy, hyperthermia, targeted therapy, and/or radiation therapy.~~

~~118. The method of any one of claims 110 to 117, wherein the subject is a mammal, a canine, a feline, an equine, a murine, or a human patient.~~

~~119~~28. ~~A method for treating a cancer in a subject selected for the treatment, comprising administering~~ Use of an isolated or engineered cell of any one of claims ~~87~~18 to ~~90~~20 or a cell population of claim ~~91 or 92~~21 in the manufacture of a medicament for treating a cancer in a subject selected for the treatment~~to the subject~~.

~~120. The method of claim 119, wherein the subject is selected if a cancer cell of the subject expresses either or both of: the first TAA of claim 1(a) or BCMA of claim 1(b), and/or the second TAA of claim 1(a) or the CS1 of claim 1(b).~~

~~121. The method of claim 120, wherein the TAA expression is determined by contacting a sample of the subject with an antigen binding domain recognizing and binding the TAA or BCMA or CS1 in vitro or in vivo and detecting binding between the sample and the antigen binding domain.~~

~~122. The method of claim 121, wherein the antigen binding domain further comprises a detectable marker.~~

~~123. The method of any one of claims 119 to 122, wherein the isolated or engineered cell is autologous to the subject in need.~~

~~124. The method of any one of claims 119 to 122, wherein the isolated or engineered cell is allogenic to the subject in need.~~

~~125. The method of any one of claims 119 to 124, further comprising administering to the subject an effective amount of a cytoreductive therapy or a therapy that upregulates the expression of a TAA.~~

~~126. The method of claim 125, wherein the cytoreductive therapy comprises chemotherapy, cryotherapy, hyperthermia, targeted therapy, and/or radiation therapy.~~

~~127. The method of any one of claims 119 to 126, wherein the subject is a mammal, a canine, a feline, an equine, a murine, or a human patient.~~

~~128. The method of any one of claims 110 to 127, wherein the administration is applied to the subject as a first line therapy, or a second line therapy, or third line therapy, or a fourth line therapy.~~

~~129~~29. The method of any one of claims ~~101~~24 to ~~128~~26 or the use of claim 27 or 28, wherein the cancer is multiple myeloma (MM).

~~130. A kit comprising an optional instructions for use and one or more of the following: a polypeptide of any one of claims 1 to 66, a polynucleotide of any one of claims 67 to 75, a vector of any one of claims 76 to 82, an isolated or engineered cell of any one of claims 83 to 90, a cell population of claim 91 or 92, a composition of claim 93 or 94, or an isolated complex of claim 95.~~