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(54) **COMBINATION THERAPIES FOR
TREATING CANCER**

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(57) **ABSTRACT**

Disclosed herein are methods and materials for treating
cancer. The disclosure further provides methods and mate-
rials for using one or more antigen binding proteins (for
example anti-B-cell maturation antigen (BCMA) antigen
binding proteins) and one or more T cell engagers for
treating a subject having cancer.

Specification includes a Sequence Listing.

COMBINATION THERAPIES FOR TREATING CANCER

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application Ser. No. 63/194,547, filed on May 28, 2021, the disclosure of which is herein incorporated by reference in its entirety.

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY

[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 May 13, 2022, is named Sequence Listing 009442_00184_ST25.txt and is 60 kilobytes in size.

FIELD OF THE DISCLOSURE

[0003] This disclosure relates to methods and materials for treating cancer. For example, this disclosure provides methods and materials for using one or more antibody-drug conjugates (ADCs) and one or more T cell engagers for treating a mammal (e.g., a human) having cancer. The disclosure further provides methods and materials for using one or more antigen binding proteins (for example anti-B-cell maturation antigen (BCMA) antigen binding protein) and one or more T cell engagers for treating a subject having cancer.

BACKGROUND INFORMATION

[0004] Multiple myeloma (MM) is an incurable malignancy and accounts for 1% of all cancers and for 10% of all hematologic malignancies. A variety of drugs and combination treatments have been evaluated and found effective in treating multiple myeloma (National Comprehensive Cancer Network, 2016; Moreau, San Miguel et al., 2017). However, most, if not all, of these patients inevitably relapse (Richardson, Barlogie et al., 2003; Richardson, Barlogie et al., 2006; Jagannath, Barlogie et al., 2008).

[0005] Currently, there remains a need in the immunotherapy field for alternative or improved compositions and methods for more efficiently treating autoimmune disease and cancer.

SUMMARY OF THE INVENTION

[0006] This disclosure provides methods and materials for treating cancer. For example, this disclosure provides methods and materials for using one or more molecules where each molecule includes: (i) an anti-BCMA antigen binding protein or ADC having binding specificity for a BCMA polypeptide and one or more T cell engagers for treating a subject having cancer. In some cases, a mammal (e.g., a human such as a human having cancer) can be administered a combination treatment disclosed herein comprising (a) an anti-BCMA antigen binding protein or ADC having binding specificity for a BCMA polypeptide and (b) one or more T cell engagers.

[0007] Disclosed herein are combinations comprising an anti-BCMA antigen binding protein and a T cell engager. In some cases, the T cell engager binds to CD3. In some cases, the anti-BCMA antigen binding protein comprises an antibody. In some cases, the antibody is a monoclonal antibody.

In some cases, the monoclonal antibody is an IgG1. In some cases, the antibody is afucosylated. In some embodiments, the antibody is fucosylated. In some embodiments, the antibody is sialylated. In some embodiments, the antibody is glycosylated. In some embodiments, the antibody is galactosylated. In some cases, the anti-BCMA antigen binding protein is human, humanized or chimeric. In some cases, the anti-BCMA antigen binding protein comprises a CDRH1 comprising the amino acid sequence set out in SEQ ID NO:1; a CDRH2 comprising the amino acid sequence set out in SEQ ID NO:2; a CDRH3 comprising the amino acid sequence set out in SEQ ID NO:3; a CDRL1 comprising the amino acid sequence set out in SEQ ID NO:4; a CDRL2 comprising the amino acid sequence set out in SEQ ID NO:5; and a CDRL3 comprising the amino acid sequence set out in SEQ ID NO:6. In some cases, the anti-BCMA antigen binding protein comprises a heavy chain variable region (VH) comprising the amino acid sequence set out in SEQ ID NO:7; and a light chain variable region (VL) comprising the amino acid sequence set out in SEQ ID NO: 8. In some cases, the anti-BCMA antigen binding protein comprises a heavy chain (H) comprising the amino acid sequence set out in SEQ ID NO:9 and a light chain (L) comprising the amino acid sequence set out in SEQ ID NO:10. In some cases, the anti-BCMA antigen binding protein is an immunoconjugate. In some cases, the anti-BCMA antigen binding protein is an immunoconjugate comprising an antibody conjugated to a cytotoxin. In some cases, the cytotoxin is MMAE or MMAF. In some cases, the cytotoxin is MMAF. In some embodiments, the cytotoxin is AFP, MMAF, MMAE, AEB, AEVB or auristatin E. In some embodiments, the cytotoxin is paclitaxel, docetaxel, CC-1065, SN-38, topotecan, morpholino-doxorubicin, rhizoxin, cyanomorpholino-doxorubicin, dolastatin-10, echinomycin, combretastatin, calicheamicin, or netropsin. In some embodiments, the cytotoxin is an auristatin, a maytansinoid, or calicheamicin. In some embodiments, the cytotoxin is vincristine, vinblastine, vindesine, vinorelbine, VP-16, camptothecin, epothilone A, epothilone B, nocodazole, colchicines, colcemid, estramustine, cemadotin, discodermolide, maytansinol, maytansine, DM1, DM2, DM3, DM4 or eleutherobin. In some cases, the anti-BCMA antigen binding protein is belantamab mafodotin. In some cases, belantamab mafodotin is present in the combination at a dose of at least about 0.5 mg/kg, 0.95 mg/kg, 1.0 mg/kg, 1.25 mg/kg, 1.4 mg/kg, 1.7 mg/kg, 1.9 mg/kg, 2.5 mg/kg, or 3.4 mg/kg. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is 0.95 mg/kg. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is 1.0 mg/kg. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is 1.4 mg/kg. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is 1.9 mg/kg. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is 1.92 mg/kg. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is 2.5 mg/kg. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is 3.4 mg/kg. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is administered to the subject every week. In some embodiments, the therapeutically

effective dose of the anti-BCMA antigen binding protein is administered to the subject every 2 weeks. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is administered to the subject every 3 weeks. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is administered to the subject every 4 weeks. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is administered to the subject every 5 weeks. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is administered to the subject every 6 weeks. In some embodiments, dosage of the therapeutically effective dose of the anti-BCMA antigen binding protein is step-down to a lower dose described herein following a first administration. In some embodiments, 3.4 mg/kg dosage of the therapeutically effective dose of the anti-BCMA antigen binding protein is step-down to a 1.9 mg/kg dose, 1.4 mg/kg or less. In some embodiments, a 2.5 mg/kg dosage of the therapeutically effective dose of the anti-BCMA antigen binding protein is step-down to a 1.9 mg/kg dose, 1.4 mg/kg or less. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is administered to the subject on day 1, day 8 and thereafter every 3-12 weeks. In some cases, the T cell engager is a bispecific T cell engager. In some cases, the T cell engager is selected from the group consisting of Cevostamab, Talquetamab, Teclistimab, PF-3135, TNB-383B, REGN5458, blinatumomab, and solitomab. In some cases, the T cell engager is an anti-FCRH5 T cell engager. In some cases, the T cell engager is Cevostamab. In some embodiments, the T cell engager comprises the sequences set out in SEQ ID NO:11, 12, 13 and 14. In some cases, the combination comprises at least about 1.5 mg, 2 mg, 3 mg, 3.6 mg, 10 mg, 15 mg, 20 mg, 90 mg, or 132 mg Cevostamab. In some cases, the T cell engager is an anti-GPRC5D T cell engager. In some cases, the T cell engager is Talquetamab. In some cases, the T cell engager is an anti-BCMA T cell engager. In some cases, the T cell engager is selected from the group consisting of Teclistimab, PF-3135, TNB-383B, and REGN5458. In some cases, the T cell engager is selected from the group consisting of CC-93269, AMG701, JNJ-7957, and GBR 1342. In some cases, the T cell engager does not bind ICOS. In some cases, the T cell engager does not bind CD38. In some cases, the combination comprises a pharmaceutically acceptable carrier. In some cases, the combination further comprising an adjuvant.

[0008] Disclosed herein are methods of treating cancer. In some cases, the method comprises treating cancer in a subject in need thereof comprising administering to the subject a therapeutically effective dose of a combination disclosed herein. In some cases, the cancer is selected from the group consisting of multiple myeloma, chronic lymphocytic leukemia, Waldenstrom macroglobulinemia, and non-Hodgkin's lymphoma. In some cases, the cancer is multiple myeloma. In some cases, the cancer is relapsed and/or refractory multiple myeloma. In some cases, the subject has received at least one previous cancer treatment. In some cases, the therapeutically effective dose of the combination is administered to the subject at least about once every 1-60 days. In some cases, the therapeutically effective dose of the combination is administered to the subject at least about once every 21 days. In some cases, the therapeutically effective dose of the combination is administered to the

subject at least about once every 8 days. In some cases, administering the therapeutically effective dose of the combination reduces ocular toxicity as compared to administering a therapeutically effective amount of the anti-BCMA antigen binding protein alone. In some cases, the anti-BCMA antigen binding protein is belantamab mafodotin. In some cases, ocular toxicity is at least one of: changes in corneal epithelium, dry eyes, irritation, redness, blurred vision, dry eyes, photophobia, or changes in visual acuity. In some cases, ocular toxicity is measured by at least one of the following methods: best corrected visual acuity, documentation of manifest refraction and the method used to obtain best corrected visual acuity, current glasses prescription (if applicable), intraocular pressure measurement, anterior segment (slit lamp) examination including fluorescein staining of the cornea and lens examination, dilated fundoscopic examination, or an ocular surface disease index (OSDI). In some cases, an anti-BCMA antigen binding protein disclosed herein is administered to a subject in a dose of at least about 0.5 mg/kg, 0.95 mg/kg, 1.25 mg/kg, 1.4 mg/kg, 1.7 mg/kg, 1.9 mg/kg, 1.92 mg/kg, 2.5 mg/kg, or 3.4 mg/kg. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is 0.95 mg/kg. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is 1.0 mg/kg. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is 1.4 mg/kg. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is 1.9 mg/kg. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is 1.92 mg/kg. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is 2.5 mg/kg. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is 3.4 mg/kg. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is administered to the subject every week. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is administered to the subject every 2 weeks. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is administered to the subject every 3 weeks. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is administered to the subject every 4 weeks. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is administered to the subject every 5 weeks. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is administered to the subject every 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, or 12 weeks. In some embodiments, dosage of the therapeutically effective dose of the anti-BCMA antigen binding protein is step-down to a lower dose described herein following a first administration. In some embodiments, 3.4 mg/kg dosage of the therapeutically effective dose of the anti-BCMA antigen binding protein is step-down to a 1.9 mg/kg dose, 1.4 mg/kg or less. In some embodiments, a 2.5 mg/kg dosage of the therapeutically effective dose of the anti-BCMA antigen binding protein is step-down to a 1.9 mg/kg dose, 1.4 mg/kg or less. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is administered to the subject on day 1, day 8 and thereafter every 3-12 weeks.

[0009] Disclosed herein are the manufacture of a medicament for use. In some cases, disclosed herein are combinations for use in the manufacture of a medicament for treatment of cancer. Disclosed herein are the use of a combination disclosed herein for the treatment of cancer.

[0010] Disclosed herein are kits. In some cases, a kit disclosed herein is for use in treatment of cancer. In some cases, a kit disclosed herein comprises a combination disclosed herein and instructions for use in the treatment of cancer.

[0011] Disclosed herein are pre-filled syringes or autoinjector devices. In some cases, a pre-filled syringe or autoinjector device disclosed herein comprises a combination disclosed herein.

[0012] Unless otherwise defined, 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 invention pertains. Although methods and materials similar or equivalent to those described herein can be used to practice the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

[0013] The details of one or more embodiments of the invention are set forth in the accompanying description below. Other features, objects, and advantages of the invention will be apparent from the description and from the claims.

DETAILED DESCRIPTION

Combination

[0014] This disclosure provides methods and materials for treating cancer. In some cases, disclosed herein is a combination comprising an anti-BCMA antigen binding protein and a T cell engager for use in treating cancer or other B-cell mediated disease or disorders.

[0015] The term “combination” described herein refers to at least two therapeutic agents. As used herein the term “therapeutic agent” is understood to mean a substance that produces a desired effect in a tissue, system, animal, mammal, human, or other subject. In one embodiment, the combination can contain an additional therapeutic agent, such as, for example, an additional cancer therapeutic agent. In one embodiment the additional cancer therapeutic is an immunomodulatory imide drug (IMiD) such as thalidomide, lenalidomide, pomalidomide, apremilast, or other thalidomide analogs. In some embodiment, the additional cancer therapeutic may be carfilzomib, daratumumab, isatuximab, ixazomib, marizomib, oprozomib, or a pharmaceutically acceptable salt thereof. In some embodiments, an additional cancer therapeutic agent is a PD-1 inhibitor. In some cases, the PD-1 inhibitor is selected from the group consisting of PDR001, Nivolumab, Pembrolizumab, Pidilizumab, MEDI0680, REGN2810, TSR-042, PF-06801591, and AMP-224. In some cases, the PD-1 inhibitor is Jemperi. In some embodiments, an additional cancer therapeutic agent is a PD-L1 inhibitor. In some cases, the PD-L1 inhibitor is selected from the group consisting of FAZ053, Atezolizumab, Avelumab, Durvalumab, and BMS-93655. In some embodiments, an additional cancer therapeutic agent is a CTLA-4 inhibitor. In some cases, the CTLA-4 inhibitor is

Ipilimumab or Tremelimumab. In some cases, an additional cancer therapeutic agent is a TIM-3 inhibitor. In some cases, the TIM-3 inhibitor is MGB453 or TSR-022. In some embodiments, an additional cancer therapeutic agent is a LAG-3 inhibitor. In some cases the LAG-3 inhibitor is selected from the group consisting of LAG525, BMS-986016, and TSR-033. In some embodiments, an additional cancer therapeutic agent is an mTOR inhibitor. In some cases the mTOR inhibitor is RAD001 or rapamycin.

[0016] The administration of the combinations of the disclosure may be advantageous over the individual therapeutic agents in that the combinations may provide one or more of the following improved properties when compared to the individual administration of a single therapeutic agent alone: i) a greater anticancer effect than the most active single agent, ii) synergistic or highly synergistic anticancer activity, iii) a dosing protocol that provides enhanced anticancer activity with reduced side effect profile, iv) a reduction in the toxic effect profile, v) an increase in the therapeutic window, or vi) an increase in the bioavailability of one or both of the therapeutic agents.

[0017] The combinations described herein can be in the form of a pharmaceutical composition. A “pharmaceutical composition” contains a combination described herein, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The carrier(s), diluent(s) or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation, capable of pharmaceutical formulation, and not deleterious to the recipient thereof. In one embodiment, each therapeutic agent in a combination is individually formulated into its own pharmaceutical composition and each of the pharmaceutical compositions are administered to treat cancer. In this embodiment, each of the pharmaceutical compositions may have the same or different carriers, diluents or excipients. For example, in one embodiment, a first pharmaceutical composition contains an anti-BCMA antigen binding protein or ADC having binding specificity for a BCMA polypeptide, a second pharmaceutical composition contains one or more T cell engagers, and the first and second pharmaceutical compositions are both administered to treat cancer. In another embodiment, each therapeutic agent in a combination is formulated together into a single pharmaceutical composition and administered to treat cancer. For example, in one embodiment, a single pharmaceutical composition contains both an anti-BCMA antigen binding protein or ADC having binding specificity for a BCMA polypeptide and one or more T cell engagers and is administered as a single pharmaceutical composition to treat cancer.

Anti-BCMA Antigen Binding Protein

[0018] The term “anti-BCMA antigen binding protein” as used herein refers to antibodies and other protein constructs, such as domains, which are capable of binding to BCMA. The terms “BCMA binding protein” and “anti-BCMA antigen binding protein” are used interchangeably herein.

[0019] The anti-BCMA antigen binding proteins described herein may bind to human BCMA having, including, for example, human BCMA containing the amino acid sequence of GenBank Accession Number Q02223.2, or genes encoding human BCMA having at least 90 percent homology or at least 90 percent identity thereto.

[0020] Exemplary anti-BCMA antigen binding proteins and methods of making the same are disclosed in Interna-

tional Publication No. WO2012/163805 which is incorporated by reference herein in its entirety. Additional exemplary anti-BCMA antigen binding proteins include those described in WO2016/014789, WO2016/090320, WO2016/090327, WO2016/020332, WO2016/079177, WO2014/122143, WO2014/122144, WO2017/021450, WO2016/014565, WO2014/068079, WO2015/166649, WO2015/158671, WO2015/052536, WO2014/140248, WO2013/072415, WO2013/072406, WO2014/089335, US2017/165373, WO2013/154760, WO2018/201051 and WO2017/051068, each of which is incorporated by reference herein in its entirety.

[0021] The term “antigen binding protein” as used herein refers to antibodies and other protein constructs, such as domains, which are capable of binding to the antigen.

[0022] The term “antibody” is used herein in the broadest sense to refer to molecules with an immunoglobulin-like domain (for example IgG, IgM, IgA, IgD or IgE) and includes monoclonal, recombinant, polyclonal, chimeric, human, humanized, multispecific antibodies, including bispecific antibodies, and heteroconjugate antibodies; a single variable domain (e.g., a domain antibody (DAB)), antigen binding antibody fragments, Fab, F(ab')₂, Fv, disulphide linked Fv, single chain Fv, disulphide-linked scFv, diabodies, TANDABS, etc. and modified versions of any of the foregoing (for a summary of alternative “antibody” formats see Holliger and Hudson, *Nature Biotechnology*, 2005, Vol 23, No. 9, 1126-1136).

[0023] In some embodiments, a BCMA binding protein disclosed herein may be derived from rat, mouse, primate (e.g. cynomolgus, Old World monkey or Great Ape) or human. The BCMA binding protein may be a human, humanized or chimeric antibody. The BCMA binding protein may comprise a constant region, which may be of any isotype or subclass. The constant region may be of the IgG isotype, for example IgG1, IgG2, IgG3, IgG4 or variants thereof. The BCMA binding protein constant region may be IgG1.

[0024] The term, “full”, “whole” or “intact” antibody, used interchangeably herein, refers to a heterotetrameric glycoprotein. An intact antibody is composed of two identical heavy chains (HCs) and two identical light chains (LCs) linked by covalent disulphide bonds. This H₂L₂ structure folds to form three functional domains comprising two antigen-binding fragments, known as ‘Fab’ fragments, and a ‘Fc’ crystallisable fragment. The Fab fragment is composed of the variable domain at the amino-terminus, variable heavy (VH) or variable light (VL), and the constant domain at the carboxyl terminus, CH1 (heavy) and CL (light). The Fc fragment is composed of two domains formed by dimerization of paired CH2 and CH3 regions. The Fc may elicit effector functions by binding to receptors on immune cells or by binding C1q, the first component of the classical complement pathway. The five classes of antibodies IgM, IgA, IgG, IgE and IgD are defined by distinct heavy chain amino acid sequences, which are called μ , α , γ , ϵ and δ respectively, each heavy chain can pair with either a K or λ light chain. The majority of antibodies in the serum belong to the IgG class, there are four isotypes of human IgG (IgG1, IgG2, IgG3 and IgG4), the sequences of which differ mainly in their hinge region.

[0025] As used herein, “about” means plus or minus 10%.

[0026] Fully human antibodies can be obtained using a variety of methods, for example using yeast-based libraries

or transgenic animals (e.g. mice) that can produce repertoires of human antibodies. Yeast presenting human antibodies on their surface that bind to an antigen of interest can be selected using FACS (Fluorescence-Activated Cell Sorting) based methods or by capture on beads using labelled antigens. Transgenic animals that have been modified to express human immunoglobulin genes can be immunized with an antigen of interest and antigen-specific human antibodies isolated using B-cell sorting techniques. Human antibodies produced using these techniques can then be characterized for desired properties such as affinity, developability and selectivity.

[0027] In some aspects, alternative antibody formats can be used. Alternative antibody formats include alternative scaffolds in which the one or more CDRs of the BCMA antibody can be arranged onto a suitable non-immunoglobulin protein scaffold or skeleton, such as an affibody, a SpA scaffold, an LDL receptor class A domain, an avimer (see, e.g., U.S. Patent Application Publication Nos. 2005/0053973, 2005/0089932, 2005/0164301) or an EGF domain.

[0028] The term “domain” refers to a folded polypeptide structure which retains its tertiary structure independent of the rest of the polypeptide. Generally, domains are responsible for discrete functional properties of polypeptides and in many cases may be added, removed or transferred to other polypeptides without loss of function of the remainder of the protein and/or of the domain.

[0029] The term “single variable domain” refers to a folded polypeptide domain comprising sequences characteristic of antibody variable domains. It therefore includes complete antibody variable domains such as VH, VHH and VL and modified antibody variable domains, for example, in which one or more loops have been replaced by sequences which are not characteristic of antibody variable domains, or antibody variable domains which have been truncated or comprise N- or C-terminal extensions, as well as folded fragments of variable domains which retain at least the binding activity and specificity of the full-length domain. A single variable domain can bind an antigen or epitope independently of a different variable region or domain. A “domain antibody” or “DAB” may be considered the same as a “single variable domain”. A single variable domain may be a human single variable domain, but also includes single variable domains from other species such as rodent (for example, as disclosed in WO 00/29004 A1), nurse shark and Camelid VHH DABs. Camelid VHH are immunoglobulin single variable domain polypeptides that are derived from species including camel, llama, alpaca, dromedary, and guanaco, which produce heavy chain antibodies naturally devoid of light chains. Such VHH domains may be humanized according to standard techniques available in the art, and such domains are considered to be “single variable domains”. As used herein, VH includes camelid VHH domains.

[0030] An antigen binding fragment, BCMA binding protein fragment, functional fragment, biologically active fragment or an immunologically effective fragment may comprise partial heavy or light chain variable sequences. Fragments are at least 5, 6, 8 or 10 amino acids in length. Alternatively, the fragments are at least 15, at least 20, at least 50, at least 75, or at least 100 amino acids in length.

[0031] An antigen binding fragment may be provided by means of arrangement of one or more CDRs on non-antibody protein scaffolds. “Protein Scaffold” as used herein

includes but is not limited to an immunoglobulin (Ig) scaffold, for example an IgG scaffold, which may be a four chain or two chain antibody, or which may comprise only the Fc region of an antibody, or which may comprise one or more constant regions from an antibody, which constant regions may be of human or primate origin, or which may be an artificial chimera of human and primate constant regions.

[0032] The protein scaffold may be an Ig scaffold, for example an IgG, or IgA scaffold. The IgG scaffold may comprise some or all the domains of an antibody (i.e. CH1, CH2, CH3, VH, VL). An antigen binding protein disclosed herein may comprise an IgG scaffold selected from IgG1, IgG2, IgG3, IgG4 or IgG4PE. For example, the scaffold may be IgG1. The scaffold may consist of, or comprise, the Fc region of an antibody, or is a part thereof.

[0033] The protein scaffold may be a derivative of a scaffold selected from the group consisting of CTLA-4, lipocalin, Protein A derived molecules such as Z-domain of Protein A (Affibody, SpA), A-domain (Avimer/Maxibody); heat shock proteins such as GroEl and GroES; transferrin (trans-body); ankyrin repeat protein (DARPin); peptide aptamer; C-type lectin domain (Tetranectin); human γ -crystallin and human ubiquitin (affilins); PDZ domains; scorpion toxin kunitz type domains of human protease inhibitors; and fibronectin/adnectin; which has been subjected to protein engineering in order to obtain binding to an antigen other than the natural ligand.

[0034] “Antigen binding site” refers to a site on an antigen binding protein which is capable of specifically binding to an antigen, this may be a single variable domain, or it may be paired VH/VL domains as can be found on a standard antibody. Single-chain Fv (scFv) domains can also provide antigen-binding sites.

[0035] The term multi-specific antigen binding protein refers to an antigen binding protein that comprises at least two different antigen binding sites. Each of these antigen-binding sites is capable of binding to a different epitope, which may be present on the same antigen or different antigens. The multi-specific antigen binding protein may have specificity for more than one antigen, for example two antigens, or three antigens, or four antigens.

[0036] Classification and formats of bispecific antibodies are comprehensively described in reviews by Labrijn et al 2019 and Brinkmann and Kontermann 2017. Bispecifics may be generally classified as having a symmetric or asymmetric architecture. Bispecifics may have an Fc or may be fragment-based (lacking an Fc). Fragment based bispecifics combine multiple antigen-binding antibody fragments in one molecule without an Fc region e.g. Fab-scFv, Fab-scFv2, orthogonol Fab-Fab, Fab-Fv, tandem scFc (e.g. BiTE and BiKE molecules), Diabody, DART, TandAb, scDiabody, tandem dAb etc.

[0037] Symmetric formats combine multiple binding specificities in a single polypeptide chain or single HL pair including Fc-fusion proteins of fragment-based formats and formats whereby antibody fragments are fused to regular antibody molecules. Examples of symmetric formats may include DVD-Ig, TVD-Ig, CODV-Ig, (scFv)4-Fc, IgG-(scFv)2, Tetravalent DART-Fc, F(ab)₄CrossMab, IgG-HC-scFv, IgG-LC-scFv, mAb-dAb etc.

[0038] Asymmetric formats retain as closely as possible the native architecture of natural antibodies by forcing correct HL chain pairing and/or promoting H chain heterodi-

merization during the co-expression of three (if common heavy or light chains are used) or four polypeptide chains e.g. Triomab, asymmetric reengineering technology immunoglobulin (ART-Ig), CrossMab, Biclomics common light chain, ZW1 common light chain, DuoBody and knobs into holes (KiH), DuetMab, $\kappa\lambda$ body, Xmab, YBODY, HET-mAb, HET-Fab, DART-Fc, SEEDbody, mouse/rat chimeric IgG

[0039] Bispecific formats also include an antibody fused to a non-Ig scaffold such as Affimabs, Fynomabs, Zybodies, and Anticalin-IgG fusions, ImmTAC.

[0040] In some embodiments, an antigen binding protein described herein is a multi-specific antigen binding protein.

[0041] The term “chimeric antigen receptor” (“CAR”) as used herein, refers to an engineered receptor which consists of an extracellular antigen binding domain (which is usually derived from a monoclonal antibody, or fragment thereof, e.g. a VH domain and a VL domain in the form of a scFv), optionally a spacer region, a transmembrane region, and one or more intracellular effector domains. CARs have also been referred to as chimeric T cell receptors or chimeric immunoreceptors (CIRs). CARs are genetically introduced into hematopoietic cells, such as T cells, to redirect T cell specificity for a desired cell-surface antigen, resulting in a CAR-T therapeutic. In some embodiments, a CAR comprises an anti-BCMA antigen binding protein disclosed herein.

[0042] The term “spacer region” as used herein, refers to an oligo- or polypeptide that functions to link the transmembrane domain to the target binding domain. This region may also be referred to as a “hinge region” or “stalk region”. The size of the spacer can be varied depending on the position of the target epitope in order to maintain a set distance (e.g. 14 nm) upon CAR:target binding.

[0043] The term “transmembrane domain” as used herein refers to the part of the CAR molecule which traverses the cell membrane.

[0044] The term “intracellular effector domain” (also referred to as the “signaling domain”) as used herein refers to the domain in the CAR which is responsible for intracellular signaling following the binding of the antigen binding domain to the target. The intracellular effector domain is responsible for the activation of at least one of the normal effector functions of the immune cell in which the CAR is expressed. For example, the effector function of a T cell can be a cytolytic activity or helper activity including the secretion of cytokines.

[0045] It will be appreciated by a person skilled in the art that VH and/or VL domains disclosed herein may be incorporated, e.g. in the form of a scFv, into CAR-T therapeutics.

[0046] Affinity, also referred to as “binding affinity”, is the strength of binding at a single interaction site, i.e. of one molecule, e.g. a BCMA binding protein of the disclosure, to another molecule, e.g. its target antigen, at a single binding site. The binding affinity of an antigen binding protein to its target may be determined by equilibrium methods (e.g. enzyme-linked immunoabsorbent assay (ELISA) or radioimmunoassay (RIA)), or kinetics (e.g. BIACORE analysis).

[0047] Avidity, also referred to as functional affinity, is the cumulative strength of binding at multiple interaction sites, e.g. the sum total of the strength of binding of two molecules (or more, e.g. in the case of a bispecific or multispecific molecule) to one another at multiple sites, e.g. taking into account the valency of the interaction.

[0048] In an embodiment, the equilibrium dissociation constant (KD) of an antigen binding protein disclosed herein—antigen interaction is 100 nM or less, 10 nM or less, 2 nM or less or 1 nM or less. Alternatively, the KD may be between 5 and 10 nM; or between 1 and 2 nM. The KD may be between 1 pM and 500 pM; or between 500 pM and 1 nM. A skilled person will appreciate that the smaller the KD numerical value, the stronger the binding. The reciprocal of KD (i.e. 1/KD) is the equilibrium association constant (KA) having units M⁻¹. A skilled person will appreciate that the larger the KA numerical value, the stronger the binding.

[0049] The dissociation rate constant (kd) or “off-rate” describes the stability of the antigen binding protein-complex, i.e. the fraction of complexes that decay per second. For example, a kd of 0.01 s⁻¹ equates to 1% of the complexes decaying per second. In an embodiment, the dissociation rate constant (kd) is 1×10⁻³ s⁻¹ or less, 1×10⁻⁴ s⁻¹ or less, 1×10⁻⁵ s⁻¹ or less, or 1×10⁻⁶ s⁻¹ or less. The kd may be between 1×10⁻⁵ s⁻¹ and 1×10⁻⁴ s⁻¹; or between 1×10⁻⁴ s⁻¹ and 1×10⁻³ s⁻¹. In some embodiments, the kd of an antigen binding protein disclosed herein is 2.06×10⁻⁴ s⁻¹ or less, 1.58×10⁻⁴ s⁻¹ or less, 1.7×10⁻⁴ s⁻¹ or less, or 5.68×10⁻⁴ s⁻¹ or less, 6.78×10⁻⁴ s⁻¹ or less, 8.26×10⁻⁴ s⁻¹ or less, 5.15×10⁻⁴ s⁻¹ or less, or 5.68×10⁻⁴ s⁻¹ or less.

[0050] The association rate constant (ka) or “on-rate” describes the rate of antigen binding protein-complex formation. In an embodiment, the association rate constant (ka) is 6.49×10⁶ M⁻¹s⁻¹, 4.65×10⁶ M⁻¹s⁻¹, 3.27×10⁶ M⁻¹s⁻¹, 8.28×10⁶ M⁻¹s⁻¹, 1.47×10⁷ M⁻¹s⁻¹, 1.10×10⁷ M⁻¹s⁻¹, 5.90×10⁶ M⁻¹s⁻¹.

[0051] It will be apparent to those skilled in the art that the term “derived” is intended to define not only the source in the sense of it being the physical origin for the material but also to define material which is structurally identical to the material but which does not originate from the reference source.

[0052] By “isolated” it is intended that the molecule, such as a BCMA binding protein, is removed from the environment in which it may be found in nature. For example, the molecule may be purified away from substances with which it would normally exist in nature. For example, the BCMA binding protein can be purified to at least 95%, 96%, 97%,

portion of an immunoglobulin. Thus, “CDRs” as used herein refers to all three heavy chain CDRs, all three light chain CDRs, all heavy and light chain CDRs, or at least two CDRs.

[0054] Throughout this specification, amino acid residues in variable domain sequences and variable domain regions within full-length antigen binding sequences, e.g. within an antibody heavy chain sequence or antibody light chain sequence, are numbered according to the Kabat numbering convention. Similarly, the terms “CDR”, “CDRL1”, “CDRL2”, “CDRL3”, “CDRH1”, “CDRH2”, “CDRH3” used in the Examples follow the Kabat numbering convention. For further information, see Kabat et al., Sequences of Proteins of Immunological Interest, 4th Ed., U.S. Department of Health and Human Services, National Institutes of Health (1987).

Variants

[0055] It will be apparent to those skilled in the art that there are alternative numbering conventions for amino acid residues in variable domain sequences and full-length antibody sequences. There are also alternative numbering conventions for CDR sequences, for example those set out in Chothia et al. (1989) Nature 342: 877-883. For example, the structure and protein folding of a BCMA binding protein may mean that other residues are considered part of the CDR sequence and would be understood to be so by a skilled person.

[0056] Other numbering conventions for CDR sequences available to a skilled person include “AbM” (University of Bath) and “contact” (University College London) methods. The minimum overlapping region using at least two of the Kabat, Chothia, AbM and contact methods can be determined to provide the “minimum binding unit”. The minimum binding unit may be a sub-portion of a CDR.

[0057] Table 1 below represents one definition using each numbering convention for each CDR or binding unit. The Kabat numbering scheme is used in Table 1 to number the variable domain amino acid sequence. It should be noted that some of the CDR definitions may vary depending on the individual publication used.

TABLE 1

	Kabat CDR	Chothia CDR	AbM CDR	Contact CDR	Minimum Binding Unit
H1	31-35/35A/35B	26-32/33/34	26-35/35A/35B	30-35/35A/35B	31-32
H2	50-65	52-56	50-58	47-58	52-56
H3	95-102	95-102	95-102	93-101	95-101
L1	24-34	24-34	24-34	30-36	30-34
L2	50-56	50-56	50-56	46-55	50-55
L3	89-97	89-97	89-97	89-96	89-96

98% or 99%, or greater with respect to a culture media containing the BCMA binding protein. The BCMA binding proteins and antibodies disclosed herein may be isolated BCMA binding proteins and antibodies.

[0053] “CDRs” are defined as the complementarity determining region amino acid sequences of an antigen binding protein. These are the hypervariable regions of immunoglobulin heavy and light chains. There are three heavy chain and three light chain CDRs (or CDR regions) in the variable

[0058] Accordingly, a BCMA binding protein is provided, which comprises any one or a combination of the following CDRs: CDRH1 of SEQ ID NO:1, CDRH2 of SEQ ID NO:2, CDRH3 of SEQ ID NO:3, CDRL1 of SEQ ID NO:4, CDRL2 of SEQ ID NO:5, CDRL3 of SEQ ID NO:6. CDRs may be modified by at least one amino acid substitution, deletion or addition, wherein the variant antigen binding protein substantially retains the biological characteristics of the unmodified protein, such as binding to the antigen.

TABLE 2

Exemplary CDR sequences for an anti-BCMA antigen binding protein.			
	Sequence	SEQ ID NO	
V _H CDR1	NYWMH	1	
V _H CDR2	ATYRGHSDDTYNQKFKG	2	
V _H CDR3	GAITYDGYDVLND	3	
V _L CDR1	SASQDISNYLN	4	
V _L CDR2	YTSNLHS	5	
V _L CDR3	QQYRKLPWT	6	

[0059] It will be appreciated that each of CDR H1, H2, H3, L1, L2, L3 may be modified alone or in combination with any other CDR, in any permutation or combination. In one embodiment, a CDR is modified by the substitution, deletion or addition of up to 3 amino acids, for example 1 or 2 amino acids, for example 1 amino acid. Typically, the modification is a substitution, particularly a conservative substitution, for example as shown in Table 3 below.

TABLE 3

Substitutions.	
Side chain	Members
Hydrophobic	Met, Ala, Val, Leu, Ile
Neutral hydrophilic	Cys, Ser, Thr
Acidic	Asp, Glu
Basic	Asn, Gln, His, Lys, Arg
Residues that influence chain orientation	Gly, Pro
Aromatic	Trp, Tyr, Phe

[0060] For example, in a variant CDR, the flanking residues that comprise the CDR as part of alternative definition (s) e.g. Kabat or Chothia, may be substituted with a conservative amino acid residue.

[0061] The VH or VL (or HC or LC) sequence disclosed herein may be a variant sequence with up to 10 amino acid substitutions, additions or deletions. For example, the variant sequence may have up to 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitution(s), addition(s) or deletion(s). The sequence variation may exclude one or more or all of the CDRs, for example the CDRs are the same as the VH or VL (or HC or LC) sequence and the variation is in the remaining portion of the VH or VL (or HC or LC) sequence, so that the CDR sequences are fixed and intact.

[0062] Alternatively, the heavy chain variable region may have 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, 99% or greater or 100% identity to an amino acid sequence described herein for an antibody; and the light chain variable region may have 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, 99% or greater, or 100% identity to an amino acid sequence disclosed herein for an antibody.

[0063] The heavy chain variable region of an antibody or amino acid sequence disclosed herein may be a variant which may contain 30, 25, 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions, insertions or deletions. The light chain variable region of an antibody or amino acid

sequence disclosed herein may be a variant which may contain 30, 25, 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions, insertions or deletions.

[0064] The term “epitope” as used herein refers to that portion of the antigen that makes contact with a particular binding domain of an antigen binding protein, also known as the paratope. An epitope may be linear or conformational/discontinuous. A conformational or discontinuous epitope comprises amino acid residues that are separated by other sequences, i.e. not in a continuous sequence in the antigen’s primary sequence assembled by tertiary folding of the polypeptide chain. Although the residues may be from different regions of the polypeptide chain, they are in close proximity in the three dimensional structure of the antigen. In the case of multimeric antigens, a conformational or discontinuous epitope may include residues from different peptide chains. Particular residues comprised within an epitope can be determined through computer modelling programs or via three-dimensional structures obtained through methods known in the art, such as X-ray crystallography. Epitope mapping can be carried out using various techniques known to persons skilled in the art as described in publications such as *Methods in Molecular Biology ‘Epitope Mapping Protocols’*, Mike Schutkowski and Ulrich Reineke (volume 524, 2009) and Johan Rockberg and Johan Nilvebrant (volume 1785, 2018).

[0065] Exemplary methods include peptide based approaches such as pepscan whereby a series of overlapping peptides are screened for binding using techniques such as ELISA or by in vitro display of large libraries of peptides or protein mutants, e.g. on phage. Detailed epitope information can be determined by structural techniques including X-ray crystallography, solution nuclear magnetic resonance (NMR) spectroscopy and cryogenic-electron microscopy (cryo-EM). Mutagenesis, such as alanine scanning, is an effective approach whereby loss of binding analysis is used for epitope mapping. Another method is hydrogen/deuterium exchange (HDX) combined with proteolysis and liquid-chromatography mass spectrometry (LC-MS) analysis to characterize discontinuous or conformational epitopes.

Percent Identity

[0066] “Percent identity” between a query nucleic acid sequence and a subject nucleic acid sequence is the “Identities” value, expressed as a percentage, that is calculated using a suitable algorithm or software, such as BLASTN, FASTA, DNASTAR Lasergene, GeneDoc, Bioedit, EMBOSS needle or EMBOSS infoalign, over the entire length of the query sequence after a pair-wise global sequence alignment has been performed using a suitable algorithm or software, such as BLASTN, FASTA, ClustalW, MUSCLE, MAFFT, EMBOSS Needle, T-Coffee, and DNASTAR Lasergene. Importantly, a query nucleic acid sequence may be described by a nucleic acid sequence identified in one or more claims herein.

[0067] “Percent identity” between a query amino acid sequence and a subject amino acid sequence is the “Identities” value, expressed as a percentage, that is calculated using a suitable algorithm or software, such as BLASTP, FASTA, DNASTAR Lasergene, GeneDoc, Bioedit, EMBOSS needle or EMBOSS infoalign, over the entire length of the query sequence after a pair-wise global sequence alignment has been performed using a suitable algorithm/software such as BLASTP, FASTA, ClustalW,

MUSCLE, MAFFT, EMBOSS Needle, T-Coffee, and DNASTAR Lasergene. Importantly, a query amino acid sequence may be described by an amino acid sequence identified in one or more claims herein.

[0068] The query sequence may be 100% identical to the subject sequence, or it may include up to a certain integer number of amino acid or nucleotide alterations as compared to the subject sequence such that the % identity is less than 100%. For example, the query sequence is at least 50, 60, 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99% identical to the subject sequence. Such alterations include at least one amino acid deletion, substitution (including conservative and non-conservative substitution), or insertion, and wherein said alterations may occur at the amino- or carboxy-terminal positions of the query sequence or anywhere between those terminal positions, interspersed either individually among the amino acids or nucleotides in the query sequence or in one or more contiguous groups within the query sequence.

[0069] The % identity may be determined across the entire length of the query sequence, including the CDRs. Alternatively, the % identity may exclude one or more or all of the CDRs, for example all of the CDRs are 100% identical to the subject sequence and the % identity variation is in the remaining portion of the query sequence, e.g. the framework sequence, so that the CDR sequences are fixed and intact. In some embodiments, an anti-BCMA binding protein disclosed herein comprises a sequence that is at least about 50, 60, 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99% identical to a sequence disclosed herein.

Modifications

[0070] The terms “peptide”, “polypeptide” and “protein” each refers to a molecule comprising two or more amino acid residues. A peptide may be monomeric or polymeric.

[0071] Fc engineering methods can be applied to modify the functional or pharmacokinetics properties of an antibody. Effector function may be altered by making mutations in the Fc region that increase or decrease binding to C1q or Fcγ receptors and modify CDC or ADCC activity respectively. Modifications to the glycosylation pattern of an antibody can also be made to change the effector function. The in vivo half-life of an antibody can be altered by making mutations that affect binding of the Fc to the FcRn (Neonatal Fc Receptor).

[0072] The term “Effector Function” as used herein refers to one or more of antibody-mediated effects including antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-mediated complement activation including complement-dependent cytotoxicity (CDC), complement-dependent cell-mediated phagocytosis (CDCP), antibody dependent complement-mediated cell lysis (ADCML), and Fc-mediated phagocytosis or antibody-dependent cellular phagocytosis (ADCP).

[0073] The interaction between the Fc region of an antigen binding protein or antibody and various Fc receptors (FcR), including FcγRI (CD64), FcγRII (CD32), FcγRIII (CD16), FcRn, C1q, and type II Fc receptors is believed to mediate the effector functions of the antigen binding protein or antibody. Significant biological effects can be a consequence of effector functionality. Usually, the ability to mediate effector function requires binding of the antigen binding protein or antibody to an antigen and not all antigen binding proteins or antibodies will mediate every effector function.

[0074] Effector function can be assessed in a number of ways including, for example, evaluating ADCC effector function of antibody coated to target cells mediated by Natural Killer (NK) cells via FcγRIII, or monocytes/macrophages via FcγRI, or evaluating CDC effector function of antibody coated to target cells mediated by complement cascade via C1q. For example, an antigen binding protein of the present invention can be assessed for ADCC effector function in a Natural Killer cell assay. Examples of such assays can be found in Shields et al, 2001, *The Journal of Biological Chemistry*, Vol. 276, p. 6591-6604; Chappel et al, 1993, *The Journal of Biological Chemistry*, Vol 268, p. 25124-25131; Lazar et al, 2006, *PNAS*, 103; 4005-4010.

[0075] Examples of assays to determine CDC function include those described in J Imm Meth, 1995, 184: 29-38.

[0076] The effects of mutations on effector functions (e.g., FcRn binding, FcγRs and C1q binding, CDC, ADCML, ADCC, ADCP) can be assessed, e.g., as described in Grevys et al., *J Immunol.* 2015 Jun. 1; 194(11): 5497-5508, or Tam et al., *Antibodies* 2017, 6(3); Monnet et al., 2014 *mAbs*, 6:2, 422-436.

[0077] Throughout this specification, amino acid residues in Fc regions, in antibody sequences or full-length antigen binding protein sequences, are numbered according to the EU index numbering convention.

[0078] Human IgG1 constant regions containing specific mutations have been shown to enhance binding to Fc receptors. In some cases these mutations have also been shown to enhance effector functions, such as ADCC and CDC, as described below. Antigen binding proteins of the present invention may include any of the following mutations.

[0079] Enhanced CDC: Fc engineering can be used to enhance complement-based effector function. For example (with reference to IgG1), K326W/E333S; S267E/H268F/S324T; and IgG1/IgG3 cross subclass can increase C1q binding; E345R (Diebolder et al., *Science* 2014; 343: 1260-1293) and E345R/E430G/S440Y results in preformed IgG hexamers (Wang et al., *Protein Cell.* 2018 January; 9(1): 63-73).

[0080] Enhanced ADCC: Fc engineering can be used to enhance ADCC. For example (with reference to IgG1), F243L/R292P/Y300L/V305I/P396L; S239D/I332E; and S298A/E333A/K334A increase FcγRIIIa binding; S239D/I332E/A330L increases FcγRIIIa binding and decreases FcγRIIb binding; G236A/S239D/I332E improves binding to FcγRIIa, improves the FcγRIIa/FcγRIIb binding ratio (activating/inhibitory ratio), and enhances phagocytosis of antibody-coated target cells by macrophages. An asymmetric Fc in which one heavy chain contains L234Y/L235Q/G236W/S239M/H268D/D270E/S298A mutations and D270E/K326D/A330M/K334E in the opposing heavy chain, increases affinity for FcγRIIIa F158 (a lower-affinity allele) and FcγRIIIa V158 (a higher-affinity allele) with no increased binding affinity to inhibitory FcγRIIb (Mimoto et al., 2013).

[0081] Enhanced ADCP: Fc engineering can be used to enhance ADCP. For example (with reference to IgG1), G236A/S239D/I332E increases FcγRIIa binding and increases FcγRIIIa binding (Richards J et al., *Mol. Cancer Ther.* 2008; 7: 2517-2527).

[0082] Increased co-engagement: Fc engineering can be used to increase co-engagement with FcRs. For example (with reference to IgG1), S267E/L328F increases FcγRIIb

binding; N325S/L328F increases FcγRIIa binding and decreases FcγRIIIa binding (Wang et al. 2018).

Glycosylation

[0083] An antigen binding protein of the present invention may comprise a heavy chain constant region with an altered glycosylation profile, such that the antigen binding protein has an enhanced effector function, e.g. enhanced ADCC, enhanced CDC, or both enhanced ADCC and CDC. Examples of suitable methodologies to produce antigen binding proteins with an altered glycosylation profile are described in WO2003011878, WO2006014679 and EP1229125, all of which can be applied to the antigen binding proteins of the present invention.

[0084] The absence of the α1,6 innermost fucose residues on the Fc glycan moiety on N297 of IgG1 antibodies enhances affinity for FcγRIIIA. As such, afucosylated or low fucosylated monoclonal antibodies may have increased therapeutic efficacy (Shields et al., J Biol Chem. 2002, 277(30): 26733-40 and Monnet et al., 2014, mAbs, 6:2, 422-436).

Potelligent

[0085] The present disclosure also provides a method of producing an antigen binding protein according to the invention comprising the steps of:

[0086] a) culturing a recombinant host cell comprising an expression vector comprising the isolated nucleic acid as described herein, wherein the FUT8 gene encoding alpha-1,6-fucosyltransferase has been inactivated in the recombinant host cell; and

[0087] b) recovering the antigen binding protein.

[0088] Such methods for the production of antigen binding proteins can be performed, for example, using the POTEILLIGENT technology system available from BioWa, Inc. (Princeton, NJ) in which CHOK1SV cells lacking a functional copy of the FUT8 gene produce monoclonal antibodies having enhanced ADCC activity that is increased relative to an identical monoclonal antibody produced in a cell with a functional FUT8 gene as described in U.S. Pat. Nos. 7,214,775, 6,946,292, WO0061739 and WO0231240, all of which are incorporated herein by reference. Those of ordinary skill in the art will also recognize other appropriate systems.

[0089] In an embodiment of the disclosure, the antigen binding protein is produced in a host cell in which the FUT8 gene has been inactivated. In an embodiment of the invention, the antigen binding protein is produced in a $-/-$ FUT8 host cell. In an embodiment of the invention, the antigen binding protein is afucosylated at Asn297 (IgG1)

[0090] In some embodiments, it may be desirable to modify the effector function of an antigen binding protein disclosed herein, for instance, to enhance ADCC or CDC, half-life, etc. In an embodiment, an antigen binding protein may be Fc disabled. One way to achieve Fc disablement comprises the substitutions of alanine residues at positions 235 and 237 (EU index numbering) of the heavy chain constant region. Alternatively, an antigen binding protein may be Fc enabled and not comprise the alanine substitutions at positions 235 and 237. An antigen binding protein may have a half-life of at least 6 hours, at least 1 day, at least

2 days, at least 3 days, at least 4 days, at least 5 days, at least 7 days, or at least 9 days in vivo in humans, or in a murine animal model.

[0091] Mutational changes to the Fc effector portion of the antibody can be used to change the affinity of the interaction between the FcRn and antibody to modulate antibody turnover. The half-life of the antibody can be extended in vivo. This could be beneficial to patient populations as maximal dose amounts and maximal dosing frequencies could be achieved as a result of maintaining in vivo IC_{50} for longer periods of time.

[0092] In some embodiments, an antigen binding protein comprising a constant region may have reduced ADCC and/or complement activation or effector functionality. The constant domain may comprise a naturally disabled constant region of IgG2 or IgG4 isotype or a mutated IgG1 constant domain. Examples of suitable modifications are described in EP0307434. One way to achieve Fc disablement comprises the substitutions of alanine residues at positions 235 and 237 (EU index numbering) of the heavy chain constant region, i.e. L235A and G237A (commonly referred to as “LAGA” mutations). Another example comprises substitution with alanines at positions 234 and 235 (EU index numbering), i.e. L234A and L235A (commonly referred to as “LALA” mutations). In some embodiments, the Fc effector function of an antigen binding protein disclosed herein has been disabled using the LAGA mutation.

[0093] Additional alterations and mutations to decrease effector function include: (with reference to IgG1 unless otherwise noted): a glycosylated N297A or N297Q or N297G; L235E; IgG4:F234A/L235A; and chimeric IgG2/IgG4. IgG2: H268Q/V309L/A330S/P331S, and IgG2: V234A/G237A/P238S/H268A/V309L/A330S/P331S can reduce FcγR and C1q binding (Wang et al. 2018 and U.S. Pat. No. 8,961,967).

[0094] Other mutations that decrease effector function include L234F/L235E/P331S; a chimeric antibody created using the CH1 and hinge region from human IgG2 and the CH2 and CH3 regions from human IgG4; IgG2m4, based on the IgG2 isotype with four key amino acid residue changes derived from IgG4 (H268Q, V309L, A330S and P331S); IgG26 which contains V234A/G237A/P238S/H268A/V309L/A330S/P331S substitutions to eliminate affinity for Fcγ receptors and C1q complement protein; IgG2m4 (H268Q/V309L/A330S/P331S, changes to IgG4); IgG4 (S228P/L234A/L235A); huIgG1 L234A/L235A (AA); huIgG4 S228P/L234A/L235A; IgG1σ (L234A/L235A/G237A/P238S/H268A/A330S/P331S); IgG4σ1 (S228P/F234A/L235A/G237A/P238S); and IgG4σ2 (S228P/F234A/L235A/G236/G237A/P238S) (Tam et al., Antibodies 2017, 6(3)).

[0095] In some embodiments, an antigen binding protein disclosed herein may comprise one or more modifications selected from a mutated constant domain such that the antibody has enhanced effector functions/ADCC and/or complement activation. Examples of suitable modifications are described in Shields et al. J. Biol. Chem. (2001) 276: 6591-6604, Lazar et al. PNAS (2006) 103:4005-4010 and U.S. Pat. No. 6,737,056, WO2004063351 and WO2004029207. The antigen binding protein may comprise a constant domain with an altered glycosylation profile such that the antigen binding protein has enhanced effector functions/ADCC and/or complement activation. Examples of suitable methodologies to produce an antigen binding pro-

tein with an altered glycosylation profile are described in WO2003/011878, WO2006/014679 and EP1229125.

Half-Life

[0096] Half-life refers to the time required for the serum concentration of an antigen binding protein to reach half of its original value. The serum half-life of proteins can be measured by pharmacokinetic studies according to the method described by Kim et al., 1994, *Eur. J. of Immuno.* 24: 542-548. According to this method, radio-labelled protein is injected intravenously into mice and its plasma concentration is periodically measured as a function of time, for example, at about 3 minutes to about 72 hours after the injection. Other methods for pharmacokinetic analysis and determination of the half-life of a molecule will be familiar to those skilled in the art.

[0097] Antigen binding proteins of the present invention may have amino acid modifications that increase the affinity of the constant domain or fragment thereof for FcRn. Increasing the half-life (i.e., serum half-life) of therapeutic and diagnostic IgG antibodies and other bioactive molecules has many benefits including reducing the amount and/or frequency of dosing of these molecules. In one embodiment, an antigen binding protein of the invention comprises all or a portion (an FcRn binding portion) of an IgG constant domain having one or more of the following amino acid modifications.

[0098] For example, with reference to IgG1, M252Y/S254T/T256E (commonly referred to as “YTE” mutations) and M428L/N434S (commonly referred to as “LS” mutations) increase FcRn binding at pH 6.0 (Wang et al. 2018).

[0099] Half-life can also be enhanced by T250Q/M428L, V259I/V308F/M428L N434A, and T307A/E380A/N434A mutations (with reference to IgG1 and Kabat numbering) (Monnet et al.).

[0100] Half-life and FcRn binding can also be extended by introducing H433K and N434F mutations (commonly referred to as “HN” or “NHance” mutations) (with reference to IgG1) (WO2006/130834).

[0101] WO00/42072 discloses a polypeptide comprising a variant Fc region with altered FcRn binding affinity, which polypeptide comprises an amino acid modification at any one or more of amino acid positions 238, 252, 253, 254, 255, 256, 265, 272, 286, 288, 303, 305, 307, 309, 311, 312, 317, 340, 356, 360, 362, 376, 378, 380, 386, 388, 400, 413, 415, 424, 433, 434, 435, 436, 439, and 447 of the Fc region (EU index numbering).

[0102] WO02/060919 discloses a modified IgG comprising an IgG constant domain comprising one or more amino acid modifications relative to a wild-type IgG constant domain, wherein the modified IgG has an increased half-life compared to the half-life of an IgG having the wild-type IgG constant domain, and wherein the one or more amino acid modifications are at one or more of positions 251, 253, 255, 285-290, 308-314, 385-389, and 428-435.

[0103] Shields et al. (2001, *J Biol Chem*; 276:6591-604) used alanine scanning mutagenesis to alter residues in the Fc region of a human IgG1 antibody and then assessed the binding to human FcRn. Positions that effectively abrogated binding to FcRn when changed to alanine include 1253, S254, H435, and Y436. Other positions showed a less pronounced reduction in binding as follows: E233-G236, R255, K288, L309, S415, and H433. Several amino acid positions exhibited an improvement in FcRn binding when

changed to alanine; notable among these are P238, T256, E272, V305, T307, Q311, D312, K317, D376, E380, E382, S424, and N434. Many other amino acid positions exhibited a slight improvement (D265, N286, V303, K360, Q362, and A378) or no change (S239, K246, K248, D249, M252, E258, T260, S267, H268, S269, D270, K274, N276, Y278, D280, V282, E283, H285, T289, K290, R292, E293, E294, Q295, Y296, N297, S298, R301, N315, E318, K320, K322, S324, K326, A327, P329, P331, E333, K334, T335, S337, K338, K340, Q342, R344, E345, Q345, Q347, R356, M358, T359, K360, N361, Y373, S375, S383, N384, Q386, E388, N389, N390, K392, L398, S400, D401, K414, R416, Q418, Q419, N421, V422, E430, T437, K439, S440, S442, S444, and K447) in FcRn binding.

[0104] The most pronounced effect with respect to improved FcRn binding was found for combination variants. At pH 6.0, the E380A/N434A variant showed over 8-fold better binding to FcRn, relative to native IgG1, compared with 2-fold for E380A and 3.5-fold for N434A. Adding T307A to this resulted in a 12-fold improvement in binding relative to native IgG1. In one embodiment the antigen binding protein of the invention comprises the E380A/N434A mutations and has increased binding to FcRn.

[0105] Dall’Acqua et al. (2002, *J Immunol.*; 169:5171-80) describes random mutagenesis and screening of human IgG1 hinge-Fc fragment phage display libraries against mouse FcRn. They disclosed random mutagenesis of positions 251, 252, 254-256, 308, 309, 311, 312, 314, 385-387, 389, 428, 433, 434, and 436. The major improvements in IgG1-human FcRn complex stability occur when substituting residues located in a band across the Fc-FcRn interface (M252, S254, T256, H433, N434, and Y436) and to lesser extent substitutions of residues at the periphery, such as V308, L309, Q311, G385, Q386, P387, and N389. The variant with the highest affinity to human FcRn was obtained by combining the M252Y/S254T/T256E (“YTE”) and H433K/N434F/Y436H mutations and exhibited a 57-fold increase in affinity relative to the wild-type IgG1. The in vivo behavior of such a mutated human IgG1 exhibited a nearly 4-fold increase in serum half-life in cynomolgus monkey as compared to wild-type IgG1.

[0106] The present invention therefore provides an antigen binding protein with optimized binding to FcRn. In a preferred embodiment, the antigen binding protein comprises at least one amino acid modification in the Fc region of said antigen binding protein, wherein said modification is at an amino acid position selected from the group consisting of 226, 227, 228, 230, 231, 233, 234, 239, 241, 243, 246, 250, 252, 256, 259, 264, 265, 267, 269, 270, 276, 284, 285, 288, 289, 290, 291, 292, 294, 297, 298, 299, 301, 302, 303, 305, 307, 308, 309, 311, 315, 317, 320, 322, 325, 327, 330, 332, 334, 335, 338, 340, 342, 343, 345, 347, 350, 352, 354, 355, 356, 359, 360, 361, 362, 369, 370, 371, 375, 378, 380, 382, 384, 385, 386, 387, 389, 390, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 403, 404, 408, 411, 412, 414, 415, 416, 418, 419, 420, 421, 422, 424, 426, 428, 433, 434, 438, 439, 440, 443, 444, 445, 446 and 447 of the Fc region.

[0107] Additionally, various publications describe methods for obtaining physiologically active molecules with modified half-lives, either by introducing an FcRn-binding polypeptide into the molecules (WO97/43316, U.S. Pat. Nos. 5,869,046, 5,747,035, WO96/32478 and WO91/14438) or by fusing the molecules with antibodies whose FcRn-binding affinities are preserved, but affinities for other Fc

receptors have been greatly reduced (WO99/43713), or fusing with FcRn binding domains of antibodies (WO00/09560, U.S. Pat. No. 4,703,039).

[0108] FcRn affinity enhanced Fc variants to improve both antibody cytotoxicity and half-life were identified in screens at pH 6.0. The selected IgG variants can be produced as low fucosylated molecules. The resulting variants show increased serum persistence in hFcRn mice, as well as conserved enhanced ADCC (Monnet et al.) Exemplary variants include (with reference to IgG1 and Kabat numbering): P230T/V303A/K322R/N389T/F404L/N434S; P228R/N434S; Q311R/K334R/Q342E/N434Y; C226G/Q386R/N434Y; T307P/N389T/N434Y; P230S/N434S; P230T/V305A/T307A/A378V/L398P/N434S; P230T/P387S/N434S; P230Q/E269D/N434S; N276S/A378V/N434S; T307A/N315D/A330V/382V/N389T/N434Y; T256N/A378V/S383N/N434Y; N315D/A330V/N361D/A387V/N434Y; V259I/N315D/M428L/N434Y; P230S/N315D/M428L/N434Y; F241L/V264E/T307P/A378V/H433R; T250A/N389K/N434Y; V305A/N315D/A330V/P395A/N434Y; V264E/Q386R/P396L/N434S/K439R; E294del/T307P/N434Y (wherein 'del' indicates a deletion).

Antibody Drug Conjugate

[0109] Also provided is an immunoconjugate (interchangeably referred to as an "antibody-drug conjugate", "ADC" or "antigen binding protein-drug conjugate") comprising an antigen binding protein according to the invention conjugated to one or more drugs, such as a cytotoxic agent, such as a chemotherapeutic agent, an immunotherapeutic agent, a growth inhibitory agent, a toxin (e.g., a protein toxin, such as an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), an antiviral agent, a radioactive isotope (i.e., a radioconjugate), an antibiotic, or a small interfering RNA (siRNA).

[0110] Immunoconjugates have been used for the local delivery of cytotoxic agents, i.e., drugs that kill or inhibit the growth or proliferation of cells, in the treatment of cancer (Lambert, J. (2005) *Curr. Opin. in Pharmacology* 5:543-549; Wu et al. (2005) *Nature Biotechnology* 23(9):1137-1146; Payne, G. (2003) *i* 3:207-212; Syrigos and Epenetos (1999) *Anticancer Research* 19:605-614; Niculescu-Duvaz and Springer (1997) *Adv. Drug Deliv. Rev.* 26:151-172; U.S. Pat. No. 4,975,278). Immunoconjugates allow for, inter alia, the targeted delivery of a drug moiety to a tumor, and intracellular accumulation therein, where systemic administration of unconjugated drugs may result in unacceptable levels of toxicity to normal cells (Tsuchikama and An, *Protein and Cell*, (2018) 9: 33-46). Immunoconjugates can enable selective delivery of a potent cytotoxic payload to target cancer cells, resulting in improved efficacy, reduced systemic toxicity, and preferable pharmacokinetics (PK)/pharmacodynamics (PD) and biodistribution compared to traditional chemotherapy (Tsuchikama and An 2018); Beck A. et al (2017) *Nature Rev. Drug Disc.* 16: 315-337).

[0111] Both polyclonal antibodies and monoclonal antibodies have been reported as useful in these strategies (Rowland et al., (1986) *Cancer Immunol. Immunother.* 21:183-87). Drugs used in these methods include daunomycin, doxorubicin, methotrexate, and vindesine (Rowland et al., (1986) *supra*). Toxins used in antibody-toxin conjugates include bacterial toxins such as diphtheria toxin, plant toxins such as ricin, small molecule toxins such as geldanamycin (Mandler et al (2000) *J. Nat. Cancer Inst.* 92(19):1573-1581;

Mandler et al (2000) *Bioorganic & Med. Chem. Letters* 10:1025-1028; Mandler et al (2002) *Bioconjugate Chem.* 13:786-791), maytansinoids (EP 1391213; Liu et al., (1996) *Proc. Natl. Acad. Sci. USA* 93:8618-8623), and calicheamicin (Lode et al (1998) *Cancer Res.* 58:2928; Hinman et al (1993) *Cancer Res.* 53:3336-3342).

[0112] In certain embodiments, an immunoconjugate comprises an antigen binding protein, such as an antibody, and a drug, such as toxin, such as a chemotherapeutic agent. The drug can be modified (e.g., via standard synthetic chemistry) to allow its chemical attachment (e.g., to contain a reaction handle to allow its chemical attachment) to a reactive end of a linker that joins the drug to the antigen binding protein.

Drug Component of Immunoconjugate

[0113] Drugs, such as chemotherapeutic agents, useful in the generation of immunoconjugates are described herein. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolacca americana* proteins (PAPI, PAPII, and PAP-S), *Momordica charantia* inhibitor, curcumin, croton, *Sapaonaria officinalis* inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. See, e.g., WO 93/21232 published Oct. 28, 1993.

[0114] In addition to toxins, a radioactive material, such as a radionucleotide, may be used as the drug in an ADC. A variety of radionucleotides are available for the production of radioconjugated antibodies. Examples include ²¹²Bi, ¹³¹I, ¹³¹In, ⁹⁰Y, and ¹⁸⁶Re.

[0115] Antigen binding proteins (such as antibodies) of the present invention may also be conjugated to one or more toxins, including, but not limited to, a calicheamicin, a maytansinoid, a dolastatin, an auristatin, a tricothecene, and CC1065, and a derivative of these toxins that have toxin activity. Suitable cytotoxic agents include, but are not limited to, an auristatin including dovaline-valine-dolaisoleu-nine-dolaproine-phenylalanine (MMAF) and monomethyl auristatin E (MMAE) as well as an ester form of MMAE, a DNA minor groove binding agent, a DNA minor groove alkylating agent, an enediyne, a lexitropsin, a duocarmycin, a taxane (such as paclitaxel and docetaxel), a puromycin, a dolastatin, a maytansinoid, and a vinca alkaloid. Specific cytotoxic agents include topotecan, morpholino-doxorubicin, rhizoxin, cyanomorpholino-doxorubicin, dolastatin-10, echinomycin, combretastatin, calicheamicin, maytansine, DM-1, DM-4, and netropsin. Other suitable cytotoxic agents include anti-tubulin agents, such as an auristatin, a vinca alkaloid, a podophyllotoxin, a taxane, a baccatin derivative, a cryptophycin, a maytansinoid, a combretastatin, or a dolastatin. Antitubulin agents include dimethylvaline-valine-dolaisoleu-nine-dolaproine-phenylalanine-p-phenylenediamine (AFP), MMAF, MMAE, auristatin E, vincristine, vinblastine, vindesine, vinorelbine, VP-16, camptothecin, paclitaxel, docetaxel, epothilone A, epothilone B, nocodazole, colchicines, colcemid, estramustine, cemadotin, discodermolide, maytansine, DM-1, DM-4, and eleutherobin.

[0116] Antibody drug conjugates can be produced by conjugating the anti-tubulin agent monomethylauristatin E (MMAE) or monomethylauristatin F (MMAF) to an antigen binding protein (such as an antibody). In the case of MMAE,

the linker can consist of a thiol-reactive maleimide, a caproyl spacer, the dipeptide valine-citrulline, or p-amino-benzyloxycarbonyl, a self-immolative fragmenting group. In the case of MMAF, a protease-resistant maleimidocaproyl linker can be used. The conjugation process leads to heterogeneity in drug-antibody attachment, varying in both the number of drugs bound to each antibody molecule (mole ratio [MR]), and the site of attachment. The most prevalent species is the material with an MR=4; less prevalent are materials with MR of 0, 2, 6, and 8. The overall average drug-to-antibody MR is approximately 4.

Auristatins and Dolastatins

[0117] In some embodiments, the immunoconjugate comprises an antigen binding protein (such as an antibody) conjugated to a dolastatin or a dolostatin peptidic analog or derivative, an auristatin (U.S. Pat. Nos. 5,635,483; 5,780,588). Dolastatins and auristatins have been shown to interfere with microtubule dynamics, GTP hydrolysis, and nuclear and cellular division (Woyke et al. (2001) *Antimicrob. Agents and Chemother.* 45(12):3580-3584) and have anticancer (U.S. Pat. No. 5,663,149) and antifungal activity (Pettit et al. (1998) *Antimicrob. Agents Chemother.* 42:2961-2965). The dolastatin or auristatin (a pentapeptide derivative of dolastatin) drug moiety may be attached to the antibody through the N (amino) terminus or the C (carboxyl) terminus of the peptidic drug moiety (WO 02/088172).

[0118] Exemplary auristatin embodiments include the N-terminus linked monomethylauristatin drug moieties DE and DF, disclosed in "Monomethylvaline Compounds Capable of Conjugation to Ligands," U.S. Pat. No. 7,498,298. As used herein, the abbreviation "MMAE" refers to monomethyl auristatin E. As used herein the abbreviation "MMAF" refers to dovaline-valine-dolaisoleuine-dolaproline-phenylalanine.

[0119] Typically, peptide-based drug moieties can be prepared by forming a peptide bond between two or more amino acids and/or peptide fragments. Such peptide bonds can be prepared, for example, according to the liquid phase synthesis method (see E. Schroder and K. Lubke, "The Peptides," volume 1, pp 76-136, 1965, Academic Press) that is well known in the field of peptide chemistry. The auristatin/dolastatin drug moieties may be prepared according to the methods of: U.S. Pat. Nos. 5,635,483; 5,780,588; Pettit et al. (1989) *J. Am. Chem. Soc.* 111:5463-5465; Pettit et al. (1998) *Anti-Cancer Drug Design* 13:243-277; Pettit, G. R., et al. *Synthesis*, 1996, 719-725; and Pettit et al. (1996) *J. Chem. Soc. Perkin Trans.* 15:859-863. See also Doronina (2003) *Nat Biotechnol* 21(7):778-784; "Monomethylvaline Compounds Capable of Conjugation to Ligands," U.S. Pat. No. 7,498,298, (disclosing, e.g., linkers and methods of preparing monomethylvaline compounds such as MMAE and MMAF conjugated to linkers). Biologically active organic compounds that act as cytotoxic agents, specifically pentapeptides, are disclosed in U.S. Pat. Nos. 6,884,869; 7,498,298; 7,098,308; 7,256,257; and 7,423,116.

Maytansine and Maytansinoids

[0120] Maytansinoids are mitototic inhibitors that act by inhibiting tubulin polymerization. Maytansine was first isolated from the east African shrub *Maytenus serrata* (U.S. Pat. No. 3,896,111). Subsequently, it was discovered that certain microbes also produce maytansinoids, such as may-

tansinol and C-3 maytansinol esters (U.S. Pat. No. 4,151,042). Highly cytotoxic maytansinoid drugs can be prepared from ansamitocin precursors produced by fermentation of microorganisms such as *Actinosynnema*. Methods for isolating ansamitocins are described in U.S. Pat. No. 6,573,074. Synthetic maytansinol and derivatives and analogues thereof are disclosed, for example, in U.S. Pat. Nos. 4,137,230; 4,248,870; 4,256,746; 4,260,608; 4,265,814; 4,294,757; 4,307,016; 4,308,268; 4,308,269; 4,309,428; 4,313,946; 4,315,929; 4,317,821; 4,322,348; 4,331,598; 4,361,650; 4,364,866; 4,424,219; 4,450,254; 4,362,663; and 4,371,533.

[0121] Antibody-maytansinoid conjugates are prepared by chemically linking an antigen binding protein (such as an antibody) to a maytansinoid molecule without significantly diminishing the biological activity of either the antibody or the maytansinoid molecule. See, e.g., U.S. Pat. No. 5,208,020. An average of 3-4 maytansinoid molecules conjugated per antibody molecule has shown efficacy in enhancing cytotoxicity of target cells without negatively affecting the function or solubility of the antibody, although even one molecule of toxin/antibody would be expected to enhance cytotoxicity over the use of naked antibody. Maytansinoids are well known in the art and can be synthesized by known techniques or isolated from natural sources. Suitable maytansinoids are disclosed, for example, in U.S. Pat. No. 5,208,020 and in the other patents and nonpatent publications referred to hereinabove. Maytansinoids are maytansinol and maytansinol analogues modified in the aromatic ring or at other positions of the maytansinol molecule, such as various maytansinol esters. Methods for preparing maytansinoids for linkage with antibodies are disclosed, e.g., in U.S. Pat. Nos. 6,570,024 and 6,884,874.

Calicheamicin

[0122] The calicheamicin family of antibiotics is capable of producing double-stranded DNA breaks at sub-picomolar concentrations. For the preparation of conjugates of the calicheamicin family, see, e.g., U.S. Pat. Nos. 5,712,374, 5,714,586, 5,739,116, 5,767,285, 5,770,701, 5,770,710, 5,773,001, and 5,877,296. Structural analogues of calicheamicin that may be used include, but are not limited to, 11, 21, 31, N-acetyl 11, PSAG and 11 (Hinman et al., *Cancer Research* 53:3336-3342 (1993), Lode et al., *Cancer Research* 58:2925-2928 (1998) and the aforementioned U.S. patents). Another anti-tumor drug that the antibody can be conjugated to is QFA, which is an antifolate. Both calicheamicin and QFA have intracellular sites of action and do not readily cross the plasma membrane. Therefore, cellular uptake of these agents through antibody mediated internalization greatly enhances their cytotoxic effects.

Other Cytotoxic Agents

[0123] Other cytotoxic agents, such as antitumor agents, that can be conjugated to an antigen binding protein (such as an antibody) include BCNU, streptozocin, vincristine and 5-fluorouracil, the family of agents known collectively LL-E33288 complex described in U.S. Pat. Nos. 5,053,394 and 5,770,710, as well as esperamicins (U.S. Pat. No. 5,877,296).

[0124] Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain,

modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolacca americana* proteins (PAPI, PAPII, and PAP-S), *Momordica charantia* inhibitor, curcin, crotin, *Sapaonaria officinalis* inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin and the tricothecenes. See, for example, WO 93/21232 published Oct. 28, 1993.

[0125] The present invention further contemplates an immunoconjugate formed between an antigen binding protein (such as an antibody) and a compound with nucleolytic activity (e.g., a ribonuclease or a DNA endonuclease such as a deoxyribonuclease; DNase).

[0126] For selective destruction of the tumor, the antigen binding protein (such as an antibody) may comprise a highly radioactive atom. A variety of radioactive isotopes are available for the production of radioconjugated antibodies. Examples include At211, I131, I125, Y90, Re186, Re188, Sm153, Bi212, P32, Pb212 and radioactive isotopes of Lu. When the conjugate is used for detection, it may comprise a radioactive atom for scintigraphic studies, for example tc99m or I123, or a spin label for nuclear magnetic resonance (NMR) imaging (also known as magnetic resonance imaging, mri), such as iodine-123 again, iodine-131, indium-111, fluorine-19, carbon-13, nitrogen-15, oxygen-17, gadolinium, manganese or iron.

[0127] The radio- or other labels may be incorporated in the conjugate in known ways. For example, the peptide may be biosynthesized or may be synthesized by chemical amino acid synthesis using suitable amino acid precursors involving, for example, fluorine-19 in place of hydrogen. Labels such as tc99m or I123, Re186, Re188 and In111 can be attached via a cysteine residue in the peptide. Yttrium-90 can be attached via a lysine residue. The IODOGEN method (Fraker et al. (1978) Biochem. Biophys. Res. Commun. 80: 49-57) can be used to incorporate iodine-123. "Monoclonal Antibodies in Immunoscintigraphy" (Chatal, CRC Press 1989) describes other methods in detail.

[0128] In some cases, an anti-BCMA antigen binding protein disclosed herein is an immunoconjugate comprising an antigen binding protein according to the disclosure as herein described including, but not limited to, an antibody conjugated to one or more cytotoxic agents, such as a chemotherapeutic agent, a drug, a growth inhibitory agent, a toxin (e.g., a protein toxin, an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate). In some cases, the anti-BCMA antigen binding protein is conjugated to a toxin such as an auristatin, e.g., monomethyl auristatin E (MMAE) or monomethyl auristatin F (MMAF). In some embodiments, the anti-BCMA antigen binding protein is conjugated to AFP, MMAF, MMAE, AEB, AEVB or auristatin E. In some embodiments, the anti-BCMA antigen binding protein is conjugated to paclitaxel, docetaxel, CC-1065, SN-38, topotecan, morpholino-doxorubicin, rhizoxin, cyanomorpholino-doxorubicin, dolastatin-10, echinomycin, combretastatin, calicheamicin, or netropsin. In some embodiments, the anti-BCMA antigen binding protein is conjugated to an auristatin, a maytansinoid, or calicheamicin. In some embodiments, the anti-BCMA antigen binding protein is conjugated to AFP, MMAP, MMAE, AEB, AEVB, auristatin E, vincristine, vinblastine, vindesine, vinorelbine, VP-16, camptothecin, paclitaxel, docetaxel, epothilone A, epothilone B, nocodazole, colchicines,

colcimid, estramustine, cemadotin, discodermolide, maytansinol, maytansine, DM1, DM2, DM3, DM4 or eleutherobin.

[0129] In some cases, an anti-BCMA antigen binding protein conjugated to a toxin can include a heavy chain having a V_H CDR1 comprising, consisting essentially of, or consisting of the amino acid sequence set forth in SEQ ID NO:1, a V_H CDR2 comprising, consisting essentially of, or consisting of the amino acid sequence set forth in SEQ ID NO:2, and a V_H CDR3 comprising, consisting essentially of, or consisting of the amino acid sequence set forth in SEQ ID NO:3. For example, an anti-BCMA antigen binding protein conjugated to a toxin described herein can include a heavy chain variable region including the amino acid sequence set forth in SEQ ID NO:7. In some cases, an anti-BCMA antigen binding protein conjugated to a toxin described herein can include a heavy chain comprising the amino acid sequence set forth in SEQ ID NO:9.

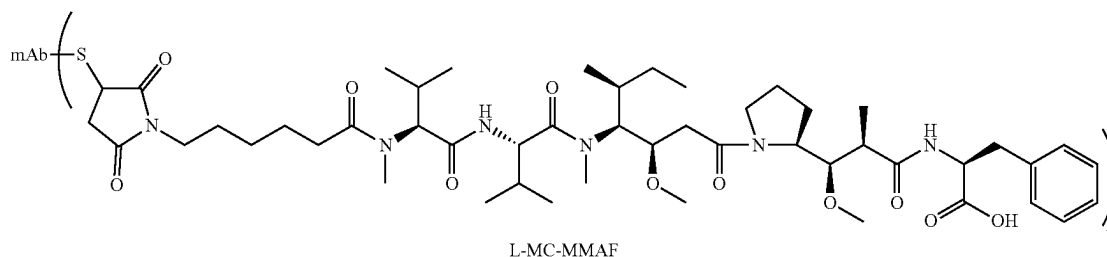
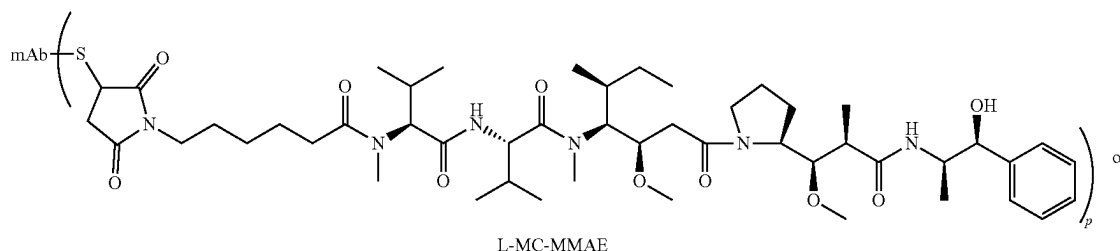
[0130] In some cases, an anti-BCMA antigen binding protein conjugated to a toxin can include a light chain having a V_L CDR1 comprising, consisting essentially of, or consisting of the amino acid sequence set forth in SEQ ID NO:4, a V_L CDR2 comprising, consisting essentially of, or consisting of the amino acid sequence set forth in SEQ ID NO:5, and a V_L CDR3 comprising, consisting essentially of, or consisting of the amino acid sequence set forth in SEQ ID NO:6. An anti-BCMA antigen binding protein conjugated to a toxin described herein can include a light chain variable region including the amino acid sequence set forth in SEQ ID NO:8. In some cases, an anti-BCMA antigen binding protein conjugated to a toxin described herein can include a light chain comprising the amino acid sequence set forth in SEQ ID NO:10.

[0131] In some cases, an anti-BCMA antigen binding protein conjugated to a toxin can include a heavy chain having a V_H CDR1 including the amino acid sequence set forth in SEQ ID NO:1, a V_H CDR2 including the amino acid sequence set forth in SEQ ID NO:2, and a V_H CDR3 including the amino acid sequence set forth in SEQ ID NO:3, and can include a light chain having a V_L CDR1 including the amino acid sequence set forth in SEQ ID NO:4, a V_L CDR2 including the amino acid sequence set forth in SEQ ID NO:5, and a V_L CDR3 including the amino acid sequence set forth in SEQ ID NO:6. For example, an anti-BCMA antigen binding protein conjugated to a toxin can include a heavy chain variable region including the amino acid sequence set forth in SEQ ID NO:7 and can include a light chain variable region including the amino acid sequence set forth in SEQ ID NO:8. In some cases an anti-BCMA antigen binding protein conjugated to a toxin described herein can include a heavy chain comprising the amino acid sequence set forth in SEQ ID NO:9 and can include a light chain comprising the amino acid sequence set forth in SEQ ID NO:10.

[0132] In some embodiments, an anti-BCMA antigen binding protein disclosed herein comprises the heavy chain variable region of SEQ ID NO:19, 23 or 27. In some embodiments, an anti-BCMA antigen binding protein disclosed herein comprises the light chain variable region of SEQ ID NO:20, 24 or 28. In some embodiments, an anti-BCMA antigen binding protein disclosed herein comprises the heavy chain region of SEQ ID NO:21, 25, 30, or 32. In some embodiments, an anti-BCMA antigen binding protein

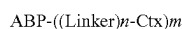
disclosed herein comprises the light chain region of SEQ ID NO:22, 26, 31 or 33. In some embodiments, an anti-BCMA antigen binding protein disclosed herein comprises the heavy chain variable region of SEQ ID NO:19 and the light chain variable region of SEQ ID NO:20, the heavy chain variable region of SEQ ID NO:23 and the light chain

[0141] In some cases, the anti-BCMA antigen binding protein is an immunoconjugate containing a monoclonal antibody linked to MMAE or MMAF. In another embodiment, the anti-BCMA antigen binding protein is an immunoconjugate containing a monoclonal antibody linked to MMAE or MMAF by an MC linker as depicted in the following structures:



variable region of SEQ ID NO:24, or the heavy chain variable region of SEQ ID NO:27 and the light chain variable region of SEQ ID NO:28. In some embodiments, an anti-BCMA antigen binding protein disclosed herein comprises the heavy chain region of SEQ ID NO:21 and the light chain of SEQ ID NO:22, the heavy chain region of SEQ ID NO: 25 and the light chain of SEQ ID NO:26, the heavy chain region of SEQ ID NO:30 and the light chain of SEQ ID NO:31 or the heavy chain region of SEQ ID NO:32 and the light chain of SEQ ID NO:33. In some embodiments, an anti-BCMA antigen binding protein disclosed herein is an scFV-fc comprising SEQ ID NO:29.

[0133] In some cases, the anti-BCMA antigen binding protein is an immunoconjugate having the following general structure:



[0134] wherein

[0135] ABP is an antigen binding protein

[0136] Linker is either absent or any a cleavable or non-cleavable linker

[0137] Ctx is any cytotoxic agent described herein

[0138] n is 0, 1, 2, or 3 and

[0139] m is 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10.

[0140] Exemplary linkers include 6-maleimidocaproyl (MC), maleimidopropanoyl (MP), valine-citrulline (val-cit), alanine-phenylalanine (ala-phe), p-aminobenzoyloxycarbonyl (PAB), N-Succinimidyl 4-(2-pyridylthio)pentanoate (SPP), N-succinimidyl 4-(N-maleimidomethyl)cyclohexane-1 carboxylate (SMCC), and N-succinimidyl 4-iodoacetyl aminobenzoate (SIAB).

[0142] In some cases, the anti-BCMA antigen binding protein is the antibody belantamab. In another embodiment, the anti-BCMA antigen binding protein is the immunoconjugate belantamab mafodotin.

[0143] In some cases, the conjugated antibodies (antibody-drug conjugates or ADCs) of the present disclosure are powerful anti-cancer agents designed to allow specific targeting of highly potent cytotoxic agents to tumor cells while sparing healthy tissues. Despite the use of tumor-specific antibodies, the emerging clinical data with ADCs indicates that adverse events frequently occur before ADCs have reached their optimal therapeutic dose. As such, despite these ADCs being highly active in preclinical tumor models their therapeutic window in the clinic is narrow and dosing regimens seem hampered by dose-limiting toxicities that could not always be predicted based on data from preclinical models.

[0144] Therapies which could be combined to synergistically enhance therapeutic efficacy without worsening the safety profile would be a major advancement in the treatment of cancer patients particularly with regards to the incidence and severity of treatment-emergent adverse events such as ocular toxicity.

[0145] Fundamentally, a combination with a drug which could enhance the efficacy of doses leading to overall responses rates (ORR) which are markedly higher whilst having the best benefit-risk profile would lead to a paradigm shift in the management of patients treated with such antigen binding proteins.

Disorders

[0146] In some cases, a combination disclosed herein treats a B-cell disorder. B-cell disorders can be divided into

defects of B-cell development/immunoglobulin production (immunodeficiencies) and excessive/uncontrolled proliferation (lymphomas, leukemias). As used herein, B-cell disorder refers to both types of diseases, and methods are provided for treating B-cell disorders with an antigen binding protein.

[0147] Examples of cancers and in particular B-cell mediated or plasma cell mediated diseases or antibody mediated diseases or disorders include Multiple Myeloma (MM), chronic lymphocytic leukemia (CLL), Follicular Lymphoma (FL), Diffuse Large B-Cell Lymphoma (DLBCL), Non-secretory multiple myeloma, Smoldering multiple myeloma, Monoclonal gammopathy of undetermined significance (MGUS), Solitary plasmacytoma (Bone, Extramedullary), Lymphoplasmacytic lymphoma (LPL), Waldenström's Macroglobulinemia, Plasma cell leukemia, Heavy chain disease, Systemic lupus erythematosus (SLE), POEMS syndrome/osteosclerotic myeloma, Type I and II cryoglobulinemia, Light chain deposition disease, Goodpasture's syndrome, Idiopathic thrombocytopenic purpura (ITP), Acute glomerulonephritis, Pemphigus and Pemphigoid disorders, and Epidermolysis bullosa acquisita; or any Non-Hodgkin's Lymphoma B-cell leukemia (NHL) and Hodgkin's lymphoma (HL). In some cases, the disease or disorder is selected from the group consisting of Multiple Myeloma (MM), Non-Hodgkin's Lymphoma B-cell leukemia (NHL), Follicular Lymphoma (FL), and Diffuse Large B-Cell Lymphoma (DLBCL). In some cases, the disease is Multiple Myeloma or Non-Hodgkin's Lymphoma B-cell leukemia (NHL). In some cases, the disease is Multiple Myeloma.

[0148] In some cases, the cancer may be a hematopoietic (or hematologic or haematological or blood-related) cancer, for example, cancers derived from blood cells or immune cells, which may be referred to as "liquid tumors". In some cases, the cancer is a B-cell related cancer and particularly a BCMA-expressing cancer. In some cases, the cancer is a leukemia such as chronic myelocytic leukemia, acute myelocytic leukemia, chronic lymphocytic leukemia and acute lymphocytic leukemia. In another case, the cancer is a lymphoma such as non-Hodgkin's lymphoma, Hodgkin's lymphoma; and the like. In another case the cancer is a plasma cell malignancy such as multiple myeloma, and Waldenström's macroglobulinemia. In some embodiments, a combination disclosed herein treats AL amyloidosis.

[0149] In some cases, the cancer is multiple myeloma. In some cases, the cancer is relapsed and/or refractory multiple myeloma. In some cases, the patient with relapsed and/or refractory multiple myeloma has been previously treated with at least one, at least two, at least three or at least four therapeutics to treat the multiple myeloma.

Prior Treatment

[0150] In some cases, a subject described herein may have had 0, 1, 2, 3, or 4 or more prior lines of treatment before being treated with the combinations described herein. In another embodiment, the subject may have relapsed and/or refractory multiple myeloma and have had 0, 1, 2, 3, or 4 or more prior lines of treatment before being treated with the combinations described herein. In another embodiment, the subject has been previously treated with at least 3 prior lines that may include the following: an immunomodulatory drug (IMiD), a proteasome inhibitor (PI) and anti-CD38 treatment (e.g., daratumumab) or combinations thereof. Lines of

therapy may be defined by consensus panel of the International Myeloma Workshop (IMWG) [Rajkumar, 2011].

[0151] In some cases, a subject may have had 0, 1, 2, 3, or 4 or more prior lines of treatment before being treated with the combinations described herein, wherein the one or more of the prior lines of treatment were unsuccessful. In some cases, adverse events connected to the prior line of treatment forced discontinuation of the prior line of treatment. When a mammal (e.g., a human) that can be treated as described herein is a mammal that has had 0, 1, 2, 3, or 4 or more prior lines of treatment before being treated as described herein, the prior treatment can be any appropriate treatment. For example, a mammal that has had 0, 1, 2, 3, or 4 or more prior lines of treatment before being treated as described herein, can have been previously treated with an immunomodulatory drug (IMiD), a proteasome inhibitor (PI), an anti-CD38 treatment or combinations thereof.

[0152] In some cases, a subject that had prior lines of treatment may have a cancer that is recurrent, relapsed, and/or refractory. In some cases, a cancer can be a primary cancer. In some cases, a cancer can be a metastatic cancer. In some cases, a cancer can be a chemo-resistant cancer. In some cases, a cancer can be a B cell cancer (e.g., leukemias and lymphomas). Examples of cancers that can be treated as described herein include, without limitation, multiple myeloma (MM), chronic lymphocytic leukemia (CLL), chronic myelocytic leukemia, acute myelocytic leukemia, acute lymphocytic leukemia, follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), non-secretory multiple myeloma, smoldering multiple myeloma, monoclonal gammopathy of undetermined significance (MGUS), solitary plasmacytoma (e.g., solitary plasmacytoma of the bone and extramedullary solitary plasmacytoma), lymphoplasmacytic lymphoma (LPL), Waldenström's macroglobulinemia, plasma cell leukemia, heavy chain disease, systemic lupus erythematosus (SLE), POEMS syndrome, osteosclerotic myeloma, Type I and II cryoglobulinemia, light chain deposition disease, Goodpasture's syndrome, idiopathic thrombocytopenic purpura (ITP), acute glomerulonephritis, pemphigus and pemphigoid disorders, epidermolysis bullosa acquisita, non-Hodgkin's lymphomas, B-cell leukaemia, and Hodgkin's lymphomas.

STATEMENT OF USE

[0153] In some cases, a combination disclosed herein can be used to treat a disease or condition for which a BCMA antigen binding protein is indicated, for example a cancer. Such a treatment may comprise: (i) an anti-BCMA antigen binding protein or an ADC having binding specificity for a BCMA polypeptide and (ii) one or more T cell engagers. In some cases, a mammal (e.g., a human such as a human having cancer) can be administered: (i) a polypeptide comprising an anti-BCMA antigen binding protein or an ADC having binding specificity for a BCMA polypeptide and (ii) one or more T cell engagers. In some cases, a combination disclosed herein targets the cytotoxic agent of the ADC to cells (e.g., cancer cells) expressing a BCMA polypeptide (e.g., expressing a BCMA polypeptide on the cell surface) and to stimulate (e.g., induce or enhance) an immune response against cells (e.g., cancer cells) expressing a cancer related antigen. In some cases, a BCMA antigen binding protein and a T cell engager can be bound to the same cancer cell. In some cases, an anti-BCMA antigen binding protein and a T cell engager can be bound to different cancer cells.

In some cases, an anti-BCMA antigen binding protein and a T cell engager can interact with the same or different cancer cells.

[0154] In some cases, combinations disclosed herein are for the treatment of a subject. The terms “individual”, “subject” and “patient” are used herein interchangeably. The subject is typically a human. The subject may also be a mammal, such as a mouse, rat or primate (e.g. a marmoset or monkey). The subject can be a non-human animal. The subject to be treated may be a farm animal for example, a cow or bull, sheep, pig, ox, goat or horse or may be a domestic animal such as a dog or cat. The animal may be any age, or a mature adult animal. In some embodiments, treatment may be therapeutic, prophylactic or preventative. The subject may be one who is in need thereof. Those in need of treatment may include individuals already suffering from a medical disease in addition to those who may develop the disease in the future.

[0155] Thus, the compositions described herein can be used for prophylactic or preventative treatment. In this case, the compositions described herein is administered to an individual in order to prevent or delay the onset of one or more aspects or symptoms of a disease. The subject can be asymptomatic. The subject may have a genetic predisposition to the disease. In some embodiments, a prophylactically effective amount of a combination disclosed herein is administered to such an individual. In some embodiments, a prophylactically effective amount is an amount which prevents or delays the onset of one or more aspects or symptoms of a disease described herein.

[0156] A combination disclosed herein may also be used in methods of therapy. The term “therapy” encompasses alleviation, reduction, or prevention of at least one aspect or symptom of a disease. For example, a combination disclosed herein may be used to ameliorate or reduce one or more aspects or symptoms of a disease described herein.

[0157] In some cases, a combination described herein is used in an effective amount for therapeutic, prophylactic or preventative treatment. In some cases, a therapeutically effective amount of a combination described herein is an amount effective to ameliorate or reduce one or more aspects or symptoms of the disease. In some cases, a combination disclosed herein may also have a generally beneficial effect on the subject’s health, for example it can increase the subject’s expected longevity.

[0158] A combination described herein need not affect a complete cure or eradicate every symptom or manifestation of the disease to constitute a viable therapeutic treatment. As is recognized in the pertinent field, drugs employed as therapeutic agents may reduce the severity of a given disease state but need not abolish every manifestation of the disease to be regarded as useful therapeutic agents. Similarly, a prophylactically administered treatment need not be completely effective in preventing the onset of a disease in order to constitute a viable prophylactic agent. Simply reducing the impact of a disease (for example, by reducing the number or severity of its symptoms, or by increasing the effectiveness of another treatment, or by producing another beneficial effect), or reducing the likelihood that the disease will occur (for example by delaying the onset of the disease) or worsen in a subject, is sufficient.

[0159] In some cases, the materials and methods provided herein can be used to reduce or eliminate the number of cancer cells present within a mammal (e.g., a human) having

cancer. For example, a mammal in need thereof (e.g., a mammal having cancer) can be administered an anti-BCMA antigen binding protein and a T cell engager to reduce the number of cancer cells present within a mammal having cancer (e.g., the number of cancer cells present in a sample obtained from a mammal having cancer) by, for example, at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, 95, or more percent. In some cases, there are no cancer cells present within a sample obtained from a mammal having cancer. For example, a mammal in need thereof (e.g., a mammal having cancer) can be administered an anti-BCMA antigen binding protein and a T cell engager to reduce the size (e.g., volume) of one or more tumors present within a mammal having cancer by, for example, at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, 95, or more percent. In some cases, the number of cancer cells present within a mammal being treated can be monitored. Any appropriate method can be used to determine whether or not the number of cancer cells present within a mammal is reduced. For example, imaging techniques can be used to assess the number of cancer cells present within a mammal.

[0160] In some cases, the materials and methods provided herein can be used to improve survival of a mammal (e.g., a human) having cancer. For example, a mammal in need thereof (e.g., a mammal having cancer) can be administered an anti-BCMA antigen binding protein and a T cell engager to improve survival of the mammal. For example, the materials and methods described herein can be used to improve the survival of a mammal having cancer by, for example, by at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, 95, or more percent. For example, the materials and methods described herein can be used to improve the survival of a mammal having cancer by, for example, at least about 3 months (e.g., at least about 3 months, at least about 6 months, at least about 8 months, at least about 10 months, at least about 1 year, at least about 1.5 years, at least about 2 years, at least about 2.5 years, at least about 3 years, at least about 4 years, at least about 5 years, or more).

[0161] In some cases, the materials and methods provided herein can be used to treat of mammal (e.g., a human) having cancer such that the mammal can experience minimal, reduced, or no side effects. For example, when administered a combination disclosed herein (for example an anti-BCMA antigen binding protein and a T cell engager) the mammal can experience minimal, reduced, or no side effects as compared to a mammal having cancer and is administered the anti-BCMA antigen binding protein alone or the T cell engager alone. Examples of side effects that can be experienced by a mammal having cancer includes without limitation, one or more side effects selected from vision or eye changes such as findings on eye exam (keratopathy), decreased vision or blurred vision, nausea, low blood cell counts, fever, infusion-related reactions, tiredness, changes in kidney or liver function blood tests, thrombocytopenia, ocular toxicity (e.g., changes in corneal epithelium, dry eyes, irritation, redness, blurred vision, dry eyes, photophobia, and changes in visual acuity).

[0162] In some cases, provided is a combination comprising an anti-BCMA antigen binding protein and a T cell engager for use in preventing and/or reducing ocular toxicity in a patient with cancers, such as multiple myeloma. In one embodiment, ocular toxicity is prevented or reduced when compared to a patient treated with the anti-BCMA antigen binding protein alone (monotherapy). In some embodi-

ments, a combination disclosed herein, for example an anti-BCMA antigen binding protein and a T cell engager, decreases/slows the decline from baseline of 1 line on Snellen Visual Acuity as compared to treatment with the anti-BCMA antigen binding protein alone. In some embodiments, a combination disclosed herein, for example an anti-BCMA antigen binding protein and a T cell engager, decreases/slows the decline from baseline of 2 or 3 lines on Snellen Visual Acuity as compared to treatment with the anti-BCMA antigen binding protein alone. In some embodiments, a combination disclosed herein, for example an anti-BCMA antigen binding protein and a T cell engager, decreases/slows the decline from baseline by more than 3 lines on Snellen Visual Acuity as compared to treatment with the anti-BCMA antigen binding protein alone. In some embodiments, a combination disclosed herein, for example an anti-BCMA antigen binding protein and a T cell engager, decreases/slows the change from baseline on Snellen Visual Acuity as compared to treatment with the anti-BCMA antigen binding protein alone. In some embodiments, a combination disclosed herein, for example an anti-BCMA antigen binding protein and a T cell engager, decreases/slows the decrease in log MAR (logarithm of the minimum angle of resolution) units from baseline as compared to treatment with the anti-BCMA antigen binding protein alone. In some embodiments, a combination disclosed herein, for example an anti-BCMA antigen binding protein and a T cell engager, decreases/slows or prevents the progression of mild superficial keratopathy, moderate superficial keratopathy, severe superficial keratopathy or corneal epithelial defect in a subject as compared to treatment with the anti-BCMA antigen binding protein alone. In some embodiments, a combination disclosed herein, for example an anti-BCMA antigen binding protein and a T cell engager, prevents mild superficial keratopathy, moderate superficial keratopathy, severe superficial keratopathy or corneal epithelial defect in a subject as compared to treatment with the anti-BCMA antigen binding protein alone.

[0163] “Ocular toxicity” refers to any unintended exposure of a therapeutic agent to ocular tissue. Ocular toxicity can include: changes in corneal epithelium, dry eyes, irritation, redness, blurred vision, dry eyes, photophobia, and/or changes in visual acuity.

[0164] Ophthalmic examination may be conducted by an ophthalmologist or optometrist. An ophthalmic examination may include one or more of the following:

- [0165]** 1. Best corrected visual acuity,
- [0166]** 2. Documentation of manifest refraction and the method used to obtain best corrected visual acuity,
- [0167]** 3. Current glasses prescription (if applicable),
- [0168]** 4. Intraocular pressure measurement,
- [0169]** 5. Anterior segment (slit lamp) examination including fluorescein staining of the cornea and lens examination,
- [0170]** 6. Dilated funduscopy examination, and/or
- [0171]** 7. An ocular surface disease index (OSDI) which is visual function questionnaire that assess the impact of potential ocular change in vision on function and health-related quality of life.

[0172] The above methods are known and practiced by those skilled in the art. The ophthalmic examination may occur before, during, and/or after treatment.

[0173] In one aspect of the disclosure, there is provided a method of treating cancer in a subject in need thereof

comprising administering a therapeutically effective dose of an anti-BCMA antigen binding protein and a T cell engager according to the disclosure.

T Cell Engager

[0174] Disclosed herein are combinations comprising (i) a polypeptide comprising an anti-BCMA antigen binding protein or an ADC having binding specificity for a BCMA polypeptide and (ii) one or more T cell engagers. A T cell engager disclosed herein can be directed against a T cell and a tumor associated antigen. Any appropriate T cell engager (s) can be used to treat a mammal (e.g., a human) having cancer as described herein. In some cases, a T cell engager can be a bispecific T cell engager (BiTE). In some cases, a T cell engager described herein is a bispecific T cell engager that binds to CD3 and BCMA (CD3xBCMA). In some cases, a T cell engager described herein is a bispecific T cell engager that binds to CD3 and GPRC5D (CD3xGPRC5D). In some cases, a T cell engager described herein is a bispecific T cell engager that binds to CD3 and FcRH5 (CD3xFcRH5). In some cases, a T cell engager can be a checkpoint-inhibitory T cell engager (CiTE). In some cases, a T cell engager can be a simultaneous multiple interaction T cell engager (SMITE). In some cases, a T cell engager can be a trispecific killer engager (TriKE). In some embodiments, a T cell engager disclosed herein binds to BCMA. In some embodiments, a T cell engager disclosed herein binds to GPRC5D. In some embodiments, a T cell engager disclosed herein binds to FcRH5. In some embodiments, a T cell engager disclosed herein binds to CD38. In some embodiments, a T cell engager disclosed herein does not bind to BCMA. In some embodiments, a T cell engager disclosed herein does not bind to GPRC5D. In some embodiments, a T cell engager disclosed herein does not bind to FcRH5. In some embodiments, a T cell engager disclosed herein does not bind to CD38.

[0175] In some cases, a T cell engager disclosed herein binds human CD3. In some cases, CD3 is an activating T cell antigen. An “activating T cell antigen” as used herein can refer to an antigenic determinant expressed on the surface of a T lymphocyte, particularly a cytotoxic T lymphocyte, which is capable of inducing T cell activation upon interaction with an antigen binding molecule. Specifically, interaction of an antigen binding molecule with an activating T cell antigen may induce T cell activation by triggering the signaling cascade of the T cell receptor complex. In some cases, a T cell engager disclosed herein is capable of inducing T cell activation. “T cell activation” as used herein can refer to one or more cellular response of a T lymphocyte, particularly a cytotoxic T lymphocyte, selected from: proliferation, differentiation, cytokine secretion, cytotoxic effector molecule release, cytotoxic activity, and expression of activation markers. In some cases, a T cell engager disclosed herein is bispecific. In some cases, a T cell engager disclosed herein binds at least one surface molecule that is expressed on human tumor cells. In some cases, a T cell engager disclosed herein binds to BCMA, CD19, CD20, CD30, CD33, CD38, CD44, CD123, CD138, CEA, CLEC12A, CS-1, EGFR, EGFRvIII, EPCAM, DLL3, LGR5, MSLN, FOLR1, FOLR3, HER2, HM1.24, MCSP, PSMA or a combination thereof.

[0176] Examples of T cell engagers that can be used to treat a mammal having cancer as described herein can comprise, without limitation, cevostamab, talquetamab,

teclistimab, PF-3135, TNB-383B, REGN5458, blinatumo-
mab, solitomab, sibrotuzumab, fresolimumab, defactinib
AZD4547 or a combination thereof. In some cases, a com-
bination disclosed herein comprises Teclistimab, PF-3135,
TNB-383B, REGN5458 or a combination thereof. In some
cases, a combination disclosed herein comprises CC-93269,
AMG701, JNJ-7957, GBR 1342 or a combination thereof.
In some cases, a combination disclosed herein comprises
Talquetamab. In some cases, a combination disclosed herein
comprises Cevostamab. In some cases, a composition dis-
closed herein comprises at least about 1 mg, 1.5 mg, 2 mg,
3 mg, 3.6 mg, 10 mg, 15 mg, 20 mg, 90 mg, or 132 mg
Cevostamab.

[0177] Cevostamab is a bispecific T-cell engager antibody
composed of two single-chain variable fragments (scFv),
one directed against the tumor-associated antigen Fc recep-
tor-like protein 5 (FCRH5; CD307; FCRL5; IRTA2;
BXMAS1) and one that is directed against the CD3 antigen
found on T lymphocytes. In some cases, upon administration
of cevostamab, the bispecific antibody binds to both the CD3
antigen on cytotoxic T lymphocytes (CTLs) and FCRH5
found on FCRH5-expressing tumor cells. In some cases, this
activates and crosslinks CTLs with FCRH5-expressing
tumor cells, which results in the CTL-mediated cell death of
FCRH5-expressing tumor cells. In some cases, FCRH5, an
immune receptor translocation-associated protein/Fc recep-
tor homolog (IRTA/FCRH) family member and a B-cell
lineage marker, is overexpressed on myeloma cells.

[0178] In some embodiments, the T cell engager com-
prises a scFv that is specific for FCRL5 and comprises a
heavy chain variable region having at least 80%, 90%, 91%,
92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%
sequence identity to the amino acid sequence set out in SEQ
ID NO:11. In some embodiments, the T cell engager com-
prises a scFv that is specific for FCRL5 and comprises a
light chain variable region having at least 80%, 90%, 91%,
92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%
sequence identity to the amino acid sequence set out in SEQ
ID NO:12. In some embodiments, the T cell engager com-
prises a scFv that is specific for FCRL5 and comprises a
heavy chain variable region having the amino acid sequence
set out in SEQ ID NO:11. In some embodiments, the T cell
engager comprises a scFv that is specific for FCRL5 and
comprises a light chain variable region having the amino
acid sequence set out in SEQ ID NO:12. In some embodi-
ments, the T cell engager comprises an activating T cell
antigen binding scFv that is specific for CD3 and comprises
a heavy chain variable region having at least 80%, 90%,
91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%
sequence identity to the amino acid sequence set out in SEQ
ID NO:13. In some embodiments, the T cell engager com-
prises an activating T cell antigen binding scFv that is
specific for CD3 and comprises a light chain variable region
having at least 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%,
97%, 98%, 99% or 100% sequence identity to the amino
acid sequence set out in SEQ ID NO:14. In some embodi-
ments, the T cell engager comprises an activating T cell
antigen binding scFv that is specific for CD3 and comprises
a heavy chain variable region having the amino acid
sequence set out in SEQ ID NO:13. In some embodiments,
the T cell engager comprises an activating T cell antigen
binding scFv that is specific for CD3 and comprises a light
chain variable region having the amino acid sequence set out
in SEQ ID NO:14. In some embodiments, the T cell engager

comprises the sequences out in SEQ ID NO:11, 12, 13 and
14. In some embodiments, the T cell engager comprises an
amino acid sequence having at least 80%, 90%, 91%, 92%,
93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence
identity to the heavy chain set out in SEQ ID NO: 15 and 17.
In some embodiments, the T cell engager comprises an
amino acid sequence having at least 80%, 90%, 91%, 92%,
93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence
identity to the light chain set out in SEQ ID NO: 16 and 18.
In some embodiments, the T cell engager comprises an
amino acid sequence having a heavy chain set out in SEQ ID
NO: 15 and 17; and a light chain set out in SEQ ID NO: 16
and 18.

TABLE 4		
Exemplarily T cell engager sequence.		
	Amino Acid Sequence	SEQ ID NO
FCRL5	EVQLVESGPGGLVKPSETLSLTCTVSGFSLTRFG	11
Target :	VHWVRQPPGKGLEWLGVIWRGGSTDYNAAFVSR	
Heavy	LTISKDNSKNQVSLKLSSVTAADTAVYYCSNHV	
Chain	YGSSDYALDNWGQGLTVTVSS	
Variable		
FCRL5	DIQMTQSPSSLSASVGDRTVITCKASQDVRLNV	12
Target :	VWFQKPKGKAPKLLIYSGSYRYSGVPSRFSGSG	
Light	SGTDFTLTISSLQPEDFATYYCQQHYSPPYTFG	
Chain	QGTKVEIK	
Variable		
CD3	EVQLVQSGAEVKKPGASVKVSCKASGFTFTSY	13
Target :	IHWVRQAPGQGLEWIGWIYPENDNTKYNEKFKD	
Heavy	RVTITADTSTSTAYLELSSLRSEDVAVYYCARD	
Chain	GYSRYFFDYWGQGLTVTVSS	
Variable		
CD3	DIVMTQSPDSLAVSLGERATINCKSSQSLNSR	14
Target :	TRKNYLAWYQKPGQSPKLLIYWTSTRKSGVPD	
Light	RFGSGSGTDFTLTISSLQAEDEVAVYYCKQSF	
Chain	LRTFGQGTKVEIK	
Variable		

[0179] Talquetamab is a bispecific humanized monoclonal
antibody against human CD3 and human G-protein coupled
receptor family C group 5 member D (GPCR5D), a tumor-
associated antigen. In some cases, upon administration,
Talquetamab binds to both CD3 on T cells and GPCR5D
expressed on certain tumor cells. In some cases, this results
in the cross-linking of T cells and tumor cells, and induces
a potent cytotoxic T-lymphocyte (CTL) response against
GPCR5D-expressing tumor cells. In some cases, GPCR5D
is overexpressed on certain tumors, such as multiple
myeloma, while minimally expressed on normal, healthy
cells, and plays a key role in tumor cell proliferation.

[0180] Blinatumomab is a recombinant, single-chain, anti-
CD19/anti-CD3 bispecific monoclonal antibody. Blinatumo-
mab possesses two antigen-recognition sites, one for the
CD3 complex, and one for CD19, a tumor-associated anti-
gen overexpressed on the surface of B cells. In some cases,
Blinatumomab brings CD19-expressing tumor B-cells and
cytotoxic T lymphocytes (CTLs) and helper T lymphocytes
(HTLs) together that result in the CTL- and HTL-mediated
cell death of CD19-expressing B-lymphocytes.

[0181] Solitomab is a recombinant bispecific monoclonal
antibody directed against both CD3 and epithelial cell
adhesion molecule (EpCAM). In some cases, Solitomab

attaches to both CD3-expressing T lymphocytes and EpCAM-expressing tumor cells, thereby selectively cross-linking tumor and T lymphocytes. In some cases, this results in the recruitment of cytotoxic T lymphocytes (CTL) to T lymphocyte/tumor cell aggregates and the CTL-mediated death of EpCAM-expressing tumor cells.

[0182] REGN5458 is a human bispecific T-cell engager antibody composed of two single-chain variable fragments (scFvs): one directed against BCMA and another directed against the CD3 antigen expressed on T lymphocytes. In some cases, upon administration, anti-BCMA/anti-CD3 REGN5458 binds to both CD3 on cytotoxic T lymphocytes (CTLs) and BCMA on BCMA-expressing tumor cells. In some cases, this activates and redirects CTLs to BCMA-expressing tumor cells, leading to CTL-mediated killing of BCMA-expressing tumor cells.

[0183] TNB-383B is a bispecific antibody directed against the tumor associated antigen BCMA and against the CD3 antigen found on T lymphocytes. TNB-383B is composed of two aBCMA moieties in sequence on one arm, a single aCD3 arm, and a silenced IgG4 Fc. In some cases, upon administration of anti-aBCMA/aCD3 T-cell engaging bispecific antibody TNB-383B, this bispecific antibody binds to both CD3 on cytotoxic T lymphocytes (CTLs) and BCMA found on BCMA-expressing tumor cells. In some cases, this activates and redirects CTLs to BCMA-expressing tumor cells, which results in the CTL-mediated cell death of BCMA-expressing tumor cells.

Dosage

[0184] In some cases, provided herein are combinations comprising a therapeutically effective dose of an anti-BCMA antigen binding protein comprising CDRH1 according to SEQ ID NO:1; CDRH2 according to SEQ ID NO:2; CDRH3 according to SEQ ID NO:3; CDRL1 according to SEQ ID NO:4; CDRL2 according to SEQ ID NO:5; and CDRL3 according to SEQ ID NO:6; and a T cell engager, for use in the treatment of cancer.

[0185] In some cases, provided herein are combinations comprising a therapeutically effective dose of an anti-BCMA antigen binding protein comprising heavy chain variable region (VH) according to SEQ ID NO:7; and a light chain variable region (VL) according to SEQ ID NO:8; and a T cell engager, for use in the treatment of cancer.

[0186] In some cases, provided herein are combinations comprising a therapeutically effective dose of an anti-BCMA antigen binding protein comprising heavy chain (H) according to SEQ ID NO:9 and a light chain (L) according to SEQ ID NO:10; and a T cell engager, for use in the treating cancer.

[0187] In some embodiments, an anti-BCMA antigen binding protein disclosed herein comprises the heavy chain variable region of SEQ ID NO:19, 23 or 27. In some embodiments, an anti-BCMA antigen binding protein disclosed herein comprises the light chain variable region of SEQ ID NO:20, 24 or 28. In some embodiments, an anti-BCMA antigen binding protein disclosed herein comprises the heavy chain region of SEQ ID NO:21, 25, 30, or 32. In some embodiments, an anti-BCMA antigen binding protein disclosed herein comprises the light chain region of SEQ ID NO:22, 26, 31 or 33. In some embodiments, an anti-BCMA antigen binding protein disclosed herein comprises the heavy chain variable region of SEQ ID NO:19 and the light chain variable region of SEQ ID NO:20, the heavy chain

variable region of SEQ ID NO:23 and the light chain variable region of SEQ ID NO:24, or the heavy chain variable region of SEQ ID NO:27 and the light chain variable region of SEQ ID NO:28. In some embodiments, an anti-BCMA antigen binding protein disclosed herein comprises the heavy chain region of SEQ ID NO:21 and the light chain of SEQ ID NO:22, the heavy chain region of SEQ ID NO: 25 and the light chain of SEQ ID NO:26, the heavy chain region of SEQ ID NO:30 and the light chain of SEQ ID NO:31 or the heavy chain region of SEQ ID NO:32 and the light chain of SEQ ID NO:33. In some embodiments, an anti-BCMA antigen binding protein disclosed herein is an scFV-fc comprising SEQ ID NO:29.

[0188] In some cases, combinations disclosed herein, when in a pharmaceutical preparation, is present in unit dose form. In some embodiments, the dosage regimen will be determined by a medical profession and/or clinical factors. As is well known in the medical arts, dosages for any one patient depend upon many factors, including the patient's size, body surface area, age, the combination to be administered, sex, time and route of administration, general health, and other drugs being administered concurrently. Exemplary doses can vary according to the size and health of the individual being treated, as well as the condition being treated.

[0189] Suitable doses of the anti-BCMA antigen binding proteins described herein may be calculated for patients according to their weight, for example suitable doses may be in the range of about 0.1 mg/kg to about 20 mg/kg, for example about 1 mg/kg to about 20 mg/kg, for example about 10 mg/kg to about 20 mg/kg or for example about 1 mg/kg to about 15 mg/kg, for example about 10 mg/kg to about 15 mg/kg.

[0190] In some cases, the therapeutically effective dose of the anti-BCMA antigen binding protein is in the range of about 0.03 mg/kg to about 4.6 mg/kg. In yet another embodiment, the therapeutically effective dose of the anti-BCMA antigen binding protein is 0.03 mg/kg, 0.06 mg/kg, 0.12 mg/kg, 0.24 mg/kg, 0.48 mg/kg, 0.96 mg/kg, 1.92 mg/kg, 2.5 mg/kg, 3.4 mg/kg, or 4.6 mg/kg. In yet another embodiment, the therapeutically effective dose of the anti-BCMA antigen binding protein is 1.9 mg/kg, 2.5 mg/kg or 3.4 mg/kg.

[0191] In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is 0.95 mg/kg. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is 1.0 mg/kg. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is 1.4 mg/kg. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is 1.9 mg/kg. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is 1.92 mg/kg. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is 2.5 mg/kg. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is 3.4 mg/kg. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is administered to the subject every week. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is administered to the subject every 2 weeks. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is administered to the subject every

3 weeks. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is administered to the subject every 4 weeks. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is administered to the subject every 5 weeks. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is administered to the subject every 6 weeks. In some embodiments, dosage of the therapeutically effective dose of the anti-BCMA antigen binding protein is step-down to a lower dose described herein following a first administration. In some embodiments, 3.4 mg/kg dosage of the therapeutically effective dose of the anti-BCMA antigen binding protein is step-down to a 1.9 mg/kg dose, 1.4 mg/kg or less. In some embodiments, a 2.5 mg/kg dosage of the therapeutically effective dose of the anti-BCMA antigen binding protein is step-down to a 1.9 mg/kg dose, 1.4 mg/kg or less. In some embodiments, the therapeutically effective dose of the anti-BCMA antigen binding protein is administered to the subject on day 1, day 8 and thereafter every 3-12 weeks.

[0192] Suitable doses of a T cell engager described herein may be calculated for patients according to their weight, for example suitable doses may be in the range of about 0.1 mg/kg to about 30 mg/kg, for example about 5 mg/kg to about 20 mg/kg, or for example about 10 mg/kg to about 20 mg/kg.

[0193] In some cases, the therapeutically effective dose of the T cell engager is about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, about 17 mg/kg, about 18 mg/kg, about 19 mg/kg, or about 20 mg/kg.

[0194] In one aspect there is provided a combination comprising belantamab mafodotin and a T cell engager for use in the treatment of cancer, wherein belantamab mafodotin is administered at least about 0.5 mg/kg, 0.95 mg/kg, 1 mg/kg, 1.4 mg/kg, 1.9 mg/kg, 1.92 mg/kg, 2.5 mg/kg, or 3.4 mg/kg and the T cell engager (for example Cevostamab) is administered at least about 2 mg, 3 mg, 3.6 mg, 10 mg, 15 mg, 20 mg, 50 mg, 100 mg, or 150 mg.

[0195] In one aspect there is provided a combination comprising belantamab mafodotin and a T cell engager for use in the treatment of cancer, wherein belantamab mafodotin is administered at 0.5 mg/kg, 0.95 mg/kg, 1 mg/kg, 1.4 mg/kg, 1.9 mg/kg, 1.92 mg/kg, 2.5 mg/kg, or 3.4 mg/kg on day 1 of a 21-day cycle and the T cell engager (for example Cevostamab) is administered at 2 mg, 3 mg, 3.6 mg, 10 mg, 15 mg, 20 mg, 50 mg, 100 mg, or 150 mg on day 1 of a 21-day cycle.

[0196] In one aspect there is provided a combination comprising belantamab mafodotin and a T cell engager for use in the treatment of cancer, wherein belantamab mafodotin is administered at 0.5 mg/kg, 0.95 mg/kg, 1 mg/kg, 1.4 mg/kg, 1.9 mg/kg, 1.92 mg/kg, 2.5 mg/kg, or 3.4 mg/kg on day 1 of a 21-day cycle and the T cell engager (for example Cevostamab) is administered at 2 mg, 3 mg, 3.6 mg, 10 mg, 15 mg, 20 mg, 50 mg, 100 mg, or 150 mg on day 1 of a 8-day cycle.

[0197] In one aspect there is provided a combination comprising belantamab mafodotin and a T cell engager for use in the treatment of cancer, wherein belantamab mafodotin is administered at 0.5 mg/kg, 0.95 mg/kg, 1 mg/kg, 1.4 mg/kg, 1.9 mg/kg, 1.92 mg/kg, 2.5 mg/kg, or 3.4 mg/kg on day 1 of a 21-day cycle and the T cell engager (for example

Cevostamab) is administered at 2 mg, 3 mg, 3.6 mg, 10 mg, 15 mg, 20 mg, 50 mg, 100 mg, or 150 mg on day 1 of a 15-day cycle.

[0198] In one aspect there is provided a combination comprising belantamab mafodotin and a T cell engager for use in the treatment of cancer, wherein belantamab mafodotin is administered at 0.5 mg/kg, 0.95 mg/kg, 1 mg/kg, 1.4 mg/kg, 1.9 mg/kg, 1.94 mg/kg, 2.5 mg/kg, or 3.4 mg/kg and half of the dose is administered on day 1 and half of the dose is administered on day 8 of a 21-day cycle; and a T cell engager (for example Cevostamab) is administered at 2 mg, 3 mg, 3.6 mg, 10 mg, 15 mg, 20 mg, 50 mg, 100 mg, or 150 mg.

[0199] In one aspect there is provided a combination comprising belantamab mafodotin and a T cell engager for use in the treatment of multiple myeloma, wherein belantamab mafodotin is administered at 0.5 mg/kg, 0.95 mg/kg, 1 mg/kg, 1.4 mg/kg, 1.9 mg/kg, 1.92 mg/kg, 2.5 mg/kg, or 3.4 mg/kg and the T cell engager (for example Cevostamab) is administered at 2 mg, 3 mg, 3.6 mg, 10 mg, 15 mg, 20 mg, 50 mg, 100 mg, or 150 mg.

[0200] In one aspect there is provided a combination comprising belantamab mafodotin and a T cell engager for use in the treatment of multiple myeloma, wherein belantamab mafodotin is administered at 0.5 mg/kg, 0.95 mg/kg, 1 mg/kg, 1.4 mg/kg, 1.9 mg/kg, 1.92 mg/kg, 2.5 mg/kg, or 3.4 mg/kg and half of the dose is administered on day 1 and half of the dose is administered on day 8 of a 21-day cycle; and the T cell engager (for example Cevostamab) is administered at 2 mg, 3 mg, 3.6 mg, 10 mg, 15 mg, 20 mg, 50 mg, 100 mg, or 150 mg on days 1-7 of a 21-day cycle.

[0201] In some cases, the subject has received at least one previous cancer treatment. In some cases, the therapeutically effective dose of the combination is administered to the subject at least about once every 1-60 days. In some cases, the therapeutically effective dose of the composition is administered to the subject at least about once every 21 days. In some cases, the therapeutically effective dose of the composition is administered to the subject at least about once every 8 days.

Route of Administration

[0202] In some cases, (i) a polypeptide comprising an anti-BCMA antigen binding protein or an ADC having binding specificity for a BCMA polypeptide and (ii) one or more T cell engagers can be administered to a mammal at the same time (e.g., in a single composition). In some cases, (i) a polypeptide comprising an anti-BCMA antigen binding protein or an ADC having binding specificity for a BCMA polypeptide and (ii) one or more T cell engagers can be administered to a subject separately. When administered separately, this may occur simultaneously or sequentially in any order (by the same or by different routes of administration). Such sequential administration may be close in time or remote in time. The dose of a therapeutic agents of the combination or pharmaceutical composition thereof and the further therapeutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

[0203] In some embodiments, the dosage is administered a single time or multiple times, for example daily, weekly, biweekly, or monthly, hourly, or is administered upon recurrence, relapse or progression of a disease or condition being treated. In some embodiments, administration of a dose may

be by slow continuous infusion over a period of from about 2 to about 24 hours, such as from about 2 to about 12 hours, or from about 2 to about 6 hours.

[0204] In some embodiments, a pharmaceutical composition disclosed herein comprises the combination for parenteral, transdermal, intraluminal, intraarterial, intrathecal and/or intranasal administration or by direct injection into tissue. In some embodiments, the pharmaceutical composition is administered to a patient via infusion or injection. In one embodiment, provided are pharmaceutical compositions comprising a BCMA binding protein and a T cell engager for intravenous administration. In some embodiments, provided are pharmaceutical compositions comprising a BCMA binding protein and a T cell engager for subcutaneous administration. In some embodiment, a pharmaceutical composition described herein is administered to a subject transarterially, subcutaneously, intradermally, intratumorally, intranodally, intramedullary, intramuscularly, by intravenous (i.v.) injection, by intravenous (i.v.) infusion, or intraperitoneally. In some embodiments, the combination is administered to a subject by intradermal or subcutaneous injection.

[0205] In one embodiment, one or more therapeutic agents of a combination are administered intravenously. In another embodiment, one or more therapeutic agents of a combination are administered intratumorally. In another embodiment, one or more therapeutic agents of a combination are administered orally. In another embodiment, one or more therapeutic agents of a combination are administered systemically, e.g., intravenously, and one or more other therapeutic agents of a combination of are administered intratumorally. In another embodiment, all therapeutic agents of a combination disclosed herein are administered systemically, e.g., intravenously. In an alternative embodiment, all therapeutic agents of the combination described herein are administered intratumorally. In any of the embodiments, e.g., in this paragraph, the therapeutic agents of the disclosure are administered as one or more pharmaceutical compositions.

Pharmaceutical Composition

[0206] In some embodiments, a pharmaceutical composition is prepared by per se known methods for the preparation of pharmaceutically acceptable compositions that are administered to subjects, such that an effective quantity of a BCMA binding protein+T cell engager is combined in a mixture with a pharmaceutically acceptable carrier. Suitable carriers are described, for example, in Remington's Pharmaceutical Sciences (Remington's Pharmaceutical Sciences, 20th ed., Mack Publishing Company, Easton, Pa., USA, 2000). On this basis, the compositions may include, albeit not exclusively, solutions of the substances in association with one or more pharmaceutically acceptable carriers or diluents, and contained in buffered solutions with a suitable pH and iso-osmotic with the physiological fluids. In some embodiments, a pharmaceutical composition disclosed herein is acidic. In some embodiments, a pharmaceutical composition disclosed herein is basic. In some embodiments, a pharmaceutical composition can have a pH of about 1, 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, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, or about 14.

[0207] In some embodiments, suitable pharmaceutically acceptable carriers include essentially chemically inert and nontoxic compositions that do not interfere with the effectiveness of the biological activity of the pharmaceutical

composition. Examples of suitable pharmaceutical carriers include, but are not limited to, water, saline solutions, glycerol solutions, N-(1(2,3-dioleoyloxy)propyl)N,N,N-trimethylammonium chloride (DOTMA), dioleoylphosphatidylethanolamine (DOPE), and liposomes. In some embodiments, such compositions contain a therapeutically effective amount of a BCMA binding protein and T cell engager disclosed herein, together with a suitable amount of carrier so as to provide the form for direct administration to a subject.

[0208] Pharmaceutical compositions may include, without limitation, lyophilized powders or aqueous or non-aqueous sterile injectable solutions or suspensions, which may further contain antioxidants, buffers, bacteriostats and solutes that render the compositions substantially compatible with the tissues or the blood of an intended recipient. Other components that may be present in such compositions include water, surfactants (such as Tween), alcohols, preservatives, polyols, glycerin and vegetable oils, for example. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, tablets, or concentrated solutions or suspensions.

[0209] A pharmaceutical composition disclosed herein may be formulated into a variety of forms and administered by a number of different means. A pharmaceutical formulation can be administered orally, rectally, or parenterally, in formulations containing conventionally acceptable carriers, adjuvants, and vehicles as desired. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, or intrasternal injection and infusion techniques. Administration includes injection or infusion, including intra-arterial, intracardiac, intracerebroventricular, intradermal, intraduodenal, intramedullary, intramuscular, intraosseous, intraperitoneal, intrathecal, intravascular, intravenous, intravitreal, epidural and subcutaneous), inhalational, transdermal, transmucosal, sublingual, buccal and topical (including epicutaneous, dermal, enema, eye drops, ear drops, intranasal, vaginal) administration. In some exemplary embodiments, a route of administration is via an injection such as an intramuscular, intravenous, subcutaneous, or intraperitoneal injection.

[0210] Liquid formulations may include an oral formulation, an intravenous formulation, an intranasal formulation, an ocular formulation, an otic formulation, an aerosol, and the like. In certain embodiments, a combination of various formulations is administered. In certain embodiments a composition is formulated for an extended release profile.

[0211] Pharmaceutical compositions of the disclosure can be administered in combination with other therapeutics or treatments. In some embodiments, a treatment for a subject can be a surgery, radiation, chemotherapy, a nutrition regime, a physical activity, an immunotherapy, a pharmaceutical composition, a cell transplantation, a blood fusion, or any combination thereof. In some cases, the combination disclosed herein is administered to a mammal having cancer together with one or more additional agents/therapies used to treat cancer. Examples of additional agents/therapies used to treat cancer include, without limitation, surgery, radiation therapies, chemotherapies, targeted therapies (e.g., monoclonal antibody therapies), hormonal therapies, angiogenesis inhibitors, immunosuppressants, checkpoint blockade therapies (e.g., anti-PD-1 antibody therapy, anti-PD-L1 antibody therapy, and/or anti-CTLA4 antibody therapy), bone marrow transplants.

[02112] In some embodiments, a combination/formulation disclosed herein is stable. In some embodiments, a “stable” formulation is one in which the combination therein essentially retains its physical and/or chemical stability and/or biological activity upon storage. Various analytical techniques for measuring protein stability are available in the art and are reviewed in *Peptide and Protein Drug Delivery*, 247-301, Vincent Lee Ed., Marcel Dekker, Inc., New York, N.Y., Pubs (1991) and Jones, A. *Adv. Drug Delivery Rev.* 10: 29-90 (1993), for example. Stability can be measured at a selected temperature for a selected time period. In some embodiments, the formulation is stable at ambient temperature or at 40°C for at least 1 month and/or stable at 2-8° C. for at least 1 to 2 years. In some embodiments, the formulation is stable following freezing (e.g. to -70° C.) and thawing. In some embodiments, a protein “retains its physical stability” in a formulation if it shows little to no change in aggregation, precipitation and/or denaturation as observed by visual examination of color and/or clarity, or as measured by UV light scattering (measures visible aggregates) or size exclusion chromatography (SEC). SEC measures soluble aggregates that are not necessarily a precursor for visible aggregates. In some embodiments, a protein “retains its chemical stability” in a formulation if the chemical stability at a given time is such that the protein is considered to retain its biological activity. Chemically degraded species may be biologically active and chemically unstable. Chemical stability can be assessed by detecting and quantifying chemically altered forms of the protein. Chemical alteration may involve size modification (e.g. clipping) which can be evaluated using SEC, SDS-PAGE and/or matrix-assisted laser desorption ionization/time-of-flight mass spectrometry (MALDI/TOF MS), for example. Other types of chemical alteration include charge alteration (e.g. occurring as a result of deamidation) which can be evaluated by ion-exchange chromatography, for example.

[02113] In some embodiments, a BCMA binding protein “retains its biological activity” in a pharmaceutical formulation, if the biological activity of the BCMA binding protein at a given time is within about 10% (within the errors of the assay) of the biological activity exhibited at the time the pharmaceutical formulation was prepared as determined in an antigen binding assay, for example. In some embodiments, a T cell engager “retains its biological activity” in a pharmaceutical formulation, if the biological activity of the T cell engager at a given time is within about 10% (within the errors of the assay) of the biological activity exhibited at the time the pharmaceutical formulation was prepared as determined in an antigen binding assay, for example.

[02114] In some embodiments, a buffer disclosed herein refers to a buffered solution that resists changes in pH by the action of its acid-base conjugate components. In some embodiments, a buffer can be phosphate, citrate and other organic acids. In some embodiments, a buffer is selected from the group consisting of sodium acetate, sodium carbonate, citrate, glycylglycine, histidine, glycine, lysine, arginine, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium phosphate, sodium citrate, sodium borate, tris(hydroxymethyl)-aminomethan, bicine, tricine, malic acid, succinate, maleic acid, fumaric acid, tartaric acid, aspartic acid or mixtures thereof. A composition disclosed herein can comprise antioxidants including ascorbic acid and/or methionine. In some embodiments, a composition disclosed herein comprises a preservative. In some

embodiments, a preservative is a compound which can be included in a formulation to essentially reduce microbial including bacterial action therein, thus facilitating the production of a multi-use formulation, for example. Examples of potential preservatives include octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

[02115] In some embodiments, a combination disclosed herein may further comprise a chemotherapeutic agent, cytotoxic agent, cytokine, growth inhibitory agent, anti-hormonal agent, and/or cardioprotectant. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

[02116] In some embodiments, a combination disclosed herein is prepared in a sustained-release preparation. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the combination or portions thereof, which matrices are in the form of shaped articles, e.g. films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides, copolymers of L-glutamic acid and γ ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid.

[02117] In some embodiments, disclosed herein are pharmaceutical compositions comprising a BCMA binding protein and a T cell engager which is present in a concentration from 1 mg/ml to 500 mg/ml, and wherein the pharmaceutical composition has a pH from 2.0 to 10.0. The pharmaceutical composition may further comprise a buffer system, preservative(s), tonicity agent(s), chelating agent(s), stabilizers and surfactants. In some embodiments, the pharmaceutical composition is an aqueous formulation, for example, formulation comprising water. Such formulation is typically a solution or a suspension. In a further embodiment, the pharmaceutical formulation is an aqueous solution. In some embodiments, an aqueous formulation is a formulation comprising at least 50% w/w water. In some embodiments an aqueous solution is defined as a solution comprising at least 50% w/w water. In some embodiments, the pharmaceutical composition is a stable liquid aqueous pharmaceutical formulation comprising a combination described herein.

[02118] The pharmaceutical compositions may also comprise additional stabilizing agents, that may further enhance stability of a therapeutically active combination. Stabilizing

agents of can include, but are not limited to, methionine and EDTA, which protect polypeptides against methionine oxidation, and a nonionic surfactant, which protects polypeptides against aggregation associated with freeze-thawing or mechanical shearing. In some embodiments, the pharmaceutical composition may further comprise a surfactant. The surfactant may be selected from a detergent, ethoxylated castor oil, polyglycolized glycerides, acetylated monoglycerides, sorbitan fatty acid esters, polyoxypropylene-polyoxyethylene block polymers (eg. poloxamers such as PLURONIC F68, poloxamer 188 and 407, Triton X-100), polyoxyethylene sorbitan fatty acid esters, polyoxyethylene and polyethylene derivatives such as alkylated and alkoxy-ylated derivatives (tweens, e.g., Tween-20, Tween-40, Tween-80 and Brij-35), monoglycerides or ethoxylated derivatives thereof, diglycerides or polyoxyethylene derivatives thereof, alcohols, glycerol, lectins and phospholipids (e.g., phosphatidyl serine, phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl inositol, diphosphatidyl glycerol and sphingomyelin), derivatives of phospholipids (e.g., dipalmitoyl phosphatidic acid) and lysophospholipids (e.g., palmitoyl lysophosphatidyl-L-serine and 1-acyl-sn-glycerol-3-phosphate esters of ethanolamine, choline, serine or threonine) and alkyl, alkoxy (alkyl ester), alkoxy (alkyl ether)-derivatives of lysophosphatidyl and phosphatidylcholines, e.g. lauroyl and myristoyl derivatives of lysophosphatidylcholine, dipalmitoylphosphatidylcholine, and modifications of the polar head group, that is cholines, ethanolamines, phosphatidic acid, serines, threonines, glycerol, inositol, and the positively charged DODAC, DOTMA, DCP, BISHOP, lysophosphatidylserine and lysophosphatidylthreonine, and glycerophospholipids (e.g., cephalins), glyceroglycolipids (e.g., galactopyransoide), sphingoglycolipids (e.g., ceramides, gangliosides), dodecylphosphocholine, hen egg lysolecithin, fusidic acid derivatives (e.g., sodium taurodihydrofusidate, etc.), long-chain fatty acids and salts thereof C6-C12 (e.g., oleic acid and caprylic acid), acylcar- nitines and derivatives, N-acylated derivatives of lysine, arginine or histidine, or side-chain acylated derivatives of lysine or arginine, N-acylated derivatives of dipeptides comprising any combination of lysine, arginine or histidine and a neutral or acidic amino acid, N-acylated derivative of a tripeptide comprising any combination of a neutral amino acid and two charged amino acids, DSS (docusate sodium, CAS registry no [577-11-7]), docusate calcium, CAS registry no [128-49-4]), docusate potassium, CAS registry no [7491-09-0]), SDS (sodium dodecyl sulphate or sodium lauryl sulphate), sodium caprylate, cholic acid or derivatives thereof, bile acids and salts thereof and glycine or taurine conjugates, ursodeoxycholic acid, sodium cholate, sodium deoxycholate, sodium taurocholate, sodium glycocholate, N-Hexadecyl-N,N-dimethyl-3-ammonio-1-propane-sulfonate, anionic (alkyl-aryl-sulphonates) monovalent surfactants, zwitterionic surfactants (e.g., N-alkyl-N,N-dimethylammonio-1-propanesulfonates, 3-cholamido-1-propyldimethylammonio-1-propanesulfonate, cationic surfactants (quaternary ammonium bases) (e.g., cetyl-trimethylammonium bromide, cetylpyridinium chloride), non-ionic surfactants (e.g., Dodecyl β -D-glucopyranoside), poloxamines (e.g., Tetronic's), which are tetrafunctional block copolymers derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine, or the surfactant may be selected from the group of imidazoline derivatives, or mixtures thereof.

Kits

[0219] A kit-of-parts comprising a pharmaceutical composition together with instructions for use is further provided. For convenience, the kit-of-parts may comprise reagents in predetermined amounts with instructions for use.

[0220] In some embodiments, disclosed herein are kits comprising a BCMA binding protein and a T cell engager disclosed herein. A kit may include a plurality of syringes, ampules, foil packets, or blister packs, each containing a single unit dose of a kit component described herein. Containers of a kit may be airtight, waterproof (e.g., impermeable to changes in moisture or evaporation), and/or light-tight. A kit may include a device suitable for administration of the component, e.g., a syringe, inhalant, pipette, forceps, measured spoon, dropper (e.g., eye dropper), swab (e.g., a cotton swab or wooden swab), or any such delivery device. In some embodiments, the device may be a medical implant device, e.g., packaged for surgical insertion. A kit disclosed herein may comprise one or more reagents or instruments which enable the method to be carried out.

[0221] In addition to the above components, instructions for use may be provided in a kit. These instructions may be present in the kit in a variety of forms, such as printed information on a suitable medium or substrate (e.g., a piece or pieces of paper on which the information is printed), in the packaging of the kit, in a package insert, etc. In some embodiments, instructions for use can be provided on a computer readable medium (e.g., jump/thumb drive, CD, etc.), on which the information has been recorded or at a website address which may be used via the internet to access the information at a website.

Devices

[0222] Another aspect of the disclosure provides a pre-filled syringe or autoinjector device, comprising a BCMA antigen binding protein, a T cell engager or a combination described herein. In some embodiments, a combination stored in a container, pre-filled syringe, injector or autoinjector device contains a BCMA antigen binding protein and a T cell engager disclosed herein.

EXAMPLES

Example 1: Treating Cancer

[0223] A subject will be identified as having cancer. The subject will be administered a combination comprising (a) an anti-BCMA antigen binding protein or an anti-BCMA ADC and (b) a T cell engager.

Example 2: Treating Cancer

[0224] A subject will be identified as having cancer. The subject will be administered (a) an anti-BCMA antigen binding protein or an anti-BCMA ADC and (b) a T cell engager in separate compositions that will be co-administered. For example, the subject having cancer will be co-administered a first composition including one or more ADCs having binding specificity for a BCMA polypeptide and a second composition including one or more T cell engagers.

Example 3: Treating Cancer

[0225] A subject will be identified as having cancer. The subject will be administered (a) an anti-BCMA antigen binding protein or an anti-BCMA ADC and (b) a T cell engager in separate compositions that will be separately administered. For example, the subject having cancer will be separately administered a first composition including one or more ADCs having binding specificity for a BCMA polypeptide and a second composition including one or more T cell engagers.

Example 4: Treating Cancer

[0226] A subject will be identified as having cancer. The subject will be administered a combination comprising belantamab mafodotin and cevostamab.

Other Embodiments

[0227] It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

Embodiments

[0228] 1. A combination comprising:

[0229] a. an anti-BCMA antigen binding protein; and

[0230] b. a T cell engager that binds to CD3.

[0231] 2. The combination of embodiment 1, wherein the anti-BCMA antigen binding protein comprises an antibody.

[0232] 3. The combination of embodiment 2, wherein the antibody is a monoclonal antibody.

[0233] 4. The combination of embodiment 3, wherein the monoclonal antibody is an IgG1.

[0234] 5. The combination of any one of embodiments 2-4, wherein the antibody is afucosylated.

[0235] 6. The combination of any one of embodiments 1-5, wherein the anti-BCMA antigen binding protein is human, humanized or chimeric.

[0236] 7. The combination of any one of embodiments 1-6, wherein the anti-BCMA antigen binding protein comprises a CDRH1 comprising the amino acid sequence set out in SEQ ID NO:1; a CDRH2 comprising the amino acid sequence set out in SEQ ID NO:2; a CDRH3 comprising the amino acid sequence set out in SEQ ID NO:3; a CDRL1 comprising the amino acid sequence set out in SEQ ID NO:4; a CDRL2 comprising the amino acid sequence set out in SEQ ID NO:5; and a CDRL3 comprising the amino acid sequence set out in SEQ ID NO:6.

[0237] 8. The combination of any one of embodiments 1-7, wherein the anti-BCMA antigen binding protein comprises a heavy chain variable region (VH) comprising the amino acid sequence set out in SEQ ID NO:7; and a light chain variable region (VL) comprising the amino acid sequence set out in SEQ ID NO: 8.

[0238] 9. The combination of any one of embodiments 1-8, wherein the anti-BCMA antigen binding protein comprises a heavy chain (H) comprising the amino acid

sequence set out in SEQ ID NO:9 and a light chain (L) comprising the amino acid sequence set out in SEQ ID NO:10.

[0239] 10. The combination of any one of embodiments 1-9, wherein the anti-BCMA antigen binding protein is an immunoconjugate.

[0240] 11. The combination of embodiment 1-10, wherein the anti-BCMA antigen binding protein is an immunoconjugate comprising an antibody conjugated to a cytotoxin.

[0241] 12. The combination of embodiment 11, wherein the cytotoxin is MMAE or MMAF.

[0242] 13. The combination of embodiment 12, wherein the cytotoxin is MMAF.

[0243] 14. The combination of embodiment 11, wherein the cytotoxin is paclitaxel, docetaxel, CC-1065, SN-38, topotecan, morpholino-doxorubicin, rhizoxin, cyano-morpholino-doxorubicin, dolastatin-10, echinomycin, combretastatin, calicheamicin, netropsin, an auristatin, a maytansinoid, a calicheamicin, AFP, MMAP, MMAE, AEB, AEVB, vincristine, vinblastine, vindesine, vinorelbine, VP-16, camptothecin, epothilone A, epothilone B, nocodazole, colchicines, colcemid, estramustine, cemadotin, discodermolide, maytansinol, maytansine, DM1, DM2, DM3, DM4 or eleutherobin.

[0244] 15. The combination of any one of embodiments 1-14, wherein the anti-BCMA antigen binding protein is belantamab mafodotin.

[0245] 16. The combination of embodiment 15, wherein the combination comprises at least about 0.5 mg/kg, 0.95 mg/kg, 1 mg/kg, 1.4 mg/kg, 1.9 mg/kg, 1.92 mg/kg, 2.5 mg/kg or about 3.4 mg/kg belantamab mafodotin.

[0246] 17. The combination of any one of embodiments 1-16, wherein the T cell engager is a bispecific T cell engager.

[0247] 18. The combination of any one of embodiments 1-17, wherein the T cell engager is selected from the group consisting of Cevostamab, Talquetamab, Teclistimab, PF-3135, TNB-383B, REGN5458, blinatumomab, and solitomab.

[0248] 19. The combination of any one of embodiments 1-17, wherein the T cell engager is an anti-FCRH5 T cell engager.

[0249] 20. The combination of embodiment 19, wherein the T cell engager is Cevostamab.

[0250] 21. The combination of embodiment 19, wherein the combination comprises at least about 1.5 mg, 2 mg, 3 mg, 3.6 mg, 10 mg, 15 mg, 20 mg, 90 mg, or 132 mg of Cevostamab.

[0251] 22. The combination of any one of embodiments 1-17, wherein the T cell engager is an anti-GPRC5D T cell engager.

[0252] 23. The combination of embodiment 22, wherein the T cell engager is Talquetamab.

[0253] 24. The combination of any one of embodiments 1-17, wherein the T cell engager is an anti-BCMA T cell engager.

[0254] 25. The combination of any one of embodiments 1-17, wherein the T cell engager is selected from the group consisting of Teclistimab, PF-3135, TNB-383B, and REGN5458.

- [0255] 26. The combination of any one of embodiments 1-17, wherein the T cell engager is selected from the group consisting of CC-93269, AMG701, JNJ-7957, and GBR 1342.
- [0256] 27. The combination of any one of embodiments 1-17, wherein the T cell engager does not bind ICOS.
- [0257] 28. The combination of any one of embodiments 1-17, wherein the T cell engager does not bind CD38.
- [0258] 29. The combination of any one of embodiments 1-28, wherein the combination comprises a pharmaceutically acceptable carrier.
- [0259] 30. The combination of any one of embodiments 1-29, wherein the combination further comprising an adjuvant.
- [0260] 31. A method of treating cancer in a subject in need thereof comprising administering to the subject a therapeutically effective dose of the combination of any one of embodiments 1-30.
- [0261] 32. A method of treating cancer in a subject in need thereof comprising administering to the subject a therapeutically effective dose of the combination of any one of embodiments 1-30, wherein a dose of the anti-BCMA antigen binding protein is step-down to a lower dose following a first administration.
- [0262] 33. The method of embodiment 31 or 32, wherein the cancer is selected from the group consisting of multiple myeloma, chronic lymphocytic leukemia, Waldenstrom macroglobulinemia, and non-Hodgkin's lymphoma.
- [0263] 34. The method of any one of embodiments 31-33, wherein the cancer is multiple myeloma.
- [0264] 35. The method of embodiment 31 or 32, wherein the cancer is relapsed and/or refractory multiple myeloma.
- [0265] 36. The method of any one of embodiments 31-35, wherein the subject has received at least one previous cancer treatment.
- [0266] 37. The method of any one of embodiments 31-36, wherein the therapeutically effective dose is administered to the subject at least about once every 21 days.
- [0267] 38. The method of any one of embodiments 31-37, wherein the administering the therapeutically effective dose of the combination treatment reduces ocular toxicity as compared to administering a therapeutically effective amount of the anti-BCMA antigen binding protein alone.
- [0268] 39. The method of embodiment 38, wherein the anti-BCMA antigen binding protein is belantamab mafodotin.
- [0269] 40. The method of embodiment 38 or 39, wherein the ocular toxicity is at least one of: changes in corneal epithelium, dry eyes, irritation, redness, blurred vision, dry eyes, photophobia, or changes in visual acuity.
- [0270] 41. The method of any one of embodiments 38-40, wherein the ocular toxicity is measured by at least one of the following methods: best corrected visual acuity, documentation of manifest refraction and the method used to obtain best corrected visual acuity, current glasses prescription (if applicable), intraocular pressure measurement, anterior segment (slit lamp) examination including fluorescein staining of the cornea and lens examination, dilated fundusoscopic examination, or an ocular surface disease index (OSDI).
- [0271] 42. The method of any one of embodiments 31-41, wherein the anti-BCMA antigen binding protein is administered to the subject in a dose of at least about 0.5 mg/kg, 0.95 mg/kg, 1.25 mg/kg, 1.4 mg/kg, 1.7 mg/kg, 1.9 mg/kg, 1.92 mg/kg, 2.5 mg/kg or 3.4 mg/kg.
- [0272] 43. A combination of any one of embodiments 1-30, for use in the manufacture of a medicament for treatment of cancer.
- [0273] 44. A combination of any one of embodiments 1-30, for use in treatment of cancer.
- [0274] 45. A kit for use in treatment of cancer comprising:
 [0275] a. the combination of any one of embodiments 1-30; and
 [0276] b. instructions for use in the treatment of cancer.
- [0277] 46. A pre-filled syringe or autoinjector device, comprising the combination of any one of embodiments 1-30.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 33

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 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: CDRH1

<400> SEQUENCE: 1

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 1 5

<210> SEQ ID NO 2
 <211> LENGTH: 17
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
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Gly

<210> SEQ ID NO 3

<211> LENGTH: 12

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: CDRH3

<400> SEQUENCE: 3

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<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: CDRL1

<400> SEQUENCE: 4

Ser Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
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<210> SEQ ID NO 5

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: CDRL2

<400> SEQUENCE: 5

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<210> SEQ ID NO 6

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: CDRL3

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<210> SEQ ID NO 7

<211> LENGTH: 121

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: heavy chain variable region

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Asn Tyr
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

-continued

35	40	45
Gly Ala Thr Tyr Arg Gly His Ser Asp Thr Tyr Tyr Asn Gln Lys Phe		
50	55	60
Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr		
65	70	75
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys		
	85	90
Ala Arg Gly Ala Ile Tyr Asp Gly Tyr Asp Val Leu Asp Asn Trp Gly		
	100	105
Gln Gly Thr Leu Val Thr Val Ser Ser		
	115	120

<210> SEQ ID NO 8
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: light chain variable region

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly		
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Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Gln Asp Ile Ser Asn Tyr		
	20	25
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile		
	35	40
Tyr Tyr Thr Ser Asn Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly		
	50	55
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro		
65	70	75
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Arg Lys Leu Pro Trp		
	85	90
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg		
	100	105

<210> SEQ ID NO 9
 <211> LENGTH: 451
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: heavy chain region

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser		
1	5	10
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Asn Tyr		
	20	25
Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met		
	35	40
Gly Ala Thr Tyr Arg Gly His Ser Asp Thr Tyr Tyr Asn Gln Lys Phe		
	50	55
Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr		
65	70	75
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys		
	85	90

-continued

Ala	Arg	Gly	Ala	Ile	Tyr	Asp	Gly	Tyr	Asp	Val	Leu	Asp	Asn	Trp	Gly	100	105	110	
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	115	120	125	
Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	130	135	140	
Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	145	150	155	160
Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	165	170	175	
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	180	185	190	
Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	195	200	205	
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	210	215	220	
Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	225	230	235	240
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	245	250	255	
Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	260	265	270	
Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	275	280	285	
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	290	295	300	
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	305	310	315	320
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	325	330	335	
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	340	345	350	
Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	355	360	365	
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	370	375	380	
Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	385	390	395	400
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	405	410	415	
Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	420	425	430	
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	435	440	445	
Pro	Gly	Lys														450			

<210> SEQ ID NO 10

<211> LENGTH: 214

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: light chain region

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<400> SEQUENCE: 10

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 Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Gln Asp Ile Ser Asn Tyr
 20 25 30
 Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Tyr Thr Ser Asn Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Arg Lys Leu Pro Trp
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
 100 105 110
 Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
 115 120 125
 Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
 130 135 140
 Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 145 150 155 160
 Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 165 170 175
 Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
 180 185 190
 Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
 195 200 205
 Phe Asn Arg Gly Glu Cys
 210

<210> SEQ ID NO 11

<211> LENGTH: 120

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: FCRL5 Target: heavy chain variable

<400> SEQUENCE: 11

Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
 1 5 10 15
 Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Arg Phe
 20 25 30
 Gly Val His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
 35 40 45
 Gly Val Ile Trp Arg Gly Gly Ser Thr Asp Tyr Asn Ala Ala Phe Val
 50 55 60
 Ser Arg Leu Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu
 65 70 75 80
 Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ser
 85 90 95
 Asn His Tyr Tyr Gly Ser Ser Asp Tyr Ala Leu Asp Asn Trp Gly Gln
 100 105 110

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Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 12
 <211> LENGTH: 107
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: FCRL5 Target: light chain variable

<400> SEQUENCE: 12

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Arg Asn Leu
 20 25 30
 Val Val Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Ser Gly Ser Tyr Arg Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Ser Pro Pro Tyr
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> SEQ ID NO 13
 <211> LENGTH: 119
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: CD3 Target: heavy chain variable

<400> SEQUENCE: 13

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Thr Ser Tyr
 20 25 30
 Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45
 Gly Trp Ile Tyr Pro Glu Asn Asp Asn Thr Lys Tyr Asn Glu Lys Phe
 50 55 60
 Lys Asp Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Asp Gly Tyr Ser Arg Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly
 100 105 110
 Thr Leu Val Thr Val Ser Ser
 115

<210> SEQ ID NO 14
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: CD3 Target: light chain variable

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<400> SEQUENCE: 14

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Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1      5      10      15
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20     25     30
Arg Thr Arg Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35     40     45
Ser Pro Lys Leu Leu Ile Tyr Trp Thr Ser Thr Arg Lys Ser Gly Val
50     55     60
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65     70     75     80
Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Lys Gln
85     90     95
Ser Phe Ile Leu Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100    105    110

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<210> SEQ ID NO 15

<211> LENGTH: 450

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: FCRL5 Target: Heavy Chain

<400> SEQUENCE: 15

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Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1      5      10      15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Arg Phe
20     25     30
Gly Val His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35     40     45
Gly Val Ile Trp Arg Gly Gly Ser Thr Asp Tyr Asn Ala Ala Phe Val
50     55     60
Ser Arg Leu Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu
65     70     75     80
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ser
85     90     95
Asn His Tyr Tyr Gly Ser Ser Asp Tyr Ala Leu Asp Asn Trp Gly Gln
100    105    110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115    120    125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130    135    140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145    150    155    160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165    170    175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180    185    190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195    200    205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210    215    220
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly

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225	230	235	240
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile	245	250	255
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu	260	265	270
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His	275	280	285
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg	290	295	300
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys	305	310	315
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu	325	330	335
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr	340	345	350
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu	355	360	365
Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp	370	375	380
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val	385	390	395
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp	405	410	415
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His	420	425	430
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro	435	440	445
Gly Lys	450		

<210> SEQ ID NO 16
 <211> LENGTH: 214
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: FCRL5 Target: Light Chain

<400> SEQUENCE: 16

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Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Arg Asn Leu	20	25	30	
Val Val Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile	35	40	45	
Tyr Ser Gly Ser Tyr Arg Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly	50	55	60	
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro	65	70	75	80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Ser Pro Pro Tyr	85	90	95	
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala	100	105	110	
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly				

-continued

115					120					125					
Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala
130					135					140					
Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln
145					150					155					160
Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser
				165					170					175	
Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr
			180					185					190		
Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser
		195					200					205			
Phe	Asn	Arg	Gly	Glu	Cys										
210															

<210> SEQ ID NO 17

<211> LENGTH: 449

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: CD3 Target: Heavy Chain

<400> SEQUENCE: 17

Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
1				5					10					15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Phe	Thr	Phe	Thr	Ser	Tyr
			20					25					30		
Tyr	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile
		35				40						45			
Gly	Trp	Ile	Tyr	Pro	Glu	Asn	Asp	Asn	Thr	Lys	Tyr	Asn	Glu	Lys	Phe
	50					55					60				
Lys	Asp	Arg	Val	Thr	Ile	Thr	Ala	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr
65					70					75					80
Leu	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
			85					90						95	
Ala	Arg	Asp	Gly	Tyr	Ser	Arg	Tyr	Tyr	Phe	Asp	Tyr	Trp	Gly	Gln	Gly
			100					105					110		
Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
		115					120					125			
Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
	130					135					140				
Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
145				150						155					160
Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
			165					170						175	
Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
			180				185						190		
Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro
		195					200					205			
Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys
	210					215					220				
Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro
225				230						235					240
Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser

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245					250					255					
Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
			260					265					270		
Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
			275				280					285			
Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Gly	Ser	Thr	Tyr	Arg	Val
			290			295					300				
Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
305					310					315					320
Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
				325					330					335	
Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
			340					345					350		
Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Ser
			355				360					365			
Cys	Ala	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
			370			375					380				
Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
385					390					395					400
Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Val	Ser	Lys	Leu	Thr	Val	Asp	Lys
			405						410					415	
Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
			420					425					430		
Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly
			435				440					445			

Lys

<210> SEQ ID NO 18

<211> LENGTH: 219

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: CD3 Target: Light Chain

<400> SEQUENCE: 18

Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Asp	Ser	Leu	Ala	Val	Ser	Leu	Gly
1				5					10					15	
Glu	Arg	Ala	Thr	Ile	Asn	Cys	Lys	Ser	Ser	Gln	Ser	Leu	Leu	Asn	Ser
			20				25						30		
Arg	Thr	Arg	Lys	Asn	Tyr	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln
		35				40						45			
Ser	Pro	Lys	Leu	Leu	Ile	Tyr	Trp	Thr	Ser	Thr	Arg	Lys	Ser	Gly	Val
		50			55					60					
Pro	Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr
65				70					75					80	
Ile	Ser	Ser	Leu	Gln	Ala	Glu	Asp	Val	Ala	Val	Tyr	Tyr	Cys	Lys	Gln
			85					90						95	
Ser	Phe	Ile	Leu	Arg	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys
			100					105					110		
Arg	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu
			115				120					125			
Gln	Leu	Lys	Ser	Gly	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe
			130				135					140			

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Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
 145 150 155 160
 Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
 165 170 175
 Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
 180 185 190
 Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
 195 200 205
 Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 210 215

<210> SEQ ID NO 19
 <211> LENGTH: 119
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: BQ76 heavy chain variable region

<400> SEQUENCE: 19

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Lys Val Ala Pro Tyr Phe Ala Pro Phe Asp Tyr Trp Gly Gln Gly
 100 105 110
 Thr Leu Val Thr Val Ser Ser
 115

<210> SEQ ID NO 20
 <211> LENGTH: 109
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: BQ76 light chain variable region

<400> SEQUENCE: 20

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
 20 25 30
 Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45
 Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
 50 55 60
 Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
 65 70 75 80
 Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Asn Pro Pro

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85	90	95
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Leu Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> SEQ ID NO 21
 <211> LENGTH: 449
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: BQ76 heavy chain region where Xaa is K or
 absent
 <220> FEATURE:
 <221> NAME/KEY: misc_feature
 <222> LOCATION: (449)..(449)
 <223> OTHER INFORMATION: Xaa is K or absent

<400> SEQUENCE: 21

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly	
1 5 10 15	
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr	
20 25 30	
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	
35 40 45	
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val	
50 55 60	
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr	
65 70 75 80	
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys	
85 90 95	
Ala Lys Val Ala Pro Tyr Phe Ala Pro Phe Asp Tyr Trp Gly Gln Gly	
100 105 110	
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe	
115 120 125	
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu	
130 135 140	
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp	
145 150 155 160	
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu	
165 170 175	
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser	
180 185 190	
Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro	
195 200 205	
Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys	
210 215 220	
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro	
225 230 235 240	
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser	
245 250 255	
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp	
260 265 270	
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn	
275 280 285	
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val	
290 295 300	

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Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
 305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
 325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr
 340 345 350

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Ser
 355 360 365

Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
 370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
 385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys
 405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
 420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 435 440 445

Xaa

<210> SEQ ID NO 22
 <211> LENGTH: 216
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: BQ76 light chain region

<400> SEQUENCE: 22

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
 20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
 50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
 65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Asn Pro Pro
 85 90 95

Leu Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val
 100 105 110

Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
 115 120 125

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
 130 135 140

Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
 145 150 155 160

Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
 165 170 175

Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
 180 185 190

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Val	Tyr	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr
		195					200					205			

Lys	Ser	Phe	Asn	Arg	Gly	Glu	Cys
	210					215	

<210> SEQ ID NO 23
 <211> LENGTH: 111
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: BU76 heavy chain variable region

<400> SEQUENCE: 23

Asp	Ile	Val	Leu	Thr	Gln	Ser	Pro	Pro	Ser	Leu	Ala	Met	Ser	Leu	Gly
1				5					10					15	

Lys	Arg	Ala	Thr	Ile	Ser	Cys	Arg	Ala	Ser	Glu	Ser	Val	Thr	Ile	Leu
		20						25					30		

Gly	Ser	His	Leu	Ile	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro
		35				40						45			

Thr	Leu	Leu	Ile	Gln	Leu	Ala	Ser	Asn	Val	Gln	Thr	Gly	Val	Pro	Ala
	50					55					60				

Arg	Phe	Ser	Gly	Ser	Gly	Ser	Arg	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asp
65					70				75					80	

Pro	Val	Glu	Glu	Asp	Asp	Val	Ala	Val	Tyr	Tyr	Cys	Leu	Gln	Ser	Arg
			85						90					95	

Thr	Ile	Pro	Arg	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys
		100						105					110	

<210> SEQ ID NO 24
 <211> LENGTH: 111
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: BU76 heavy chain region

<400> SEQUENCE: 24

Asp	Ile	Val	Leu	Thr	Gln	Ser	Pro	Pro	Ser	Leu	Ala	Met	Ser	Leu	Gly
1				5					10					15	

Lys	Arg	Ala	Thr	Ile	Ser	Cys	Arg	Ala	Ser	Glu	Ser	Val	Thr	Ile	Leu
		20						25					30		

Gly	Ser	His	Leu	Ile	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro
		35				40						45			

Thr	Leu	Leu	Ile	Gln	Leu	Ala	Ser	Asn	Val	Gln	Thr	Gly	Val	Pro	Ala
	50					55					60				

Arg	Phe	Ser	Gly	Ser	Gly	Ser	Arg	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asp
65					70				75					80	

Pro	Val	Glu	Glu	Asp	Asp	Val	Ala	Val	Tyr	Tyr	Cys	Leu	Gln	Ser	Arg
				85					90					95	

Thr	Ile	Pro	Arg	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys
		100						105					110	

<210> SEQ ID NO 25
 <211> LENGTH: 447
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: BU76 heavy chain region where Xaa is K or absent

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (447)..(447)
<223> OTHER INFORMATION: Xaa is K or absent

<400> SEQUENCE: 25

Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1           5           10          15

Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
          20           25          30

Ser Ile Asn Trp Val Lys Arg Ala Pro Gly Lys Gly Leu Lys Trp Met
          35           40          45

Gly Trp Ile Asn Thr Glu Thr Arg Glu Pro Ala Tyr Ala Tyr Asp Phe
50           55          60

Arg Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr
65           70          75          80

Leu Gln Ile Asn Asn Leu Lys Tyr Glu Asp Thr Ala Thr Tyr Phe Cys
          85           90          95

Ala Leu Asp Tyr Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
          100          105          110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
          115          120          125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
          130          135          140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145          150          155          160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
          165          170          175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
          180          185          190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
          195          200          205

Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His
          210          215          220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225          230          235          240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
          245          250          255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
          260          265          270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
          275          280          285

Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser
          290          295          300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305          310          315          320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
          325          330          335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys Thr Leu Pro
          340          345          350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Ser Cys Ala
          355          360          365

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Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn
370						375					380				
Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser
385					390					395					400
Asp	Gly	Ser	Phe	Phe	Leu	Val	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg
			405						410					415	
Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu
			420					425					430		
His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Xaa	
	435						440					445			

<210> SEQ ID NO 26
 <211> LENGTH: 218
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: BU76 light chain region

<400> SEQUENCE: 26

Asp	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Ser	Leu	Ala	Met	Ser	Leu	Gly
1				5					10					15	
Lys	Arg	Ala	Thr	Ile	Ser	Cys	Arg	Ala	Ser	Glu	Ser	Val	Ser	Val	Ile
			20					25					30		
Gly	Ala	His	Leu	Ile	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Pro	Pro
		35					40					45			
Lys	Leu	Leu	Ile	Tyr	Leu	Ala	Ser	Asn	Leu	Glu	Thr	Gly	Val	Pro	Ala
	50					55				60					
Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asp
65				70					75					80	
Pro	Val	Glu	Glu	Asp	Asp	Val	Ala	Ile	Tyr	Ser	Cys	Leu	Gln	Ser	Arg
			85					90						95	
Ile	Phe	Pro	Arg	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu	Ile	Lys	Arg
		100					105						110		
Thr	Val	Ala	Ala	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln
		115					120					125			
Leu	Lys	Ser	Gly	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr
	130					135				140					
Pro	Arg	Glu	Ala	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser
145				150						155				160	
Gly	Asn	Ser	Gln	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr
			165					170						175	
Tyr	Ser	Leu	Ser	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys
		180					185						190		
His	Lys	Val	Tyr	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro
	195						200					205			
Val	Thr	Lys	Ser	Phe	Asn	Arg	Gly	Glu	Cys						
	210					215									

<210> SEQ ID NO 27
 <211> LENGTH: 116
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: EE11 heavy chain variable region

<400> SEQUENCE: 27

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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Lys Val Leu Gly Trp Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
 100 105 110
 Thr Val Ser Ser
 115

<210> SEQ ID NO 28
 <211> LENGTH: 109
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: EE11 light chain variable region

<400> SEQUENCE: 28

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser
 20 25 30
 Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45
 Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
 50 55 60
 Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
 65 70 75 80
 Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Tyr Pro Pro
 85 90 95
 Asp Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> SEQ ID NO 29
 <211> LENGTH: 477
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: EE11 scFV_Fc where Xaa is K or absent
 <220> FEATURE:
 <221> NAME/KEY: misc_feature
 <222> LOCATION: (477)..(477)
 <223> OTHER INFORMATION: Xaa is K or absent

<400> SEQUENCE: 29

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

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Ala	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
	35						40					45			
Ser	Ala	Ile	Ser	Gly	Ser	Gly	Gly	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val
	50					55					60				
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
	65				70					75					80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Lys	Val	Leu	Gly	Trp	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val
			100					105					110		
Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly
		115					120					125			
Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro
	130					135					140				
Gly	Thr	Leu	Ser	Leu	Ser	Pro	Gly	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg
	145				150					155					160
Ala	Ser	Gln	Ser	Val	Ser	Ser	Ser	Tyr	Leu	Ala	Trp	Tyr	Gln	Gln	Lys
				165					170					175	
Pro	Gly	Gln	Ala	Pro	Arg	Leu	Leu	Ile	Tyr	Gly	Ala	Ser	Ser	Arg	Ala
			180					185					190		
Thr	Gly	Ile	Pro	Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe
		195					200					205			
Thr	Leu	Thr	Ile	Ser	Arg	Leu	Glu	Pro	Glu	Asp	Phe	Ala	Val	Tyr	Tyr
	210					215					220				
Cys	Gln	Gln	Tyr	Gly	Tyr	Pro	Pro	Asp	Phe	Thr	Phe	Gly	Gln	Gly	Thr
	225				230					235					240
Lys	Val	Glu	Ile	Lys	Gly	Gly	Gly	Gly	Ser	Asp	Lys	Thr	His	Thr	Cys
			245						250					255	
Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu
			260					265					270		
Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu
		275					280					285			
Val	Thr	Cys	Val	Val	Val	Ala	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys
	290					295					300				
Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys
	305				310					315					320
Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu
				325					330					335	
Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys
		340						345					350		
Val	Ser	Asn	Lys	Ala	Leu	Ala	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys
		355					360					365			
Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Cys
	370					375					380				
Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Trp	Cys	Leu	Val	Lys
	385				390					395					400
Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln
			405						410					415	
Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly
		420						425					430		
Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln

-continued

435	440	445
Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn		
450	455	460
His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Xaa		
465	470	475

<210> SEQ ID NO 30
 <211> LENGTH: 449
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: EM90 heavy chain where Xaa is K or absent
 <220> FEATURE:
 <221> NAME/KEY: misc_feature
 <222> LOCATION: (449)..(449)
 <223> OTHER INFORMATION: Xaa is K or absent

<400> SEQUENCE: 30

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly		
1	5	10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ser		
	20	25 30
Gly Met Ile Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val		
	35	40 45
Gly His Ile Arg Ser Lys Thr Asp Gly Gly Thr Thr Asp Tyr Ala Ala		
	50	55 60
Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr		
	65	70 75 80
Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr		
	85	90 95
Tyr Cys Thr Thr Gly Gly Ser Gly Ser Phe Asp Tyr Trp Gly Gln Gly		
	100	105 110
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe		
	115	120 125
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu		
	130	135 140
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp		
	145	150 155 160
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu		
	165	170 175
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser		
	180	185 190
Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro		
	195	200 205
Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys		
	210	215 220
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro		
	225	230 235 240
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser		
	245	250 255
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp		
	260	265 270
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn		
	275	280 285

-continued

Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val
290						295					300				
Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
305					310					315					320
Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
			325						330					335	
Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Cys	Thr
			340					345					350		
Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Ser
		355					360					365			
Cys	Ala	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
	370					375					380				
Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
385					390					395					400
Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Val	Ser	Lys	Leu	Thr	Val	Asp	Lys
			405						410					415	
Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
			420					425					430		
Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly
		435					440					445			

Xaa

<210> SEQ ID NO 31
 <211> LENGTH: 215
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: EM90 light chain

<400> SEQUENCE: 31

Gln	Ala	Val	Val	Thr	Gln	Glu	Pro	Ser	Leu	Thr	Val	Ser	Pro	Gly	Gly
1				5					10					15	
Thr	Val	Thr	Leu	Thr	Cys	Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Thr	Ser
			20					25					30		
Asn	Tyr	Ala	Asn	Trp	Val	Gln	Glu	Lys	Pro	Gly	Gln	Ala	Phe	Arg	Gly
		35					40					45			
Leu	Ile	Gly	Gly	Thr	Asn	Lys	Arg	Ala	Pro	Gly	Thr	Pro	Ala	Arg	Phe
	50				55						60				
Ser	Gly	Ser	Leu	Leu	Gly	Gly	Lys	Ala	Ala	Leu	Thr	Leu	Ser	Gly	Ala
	65				70					75					80
Gln	Pro	Glu	Asp	Glu	Ala	Glu	Tyr	Tyr	Cys	Ala	Leu	Trp	Tyr	Ser	Asn
			85					90						95	
Leu	Trp	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu	Gly	Gln	Pro
			100					105					110		
Lys	Ala	Ala	Pro	Ser	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu	Glu	Leu
		115					120					125			
Gln	Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ile	Ser	Asp	Phe	Tyr	Pro
	130					135					140				
Gly	Ala	Val	Thr	Val	Ala	Trp	Lys	Ala	Asp	Ser	Ser	Pro	Val	Lys	Ala
	145				150				155						160
Gly	Val	Glu	Thr	Thr	Thr	Pro	Ser	Lys	Gln	Ser	Asn	Asn	Lys	Tyr	Ala
			165					170						175	
Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Glu	Gln	Trp	Lys	Ser	His	Arg

-continued

180	185	190
Ser Tyr Ser Cys Gln Val Thr	His Glu Gly Ser Thr	Val Glu Lys Thr
195	200	205
Val Ala Pro Thr Glu Cys Ser		
210	215	

<210> SEQ ID NO 32
 <211> LENGTH: 441
 <212> TYPE: PRT
 <213> ORGANISM: Artificial
 <220> FEATURE:
 <223> OTHER INFORMATION: FP31 heavy chain region

 <400> SEQUENCE: 32

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Pro Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Gly Gly Ser Gly Gly Ser Leu Pro Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Tyr Trp Pro Met Asp Ile Trp Gly Gln Gly Thr Leu Val Thr
100 105 110
Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
115 120 125
Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val
130 135 140
Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
145 150 155 160
Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
165 170 175
Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly
180 185 190
Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys
195 200 205
Val Asp Lys Thr Val Glu Arg Lys Cys Glu Val Glu Cys Pro Glu Cys
210 215 220
Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
225 230 235 240
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
245 250 255
Val Val Ala Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
260 265 270

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Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
275 280 285

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
290 295 300

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
305 310 315 320

Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
325 330 335

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
340 345 350

Thr Lys Asn Gln Val Ser Leu Thr Cys Glu Val Lys Gly Phe Tyr Pro
355 360 365

Ser Asp Ile Ser Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
370 375 380

Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
385 390 395 400

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
405 410 415

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
420 425 430

Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> SEQ ID NO 33

<211> LENGTH: 215

<212> TYPE: PRT

<213> ORGANISM: Artificial

<220> FEATURE:

<223> OTHER INFORMATION: FP31 light chain region

<400> SEQUENCE: 33

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Met Tyr Asp Ala Ser Ile Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gln Ser Trp Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175

-continued

Ser	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val
			180					185					190		
Tyr	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys
		195					200					205			
Ser	Phe	Asn	Arg	Gly	Glu	Cys									
	210					215									

1. A combination comprising:
 - a. an anti-BCMA antigen binding protein; and
 - b. a T cell engager that binds to CD3.
2. The combination of claim 1, wherein the anti-BCMA antigen binding protein comprises an antibody.
- 3.-4. (canceled)
5. The combination of claim 2, wherein the antibody is afucosylated.
6. (canceled)
7. The combination of claim 1, wherein the anti-BCMA antigen binding protein comprises a CDRH1 comprising the amino acid sequence set out in SEQ ID NO:1; a CDRH2 comprising the amino acid sequence set out in SEQ ID NO:2; a CDRH3 comprising the amino acid sequence set out in SEQ ID NO:3; a CDRL1 comprising the amino acid sequence set out in SEQ ID NO:4; a CDRL2 comprising the amino acid sequence set out in SEQ ID NO:5; and a CDRL3 comprising the amino acid sequence set out in SEQ ID NO:6.
8. The combination of claim 1, wherein the anti-BCMA antigen binding protein comprises a heavy chain variable region (V_H) comprising the amino acid sequence set out in SEQ ID NO:7; and a light chain variable region (V_L) comprising the amino acid sequence set out in SEQ ID NO:8.
9. The combination of claim 1, wherein the anti-BCMA antigen binding protein comprises a heavy chain (H) comprising the amino acid sequence set out in SEQ ID NO:9 and a light chain (L) comprising the amino acid sequence set out in SEQ ID NO:10.
10. (canceled)
11. The combination of claim 1, wherein the anti-BCMA antigen binding protein is an immunoconjugate comprising an antibody conjugated to a cytotoxin, wherein the cytotoxin is MMAE or MMAF.
- 12.-13. (canceled)
14. The combination of claim 1, wherein the anti-BCMA antigen binding protein is belantamab mafodotin.
15. (canceled)

16. The combination of claim 1, wherein the T cell engager is a bispecific T cell engager.
17. The combination of claim 23, wherein the T cell engager is selected from the group consisting of Cevostamab, Talquetamab, Teclistimab, PF-3135, TNB-383B, REGN5458, Blinatumomab, Solitomab, CC-93269, AMG701, AMG420, JNJ-7957, and GBR 1342.
18. The combination of claim 1, wherein the T cell engager is an anti-FcRH5 T cell engager.
19. The combination of claim 18, wherein the T cell engager is Cevostamab.
20. (canceled)
21. The combination of any one of claims 1-16, wherein the T cell engager is an anti-GPCR5D T cell engager.
22. The combination of claim 21, wherein the T cell engager is Talquetamab.
23. The combination of claim 1, wherein the T cell engager is an anti-BCMA T cell engager, an anti-FcRH5 T cell engager, or an anti-GPCR5D T cell engager.
- 24.-29. (canceled)
30. A method of treating cancer in a subject in need thereof comprising administering to the subject a therapeutically effective dose of the combination of claim 1.
31. (canceled)
32. The method of claim 30, wherein the cancer is selected from the group consisting of multiple myeloma, chronic lymphocytic leukemia, Waldenstrom macroglobulinemia, and non-Hodgkin's lymphoma.
33. The method of claim 30, wherein the cancer is multiple myeloma.
34. The method of claim 30, wherein the cancer is relapsed and/or refractory multiple myeloma.
- 35.-40. (canceled)
41. The method of claim 30, wherein the anti-BCMA antigen binding protein is administered to the subject in a dose of at least about 0.5 mg/kg, 0.95 mg/kg, 1 mg/kg, 1.25 mg/kg, 1.4 mg/kg, 1.7 mg/kg, 1.9 mg/kg, 1.92 mg/kg, 2.5 mg/kg or 3.4 mg/kg.
- 42.-45. (canceled)

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