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2022259766 26 Oct 2022

MULTISPECIFIC HEAVY CHAIN ANTIBODIES WITH MODIFIED HEAVY CHAIN CONSTANT REGIONS

ABSTRACT

Multispecific, human heavy chain antibodies (e.g., UniAbs™) that have modified heavy chain constant regions that impart advantageous properties are provided. The invention further concerns methods of making such antibodies, compositions, including pharmaceutical compositions, comprising such antibodies, and their use to treat disorders that are characterized by expression of one or more of the binding targets described herein.

2022259766 26 Oct 2022

MULTISPECIFIC HEAVY CHAIN ANTIBODIES WITH MODIFIED HEAVY CHAIN CONSTANT REGIONS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit of the filing date of the filing date of US Provisional Patent Application Serial No. 63/017,589, filed on April 29, 2020, as well as US Provisional Patent Application Serial No. 63/108,796, filed on November 2, 2020, the disclosures of which applications are incorporated by reference herein in their entireties.

[0001a] The entire disclosure of application AU 2021263448 is hereby incorporated by reference.

SEQUENCE LISTING

[0001b] This application contains a Sequence Listing which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention concerns multispecific, human heavy chain antibodies (e.g., UniAbs™) that have modified heavy chain constant regions that impart advantageous properties. The invention further concerns methods of making such antibodies, compositions, including pharmaceutical compositions, comprising such antibodies, and their use to treat disorders that are characterized by expression of one or more of the binding targets described herein.

BACKGROUND OF THE INVENTION

Modified Fc Regions

[0003] Advances in protein engineering have led to the successful manufacture and clinical utilization of multispecific antibodies having binding affinity to two or more targets. However, due to their heterodimeric nature, appropriate measures must be utilized to facilitate proper pairing of the desired combination of binding sequences, and thus the polypeptide subunits, in a multispecific antibody. Wang et al., *mAbs* 10:8, 1226-1235 (2018).

[0004] One approach to circumvent the problem of mispaired polypeptide subunits is known as "knobs-into-holes" (KiH), and it aims at forcing the pairing of two different antibody heavy chains by introducing

2022259766 16 Jun 2023

mutations in the CH2 and/or CH3 domains to modify the contact interface. On one chain, bulky amino acids are replaced by amino acids with short side chains to create a "hole". Conversely, amino acids with large side chains are introduced into the other heavy chain to create a "knob". By co-expressing these two heavy chains, a higher yield of heterodimer formation ("knob-hole") versus homodimer formation ("hole-hole" or "knob-knob") is observed due to the more favorable stability of the knob-hole pair (Ridgway, J.B., et al, *Protein Eng.* 9 (1996) 617-621; and WO 96/027011).

[0005] While this strategy appears attractive for achieving a desired heterodimer, other properties of the resulting multispecific antibodies are highly dependent on the specific amino acid sequence of the Fc region, namely, effector functions, such as, e.g., complement-dependent cytotoxicity (CDC) and antibody dependent cellular cytotoxicity (ADCC). Additionally, effector function activity can induce the production of cytokines, which can lead to a "cytokine storm" of unwanted inflammatory responses. Gupta et al., *Journal of Interferon & Cytokine Research* 40:1, 19-23 (2019). Acordingly, in certain settings, there is a need to reduce or altogether eliminate effector functions, for example, to avoid impairing or killing an immune cell (e.g., a T-cell) to which a multispecific antibody binds, and/or to avoid unwanted cytokine production and the resulting undesirable inflammatory responses.

[0006] Furthermore, introducing amino acid modifications into a protein can have serious drawbacks, namely, inducing an immune response by the patient against the protein based on the presence of non-native sequences. As such, the development of multispecific antibodies requires identifying sequences that are very similar in general structure to those of naturally occurring antibodies (like IgA, IgD, IgE, IgG or IgM) with minimal deviation from native sequences, but that successfully incorporate modifications that can simultaneously achieve the goals of facilitating desired heterodimerization, while also achieving a reduction or elimination of one or more effector functions.

[0007] To balance these competing requirements, the inventors focused on IgG4 Fc, whose native sequence is known to have relatively low-level effector function activity. Crescioli et al., *Curr Allergy Asthma Rep* 16:7 (2016). However, despite this seeming advantage, IgG4 is known to undergo an *in vivo* chain exchange reaction due to its particular hinge region sequence, presenting additional complications for achieving desired heterodimerization. Labrijn et al., *Nature Biotechnology* 27, 767-71 (2009). As such, there is a need for modified heavy chain constant region sequences that achieve desired heterodimerization, incorporate modifications that reduce or eliminate effector functions, and at the same time incorporate modifications that reduce or eliminate chain exchange reactions in IgG4. The molecules described herein address these and other challenges.

2022259766 16 Jun 2023

Heavy Chain Antibodies

[0008] In a conventional IgG antibody, the association of the heavy chain and light chain is due in part to a hydrophobic interaction between the light chain constant region and the CH1 constant domain of the heavy chain. There are additional residues in the heavy chain framework 2 (FR2) and framework 4 (FR4) regions that also contribute to this hydrophobic interaction between the heavy and light chains.

[0009] It is known, however, that sera of camelids (sub-order Tylopoda which includes camels, dromedaries and llamas) contain a major type of antibodies composed solely of paired H-chains (heavy-chain only antibodies or UniAbs™). The UniAbs™ of *Camelidae* (*Camelus dromedarius, Camelus bactrianus, Lama glama, Lama guanaco, Lama alpaca* and *Lama vicugna*) have a unique structure consisting of a single variable domain (VHH), a hinge region and two constant domains (CH2 and CH3), which are highly homologous to the CH2 and CH3 domains of classical antibodies. These UniAbs™ lack the first domain of the constant region (CH1) which is present in the genome, but is spliced out during mRNA processing. The absence of the CH1 domain explains the absence of the light chain in the UniAbs™, since this domain is the anchoring place for the constant domain of the light chain. Such UniAbs™ naturally evolved to confer antigen-binding specificity and high affinity by three CDRs from conventional antibodies or fragments thereof (Muyldermans, 2001; *J Biotechnol* 74:277–302; Revets et al., 2005; *Expert Opin Biol Ther* 5:111–124). Cartilaginous fish, such as sharks, have also evolved a distinctive type of immunoglobulin, designated as IgNAR, which lacks the light polypeptide chains and is composed entirely by heavy chains. IgNAR molecules can be manipulated by molecular engineering to produce the variable domain of a single heavy chain polypeptide (vNARs) (Nuttall et al. *Eur. J. Biochem.* 270, 3543-3554 (2003); Nuttall et al. *Function and Bioinformatics* 55, 187-197 (2004); Dooley et al., *Molecular Immunology* 40, 25-33 (2003)).

[00010] The ability of heavy chain-only antibodies devoid of light chain to bind antigen was established in the 1960s (Jaton *et al.* (1968) *Biochemistry*, 7, 4185-4195). Heavy chain immunoglobulin physically separated from light chain retained 80% of antigen-binding activity relative to the tetrameric antibody. Sitia et al. (1990) *Cell*, 60, 781-790 demonstrated that removal of the CH1 domain from a rearranged mouse μ gene results in the production of a heavy chain-only antibody, devoid of light chain, in mammalian cell culture. The antibodies produced retained VH binding specificity and effector functions.

[00011] Heavy chain antibodies with a high specificity and affinity can be generated against a variety of antigens through immunization (van der Linden, R. H., et al. *Biochim. Biophys. Acta.* 1431, 37-46 (1999)) and the VHH portion can be readily cloned and expressed in yeast (Frenken, L. G. J., *et al. J. Biotechnol.* 78, 11-21 (2000)). Their levels of expression, solubility and stability are significantly higher than those of classical F(ab) or Fv fragments (Ghahroudi, M. A. et al. *FEBS Lett.* 414, 521-526 (1997)).

[00012] Mice in which the λ (lambda) light (L) chain locus and/or the λ and κ (kappa) L chain loci have been functionally silenced and antibodies produced by such mice are described in U.S. Patent Nos.

7,541,513 and 8,367,888. Recombinant production of heavy chain-only antibodies in mice and rats has been reported, for example, in WO2006008548; U.S. Application Publication No. 20100122358; Nguyen et al., 2003, *Immunology*; 109(1), 93-101; Brüggemann *et al.*, *Crit. Rev. Immunol.*; 2006, 26(5):377-90; and Zou *et al.*, 2007, *J Exp Med*; 204(13): 3271–3283. The production of knockout rats via embryo microinjections of zinc-finger nucleases is described in Geurts et al., 2009, *Science*, 325(5939):433. Soluble heavy chain-only antibodies and transgenic rodents comprising a heterologous heavy chain locus producing such antibodies are described in U. S. Patent Nos. 8,883,150 and 9,365,655. CAR-T structures comprising single-domain antibodies as binding (targeting) domain are described, for example, in Iri-Sofla *et al.*, 2011, *Experimental Cell Research* 317:2630-2641 and Jamnani *et al.*, 2014, *Biochim Biophys Acta*, 1840:378-386.

B-Cell Maturation Antigen (BCMA)

[00013] BCMA, also known as tumor necrosis factor superfamily member 17 (TNFRSF17) (UniProt Q02223), is a cell surface receptor exclusively expressed on plasma cells and plasmablasts. BCMA is a receptor for two ligands in the tumor necrosis factor (TNF) superfamily: APRIL (a proliferation-inducing ligand, also known as TNFSF13; TALL-2 and TRDL-1; the high affinity ligand for BCMA) and B-cell activation factor (BAFF) (also known as BLyS; TALL-1; THANK; zTNF4; TNFSF20; and D8Ertd387e; the low affinity ligand for BCMA). APRIL and BAFF are growth factors that bind BCMA and promote survival of plasma cells. BCMA is also highly expressed on malignant plasma cells in human multiple myeloma (MM). Antibodies binding to BCMA are described, for example, in Gras et al., 1995, Int. Immunol. 7:1093-1106, WO200124811 and WO200124812. Anti-BCMA antibodies that cross-react with TACI are described in WO2002/066516. Bispecific antibodies against BCMA and CD3 are described, for example, in US 2013/0156769 A1 and US 2015/0376287 A1. An anti-BCMA antibody-MMAE or -MMAF conjugate has been reported to selectively induce killing of multiple myeloma cells (Tai et al., Blood 2014, 123(20): 3128-38). Ali et al., Blood 2016, 128(13):1688-700, have reported that in a clinical trial (#NCT02215967) chimeric antigen receptor (CAR) T-cells targeting BCMA resulted in remission of multiple myeloma in human patients.

PSMA

[00014] PSMA, also known as Prostate Specific Membrane Antigen and Glutamate Carboxypeptidase II (UniProt Q04609), is a type II transmembrane protein that has N-acetylated-alpha-linked-acidic dipeptidase, folate hydrolase and dipeptidyl-peptidase activity. It is encoded by the FOLH1 gene in humans and consists of a 19 amino acid cytoplasmic domain, a 24 amino acid transmembrane portion, and a 707 amino acid extracellular portion. The protein is enzymatically active as a non-covalent homodimer. PSMA is expressed

on prostate epithelium tissue and is upregulated in prostate cancer and the neovasculature of solid tumors. It is also expressed at low levels in healthy tissues such as the brain, kidney, and salivary glands, but its overexpression in malignant prostate tissue makes it an attractive target for the therapeutic treatment of prostate cancer. It may also be relevant for therapy or imaging of solid tumors, given its high expression in malignant neovasculature. Monoclonal antibodies, antibody-drug conjugates and chimeric antigen receptor T-cells targeting PSMA have been described for treatment of metastatic prostate cancer (Hernandez-Hoyos et al 2016, PMID: 27406985, DiPippo et al 2014, PMID: 25327986, Serganova et al 2016, PMID: 28345023). In addition, radionuclide conjugates specific to PSMA are being investigated for imaging and treatment of prostate cancer (e.g., Hofman et al., 2018 PMID: 29752180).

CD19

[00015] CD19, also known as B-Lymphocyte Surface Antigen B4 (UniProt P15391), is a cell surface receptor that is expressed on all human B-cells, but is not found on plasma cells. CD19 is a transmembrane protein that recruits cytoplasmic signaling proteins to the membrane and works within the CD19/CD21 complex to decrease the threshold for B-cell receptor signaling pathways. CD19 has a relatively large, 240 amino acid, cytoplasmic tail. The extracellular Ig-like domains are divided by a potential disulfide linked non-Ig-like domain and N-linked carbohydrate addition sites. The cytoplasmic tail contains at least nine tyrosine residues near the C-terminus, some of which have been shown to be phosphorylated. Along with CD20 and CD22, the restricted expression of CD19 to the B-cell lineage makes it an attractive target for the therapeutic treatment of B-cell malignancies. Many monoclonal antibodies and antibody drug conjugates specific to CD19 have been described (e.g., Naddafi et al. 2015, PMC4644525). In addition, anti-CD19 chimeric antigen receptor T-cells have been approved to treat leukemia (e.g., Sadelain et al. 2017, PMID: 29245005).

[00015a] It is to be understood that if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art in Australia or any other country.

SUMMARY OF THE INVENTION

[00015b] A first aspect provides a bispecific monoclonal antibody that binds to human CD3 and human BCMA, comprising:

(i) a first polypeptide subunit comprising the amino acid sequence of SEQ ID NO:49;

(ii) a second polypeptide subunit comprising the amino acid sequence of SEQ ID NO:56,

wherein the first and second polypeptide subunits together form a first binding moiety that binds to human CD3; and

(iii) a third polypeptide subunit that binds to human BCMA, comprising the amino acid sequence of SEQ ID NO:58.

[00015c] A second aspect provides a bispecific monoclonal antibody that binds to human CD3 and human BCMA, comprising:

(i) a first polypeptide subunit comprising the amino acid sequence of SEQ ID NO:49;

(ii) a second polypeptide subunit comprising the amino acid sequence of SEQ ID NO:75, wherein the first and second polypeptide subunits together form a first binding moiety that binds to human CD3; and

(iii) a third polypeptide subunit that binds to human BCMA, comprising the amino acid sequence of SEQ ID NO:76.

[00015d] A third aspect provides a human, monoclonal IgG4 bispecific antibody comprising:

(i) a first binding arm that binds to human CD3; and

(ii) a second binding arm that binds to human BCMA,

wherein the first binding arm comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO:56 and a light chain comprising the amino acid sequence of SEQ ID NO:49; and

wherein the second binding arm comprises a bivalent second heavy chain comprising the amino acid sequence of SEQ ID NO:58.

[00015e] A fourth aspect provides a human, monoclonal IgG4 bispecific antibody comprising:

(i) a first binding arm that binds to human CD3; and

(ii) a second binding arm that binds to human BCMA,

wherein the first binding arm comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO:75 and a light chain comprising the amino acid sequence of SEQ ID NO:49; and

wherein the second binding arm comprises a bivalent second heavy chain comprising the amino acid sequence of SEQ ID NO:76.

[00015f] A fifth aspect provides a pharmaceutical composition comprising the bispecific antibody of any one of the first to fourth aspects, and a pharmaceutically acceptable carrier.

[00015g] A sixth aspect provides one or more polynucleotides encoding the bispecific antibody of any one of the first to fourth aspects.

[00015h] A seventh aspect provides one or more vectors comprising the one or more polynucleotides of the sixth aspect.

[00015i] An eighth aspect provides an isolated or non-human cell comprising the one or more vectors of the seventh aspect.

[00015j] A ninth aspect provides a method of producing a bispecific antibody, comprising growing the cell of the eighth aspect under conditions permissive for expression of the bispecific antibody, and isolating the bispecific antibody from the cell.

[00015k] A tenth aspect provides a kit comprising the bispecific antibody of any one of the first to fourth aspects, and instructions for use.

[00015l] An eleventh aspect provides a method for treating a BCMA-expressing cancer in a human subject in need thereof, comprising administering to the subject a therapeutically effective amount of the bispecific antibody of any one of the first to fourth aspects.

[00015m] A twelfth aspect provides use of the bispecific antibody of any one of the first to fourth aspects in the manufacture of a medicament for treating a BCMA-expressing cancer in a human subject in need thereof.

[00016] Also disclosed are isolated multispecific antibodies comprising: a first heavy chain polypeptide subunit comprising a mutated human IgG4 constant region comprising mutations S228P, F234A, L235A, and T366W; and a second heavy chain polypeptide subunit comprising a mutated human IgG4 constant region comprising mutations S228P, F234A, L235A, T366S, L368A, and Y407V. In some embodiments, the mutated human IgG4 constant region of the first heavy chain polypeptide subunit or the mutated human IgG4 constant region of second heavy chain polypeptide subunit lacks a CH1 domain. In some embodiments, the mutated human IgG4 constant region of the first heavy chain polypeptide subunit comprises a sequence of SEQ ID NO: 73 or 55, and the mutated human IgG4 constant region of the second heavy chain polypeptide subunit comprises a sequence of SEQ ID NO: 72 or 54.

[00017] In some embodiments, multispecific antibodies in accordance with embodiments of the invention further comprise a first binding moiety that has binding specificity for CD3, comprising: a heavy chain variable domain comprising a CDR1 sequence comprising a sequence of SEQ ID NO: 36, a CDR2 sequence comprising a sequence of SEQ ID NO: 37, and a CDR3 sequence comprising a sequence of SEQ ID NO: 38; and a light chain variable domain comprising a CDR1 sequence comprising a sequence of SEQ ID NO: 39, a CDR2 sequence comprising a sequence of SEQ ID NO: 40, and a CDR3 sequence comprising a sequence of SEQ ID NO: 41.

[00018] In some embodiments, the CDR1, CDR2 and CDR3 sequences in the heavy chain variable domain of the first binding moiety are present in a human VH framework; and the CDR1, CDR2 and CDR3 sequences in the light chain variable domain of the first binding moiety are present in a human Vkappa framework. In some embodiments, the heavy chain variable domain of the first binding moiety comprises a sequence having at least 95% identity to SEQ ID NO: 42; and the light chain variable domain of the first binding moiety comprises a sequence having at least 95% identity to SEQ ID NO: 43. In some embodiments, the heavy chain variable domain of the first binding moiety comprises the sequence of SEQ ID NO: 42; and the light chain variable domain of the first binding moiety comprises the sequence of SEQ ID NO: 43.

[00019] In some embodiments, multispecific antibodies in accordance with embodiments of the invention further comprise a second binding moiety having binding specificity to a protein other than CD3. In some embodiments, the second binding moiety comprises a single heavy chain variable region, in a monovalent or bivalent configuration. In some embodiments, the first binding moiety comprises a light chain polypeptide subunit and a heavy chain polypeptide subunit, and wherein the second binding moiety comprises a heavy chain polypeptide subunit. In some embodiments, the light chain polypeptide subunit of the first binding moiety comprises a light chain constant domain. In some embodiments, the protein other than CD3 is a tumor-associated antigen (TAA) or a tumor-specific antigen (TSA). In some embodiments, the TAA is B-cell maturation antigen (BCMA). In some embodiments, the TAA is CD19. In some embodiments, the TAA is prostate specific membrane antigen (PSMA).

[00020] Also disclosed are pharmaceutical compositions comprising a multispecific antibody as described herein, polynucleotides encoding a multispecific antibody as described herein, vectors comprising such polynucleotides, and cells comprising such vectors.

[00021] Also disclosed are methods of producing a multispecific antibody as described herein, comprising growing a cell as described herein under conditions permissive for expression of the multispecific antibody, and isolating the multispecific antibody from the cell.

[00022] Also disclosed are methods of treatment comprising administering to an individual in need an effective dose of a multispecific antibody, or the pharmaceutical composition, described herein.

[00023] Also disclosed are use of a multispecific antibody described herein in the preparation of a medicament for the treatment of a disease or disorder in an individual in need.

[00024] Also disclosed are methods for treating a disease or condition characterized by expression of BCMA, comprising administering to an individual in need an effective dose of a multispecific antibody, or a pharmaceutical composition, described herein. In some embodiments, the disease is an autoimmune disease. In some embodiments, the disease is a cancer. In some embodiments, the cancer is a myeloma. In some embodiments, the myeloma is multiple myeloma.

[00025] Also disclosed are methods for treating a disease or condition characterized by expression of PSMA, comprising administering to an individual in need an effective dose of a multispecific antibody, or a pharmaceutical composition, described herein. In some embodiments, the disease is a cancer. In some embodiments, the cancer is prostate cancer.

[00026] Also disclosed are methods for treating a disease or condition characterized by expression of CD19, comprising administering to an individual in need an effective dose of a multispecific antibody, or a pharmaceutical composition, described herein. In some embodiments, the disorder is diffuse large B-cell lymphoma (DLBCL). In some embodiments, the disorder is acute lymphoblastic leukemia (ALL). In some embodiments, the disorder is non-Hodgkin's lymphoma (NHL). In some embodiments, the disorder is

systemic lupus erythematosus (SLE). In some embodiments, the disorder is rheumatoid arthritis (RA). In some embodiments, the disorder is multiple sclerosis (MS).

[00027] Also disclosed are kits for treating a disease or disorder in an individual in need, comprising a multispecific antibody, or a pharmaceutical composition, described herein, and instructions for use. In some embodiments, a kit further comprises at least one additional reagent. In some embodiments, the at least one additional reagent comprises a chemotherapeutic drug.

[00028] Also disclosed are bispecific three-chain antibody like molecules comprising: a first polypeptide subunit comprising: a light chain variable domain (VL) comprising a sequence of SEQ ID NO: 43; and a light chain constant domain (CL); a second polypeptide subunit comprising: a heavy chain variable domain (VH) comprising a sequence of SEQ ID NO: 42; and a heavy chain constant domain (CH) comprising a sequence of SEQ ID NO: 72 or 73; wherein the light chain variable domain and the heavy chain variable domain together form a first binding moiety that has binding specificity for CD3; and a third polypeptide subunit comprising: a heavy chain-only variable region, in a monovalent or bivalent configuration, that has binding specificity for a protein other than CD3; and a heavy chain constant domain (CH) comprising a sequence of SEQ ID NO: 54 or 55. In some embodiments, the third polypeptide subunit comprises a heavy chain-only variable region in a bivalent configuration that has binding specificity to BCMA.

[00029] Also disclosed are bispecific three-chain antibody like molecules comprising: a first polypeptide subunit comprising a sequence of SEQ ID NO: 49; a second polypeptide subunit comprising a sequence of SEQ ID NO: 56; and a third polypeptide subunit comprising a sequence of SEQ ID NO: 58.

[00030] Also disclosed are pharmaceutical compositions comprising a bispecific three-chain antibody like molecule described herein, polynucleotides encoding a bispecific three-chain antibody like molecule described herein, vectors comprising such polynucleotides, and cells comprising such vectors.

[00031] Also disclosed are methods of producing a bispecific three-chain antibody like molecule described herein, comprising growing a cell described herein under conditions permissive for expression of the bispecific three-chain antibody like molecule, and isolating the bispecific three-chain antibody like molecule from the cell.

[00032] Also disclosed are methods of treatment, comprising administering to an individual in need an effective dose of a bispecific three-chain antibody like molecule, or a pharmaceutical composition, described herein.

[00033] Also disclosed are use of a bispecific three-chain antibody like molecule described herein in the preparation of a medicament for the treatment of a disease or disorder in an individual in need.

[00034] Also disclosed are methods for treating a disease or condition characterized by expression of BCMA, comprising administering to an individual in need an effective dose of a bispecific three-chain

2022259766 16 Jun 2023

antibody like molecule, or a pharmaceutical composition, described herein. In some embodiments, the disease is an autoimmune disease. In some embodiments, the disease is a cancer. In some embodiments, the cancer is a myeloma. In some embodiments, the myeloma is multiple myeloma.

[00035] Also disclosed are kits for treating a disease or disorder in an individual in need, comprising a bispecific three-chain antibody like molecule, or a pharmaceutical composition, described herein, and instructions for use. In some embodiments, a kit further comprises at least one additional reagent. In some embodiments, the at least one additional reagent comprises a chemotherapeutic drug.

[00036] These and further embodiments will be further explained in the rest of the disclosure, including the Examples.

BRIEF DESCRIPTION OF THE DRAWINGS

[00037] FIG. 1, panels A-C, provide illustrations of various multispecific antibodies in accordance with embodiments of the invention.

2022259766 26 Oct 2022

[00038] FIG. 2, panels A-B, show images of non-reducing SDS-PAGE analyses of various antibody species purified via protein A chromatography.

[00039] FIG. 3, panel A, shows an image of non-reducing SDS-PAGE analysis of various antibody species purified via protein A chromatography. Panel B shows an image of a reducing SDS-PAGE analysis of the same antibody species shown in panel A.

[00040] FIG. 4, panels A-D are graphs depicting Fc gamma receptor – antibody interactions for various IgG1 antibody species in accordance with embodiments of the invention.

[00041] FIG. 5, panels A-E are graphs depicting Fc gamma receptor – antibody interactions for various IgG4 antibody species in accordance with embodiments of the invention.

[00042] FIG. 6, panels A-D, are graphs depicting Fc gamma receptor – antibody interactions for various IgG1 antibody species in accordance with embodiments of the invention.

[00043] FIG. 7, panels A-E are graphs depicting Fc gamma receptor – antibody interactions for various IgG4 antibody species in accordance with embodiments of the invention.

[00044] FIG. 8, panel A is a graph showing cell binding to human PSMA. FIG. 8, panel B is a graph showing cell binding to cynomolgus monkey PSMA.

[00045] FIG. 9 is a graph depicting T-cell mediated lysis of PSMA positive cells using unstimulated T-cells.

[00046] FIG. 10 is a graph depicting T-cell mediated lysis of PSMA positive cells using pre-activated T-cells.

[00047] FIG. 11 is a graph depicting percent specific lysis of PSMA negative DU145 cells as a function of multi-specific antibody concentration in the presence of pre-activated T-cells.

[00048] FIG. 12 is a graph showing binding of PSMA x CD3 bispecific antibodies to PSMA positive and negative cells.

[00049] FIG. 13 is a graph showing T-cell mediated lysis of PSMA positive cells.

[00050] FIG. 14, panel A, is a graph depicting T-cell mediated lysis of PSMA positive cells as a function of antibody concentration. Panel B, is a graph depicting cytokine (IFNγ) release as a function of antibody concentration. Panel C, is a graph depicting cytokine (IL-2) release as a function of antibody concentration.

[00051] FIG. 15, panel A, is a graph depicting T-cell proliferation as a function of antibody concentration. Panel B, is a graph depicting T-cell proliferation as a function of antibody concentration. Panel C, is a graph depicting the ratio of CD8 to CD4 of proliferated T-cells. Panel D, is a graph depicting the ratio of CD8 to CD4 of proliferated T-cells.

[00052] FIG. 16 is a graph depicting inhibition of 22Rv1 tumor growth in a tumor xenograft model.

[00053] FIG. 17 is a graph depicting %CD4+CD69+ T-cells as a function of bispecific antibody concentration for the bispecific antibodies shown in the legend.

[00054] FIG. 18 is a graph depicting %CD8+CD69+ T-cells as a function of bispecific antibody concentration for the bispecific antibodies shown in the legend.

[00055] FIG. 19 is a graph depicting %CD8+CD69+ T-cells as a function of bispecific antibody concentration for the bispecific antibodies shown in the legend.

[00056] FIG. 20 is a graph depicting %CD8+CD69+ T-cells as a function of bispecific antibody concentration for the bispecific antibodies shown in the legend.

[00057] FIG. 21, panels A-D, provide several graphs depicting bispecific antibody-mediated tumor cell lysis. Anti-CD3 x anti-BCMA bispecific antibodies were assayed for the ability to kill three different BCMA+ tumor cells and one BCMA-negative cell line through redirection of activated primary T-cells. In this experiment, tumor cells were mixed with activated pan T-cells in a 10:1 E:T ratio along with the addition of bispecific antibody. Panel A shows killing of RPMI-8226 cells, panel B shows killing of NCI-H929 cells, panel C shows killing of U-266 cells, and panel D shows killing of K562 cells, a negative control. The x-axis shows the concentration of antibody used and the y-axis shows the % lysis of tumor cells 6 hours after addition of antibody.

[00058] FIG. 22, panels A-D, provide several graphs depicting bispecific antibody-mediated IL-2 release. The level of IL-2 cytokine release was measured after resting human T-cells were cultured with various tumor cell lines and increasing doses of anti-CD3 x anti-BCMA bispecific antibody. Panel A shows IL-2 release stimulated by RPMI-8226 cells, panel B shows IL-2 release stimulated by NCI-H929 cells, panel C shows IL-2 release stimulated by U-266 cells, and panel D shows IL-2 release stimulated by K562 cells, a negative control.

[00059] FIG. 23, panels A-D, provide several graphs depicting bispecific antibody-mediated IFN-γ release. The level of IFN-γ cytokine release was measured after resting human T-cells were cultured with various tumor cell lines and increasing doses of anti-CD3 x anti-BCMA bispecific antibody. Panel A shows IFN-γ release stimulated by RPMI-8226 cells, panel B shows IFN-γ release stimulated by NCI-H929 cells, panel C shows IFN-γ release stimulated by U-266 cells, and panel D shows IFN-γ release stimulated by K562 cells, a negative control.

[00060] FIG. 24 is an image of a non-reducing SDS-PAGE analysis of various antibody species purified via protein A chromatography.

[00061] FIG. 25 is a table showing % HMW species, % Monomers, and % LMW species from samples of the indicated constructs following purification.

[00062] FIG. 26, panels A-D, are graphs depicting Fc gamma receptor – antibody interactions for various IgG4 antibody species in accordance with embodiments of the invention.

[00063] FIG. 27, panels A and B, are graphs depicting %CD4+CD69+ T-cells (panel A) and %CD8+CD69+ T-cells (panel B) as a function of bispecific antibody concentration for the CD3xBCMA bispecific antibodies shown in the legend.

[00064] FIG. 28, panels A and B, are graphs depicting %CD4+CD69+ T-cells (panel A) and %CD8+CD69+ T-cells (panel B) as a function of bispecific antibody concentration for the CD3xBCMA bispecific antibodies shown in the legend.

[00065] FIG. 29, panels A and B, are graphs depicting %CD4+CD69+ T-cells (panel A) and %CD8+CD69+ T-cells (panel B) as a function of bispecific antibody concentration for the CD3xBCMA bispecific antibodies shown in the legend.

[00066] FIG. 30, panels A and B, are graphs depicting %CD4+CD69+ T-cells (panel A) and %CD8+CD69+ T-cells (panel B) as a function of bispecific antibody concentration for the CD3xPSMA bispecific antibodies shown in the legend.

[00067] FIG. 31, panels A and B, are graphs depicting %CD4+CD69+ T-cells (panel A) and %CD8+CD69+ T-cells (panel B) as a function of bispecific antibody concentration for the CD3xPSMA bispecific antibodies shown in the legend.

[00068] FIG. 32, panels A and B, are graphs depicting %CD4+CD69+ T-cells (panel A) and %CD8+CD69+ T-cells (panel B) as a function of bispecific antibody concentration for the CD3xPSMA bispecific antibodies shown in the legend.

[00069] FIG. 33, panels A and B, are graphs depicting %CD4+CD69+ T-cells (panel A) and %CD8+CD69+ T-cells (panel B) as a function of bispecific antibody concentration for the CD3xCD19 bispecific antibodies shown in the legend.

[00070] FIG. 34, panels A and B, are graphs depicting %CD4+CD69+ T-cells (panel A) and %CD8+CD69+ T-cells (panel B) as a function of bispecific antibody concentration for the CD3xCD19 bispecific antibodies shown in the legend.

[00071] FIG. 35, panels A and B, are graphs depicting %CD4+CD69+ T-cells (panel A) and %CD8+CD69+ T-cells (panel B) as a function of bispecific antibody concentration for the CD3xCD19 bispecific antibodies shown in the legend.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[00072] The practice of the present invention will employ, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature, such as, "Molecular Cloning: A Laboratory Manual", second edition (Sambrook et al., 1989);

"Oligonucleotide Synthesis" (M. J. Gait, ed., 1984); "Animal Cell Culture" (R. I. Freshney, ed., 1987); "Methods in Enzymology" (Academic Press, Inc.); "Current Protocols in Molecular Biology" (F. M. Ausubel et al., eds., 1987, and periodic updates); "PCR: The Polymerase Chain Reaction", (Mullis et al., ed., 1994); "A Practical Guide to Molecular Cloning" (Perbal Bernard V., 1988); "Phage Display: A Laboratory Manual" (Barbas et al., 2001); Harlow, Lane and Harlow, Using Antibodies: A Laboratory Manual: Portable Protocol No. I, Cold Spring Harbor Laboratory (1998); and Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory; (1988).

[00073] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

[00074] Unless indicated otherwise, antibody residues herein are numbered according to the Kabat numbering system (*e.g.*, Kabat *et al.*, Sequences of Immunological Interest. 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)).

[00075] In the following description, numerous specific details are set forth to provide a more thorough understanding of the present invention. However, it will be apparent to one of skill in the art that the present invention may be practiced without one or more of these specific details. In other instances, well-known features and procedures well known to those skilled in the art have not been described in order to avoid obscuring the invention.

[00076] All references cited throughout the disclosure, including patent applications and publications, are incorporated by reference herein in their entirety.

I. Definitions

[00077] By "comprising" it is meant that the recited elements are required in the composition/method/kit, but other elements may be included to form the composition/method/kit etc. within the scope of the claim.

[00078] By "consisting essentially of", it is meant a limitation of the scope of composition or method described to the specified materials or steps that do not materially affect the basic and novel characteristic(s) of the subject invention.

[00079] By "consisting of", it is meant the exclusion from the composition, method, or kit of any element, step, or ingredient not specified in the claim.

[00080] Antibody residues herein are numbered according to the Kabat numbering system and the EU numbering system. The Kabat numbering system is generally used when referring to a residue in the variable domain (approximately residues 1-113 of the heavy chain) (*e.g.*, Kabat *et al.*, Sequences of Immunological Interest. 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)). The "EU numbering system" or "EU index" is generally used when referring to a residue in an immunoglobulin heavy chain constant region (e.g., the EU index reported in Kabat et al., supra). The "EU index as in Kabat" refers to the residue numbering of the human IgG1 EU antibody. Unless stated otherwise herein, references to residue numbers in the variable domain of antibodies mean residue numbering by the Kabat numbering system. Unless stated otherwise herein, references to residue numbers in the constant domain of antibodies mean residue numbering by the EU numbering system.

[00081] An "antibody" or "immunoglobulin" refers to a molecule comprising at least one heavy chain and one light chain, where the amino terminal domain of the heavy and light chains is variable in sequence, hence is commonly referred to as a variable region domain, or a variable heavy (VH) or variable light (VH) domain. The two domains conventionally associate to form a specific binding region, although as will be discussed here, specific binding can also be obtained with heavy chain-only variable sequences, and a variety of non-natural configurations of antibodies are known and used in the art.

[00082] A "functional" or "biologically active" antibody or antigen-binding molecule (including heavy chain-only antibodies and multi-specific (e.g., bispecific) three-chain antibody-like molecules (TCAs), described herein) is one capable of exerting one or more of its natural activities in structural, regulatory, biochemical or biophysical events. For example, a functional antibody or other binding molecule, e.g., a TCA, may have the ability to specifically bind an antigen and the binding may in turn elicit or alter a cellular or molecular event such as signal transduction or enzymatic activity. A functional antibody or other binding molecule, e.g., a TCA, may also block ligand activation of a receptor or act as an agonist or antagonist. The capability of an antibody or other binding molecule, e.g., a TCA, to exert one or more of its natural activities depends on several factors, including proper folding and assembly of the polypeptide chains.

[00083] The term antibody may reference a full-length heavy chain, a full length light chain, an intact immunoglobulin molecule; or an immunologically active portion of any of these polypeptides, i.e., a polypeptide that comprises an antigen binding site that immunospecifically binds an antigen of a target of interest or part thereof, such targets including but not limited to, cancer cell or cells that produce autoimmune antibodies associated with an autoimmune disease. The immunoglobulin disclosed herein can be of any type (e.g., IgG, IgE, IgM, IgD, and IgA), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule, including engineered subclasses with altered Fc portions that provide for reduced or enhanced effector cell activity. Light chains of the subject antibodies can be kappa

light chains (Vkappa) or lambda light chains (Vlambda). The immunoglobulins can be derived from any species. In one aspect, the immunoglobulin is of largely human origin.

[00084] The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. Monoclonal antibodies in accordance with the present invention can be made by the hybridoma method first described by Kohler et al. (1975) *Nature* 256:495, and can also be made via recombinant protein production methods (see, *e.g.*, U.S. Patent No. 4,816,567), for example.

[00085] The term "variable", as used in connection with antibodies, refers to the fact that certain portions of the antibody variable domains differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody for its particular antigen. However, the variability is not evenly distributed throughout the variable domains of antibodies. It is concentrated in three segments called hypervariable regions both in the light chain and the heavy chain variable domains. The more highly conserved portions of variable domains are called the framework regions (FRs). The variable domains of native heavy and light chains each comprise four FRs, largely adopting a β-sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases forming part of, the β-sheet structure. The hypervariable regions in each chain are held together in close proximity by the FRs and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site of antibodies (see Kabat *et al., Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)). The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody dependent cellular cytotoxicity (ADCC).

[00086] The term "hypervariable region" when used herein refers to the amino acid residues of an antibody which are responsible for antigen-binding. The hypervariable region generally comprises amino acid residues from a "complementarity determining region" or "CDR" (e.g., residues 31-35 (H1), 50-65 (H2) and 95-102 (H3) in the heavy chain variable domain; Kabat et al., *Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)) and/or those residues from a "hypervariable loop" residues 26-32 (H1), 53-55 (H2) and 96-101 (H3) in the heavy chain variable domain; Chothia and Lesk *J. Mol. Biol.* 196:901-917 (1987)). In some embodiments, "CDR" means a complementary determining region of an antibody as defined in Lefranc, MP et al., IMGT, the international ImMunoGeneTics database, Nucleic Acids Res., 27:209-212 (1999). "Framework Region" or

"FR" residues are those variable domain residues other than the hypervariable region/CDR residues as herein defined.

[00087] Exemplary CDR designations are shown herein, however one of skill in the art will understand that a number of definitions of the CDRs are commonly in use, including the Kabat definition (see "Zhao et al. A germline knowledge based computational approach for determining antibody complementarity determining regions." *Mol Immunol.* 2010;47:694–700), which is based on sequence variability and is the most commonly used. The Chothia definition is based on the location of the structural loop regions (Chothia et al. "Conformations of immunoglobulin hypervariable regions." *Nature.* 1989; 342:877–883). Alternative CDR definitions of interest include, without limitation, those disclosed by Honegger, "Yet another numbering scheme for immunoglobulin variable domains: an automatic modeling and analysis tool." *J Mol Biol.* 2001;309:657–670; Ofran et al. "Automated identification of complementarity determining regions (CDRs) reveals peculiar characteristics of CDRs and B-cell epitopes." *J Immunol.* 2008;181:6230–6235; Almagro "Identification of differences in the specificity-determining residues of antibodies that recognize antigens of different size: implications for the rational design of antibody repertoires." *J Mol Recognit.* 2004;17:132–143; and Padlanet al. "Identification of specificity-determining residues in antibodies." Faseb J. 1995;9:133–139., each of which is herein specifically incorporated by reference.

[00088] The terms "heavy chain-only antibody," and "heavy chain antibody" are used interchangeably herein and refer, in the broadest sense, to antibodies, or one or more portions of an antibody, e.g., one or more arms of an antibody, lacking the light chain of a conventional antibody. The terms specifically include, without limitation, homodimeric antibodies comprising the VH antigen-binding domain and the CH2 and CH3 constant domains, in the absence of the CH1 domain; functional (antigen-binding) variants of such antibodies, soluble VH variants, Ig-NAR comprising a homodimer of one variable domain (V-NAR) and five C-like constant domains (C-NAR) and functional fragments thereof; and soluble single domain antibodies (sUniDabs™). In one embodiment, a heavy chain-only antibody is composed of a variable region antigen-binding domain composed of framework 1, CDR1, framework 2, CDR2, framework 3, CDR3, and framework 4. In another embodiment, a heavy chain-only antibody is composed of an antigen-binding domain, at least part of a hinge region and CH2 and CH3 domains. In another embodiment, a heavy chain-only antibody is composed of an antigen-binding domain, at least part of a hinge region and a CH2 domain. In a further embodiment, a heavy chain-only antibody is composed of an antigen-binding domain, at least part of a hinge region and a CH3 domain. Heavy chain-only antibodies in which the CH2 and/or CH3 domain is truncated are also included herein. In a further embodiment, a heavy chain is composed of an antigen binding domain, and at least one CH (CH1, CH2, CH3, or CH4) domain but no hinge region. The heavy chain-only antibody can be in the form of a dimer, in which two heavy chains are disulfide bonded or otherwise, covalently or non-covalently, attached with each other. The heavy chain-only antibody may

belong to the IgG subclass, but antibodies belonging to other subclasses, such as IgM, IgA, IgD and IgE subclass, are also included herein. In a particular embodiment, a heavy chain antibody is of the IgG1, IgG2, IgG3, or IgG4 subtype, in particular the IgG1 subtype. In one embodiment, the heavy chain-only antibodies herein are used as a binding (targeting) domain of a chimeric antigen receptor (CAR). The definition specifically includes human heavy chain-only antibodies produced by human immunoglobulin transgenic rats (UniRat™), called UniAbs™. The variable regions (VH) of UniAbs™ are called UniDabs™, and are versatile building blocks that can be linked to Fc regions or serum albumin for the development of novel therapeutics with multi-specificity, increased potency and extended half-life. Since the homodimeric UniAbs™ lack a light chain and thus a VL domain, the antigen is recognized by one single domain, i.e., the variable domain of the heavy chain of a heavy-chain antibody (VH or VHH).

[00089] An "intact antibody chain" as used herein is one comprising a full length variable region and a full length constant region (Fc). An intact "conventional" antibody comprises an intact light chain and an intact heavy chain, as well as a light chain constant domain (CL) and heavy chain constant domains, CH1, hinge, CH2 and CH3 for secreted IgG. Other isotypes, such as IgM or IgA may have different CH domains. The constant domains may be native sequence constant domains (e.g., human native sequence constant domains) or amino acid sequence variants thereof. The intact antibody may have one or more "effector functions" which refer to those biological activities attributable to the Fc constant region (a native sequence Fc region or amino acid sequence variant Fc region) of an antibody. Examples of antibody effector functions include C1q binding; complement dependent cytotoxicity; Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; and down regulation of cell surface receptors. Constant region variants include those that alter the effector profile, binding to Fc receptors, and the like.

[00090] Depending on the amino acid sequence of the Fc (constant domain) of their heavy chains, antibodies and various antigen-binding proteins can be provided as different classes. There are five major classes of heavy chain Fc regions: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into "subclasses" (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA, and IgA2. The Fc constant domains that correspond to the different classes of antibodies may be referenced as α, δ, ε, γ, and μ, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known. Ig forms include hinge-modifications or hingeless forms (Roux et al (1998) J. Immunol. 161:4083-4090; Lund et al (2000) Eur. J. Biochem. 267:7246-7256; US 2005/0048572; US 2004/0229310). The light chains of antibodies from any vertebrate species can be assigned to one of two types, called κ (kappa) and λ (lambda), based on the amino acid sequences of their constant domains. Antibodies in accordance with embodiments of the invention can comprise kappa light chain sequences or lambda light chain sequences.

[00091] A "functional Fc region" possesses an "effector function" of a native-sequence Fc region. Non-limiting examples of effector functions include C1q binding; CDC; Fc-receptor binding; ADCC; ADCP;

down-regulation of cell-surface receptors (e.g., B-cell receptor), etc. Such effector functions generally require the Fc region to interact with a receptor, e.g., the FcγRI; FcγRIIA; FcγRIIB1; FcγRIIB2; FcγRIIIA; FcγRIIIB receptors, and the low affinity FcRn receptor; and can be assessed using various assays known in the art. A "dead" or "silenced" Fc is one that has been mutated to retain activity with respect to, for example, prolonging serum half-life, but which does not activate a high affinity Fc receptor, or which has a reduced affinity to an Fc receptor.

[00092] A "native-sequence Fc region" comprises an amino acid sequence identical to the amino acid sequence of an Fc region found in nature. Native-sequence human Fc regions include, for example, a native-sequence human IgG1 Fc region (non-A and A allotypes); native-sequence human IgG2 Fc region; native-sequence human IgG3 Fc region; and native-sequence human IgG4 Fc region, as well as naturally occurring variants thereof.

[00093] A "variant Fc region" comprises an amino acid sequence that differs from that of a native-sequence Fc region by virtue of at least one amino acid modification, preferably one or more amino acid substitution(s). Preferably, the variant Fc region has at least one amino acid substitution compared to a native-sequence Fc region or to the Fc region of a parent polypeptide, e.g., from about one to about ten amino acid substitutions, such as 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid substitutions, and preferably from about one to about five amino acid substitutions in a native-sequence Fc region or in the Fc region of the parent polypeptide. The variant Fc region herein will preferably possess at least about 80% homology with a native-sequence Fc region and/or with an Fc region of a parent polypeptide, and most preferably at least about 90% homology therewith, more preferably at least about 95% homology therewith.

[00094] The human IgG4 Fc amino acid sequence (UniProtKB No. P01861) is provided herein as SEQ ID NO: 45. Silenced IgG1 is described, for example, in Boesch, A.W., et al., "Highly parallel characterization of IgG Fc binding interactions." MAbs, 2014. 6(4): p. 915-27, the disclosure of which is incorporated herein by reference in its entirety.

[00095] Other Fc variants are possible, including, without limitation, one in which a region capable of forming a disulfide bond is deleted, or in which certain amino acid residues are eliminated at the N-terminal end of a native Fc, or a methionine residue is added thereto. Thus, in some embodiments, one or more Fc portions of an antibody can comprise one or more mutations in the hinge region to eliminate disulfide bonding. In yet another embodiment, the hinge region of an Fc can be removed entirely. In still another embodiment, an antibody can comprise an Fc variant.

[00096] Further, an Fc variant can be constructed to remove or substantially reduce effector functions by substituting (mutating), deleting or adding amino acid residues to effect complement binding or Fc receptor binding. For example, and not limitation, a deletion may occur in a complement-binding site, such as a C1q-binding site. Techniques for preparing such sequence derivatives of the immunoglobulin Fc fragment

are disclosed in International Patent Publication Nos. WO 97/34631 and WO 96/32478. In addition, the Fc domain may be modified by phosphorylation, sulfation, acylation, glycosylation, methylation, farnesylation, acetylation, amidation, and the like.

[00097] In some embodiments, an antibody comprises a variant human IgG4 CH3 domain sequence comprising a T366W mutation, which can optionally be referred to herein as an IgG4 CH3 knob sequence. In some embodiments, an antibody comprises a variant human IgG4 CH3 domain sequence comprising a T366S mutation, an L368A mutation, and a Y407V mutation, which can optionally be referred to herein as an IgG4 CH3 hole sequence. The IgG4 CH3 mutations described herein can be utilized in any suitable manner so as to place a "knob" on a first heavy chain constant region of a first monomer in an antibody dimer, and a "hole" on a second heavy chain constant region of a second monomer in an antibody dimer, thereby facilitating proper pairing (heterodimerization) of the desired pair of heavy chain polypeptide subunits in the antibody.

[00098] In some embodiments, an antibody comprises a heavy chain polypeptide subunit comprising a variant human IgG4 Fc region comprising an S228P mutation, an F234A mutation, an L235A mutation, and a T366W mutation (knob). In some embodiments, and antibody comprises a heavy chain polypeptide subunit comprising a variant human IgG4 Fc region comprising an S228P mutation, an F234A mutation, an L235A mutation, a T366S mutation, an L368A mutation, and a Y407V mutation (hole).

[00099] The term "Fc-region-comprising antibody" refers to an antibody that comprises an Fc region. The C-terminal lysine (residue 447 according to the EU numbering system) of the Fc region may be removed, for example, during purification of the antibody or by recombinant engineering of the nucleic acid encoding the antibody. Accordingly, an antibody having an Fc region according to this invention can comprise an antibody with or without K447.

[000100] Aspects of the invention include antibodies comprising a heavy chain-only variable region in a monovalent or bivalent configuration. As used herein, the term "monovalent configuration" as used in reference to a heavy chain-only variable region domain means that only one heavy chain-only variable region domain is present, having a single binding site (see FIG. 1, Panel A, right arm of antibody). In contrast, the term "bivalent configuration" as used in reference to a heavy chain-only variable region domain means that two heavy chain-only variable region domains are present (each having a single binding site), and are connected by a linker sequence (see FIG. 1, Panels B and C, right arms of antibodies). Non-limiting examples of linker sequences are discussed further herein, and include, without limitation, GS linker sequences of various lengths. When a heavy chain-only variable region is in a bivalent configuration, each of the two heavy chain-only variable region domains can have binding affinity to the same antigen, or to different antigens (e.g., to different epitopes on the same protein; to two different proteins, etc.). However, unless specifically noted otherwise, a heavy chain-only variable region denoted as being in a "bivalent

configuration" is understood to contain two identical heavy chain-only variable region domains, connected by a linker sequence, wherein each of the two identical heavy chain-only variable region domains have binding affinity to the same target antigen.

[000101] Aspects of the invention include antibodies having multi-specific configurations, which include, without limitation, bispecific, trispecific, etc. A large variety of methods and protein configurations are known and used in bispecific monoclonal antibodies (BsMAB), tri-specific antibodies, etc.

[000102] Various methods for the production of multivalent artificial antibodies have been developed by recombinantly fusing variable domains of two or more antibodies. In some embodiments, a first and a second antigen-binding domain on a polypeptide are connected by a polypeptide linker. One non-limiting example of such a polypeptide linker is a GS linker, having an amino acid sequence of four glycine residues, followed by one serine residue, and wherein the sequence is repeated n times, where n is an integer ranging from 1 to about 10, such as 2, 3, 4, 5, 6, 7, 8, or 9 (SEQ ID NO: 93). Non-limiting examples of such linkers include GGGGS (SEQ ID NO: 70) (n=1) and GGGGSGGGGS (SEQ ID NO: 71) (n=2). Other suitable linkers can also be used, and are described, for example, in Chen et al., Adv Drug Deliv Rev. 2013 October 15; 65(10): 1357-69, the disclosure of which is incorporated herein by reference in its entirety.

[000103] The term "three-chain antibody like molecule" or "TCA" is used herein to refer to antibody-like molecules comprising, consisting essentially of, or consisting of three polypeptide subunits, two of which comprise, consist essentially of, or consist of one heavy and one light chain of a monoclonal antibody, or functional antigen-binding fragments of such antibody chains, comprising an antigen-binding region and at least one CH domain. This heavy chain/light chain pair has binding specificity for a first antigen. The third polypeptide subunit comprises, consists essentially of, or consists of a heavy-chain only antibody comprising an Fc portion comprising CH2 and/or CH3 and/or CH4 domains, in the absence of a CH1 domain, and one or more antigen binding domains (e.g., two antigen binding domains) that binds an epitope of a second antigen or a different epitope of the first antigen, where such binding domain is derived from or has sequence identity with the variable region of an antibody heavy or light chain. Parts of such variable region may be encoded by V_H and/or V_L gene segments, D and J_H gene segments, or J_L gene segments. The variable region may be encoded by rearranged V_HDJ_H, V_LDJ_H, V_HJ_L, or V_LJ_L gene segments.

[000104] A TCA binding compound makes use of a "heavy chain only antibody" or "heavy chain antibody" or "heavy chain polypeptide" which, as used herein, mean a single chain antibody comprising heavy chain constant regions CH2 and/or CH3 and/or CH4 but no CH1 domain. In one embodiment, the heavy chain antibody is composed of an antigen-binding domain, at least part of a hinge region and CH2 and CH3 domains. In another embodiment, the heavy chain antibody is composed of an antigen-binding domain, at least part of a hinge region and a CH2 domain. In a further embodiment, the heavy chain antibody is composed of an antigen-binding domain, at least part of a hinge region and a CH3 domain. Heavy chain

antibodies in which the CH2 and/or CH3 domain is truncated are also included herein. In a further embodiment, the heavy chain is composed of an antigen binding domain, and at least one CH (CH1, CH2, CH3, or CH4) domain but no hinge region. The heavy chain only antibody can be in the form of a dimer, in which two heavy chains are disulfide bonded other otherwise covalently or non-covalently attached to each other, and can optionally include an asymmetric interface between one or more of the CH domains to facilitate proper pairing between polypeptide chains. The heavy-chain antibody may belong to the IgG subclass, but antibodies belonging to other subclasses, such as IgM, IgA, IgD and IgE subclass, are also included herein. In a particular embodiment, the heavy chain antibody is of the IgG1, IgG2, IgG3, or IgG4 subtype, in particular the IgG1 subtype or the IgG4 subtype. Non-limiting examples of a TCA binding compound are described in, for example, WO2017/223111 and WO2018/052503, the disclosures of which are incorporated herein by reference in their entirety.

[000105] Heavy-chain antibodies constitute about one fourth of the IgG antibodies produced by the camelids, e.g., camels and llamas (Hamers-Casterman C., et al. Nature. 363, 446-448 (1993)). These antibodies are formed by two heavy chains but are devoid of light chains. As a consequence, the variable antigen binding part is referred to as the VHH domain and it represents the smallest naturally occurring, intact, antigen-binding site, being only around 120 amino acids in length (Desmyter, A., et al. J. Biol. Chem. 276, 26285-26290 (2001)). Heavy chain antibodies with a high specificity and affinity can be generated against a variety of antigens through immunization (van der Linden, R. H., et al. Biochim. Biophys. Acta. 1431, 37-46 (1999)) and the VHH portion can be readily cloned and expressed in yeast (Frenken, L. G. J., et al. J. Biotechnol. 78, 11-21 (2000)). Their levels of expression, solubility and stability are significantly higher than those of classical F(ab) or Fv fragments (Ghahroudi, M. A. et al. FEBS Lett. 414, 521-526 (1997)). Sharks have also been shown to have a single VH-like domain in their antibodies, termed VNAR. (Nuttall et al. Eur. J. Biochem. 270, 3543-3554 (2003); Nuttall et al. Function and Bioinformatics 55, 187-197 (2004); Dooley et al., Molecular Immunology 40, 25-33 (2003)).

[000106] The term "CD3" refers to the human CD3 protein multi-subunit complex. The CD3 protein multi-subunit complex is composed to 6 distinctive polypeptide chains. These include a CD3γ chain (SwissProt P09693), a CD3δ chain (SwissProtP04234), two CD3ε chains (SwissProt P07766), and one CD3ζ chain homodimer (SwissProt 20963), and which is associated with the T-cell receptor α and β chain. The term "CD3" includes any CD3 variant, isoform and species homolog which is naturally expressed by cells (including T-cells) or can be expressed on cells transfected with genes or cDNA encoding those polypeptides, unless noted.

[000107] A "BCMA x CD3 antibody" is a multispecific heavy chain-only antibody, such as a bispecific heavy chain-only antibody, which comprises two different antigen-binding regions, one of which binds specifically to the antigen BCMA and one of which binds specifically to CD3. A "PSMA x CD3 antibody"

is a multispecific heavy chain-only antibody, such as a bispecific heavy chain-only antibody, which comprises two different antigen-binding regions, one of which binds specifically to the antigen PSMA and one of which binds specifically to CD3. A "CD19 x CD3 antibody" is a multispecific heavy chain-only antibody, such as a bispecific heavy chain-only antibody, which comprises two different antigen-binding regions, one of which binds specifically to the antigen CD19 and one of which binds specifically to CD3.

[000108] The term "BCMA" as used herein relates to human B-cell maturation antigen, also known as BCMA, CD269, and TNFRSF17 (UniProt Q02223), which is a member of the tumor necrosis receptor superfamily that is preferentially expressed in differentiated plasma cells. The extracellular domain of human BCMA consists, according to UniProt of amino acids 1-54 (or 5-51).

[000109] The term "anti-BCMA heavy chain-only antibody," and "BCMA heavy chain-only antibody" are used herein to refer to a heavy chain-only antibody as hereinabove defined, immunospecifically binding to BCMA.

[000110] The term "PSMA" as used herein refers to a type II transmembrane protein that has N-acetylated-alpha-linked acidic depeptidase, folate hydrolase and dipeptidyl-peptidase activity. The term "PSMA" includes a PSMA protein of any human and non-human animal species, and specifically includes human PSMA as well as PSMA of non-human mammals.

[000111] The term "human PSMA" as used herein includes any variants, isoforms and species homologs of human PSMA (UniProt Q04609), regardless of its source or mode of preparation. Thus, "human PSMA" includes human PSMA naturally expressed by cells and PSMA expressed on cells transfected with the human PSMA gene.

[000112] The terms "anti-PSMA heavy chain-only antibody," "PSMA heavy chain-only antibody," "anti-PSMA heavy chain antibody" and "PSMA heavy chain antibody" are used herein interchangeably to refer to a heavy chain-only antibody as hereinabove defined, immunospecifically binding to PSMA, including human PSMA, as hereinabove defined. The definition includes, without limitation, human heavy chain antibodies produced by transgenic animals, such as transgenic rats or transgenic mice expressing human immunoglobulin, including UniRats™ producing human anti-PSMA UniAb™ antibodies, as hereinabove defined.

[000113] The terms "CD19" and "cluster of differentiation 19" as used herein refer to a molecule expressed during all phases of B-cell development until terminal differentiation into plasma cells. The term "CD19" includes a CD19 protein of any human and non-human animal species, and specifically includes human CD19 as well as CD19 of non-human mammals.

[000114] The term "human CD19" as used herein includes any variants, isoforms and species homologs of human CD19 (UniProt P15391), regardless of its source or mode of preparation. Thus, "human CD19"

includes human CD19 naturally expressed by cells and CD19 expressed on cells transfected with the human CD19 gene.

[000115] The terms "anti-CD19 heavy chain-only antibody," "CD19 heavy chain-only antibody," "anti-CD19 heavy chain antibody" and "CD19 heavy chain antibody" are used herein interchangeably to refer to a heavy chain-only antibody as hereinabove defined, immunospecifically binding to CD19, including human CD19, as hereinabove defined. The definition includes, without limitation, human heavy chain antibodies produced by transgenic animals, such as transgenic rats or transgenic mice expressing human immunoglobulin, including UniRatsTM producing human anti-CD19 UniAbTM antibodies, as hereinabove defined.

[000116] "Percent (%) amino acid sequence identity" with respect to a reference polypeptide sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2.

[000117] An "isolated" antibody is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody *in situ* within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

[000118] Antibodies of the invention include multi-specific antibodies. Multi-specific antibodies have more than one binding specificity. The term "multi-specific" specifically includes "bispecific" and "trispecific," as well as higher-order independent specific binding affinities, such as higher-order polyepitopic specificity,

as well as tetravalent antibodies and antibody fragments. The terms "multi-specific antibody," "multi-specific heavy chain-only antibody," "multi-specific heavy chain antibody," and "multi-specific UniAb™" are used herein in the broadest sense and cover all antibodies with more than one binding specificity.

[000119] The multi-specific antibodies of the present invention specifically include antibodies immunospecifically binding to two or more non-overlapping epitopes on a BCMA protein, a PSMA protein, or a CD19 protein, such as a human BCMA protein, a human PSMA protein, or a human CD19 protein (i.e., bivalent and biparatopic). The multi-specific heavy chain antibodies of the present invention also specifically include antibodies immunospecifically binding to an epitope on a BCMA protein, a PSMA protein, or a CD19 protein, such as a human BCMA protein, a human PSMA protein, or a human CD19 protein and to an epitope on a different protein, such as, for example, a CD3 protein, such as human CD3 (i.e., bivalent and biparatopic). The multi-specific heavy chain antibodies of the present invention also specifically include antibodies immunospecifically binding to two or more non-overlapping or partially overlapping epitopes on a BCMA protein, a PSMA protein, or a CD19 protein, such as a human BCMA protein, a human PSMA protein, or a human CD19 protein, and to an epitope on a different protein, such as, for example, a CD3 protein, such as human CD3 protein (i.e., trivalent and biparatopic).

[000120] An "epitope" is the site on the surface of an antigen molecule to which a single antibody molecule binds. Generally an antigen has several or many different epitopes and reacts with many different antibodies. The term specifically includes linear epitopes and conformational epitopes.

[000121] "Epitope mapping" is the process of identifying the binding sites, or epitopes, of antibodies on their target antigens. Antibody epitopes may be linear epitopes or conformational epitopes. Linear epitopes are formed by a continuous sequence of amino acids in a protein. Conformational epitopes are formed of amino acids that are discontinuous in the protein sequence, but which are brought together upon folding of the protein into its three-dimensional structure.

[000122] "Polyepitopic specificity" refers to the ability to specifically bind to two or more different epitopes on the same or different target(s). As noted above, the present invention specifically includes heavy chain antibodies with polyepitopic specificities, i.e., heavy chain antibodies binding to one or more non-overlapping epitopes on a BCMA protein, a PSMA protein, or a CD19 protein, such as a human BCMA protein, a human PSMA protein, or a human CD19 protein; and heavy chain antibodies binding to one or more epitopes on a BCMA protein, a PSMA protein, or a CD19 protein, and to an epitope on a different protein, such as, for example, a CD3 protein. The term "non-overlapping epitope(s)" or "non-competitive epitope(s)" of an antigen is defined herein to mean epitope(s) that are recognized by one member of a pair of antigen-specific antibodies but not the other member. Pairs of antibodies, or antigen-binding regions targeting the same antigen on a multi-specific antibody, recognizing non-overlapping epitopes, do not compete for binding to that antigen and are able to bind that antigen simultaneously.

[000123] An antibody binds "essentially the same epitope" as a reference antibody, when the two antibodies recognize identical or sterically overlapping epitopes. The most widely used and rapid methods for determining whether two epitopes bind to identical or sterically overlapping epitopes are competition assays, which can be configured in all number of different formats, using either labeled antigen or labeled antibody. Usually, the antigen is immobilized on a 96-well plate, and the ability of unlabeled antibodies to block the binding of labeled antibodies is measured using radioactive or enzyme labels.

[000124] The term "valent" as used herein refers to a specified number of binding sites in an antibody molecule.

[000125] A "monovalent" antibody has one binding site. Thus a monovalent antibody is also monospecific.

[000126] A "multi-valent" antibody has two or more binding sites. Thus, the terms "bivalent", "trivalent", and "tetravalent" refer to the presence of two binding sites, three binding sites, and four binding sites, respectively. Thus, a bispecific antibody according to the invention is at least bivalent and may be trivalent, tetravalent, or otherwise multi-valent. A bivalent antibody in accordance with embodiments of the invention may have two binding sites to the same epitope (i.e., bivalent, monoparatopic), or to two different epitopes (i.e., bivalent, biparatopic).

[000127] A large variety of methods and protein configurations are known and used for the preparation of bispecific monoclonal antibodies (BsMAB), tri-specific antibodies, and the like.

[000128] The term "three-chain antibody like molecule" or "TCA" is used herein to refer to antibody-like molecules comprising, consisting essentially of, or consisting of three polypeptide subunits, two of which comprise, consist essentially of, or consist of one heavy chain and one light chain of a monoclonal antibody, or functional antigen-binding fragments of such antibody chains, comprising an antigen-binding region and at least one CH domain. This heavy chain/light chain pair has binding specificity for a first antigen. The third polypeptide subunit comprises, consists essentially of, or consists of a heavy chain-only antibody comprising an Fc portion comprising CH2 and/or CH3 and/or CH4 domains, in the absence of a CH1 domain, and an antigen binding domain that binds an epitope of a second antigen or a different epitope of the first antigen, where such binding domain is derived from or has sequence identity with the variable region of an antibody heavy or light chain. Parts of such variable region may be encoded by V_H and/or V_L gene segments, D and J_H gene segments, or J_L gene segments. The variable region may be encoded by rearranged V_HDJ_H, V_LDJ_H, V_HJ_L, or V_LJ_L gene segments. A TCA protein makes use of a heavy chain-only antibody as hereinabove defined.

[000129] The term "chimeric antigen receptor" or "CAR" is used herein in the broadest sense to refer to an engineered receptor, which grafts a desired binding specificity (e.g., the antigen-binding region of a monoclonal antibody or other ligand) to membrane-spanning and intracellular-signaling domains. Typically, the receptor is used to graft the specificity of a monoclonal antibody onto a T-cell to create a chimeric

antigen receptors (CAR). (*J Natl Cancer Inst,* 2015; 108(7):dvj439; and Jackson et al., *Nature Reviews Clinical Oncology*, 2016; 13:370–383). CAR-T cells are T-cells that have been genetically engineered to produce an artificial T-cell receptor for use in immunotherapy. In one embodiment, "CAR-T cell" means a therapeutic T-cell expressing a transgene encoding one or more chimeric antigen receptors comprised minimally of an extracellular domain, a transmembrane domain, and at least one cytosolic domain.

[000130] The term "human antibody" is used herein to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human antibodies herein may include amino acid residues not encoded by human germline immunoglobulin sequences, e.g., mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*. The term "human antibody" specifically includes heavy chain-only antibodies having human heavy chain variable region sequences, produced by transgenic animals, such as transgenic rats or mice, in particular UniAbs™ produced by UniRats™, as defined above.

[000131] By a "chimeric antibody" or a "chimeric immunoglobulin" is meant an immunoglobulin molecule comprising amino acid sequences from at least two different Ig loci, e.g., a transgenic antibody comprising a portion encoded by a human Ig locus and a portion encoded by a rat Ig locus. Chimeric antibodies include transgenic antibodies with non-human Fc-regions or artificial Fc-regions, and human idiotypes. Such immunoglobulins can be isolated from animals of the invention that have been engineered to produce such chimeric antibodies.

[000132] As used herein, the term "effector cell" refers to an immune cell which is involved in the effector phase of an immune response, as opposed to the cognitive and activation phases of an immune response. Some effector cells express specific Fc receptors and carry out specific immune functions. In some embodiments, an effector cell such as a natural killer cell is capable of inducing antibody-dependent cellular cytotoxicity (ADCC). For example, monocytes andmacrophages, which express FcR, are involved in specific killing of target cells and presenting antigens to other components of the immune system, or binding to cells that present antigens. In some embodiments, an effector cell may phagocytose a target antigen or target cell.

[000133] "Human effector cells" are leukocytes which express receptors such as T-cell receptors or FcRs and perform effector functions. Preferably, the cells express at least FcγRIII and perform ADCC effector function. Examples of human leukocytes which mediate ADCC include natural killer (NK) cells, monocytes, cytotoxic T-cells and neutrophils; with NK cells being preferred. The effector cells may be isolated from a native source thereof, e.g., from blood or PBMCs as described herein.

[000134] The term "immune cell" is used herein in the broadest sense, including, without limitation, cells of myeloid or lymphoid origin, for instance lymphocytes (such as B-cells and T-cells including cytolytic T-

cells (CTLs)), killer cells, natural killer (NK) cells, macrophages, monocytes, eosinophils, polymorphonuclear cells, such as neutrophils, granulocytes, mast cells, and basophils.

[000135] Antibody "effector functions" refer to those biological activities attributable to the Fc region (a native sequence Fc region or amino acid sequence variant Fc region) of an antibody. Examples of antibody effector functions include C1q binding; complement dependent cytotoxicity (CDC); Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (e.g., B-cell receptor; BCR), etc.

[000136] "Antibody-dependent cell-mediated cytotoxicity" and "ADCC" refer to a cell-mediated reaction in which nonspecific cytotoxic cells that express Fc receptors (FcRs) (e.g., Natural Killer (NK) cells, neutrophils, and macrophages) recognize bound antibody on a target cell and subsequently cause lysis of the target cell. The primary cells for mediating ADCC, NK cells, express FcγRIII only, whereas monocytes express FcγRI, FcγRII and FcγRIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, *Annu. Rev. Immunol* 9:457-92 (1991). To assess ADCC activity of a molecule of interest, an *in vitro* ADCC assay, such as that described in US Patent No. 5,500,362 or 5,821,337 may be performed. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed *in vivo*, e.g., in an animal model such as that disclosed in Clynes *et al. PNAS (USA)* 95:652-656 (1998).

[000137] "Complement dependent cytotoxicity" or "CDC" refers to the ability of a molecule to lyse a target in the presence of complement. The complement activation pathway is initiated by the binding of the first component of the complement system (C1q) to a molecule (*e.g.* an antibody) complexed with a cognate antigen. To assess complement activation, a CDC assay, e.g., as described in Gazzano-Santoro *et al.*, *J. Immunol. Methods* 202:163 (1996), may be performed.

[000138] "Binding affinity" refers to the strength of the sum total of noncovalent interactions between a single binding site of a molecule (e.g., an antibody) and its binding partner (e.g., an antigen). Unless indicated otherwise, as used herein, "binding affinity" refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (e.g., antibody and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (Kd). Affinity can be measured by common methods known in the art. Low-affinity antibodies generally bind antigen slowly and tend to dissociate readily, whereas high-affinity antibodies generally bind antigen faster and tend to remain bound.

[000139] As used herein, the "Kd" or "Kd value" refers to a dissociation constant determined by BioLayer Interferometry, using an Octet QK384 instrument (Fortebio Inc., Menlo Park, CA) in kinetics mode. For example, anti-mouse Fc sensors are loaded with mouse-Fc fused antigen and then dipped into antibody-containing wells to measure concentration dependent association rates (kon). Antibody dissociation rates

(koff) are measured in the final step, where the sensors are dipped into wells containing buffer only. The Kd is the ratio of koff/kon. (For further details see, Concepcion, J, et al., *Comb Chem High Throughput Screen*, 12(8), 791-800, 2009).

[000140] The terms "treatment", "treating" and the like are used herein to generally mean obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a disease and/or adverse effect attributable to the disease. "Treatment" as used herein covers any treatment of a disease in a mammal, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development; or (c) relieving the disease, i.e., causing regression of the disease. The therapeutic agent may be administered before, during or after the onset of disease or injury. The treatment of ongoing disease, where the treatment stabilizes or reduces the undesirable clinical symptoms of the patient, is of particular interest. Such treatment is desirably performed prior to complete loss of function in the affected tissues. The subject therapy may be administered during the symptomatic stage of the disease, and in some cases after the symptomatic stage of the disease.

[000141] A "therapeutically effective amount" is intended for an amount of active agent which is necessary to impart therapeutic benefit to a subject. For example, a "therapeutically effective amount" is an amount which induces, ameliorates or otherwise causes an improvement in the pathological symptoms, disease progression or physiological conditions associated with a disease or which improves resistance to a disorder.

[000142] The term "prostate cancer," as used herein, refers to a malignant tumor of glandular origin in the prostate gland.

[000143] The term "characterized by expression of PSMA" broadly refers to any disease or disorder in which PSMA expression is associated with or involved with one or more pathological processes that are characteristic of the disease or disorder. Such disorders include, but are not limited to, prostate cancer.

[000144] The terms "B-cell neoplasms" or "mature B-cell neoplasms" in the context of the present invention include, but are not limited to, all lymphoid leukemias and lymphomas, chronic lymphocytic leukemia, acute lymphoblastc leukemia, prolymphocytic leukemia, precursor B-lymphoblastic leukemia, hair cell leukemia, small lymphocytic lymphoma, B-cell prolymphocytic lymphoma, B-cell chronic lymphocytic leukemia, mantle cell lymphoma, Burkitt's lymphoma, follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), multiple myeloma, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, plasma cell neoplasms, such as plasma cell myeloma, plasmacytoma, monoclonal immunoglobulin deposition disease, heavy chain disease, MALT lymphoma, nodal marginal B-cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, lymphomatoid granulomatosis, non-Hodgkins lymphoma,

Hodgkins lymphoma, hairy cell leukemia, primary effusion lymphoma and AIDS-related non-Hodgkins lymphoma.

[000145] The term "characterized by expression of CD19" broadly refers to any disease or disorder in which CD19 expression is associated with or involved with one or more pathological processes that are characteristic of the disease or disorder. Such disorders include, but are not limited to, B-cell neoplasms.

[000146] The term "characterized by expression of BCMA" broadly refers to any disease or disorder in which BCMA expression is associated with or involved with one or more pathological processes that are characteristic of the disease or disorder. Such disorders include, but are not limited to, B-cell neoplasms.

[000147] The terms "subject," "individual," and "patient" are used interchangeably herein to refer to a mammal being assessed for treatment and/or being treated. In an embodiment, the mammal is a human. The terms "subject," "individual," and "patient" encompass, without limitation, individuals having cancer, individuals with autoimmune diseases, with pathogen infections, and the like. Subjects may be human, but also include other mammals, particularly those mammals useful as laboratory models for human disease, e.g., mouse, rat, etc.

[000148] The term "pharmaceutical formulation" refers to a preparation which is in such form as to permit the biological activity of the active ingredient to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the formulation would be administered. Such formulations are sterile. "Pharmaceutically acceptable" excipients (vehicles, additives) are those which can reasonably be administered to a subject mammal to provide an effective dose of the active ingredient employed.

[000149] A "sterile" formulation is aseptic or free or essentially free from all living microorganisms and their spores. A "frozen" formulation is one at a temperature below 0 °C.

[000150] A "stable" formulation is one in which the protein therein essentially retains its physical stability and/or chemical stability and/or biological activity upon storage. Preferably, the formulation essentially retains its physical and chemical stability, as well as its biological activity upon storage. The storage period is generally selected based on the intended shelf-life of the formulation. 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. Stability can be evaluated qualitatively and/or quantitatively in a variety of different ways, including evaluation of aggregate formation (for example using size exclusion chromatography, by measuring turbidity, and/or by visual inspection); by assessing charge heterogeneity using cation exchange chromatography, image capillary isoelectric focusing (icIEF) or capillary zone electrophoresis; amino-terminal or carboxy-terminal sequence analysis; mass spectrometric analysis; SDS-PAGE analysis to

2022259766 26 Oct 2022

compare reduced and intact antibody; peptide map (for example tryptic or LYS-C) analysis; evaluating biological activity or antigen binding function of the antibody; etc. Instability may involve any one or more of: aggregation, deamidation (e.g., Asn deamidation), oxidation (e.g., Met oxidation), isomerization (e.g., Asp isomeriation), clipping/hydrolysis/fragmentation (e.g., hinge region fragmentation), succinimide formation, unpaired cysteine(s), N-terminal extension, C-terminal processing, glycosylation differences, etc.

II. Detailed Description

Anti-BCMA Antibodies

[000151] The present invention relates to several families of closely related antibodies that bind to human BCMA. The variable regions of the antibodies of these families are described in US Patent Publication Nos. US20190352412 US20200157232 and US20200048348, and in PCT Publication Nos. WO2018237037 and WO2019006072, the disclosures of which applictions are incorporated by reference herein in their entireties. A non-limiting selection of representative anti-BCMA heavy chain antibody variable domain sequences are provided below in Table 1.

Table 1: Anti-BCMA heavy chain antibody variable domain amino acid sequences.

Clone ID #	**SEQ_aa_FR1_FR4**	**SEQ ID NO.**
308635	EVQLLESGGGLVQAGGSLRLSCAASGFTVSSYGMSWVRQA PGKGPEWVSGIRGSDGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYHCAKQGENDGPFDYRGQGTLVTVSS	92
308636	EVQVLESGGGLVQPGGSLRLSCAASGFTVSSYGMSWVRQPP GKGMEWVSGIRGSDGSTFYADSVKG RFTISRDNATNTLYL QMNSLRAEDTAVYYCAKQGGNDGPFDYRGQGTLVTVSS	87
308806	EVQLLESGGGLVQPGGSLRLSCAASGFTISSYGMSWVRQAP GKGVEWVSG IRGSDGTTYYADSVKGRFTISRDSSRNTLYLQ MNSLRAEDTAVYYCAKQGGNDGPFDHRGQGT LVTVSS	88
308837	EVQLLESGGGLVQPGGSLRLSCAASGFTVSSYGMSWVRQAP GKGPEWVSGIRGSDGSTYYADSVKGRFTISRDNATNTLYLQM NSLRAEDTAVYYCAKQGGNDGPFDYRGQGT LVTVSS	89
308902	EVQLLESGGGLVQPGGSLRLSCAASGFTVSSYGMSWVRQA PGKGPEWVSGIRGSDGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCAKQGENDGPFDHRGQGTLVTVSS	90
308912	EVQLLESGGGLVQPGGSLRLSCAASGFTVSSYGMSWVRQPP GKGMEWVSGIRGSDGSTYYADSVKGRFTISRDNAKNTLYLQ MNSLRAEDTAVYYCAKQGGNDGPFDYRGQGTLVTVSS	91

[000152] An anti-BCMA antibody sequence may be selected from those provided herein for development and therapeutic or other use, including, without limitation, use as a multispecific, e.g., a bispecific antibody.

In some embodiments, bispecific or multispecific antibodies are provided, which may have any of the configurations discussed herein, including, without limitation, a TCA. Bispecific antibodies comprise at least the heavy chain variable region of an antibody specific for a protein other than BCMA.

[000153] Where a protein of the invention is a bispecific antibody, one binding moiety is specific for human BCMA while the other arm may be specific for target cells, tumor associated antigens, targeting antigens, e.g., integrins, etc., pathogen antigens, checkpoint proteins, and the like. Target cells specifically include cancer cells, such as hematologic tumors, e.g., B-cell tumors, as discussed below.

[000154] Various formats of bispecific antibodies are within the ambit of the invention, including, without limitation, single chain polypeptides, two chain polypeptides, three chain polypeptides, four chain polypeptides, and multiples thereof. The bispecific antibodies herein specifically include T-cell bispecific antibodies binding to BCMA, which is selectively expressed on plasma cells (PCs) and multiple myeloma (MM), and CD3 (anti-BCMA × anti-CD3 antibodies). Such antibodies induce potent T-cell mediated killing of cells carrying BCMA, and can be used to treat tumors, in particular hematologic tumors, such as B-cell tumors, as discussed further herein.

[000155] In a preferred embodiment, a bispecific antibody is a TCA comprising: an anti-CD3 VH domain that is paired with a light chain variable domain (VL), wherein the VH domain and the VL domain together have binding affinity for CD3; a heavy chain variable domain of a heavy chain-only antibody having binding affinity to BCMA, in a monovalent or bivalent configuration; and a variant human IgG4 Fc domain comprising a first heavy chain constant region sequence comprising an S228P mutation, an F234A mutation, an L235A mutation, and a T366W mutation (knob), and a second heavy chain constant region sequence comprising an S228P mutation, an F234A mutation, an L235A mutation, a T366S mutation, an L368A mutation, and a Y407V mutation (hole). This variant, or modified, IgG4 Fc domain prevents unwanted Fab exchange, reduces effector function of the antibody, and also facilitates heterodimerization of the heavy chain polypeptide subunits to form the bispecific antibody.

[000156] In some embodiments, the present invention comprises a bispecific antibody comprising i) an anti-CD3 heavy chain comprising SEQ ID NO: 56, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and iii) an anti-BCMA heavy chain comprising SEQ ID NO: 58.

[000157] In some embodiments, the present invention comprises a bispecific antibody comprising i) an anti-CD3 heavy chain comprising SEQ ID NO: 56, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and iii) an anti-BCMA heavy chain comprising SEQ ID NO: 59.

[000158] In some embodiments, the present invention comprises a bispecific antibody comprising i) an anti-CD3 heavy chain comprising SEQ ID NO: 56, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and iii) an anti-BCMA heavy chain comprising SEQ ID NO: 58, wherein the bispecific antibody does not comprise an anti-BCMA light chain.

[000159] In some embodiments, the present invention comprises a bispecific antibody comprising an anti-CD3 heavy chain comprising i) SEQ ID NO: 56, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and iii) an anti-BCMA heavy chain comprising SEQ ID NO: 59, wherein the bispecific antibody does not comprise an anti-BCMA light chain.

[000160] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific antibody comprising an anti-CD3 heavy chain comprising SEQ ID NO: 56, an anti-CD3 light chain comprising SEQ ID NO: 49, and an anti-BCMA heavy chain comprising SEQ ID NO: 58.

[000161] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific antibody comprising i) an anti-CD3 heavy chain comprising SEQ ID NO: 56, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and iii) an anti-BCMA heavy chain comprising SEQ ID NO: 59.

[000162] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific antibody comprising i) an anti-CD3 heavy chain comprising SEQ ID NO: 56, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and an anti-BCMA heavy chain comprising SEQ ID NO: 58, wherein the bispecific antibody does not comprise an anti-BCMA light chain.

[000163] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific antibody comprising i) an anti-CD3 heavy chain comprising SEQ ID NO: 56, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and iii) an anti-BCMA heavy chain comprising SEQ ID NO: 59, wherein the bispecific antibody does not comprise an anti-BCMA light chain.

[000164] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific antibody, comprising (i) a first binding arm that binds to human CD3 and (ii) a second binding arm that binds to human BCMA, said first binding arm comprising a first heavy chain and a light chain, and said second binding arm comprising a bivalent second heavy chain, wherein said first heavy chain comprises the amino acid sequence of SEQ ID NO: 56, said light chain comprises the amino acid sequence of SEQ ID NO: 49, and said bivalent second heavy chain comprises the amino acid sequence of SEQ ID NO: 58.

[000165] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific antibody, comprising (i) a first binding arm that binds to human CD3 and (ii) a second binding arm that binds to human BCMA, said first binding arm comprising a first heavy chain and a light chain, and said second binding arm comprising a bivalent second heavy chain, wherein said first heavy chain comprises the amino acid sequence of SEQ ID NO: 56, said light chain comprises the amino acid sequence of SEQ ID NO: 49, and said bivalent second heavy chain comprises the amino acid sequence of SEQ ID NO: 59.

[000166] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific antibody, comprising (i) a first binding arm that binds to human CD3 and (ii) a second binding arm that binds to human BCMA, said first binding arm comprising a first heavy chain and a light chain, and said second binding arm comprising a bivalent second heavy chain, wherein said first heavy chain comprises

2022259766 26 Oct 2022

the amino acid sequence of SEQ ID NO: 56, said light chain comprises the amino acid sequence of SEQ ID NO: 49, and said bivalent second heavy chain comprises the amino acid sequence of SEQ ID NO: 58, and wherein said second binding arm does not comprise a light chain.

[000167] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific antibody, comprising (i) a first binding arm that binds to human CD3 and (ii) a second binding arm that binds to human BCMA, said first binding arm comprising a first heavy chain and a light chain, and said second binding arm comprising a bivalent second heavy chain, wherein said first heavy chain comprises the amino acid sequence of SEQ ID NO: 56, said light chain comprises the amino acid sequence of SEQ ID NO: 49, and said bivalent second heavy chain comprises the amino acid sequence of SEQ ID NO: 59, and wherein said second binding arm does not comprise a light chain.

[000168] In some embodiments, the present invention comprises a bispecific three-chain antibody like molecule (TCA) comprising i) an anti-CD3 heavy chain comprising SEQ ID NO: 56, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and iii) an anti-BCMA heavy chain comprising SEQ ID NO: 58.

[000169] In some embodiments, the present invention comprises a bispecific three-chain antibody like molecule (TCA) comprising i) an anti-CD3 heavy chain comprising SEQ ID NO: 56, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and iii) an anti-BCMA heavy chain comprising SEQ ID NO: 59.

[000170] In some embodiments, the present invention comprises a bispecific three-chain antibody like molecule (TCA) comprising i) an anti-CD3 heavy chain comprising SEQ ID NO: 56, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and iii) an anti-BCMA heavy chain comprising SEQ ID NO: 58, wherein the bispecific antibody does not comprise an anti-BCMA light chain.

[000171] In some embodiments, the present invention comprises a bispecific three-chain antibody like molecule (TCA) comprising an anti-CD3 heavy chain comprising i) SEQ ID NO: 56, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and iii) an anti-BCMA heavy chain comprising SEQ ID NO: 59, wherein the bispecific antibody does not comprise an anti-BCMA light chain.

[000172] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific three-chain antibody like molecule (TCA) comprising an anti-CD3 heavy chain comprising SEQ ID NO: 56, an anti-CD3 light chain comprising SEQ ID NO: 49, and an anti-BCMA heavy chain comprising SEQ ID NO: 58.

[000173] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific three-chain antibody like molecule (TCA) comprising i) an anti-CD3 heavy chain comprising SEQ ID NO: 56, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and iii) an anti-BCMA heavy chain comprising SEQ ID NO: 59.

[000174] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific three-chain antibody like molecule (TCA) comprising i) an anti-CD3 heavy chain comprising SEQ ID NO: 56,

ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and an anti-BCMA heavy chain comprising SEQ ID NO: 58, wherein the bispecific antibody does not comprise an anti-BCMA light chain.

[000175] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific three-chain antibody like molecule (TCA) comprising i) an anti-CD3 heavy chain comprising SEQ ID NO: 56, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and iii) an anti-BCMA heavy chain comprising SEQ ID NO: 59, wherein the bispecific antibody does not comprise an anti-BCMA light chain.

[000176] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific three-chain antibody like molecule (TCA) comprising (i) a first binding arm that binds to human CD3 and (ii) a second binding arm that binds to human BCMA, said first binding arm comprising a first heavy chain and a light chain, and said second binding arm comprising a bivalent second heavy chain, wherein said first heavy chain comprises the amino acid sequence of SEQ ID NO: 56, said light chain comprises the amino acid sequence of SEQ ID NO: 49, and said bivalent second heavy chain comprises the amino acid sequence of SEQ ID NO: 58.

[000177] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific three-chain antibody like molecule (TCA) comprising (i) a first binding arm that binds to human CD3 and (ii) a second binding arm that binds to human BCMA, said first binding arm comprising a first heavy chain and a light chain, and said second binding arm comprising a bivalent second heavy chain, wherein said first heavy chain comprises the amino acid sequence of SEQ ID NO: 56, said light chain comprises the amino acid sequence of SEQ ID NO: 49, and said bivalent second heavy chain comprises the amino acid sequence of SEQ ID NO: 59.

[000178] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific three-chain antibody like molecule (TCA) comprising (i) a first binding arm that binds to human CD3 and (ii) a second binding arm that binds to human BCMA, said first binding arm comprising a first heavy chain and a light chain, and said second binding arm comprising a bivalent second heavy chain, wherein said first heavy chain comprises the amino acid sequence of SEQ ID NO: 56, said light chain comprises the amino acid sequence of SEQ ID NO: 49, and said bivalent second heavy chain comprises the amino acid sequence of SEQ ID NO: 58, and wherein said second binding arm does not comprise a light chain.

[000179] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific three-chain antibody like molecule (TCA) comprising (i) a first binding arm that binds to human CD3 and (ii) a second binding arm that binds to human BCMA, said first binding arm comprising a first heavy chain and a light chain, and said second binding arm comprising a bivalent second heavy chain, wherein said first heavy chain comprises the amino acid sequence of SEQ ID NO: 56, said light chain comprises the amino acid sequence of SEQ ID NO: 49, and said bivalent second heavy chain comprises the amino acid sequence of SEQ ID NO: 59, and wherein said second binding arm does not comprise a light chain.

[000180] In some embodiments, the present invention comprises a bispecific antibody comprising i) an anti-CD3 heavy chain comprising SEQ ID NO: 75, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and iii) an anti-BCMA heavy chain comprising SEQ ID NO: 76.

[000181] In some embodiments, the present invention comprises a bispecific antibody comprising i) an anti-CD3 heavy chain comprising SEQ ID NO: 75, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and iii) an anti-BCMA heavy chain comprising SEQ ID NO: 77.

[000182] In some embodiments, the present invention comprises a bispecific antibody comprising i) an anti-CD3 heavy chain comprising SEQ ID NO: 75, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and iii) an anti-BCMA heavy chain comprising SEQ ID NO: 76, wherein the bispecific antibody does not comprise an anti-BCMA light chain.

[000183] In some embodiments, the present invention comprises a bispecific antibody comprising an anti-CD3 heavy chain comprising i) SEQ ID NO: 75, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and iii) an anti-BCMA heavy chain comprising SEQ ID NO: 77, wherein the bispecific antibody does not comprise an anti-BCMA light chain.

[000184] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific antibody comprising an anti-CD3 heavy chain comprising SEQ ID NO: 75, an anti-CD3 light chain comprising SEQ ID NO: 49, and an anti-BCMA heavy chain comprising SEQ ID NO: 76.

[000185] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific antibody comprising i) an anti-CD3 heavy chain comprising SEQ ID NO: 75, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and iii) an anti-BCMA heavy chain comprising SEQ ID NO: 77.

[000186] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific antibody comprising i) an anti-CD3 heavy chain comprising SEQ ID NO: 75, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and an anti-BCMA heavy chain comprising SEQ ID NO: 76, wherein the bispecific antibody does not comprise an anti-BCMA light chain.

[000187] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific antibody comprising i) an anti-CD3 heavy chain comprising SEQ ID NO: 75, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and iii) an anti-BCMA heavy chain comprising SEQ ID NO: 77, wherein the bispecific antibody does not comprise an anti-BCMA light chain.

[000188] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific antibody, comprising (i) a first binding arm that binds to human CD3 and (ii) a second binding arm that binds to human BCMA, said first binding arm comprising a first heavy chain and a light chain, and said second binding arm comprising a bivalent second heavy chain, wherein said first heavy chain comprises the amino acid sequence of SEQ ID NO: 75, said light chain comprises the amino acid sequence of SEQ ID NO: 49, and said bivalent second heavy chain comprises the amino acid sequence of SEQ ID NO: 76.

[000189] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific antibody, comprising (i) a first binding arm that binds to human CD3 and (ii) a second binding arm that binds to human BCMA, said first binding arm comprising a first heavy chain and a light chain, and said second binding arm comprising a bivalent second heavy chain, wherein said first heavy chain comprises the amino acid sequence of SEQ ID NO: 75, said light chain comprises the amino acid sequence of SEQ ID NO: 49, and said bivalent second heavy chain comprises the amino acid sequence of SEQ ID NO: 77.

[000190] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific antibody, comprising (i) a first binding arm that binds to human CD3 and (ii) a second binding arm that binds to human BCMA, said first binding arm comprising a first heavy chain and a light chain, and said second binding arm comprising a bivalent second heavy chain, wherein said first heavy chain comprises the amino acid sequence of SEQ ID NO: 75, said light chain comprises the amino acid sequence of SEQ ID NO: 49, and said bivalent second heavy chain comprises the amino acid sequence of SEQ ID NO: 76, and wherein said second binding arm does not comprise a light chain.

[000191] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific antibody, comprising (i) a first binding arm that binds to human CD3 and (ii) a second binding arm that binds to human BCMA, said first binding arm comprising a first heavy chain and a light chain, and said second binding arm comprising a bivalent second heavy chain, wherein said first heavy chain comprises the amino acid sequence of SEQ ID NO: 75, said light chain comprises the amino acid sequence of SEQ ID NO: 49, and said bivalent second heavy chain comprises the amino acid sequence of SEQ ID NO: 77, and wherein said second binding arm does not comprise a light chain.

[000192] In some embodiments, the present invention comprises a bispecific three-chain antibody like molecule (TCA) comprising i) an anti-CD3 heavy chain comprising SEQ ID NO: 75, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and iii) an anti-BCMA heavy chain comprising SEQ ID NO: 76.

[000193] In some embodiments, the present invention comprises a bispecific three-chain antibody like molecule (TCA) comprising i) an anti-CD3 heavy chain comprising SEQ ID NO: 75, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and iii) an anti-BCMA heavy chain comprising SEQ ID NO: 77.

[000194] In some embodiments, the present invention comprises a bispecific three-chain antibody like molecule (TCA) comprising i) an anti-CD3 heavy chain comprising SEQ ID NO: 75, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and iii) an anti-BCMA heavy chain comprising SEQ ID NO: 76, wherein the bispecific antibody does not comprise an anti-BCMA light chain.

[000195] In some embodiments, the present invention comprises a bispecific three-chain antibody like molecule (TCA) comprising an anti-CD3 heavy chain comprising i) SEQ ID NO: 75, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and iii) an anti-BCMA heavy chain comprising SEQ ID NO: 77, wherein the bispecific antibody does not comprise an anti-BCMA light chain.

[000196] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific three-chain antibody like molecule (TCA) comprising an anti-CD3 heavy chain comprising SEQ ID NO: 75, an anti-CD3 light chain comprising SEQ ID NO: 49, and an anti-BCMA heavy chain comprising SEQ ID NO: 76.

[000197] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific three-chain antibody like molecule (TCA) comprising i) an anti-CD3 heavy chain comprising SEQ ID NO: 75, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and iii) an anti-BCMA heavy chain comprising SEQ ID NO: 77.

[000198] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific three-chain antibody like molecule (TCA) comprising i) an anti-CD3 heavy chain comprising SEQ ID NO: 75, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and an anti-BCMA heavy chain comprising SEQ ID NO: 76, wherein the bispecific antibody does not comprise an anti-BCMA light chain.

[000199] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific three-chain antibody like molecule (TCA) comprising i) an anti-CD3 heavy chain comprising SEQ ID NO: 75, ii) an anti-CD3 light chain comprising SEQ ID NO: 49, and iii) an anti-BCMA heavy chain comprising SEQ ID NO: 77, wherein the bispecific antibody does not comprise an anti-BCMA light chain.

[000200] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific three-chain antibody like molecule (TCA) comprising (i) a first binding arm that binds to human CD3 and (ii) a second binding arm that binds to human BCMA, said first binding arm comprising a first heavy chain and a light chain, and said second binding arm comprising a bivalent second heavy chain, wherein said first heavy chain comprises the amino acid sequence of SEQ ID NO: 75, said light chain comprises the amino acid sequence of SEQ ID NO: 49, and said bivalent second heavy chain comprises the amino acid sequence of SEQ ID NO: 76.

[000201] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific three-chain antibody like molecule (TCA) comprising (i) a first binding arm that binds to human CD3 and (ii) a second binding arm that binds to human BCMA, said first binding arm comprising a first heavy chain and a light chain, and said second binding arm comprising a bivalent second heavy chain, wherein said first heavy chain comprises the amino acid sequence of SEQ ID NO: 75, said light chain comprises the amino acid sequence of SEQ ID NO: 49, and said bivalent second heavy chain comprises the amino acid sequence of SEQ ID NO: 77.

[000202] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific three-chain antibody like molecule (TCA) comprising (i) a first binding arm that binds to human CD3 and (ii) a second binding arm that binds to human BCMA, said first binding arm comprising a first heavy chain and a light chain, and said second binding arm comprising a bivalent second heavy chain, wherein said first

2022259766 26 Oct 2022

heavy chain comprises the amino acid sequence of SEQ ID NO: 75, said light chain comprises the amino acid sequence of SEQ ID NO: 49, and said bivalent second heavy chain comprises the amino acid sequence of SEQ ID NO: 76, and wherein said second binding arm does not comprise a light chain.

[000203] In some embodiments, the present invention comprises a human monoclonal IgG4 bispecific three-chain antibody like molecule (TCA) comprising (i) a first binding arm that binds to human CD3 and (ii) a second binding arm that binds to human BCMA, said first binding arm comprising a first heavy chain and a light chain, and said second binding arm comprising a bivalent second heavy chain, wherein said first heavy chain comprises the amino acid sequence of SEQ ID NO: 75, said light chain comprises the amino acid sequence of SEQ ID NO: 49, and said bivalent second heavy chain comprises the amino acid sequence of SEQ ID NO: 77, and wherein said second binding arm does not comprise a light chain.

Anti-CD19 Antibodies

[000204] The present invention provides a family of closely related antibodies that bind to human CD19. The variable regions of the antibodies of this family are described in PCT Publication No. WO2020018922, the disclosure of which is incorporated by reference herein in its entirety. An anti-CD19 antibody sequence may be selected from those provided herein for development and therapeutic or other use, including, without limitation, use as a multispecific, e.g., a bispecific antibody. In some embodiments, bispecific or multispecific antibodies are provided, which may have any of the configurations discussed herein, including, without limitation, a TCA. Bispecific antibodies comprise at least the heavy chain variable region of an antibody specific for a protein other than CD19.

[000205] Where a protein of the invention is a bispecific antibody, one binding moiety is specific for human CD19 while the other arm may be specific for target cells, tumor associated antigens, targeting antigens, e.g., integrins, etc., pathogen antigens, checkpoint proteins, and the like. Target cells specifically include cancer cells, such as hematologic tumors, e.g., B-cell tumors, as discussed below.

[000206] Various formats of bispecific antibodies are within the ambit of the invention, including, without limitation, single chain polypeptides, two chain polypeptides, three chain polypeptides, four chain polypeptides, and multiples thereof. The bispecific antibodies herein specifically include T-cell bispecific antibodies binding to CD19, which is selectively expressed on mature B-cells, and CD3 (anti-CD19 × anti-CD3 antibodies). Such antibodies induce potent T-cell mediated killing of cells expressing CD19, and can be used to treat tumors, in particular hematologic tumors, such as B-cell tumors, as discussed further herein.

[000207] In a preferred embodiment, a bispecific antibody is a TCA comprising: an anti-CD3 VH domain that is paired with a light chain variable domain (VL), wherein the VH domain and the VL domain together have binding affinity for CD3; a heavy chain variable domain of a heavy chain-only antibody having binding affinity to CD19, in a monovalent or bivalent configuration; and a variant human IgG4 Fc domain

comprising a first heavy chain constant region sequence comprising an S228P mutation, an F234A mutation, an L235A mutation, and a T366W mutation (knob), and a second heavy chain constant region sequence comprising an S228P mutation, an F234A mutation, an L235A mutation, a T366S mutation, an L368A mutation, and a Y407V mutation (hole). This variant, or modified, IgG4 Fc domain prevents unwanted Fab exchange, reduces effector function of the antibody, and also facilitates heterodimerization of the heavy chain polypeptide subunits to form the bispecific antibody.

Anti-PSMA Antibodies

[000208] The present invention provides a family of closely related antibodies that bind to human PSMA. The antibodies of this family are exemplified by the provided heavy chain variable region (VH) sequences of SEQ ID NOs: 24 to 54 set forth in Table 2. The families of antibodies provide a number of benefits that contribute to utility as clinically therapeutic agent(s). The antibodies include members with a range of binding affinities, allowing the selection of a specific sequence with a desired binding affinity.

Table 2. Anti-PSMA heavy chain antibody variable domain amino acid sequences.

Clone ID #	**SEQ_aa_FR1_FR4**	**SEQ ID NO.**
325920	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIGSIDYS GYTYYNPSLQSRVTISVDTSKNQFSLKLSSVTAADTAVYYNCARHKAATADFDYR GQGTLVTVSS	1
346181	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSNYFWGWIRQSPGKGLEWIGSIDYS GYTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYNCARHKAATADFDYR GQGTLVTVSS	2
346165	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIGSVDYS GYTYYNPSLQSRVTISVDTSKNQFSLKLSSVTAADTAVYYNCARHKAATADFDYR GQGTLVTVSS	3
346172	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIGSIDYS GYTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYNCARHKAATADFDYR GQGTLVTVSS	4
326109	QLQLQESGPGLVKPSETLSLTCTVSGGSISSNSYYWGWIRQSPGKGLEWLGSIYDS GSTHYNPSLKSRVIISGDTSKNQFSLKLSSVTAADTAVYYCARHKAATADFDYRG QGTLVTVSS	5
325867	QVQLVESGGGVVQPGRSLRLSCAASGFSFRSYGMHWVRQAPGKGLEWVAVIWY DGSNKYYADSVKGRFTISRDYSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYE SSGYDSLDYRGQGTLVTVSS	6
325742	QVQLVESGGGVVQPGRSLRLSCAASGFSFSSYGMHWVRQAPGKGLEWVAVIWY DGSNKYYADSVKGRFTISRDYSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYE SSGYDSLDYRGQGTLVTVSS	7
325748	QVQLVESGGGVVQPGRSLRLSCAASGFSFSSYGMHWVRQAPGKGLEGVAVIWY DGSNRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYE SSGYYSLDYRGQGTLVTVSS	8

2022259766 26 Oct 2022

Clone ID #	SEQ_aa_FR1_FR4	SEQ ID NO.
325940	QVQLVESGGGVVQPGRSLRLSCAASGFIFRSYGMHWVRQAPGKGPEWVAVIWY DGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYE SSGYYSLDYRGQGTLVTVSS	9
325836	QVQLVESGGGVVQPGRSLRLSCAASGFSFRSYGMHWVRQAPGKGLEWVAVIWY DGSNKYYADSVKGRFTISRDYSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYD SSGYDSLDYRGQGTLVTVSS	10
326027	QVQLVESGGGVVQPGRSLRLSCAASGFSFRSYGMHWVRQAPGKGLEWVAVIWY DGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYD SSGYDSLDYRGQGTLVTVSS	11
326087	QVQLVESGGGVVQPGRSLRLSCAASGFIFRSYGMHWVRQAPGKGPEWVAVIWY DGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYD SSGYDSLDYRGQGTLVTVSS	12
326084	QVQLVESGGGVVQPGRSLRLSCAASGFSFSSYGMHWVRQAPGKGLEGVAVIWY DGSNRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYD SSGYYSLDYRGQGTLVTVSS	13
326028	QVQLVESGGGVVQPGRSLRLSCAASGFSFRSYGMHWVRQAPGKGLEWVAVISY DGSNKYYADSVKGRFTISRDYSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYD SSGYDSLDYRGQGTLVTVSS	14
345497	QVQLVESGGGVVQPGRSLRLSCAASGFSFSRYGMHWVRQAPGKGLEGVAVIWY DGSNRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYE SSGYYSLDYRGQGTLVTVSS	15
326029	QVQLVESGGGVVQPGRSLRLSCAASGFSFSRYGMHWVRQAPGKGLEWVAVISY DGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPRVGYYY ETSGYYSLDYRGQGTLVTVSS	16
345461	QVQLVESGGGVVQPGRSLRLSCAASGFSFTSYGMHWVRQAPGKGLEGVAVIWY DGSNRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYE SSGYYSLDYRGQGTLVTVSS	17
345493	QVQLVESGGGVVQPGRSLRLSCAASGFSFSRYGMHWVRQAPGKGLEWVAVIWY DGSNRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYE SSGYYSLDYRGQGTLVTVSS	18
345436	QVQLVESGGGVVQPGRSLRLSCAASGFSFSRYGMHWVRQAPGKGLEGVAVIWY DGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYE SSGYYSLDYRGQGTLVTVSS	19
345443	QVQLVESGGGVVQPGRSLRLSCAASGFSFSSYGMHWVRQAPGKGLEGVAVIWY DGSNRYYADSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCAREPRIGYYYE SSGYYSLDYRGQGTLVTVSS	20
345490	QVQLVESGGGLVKPGGSLRLSCAASGFSFSSYGMHWVRQAPGKGLEGVAVIWY DGSNRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYE SSGYYSLDYRGQGTLVTVSS	21
345482	QVQLVESGGGVVQPGRSLRLSCAASGFSFSSYGMHWVRQAPGKGLEGVAVIWY DGSNRYYADSVKGRFTISRDSSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYE SSGYYSLDYRGQGTLVTVSS	22
345485	QVQLVESGGGVVQPGRSLRLSCAASGFSFRSYGMHWVRQAPGKGLEWVAVIWY DGSNKYYADSVKGRFTISRDNSKNTMYLQMNSLRAEDTAVYYCAREPRIGYYYE SSGYYSLDYRGQGTLVTVSS	23

Clone ID #	SEQ_aa_FR1_FR4	SEQ ID NO.
345463	QVQLVESGGGVVQPGRSLRLSCAASGFIFRSYGMHWVRQAPGKGPEWVAVIWY DGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYE SSGYYSLDYRGQGTLVTVSS	24
325932	QVQLVESGGGVVQPGRSLRLSCAASGFSFSSYGMHWVRQAPGKGLEGVAVIWY DGSNRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYE SSGYYSLDYRGQGTLVTVSS	25
345505	QVQLVESGGGVVQPGRSLRLSCAASGFTFISYGMHWVRQAPGKGLEGVAVIWY DGSNRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYE SSGYYSLDYRGQGTLVTVSS	26
345508	QVQLVESGGGVVQPGRSLRLSCAASGFSFSSYGMHWVRQAPGKGPEWVAVIWY DGSNRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYE SSGYYSLDYRGQGTLVTVSS	27
345480	QVQLVESGGGVVQPGRSLRLSCAASGFSFSSYGMHWVRQAPGKGLEWVAVIWY DGSNRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYE SSGYYSLDYRGQGTLVTVSS	28
326116	QVQLVESGGGVVQPGRSLRLSCAASGFSFSRYGMHWVRQAPGKGLEGVAVISY DGSNKYYADSVKGRFTISRDYSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYD SSGYDSLDYRGQGTLVTVSS	29
345509	QVQLVESGGGLVQPGGSLRLSCAASGFSFSSYGMHWVRQAPGKGLEGVAVIWY DGSNKYYADSVKGRFTISRDNSKNTMYLQMNSLRAEDTAVYYCAREPRIGYYYE SSGYYSLDYRGQGTLVTVSS	30
345444	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEGVAVIWY DGSNRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYE SSGYYSLDYRGQGTLVTVSS	31
345421	QVQLVESVGGVVQPGRSLRLSCAASGFSFSSYGMHWVRQAPGKGLEGVAVIWY DGSNRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYE SSGYYSLDYRGQGTLVTVSS	32
345447	QVQLVESGGGVVQPGRSLRLSCAASGFSFSSYGMHWVRQAPGKGLEGVAVISY DGSNRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYE SSGYYSLDYRGQGTLVTVSS	33
345510	QVQLVESGGGVVQPGRSLRLSCAASGFSFSSYGMHWVRQAPGKGLEWVAVIWY DGSNKYYADSVKGRFTISRDNSKNTMYLQMNSLRAEDTAVYYCAREPRIGYYYE SSGYYSLDYRGQGTLVTVSS	34
345438	QVQLVESGGGVVQPGRSLRLSCAASGFSFSSYGMHWVRQAPGKGPEWVAVIWY DGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPRIGYYYE SSGYYSLDYRGQGTLVTVSS	35

[000209] In a preferred embodiment, a bispecific antibody is a TCA comprising: an anti-CD3 VH domain that is paired with a light chain variable domain (VL), wherein the VH domain and the VL domain together have binding affinity for CD3; a heavy chain variable domain of a heavy chain-only antibody having binding affinity to PSMA, in a monovalent or bivalent configuration; and a variant human IgG4 Fc domain comprising a first heavy chain constant region sequence comprising an S228P mutation, an F234A mutation, an L235A mutation, and a T366W mutation (knob), and a second heavy chain constant region sequence comprising an S228P mutation, an F234A mutation, an L235A mutation, a T366S mutation, an L368A

mutation, and a Y407V mutation (hole). This variant, or modified, IgG4 Fc domain prevents unwanted Fab exchange, reduces effector function of the antibody, and also facilitates heterodimerization of the heavy chain polypeptide subunits to form the bispecific antibody.

CD3 x Target Protein three-chain antibody-like molecules (TCAs)

[000210] In some embodiments, bispecific or multi-specific antibodies are provided, which may have any of the configurations discussed herein, including, without limitation, a bispecific three-chain antibody like molecule. In some embodiments, a multi-specific antibody can comprise a heavy chain/light chain pair that has binding specificity for a first antigen (e.g., CD3), and a heavy chain from a heavy chain-only antibody. In certain embodiments, the heavy chain from the heavy chain only antibody comprises an Fc portion comprising CH2 and/or CH3 and/or CH4 domains, in the absence of a CH1 domain. In one particular embodiment, a bispecific antibody comprises a heavy chain/light chain pair that has binding specificity for an antigen on an effector cell (e.g., a CD3 protein on a T-cell), and a heavy chain from a heavy chain-only antibody comprising an antigen-binding domain that has binding specificity for BCMA, PSMA, or CD19.

[000211] In a preferred embodiment, a bispecific antibody is a TCA comprising: an anti-CD3 VH domain that is paired with a light chain variable domain (VL), wherein the VH domain and the VL domain together have binding affinity for CD3; a heavy chain variable domain of a heavy chain-only antibody having binding affinity to BCMA, PSMA, or CD19; and a variant human IgG4 Fc domain comprising a first heavy chain constant region sequence comprising an S228P mutation, an F234A mutation, an L235A mutation, and a T366W mutation (knob), and a second heavy chain constant region sequence comprising an S228P mutation, an F234A mutation, an L235A mutation, a T366S mutation, an L368A mutation, and a Y407V mutation (hole). This variant, or modified, IgG4 Fc domain prevents unwanted Fab exchange, reduces effector function of the antibody, and also facilitates heterodimerization of the heavy chain polypeptide subunits to form the bispecific antibody.

[000212] In some embodiments, a multi-specific antibody comprises a CD3-binding VH domain that is paired with a light chain variable domain. In certain embodiments, the light chain is a fixed light chain. In some embodiments, the CD3-binding VH domain comprises a CDR1 sequence of SEQ ID NO: 36, a CDR2 sequence of SEQ ID NO: 37, and a CDR3 sequence of SEQ ID NO: 38, in a human VH framework. In some embodiments, the fixed light chain comprises a CDR1 sequence of SEQ ID NO: 39, a CDR2 sequence of SEQ ID NO: 40, and a CDR3 sequence of SEQ ID NO: 41, in a human VL framework. Together, the CD3-binding VH domain and the light chain variable domain have binding affinity for CD3. In some embodiments, a CD3-binding VH domain comprises a heavy chain variable region sequence of SEQ ID NO: 42. In some embodiments, a CD3-binding VH domain comprises a sequence having at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% percent identity to the

2022259766 26 Oct 2022

heavy chain variable region sequence of SEQ ID NO: 42. In some embodiments, a fixed light chain comprises a light chain variable region sequence of SEQ ID NO: 43. In some embodiments, a fixed light chain comprises a sequence having at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% percent identity to the heavy chain variable region sequence of SEQ ID NO: 43.

[000213] Multi-specific antibodies comprising the above-described CD3-binding VH domain and light chain variable domain have advantageous properties, for example, as described in PCT Publication No. WO2018/052503, the disclosure of which is incorporated by reference herein in its entirety. Any of the multi-specific antibodies and antigen-binding domains described herein, having binding affinity to BCMA, PSMA, or CD19, can be combined with the CD3-binding domains and fixed light chain domains described herein to generate multi-specific antibodies having binding affinity to one or more BCMA epitopes, PSMA epitopes, or CD19 epitopes, as well as CD3.

Table 3. Anti-CD3 Heavy and Light Chain CDR1, CDR2, CDR3 amino acid sequences.

	SEQ_aa_CDR1	**SEQ_aa_CDR2**	**SEQ_aa_CDR3**
Heavy Chain	GFTFDDYA (SEQ ID NO: 36)	ISWNSGSI (SEQ ID NO: 37)	AKDSRGYGDYRLGGAY (SEQ ID NO: 38)
Light Chain	QSVSSN (SEQ ID NO: 39)	GAS (SEQ ID NO: 40)	QQYNNWPWT (SEQ ID NO: 41)

Table 4. Anti-CD3 heavy and light chain variable region amino acid sequences.

VH	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEW VSGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYC AKDSRGYGDYRLGGAYWGQGTLVTVSS (SEQ ID NO: 42)
VL	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYG ASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYNNWPWTFGQ GTKVEIK (SEQ ID NO: 43)

Table 5: Human IgG1 and IgG4 Fc region sequences.

Human IgG1 (UniProt No. P01857)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSDE LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK (SEQ ID NO: 44)
Human IgG4 (UniProt No. P01861)	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKS LSLSLGK (SEQ ID NO: 45)
Human IgG1 with silencing mutations (Fc region)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 46)
Human IgG4 with silencing mutations (Fc region)	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 47)

Table 6: Anti-CD3 antibody sequences.

Anti-CD3 light chain constant region sequence (kappa light chain)	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC (SEQ ID NO: 48)

Anti-CD3 full length light chain (VL + kappa CL)	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLI YGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYNNWPW TFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKV YACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 49)
Anti-CD3 heavy chain sequence (VH (F2B) + wt IgG1 Fc)	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLE WVSGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAL YYCAKDSRGYGDYRLGGAYWGQGTLVTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPC PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 50)
Anti-CD3 heavy chain sequence (VH F2B + silenced IgG1 Fc)	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLE WVSGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAL YYCAKDSRGYGDYRLGGAYWGQGTLVTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPC PAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 51)
Anti-CD3 heavy chain VH F2B (+ wt IgG4 Fc)	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLE WVSGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAL YYCAKDSRGYGDYRLGGAYWGQGTLVTVSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPE FLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKG LPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVF SCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 52)
Anti-CD3 heavy chain VH F2B (+ silenced IgG4 Fc)	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLE WVSGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAL YYCAKDSRGYGDYRLGGAYWGQGTLVTVSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCP**P**CPAPE **AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVD GVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNV FSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 53)

Silenced IgG4 (CH1 - hinge – CH2 – CH3; hole (S228P, F234A, L235A; T366S, L368A, Y407V))	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCP**P**CPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE MTKNQVSL**S**C**A**VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFL**V**SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 72)
Silenced IgG4 (CH1 - hinge – CH2 – CH3; knob (S228P, F234A, L235A; T366W))	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCP**P**CPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE MTKNQVSL**W**CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 73)
Silenced IgG4 (hinge – CH2 – CH3; hole (S228P, F234A, L235A; T366S, L368A, Y407V))	ESKYGPPCP**P**CPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT KNQVSL**S**C**A**VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL **V**SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 54)
Silenced IgG4 (hinge – CH2 – CH3; knob (S228P, F234A, L235A; T366W))	ESKYGPPCP**P**CPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT KNQVSL**W**CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 55)
Anti-CD3 full length heavy chain (VH F2B + silenced IgG4 Fc + knob (S228P, F234A, L235A; T366W)) with C-terminal Lysine (K)	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLE WVSGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAL YYCAKDSRGYGDYRLGGAYWGQGTLVTVSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCP**P**CPAPE **AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSL**W**CLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 56)

2022259766 26 Oct 2022

Anti-CD3 full length heavy chain (VH F2B + silenced IgG4 Fc + knob (S228P, F234A, L235A; T366W)) without C-terminal Lysine (K)	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLE WVSGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAL YYCAKDSRGYGDYRLGGAYWGQGTLVTVSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCP**P**CPAPE **AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSL**W**CLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLG (SEQ ID NO: 75)
Anti-CD3 full length heavy chain (VH F2B + silenced IgG4 Fc + hole (S228P, F234A, L235A; T366S, L368A, Y407V))	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLE WVSGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAL YYCAKDSRGYGDYRLGGAYWGQGTLVTVSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCP**P**CPAPE **AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSL**S**C**A**VKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL**V**SRLTVDKSRWQEG NVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 57)

Table 7: Anti-TAA antibody sequences.

Silenced IgG4 (hinge – CH2 – CH3; hole (S228P, F234A, L235A; T366S, L368A, Y407V))	ESKYGPPCP**P**CPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT KNQVSL**S**C**A**VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL **V**SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 54)
Silenced IgG4 (hinge – CH2 – CH3; knob (S228P, F234A, L235A; T366W))	ESKYGPPCP**P**CPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT KNQVSL**W**CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 55)

BCMA bivalent heavy chain (TNB-383B w GS1) + silenced IgG4 Fc hinge CH2 CH3, hole (S228P, F234A, L235A, T366S, L368A, Y407V, with C-terminal Lysine (K)	EVQLLESGGGLVQPGGSLRLSCAASGFTVSSYGMSWVRQAPGKGPE WVSGIRGSDGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKQGENDGPFDHRGQGTLVTVSSGGGGSEVQLLESGGGLVQPG GSLRLSCAASGFTVSSYGMSWVRQAPGKGPEWVSGIRGSDGSTYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKQGENDGPFDHR GQGTLVTVSSESKYGPPCP**P**CPAPE**AA**GGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSL**S**C**A**VKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFL**V**SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL SLSLGK (SEQ ID NO: 58)
BCMA bivalent heavy chain (TNB-383B w GS1) + silenced IgG4 Fc hinge CH2 CH3, hole (S228P, F234A, L235A, T366S, L368A, Y407V, without C-terminal Lysine (K)	EVQLLESGGGLVQPGGSLRLSCAASGFTVSSYGMSWVRQAPGKGPE WVSGIRGSDGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKQGENDGPFDHRGQGTLVTVSSGGGGSEVQLLESGGGLVQPG GSLRLSCAASGFTVSSYGMSWVRQAPGKGPEWVSGIRGSDGSTYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKQGENDGPFDHR GQGTLVTVSSESKYGPPCP**P**CPAPE**AA**GGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSL**S**C**A**VKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFL**V**SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL SLSLG (SEQ ID NO: 76)
BCMA bivalent heavy chain (TNB-383B w GS2) + silenced IgG4 Fc hinge CH2 CH3, hole (S228P, F234A, L235A, T366S, L368A, Y407V, with C-terminal Lysine (K)	EVQLLESGGGLVQPGGSLRLSCAASGFTVSSYGMSWVRQAPGKGPE WVSGIRGSDGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKQGENDGPFDHRGQGTLVTVSSGGGGSGGGGSEVQLLESGGG LVQPGGSLRLSCAASGFTVSSYGMSWVRQAPGKGPEWVSGIRGSDGS TYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKQGEND GPFDHRGQGTLVTVSSESKYGPPCP**P**CPAPE**AA**GGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQF NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSL**S**C**A**VKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFL**V**SRLTVDKSRWQEGNVFSCSVMHEALHNH YTQKSLSLSLGK (SEQ ID NO: 59)

BCMA bivalent heavy chain (TNB-383B w GS2) + silenced IgG4 Fc hinge CH2 CH3, hole (S228P, F234A, L235A, T366S, L368A, Y407V, without C-terminal Lysine (K)	EVQLLESGGGLVQPGGSLRLSCAASGFTVSSYGMSWVRQAPGKGPE WVSGIRGSDGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKQGENDGPFDHRGQGTLVTVSSGGGGSGGGGSEVQLLESGGG LVQPGGSLRLSCAASGFTVSSYGMSWVRQAPGKGPEWVSGIRGSDGS TYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKQGEND GPFDHRGQGTLVTVSSESKYGPPCP**P**CPAPE**AA**GGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQF NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSL**S**C**A**VKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFL**V**SRLTVDKSRWQEGNVFSCSVMHEALHNH YTQKSLSLSLG (SEQ ID NO: 77)
BCMA monovalent heavy chain (TNB-383B) + silenced IgG4 Fc hinge CH2 CH3, hole (S228P, F234A, L235A, T366S, L368A, Y407V	EVQLLESGGGLVQPGGSLRLSCAASGFTVSSYGMSWVRQAPGKGPE WVSGIRGSDGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKQGENDGPFDHRGQGTLVTVSSESKYGPPCP**P**CPAPE**AA**GGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSI EKTISKAKGQPREPQVYTLPPSQEEMTKNQVSL**S**C**A**VKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFL**V**SRLTVDKSRWQEGNVFSCS VMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 60)
PSMA monovalent heavy chain (clone ID 346181) + silenced IgG4 Fc hinge CH2 CH3, hole (S228P, F234A, L235A, T366S, L368A, Y407V, with C-terminal Lysine (K)	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSNYFWGWIRQSPGKGLE WIGSIDYSGYTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYN CARHKAATADFDYRGQGTLVTVSSESKYGPPCP**P**CPAPE**AA**GGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTKNQVSL**S**C**A**VKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFL**V**SRLTVDKSRWQEGNVFSCSVM HEALHNHYTQKSLSLSLGK (SEQ ID NO: 61)

PSMA monovalent heavy chain (clone ID 346181) + silenced IgG4 Fc hinge CH2 CH3, hole (S228P, F234A, L235A, T366S, L368A, Y407V, without C-terminal Lysine (K)	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSNYFWGWIRQSPGKGLE WIGSIDYSGYTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYN CARHKAATADFDYRGQGTLVTVSSESKYGPPCP**P**CPAPE**AA**GGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTKNQVSL**S**C**A**VKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFL**V**SRLTVDKSRWQEGNVFSCSVM HEALHNHYTQKSLSLSLG (SEQ ID NO: 81)
PSMA bivalent heavy chain (clone ID 346181) + silenced IgG4 Fc hinge CH2 CH3, hole (S228P, F234A, L235A, T366S, L368A, Y407V, with C-terminal Lysine (K)	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSNYFWGWIRQSPGKGLE WIGSIDYSGYTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYN CARHKAATADFDYRGQGTLVTVSSGGGGSGGGGSQLQLQESGPGLV KPSETLSLTCTVSGGSISSSNYFWGWIRQSPGKGLEWIGSIDYSGYTYY NPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYNCARHKAATADFD YRGQGTLVTVSSESKYGPPCP**P**CPAPE**AA**GGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREP QVYTLPPSQEEMTKNQVSL**S**C**A**VKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFL**V**SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ KSLSLSLGK (SEQ ID NO: 62)
PSMA bivalent heavy chain (clone ID 346181) + silenced IgG4 Fc hinge CH2 CH3, hole (S228P, F234A, L235A, T366S, L368A, Y407V, without C-terminal Lysine (K)	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSNYFWGWIRQSPGKGLE WIGSIDYSGYTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYN CARHKAATADFDYRGQGTLVTVSSGGGGSGGGGSQLQLQESGPGLV KPSETLSLTCTVSGGSISSSNYFWGWIRQSPGKGLEWIGSIDYSGYTYY NPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYNCARHKAATADFD YRGQGTLVTVSSESKYGPPCP**P**CPAPE**AA**GGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREP QVYTLPPSQEEMTKNQVSL**S**C**A**VKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFL**V**SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ KSLSLSLG (SEQ ID NO: 82)

PSMA monovalent heavy chain (clone ID 345497) + silenced IgG4 Fc hinge CH2 CH3, hole (S228P, F234A, L235A, T366S, L368A, Y407V, with C-terminal Lysine (K)	QVQLVESGGGVVQPGRSLRLSCAASGFSFSRYGMHWVRQAPGKGLE GVAVIWYDGSNRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTA VYYCAREPRIGYYYESSGYYSLDYRGQGTLVTVSSESKYGPPCP**P**CP APE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSL**S**C**A**VK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL**V**SRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 63)
PSMA monovalent heavy chain (clone ID 345497) + silenced IgG4 Fc hinge CH2 CH3, hole (S228P, F234A, L235A, T366S, L368A, Y407V, without C-terminal Lysine (K)	QVQLVESGGGVVQPGRSLRLSCAASGFSFSRYGMHWVRQAPGKGLE GVAVIWYDGSNRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTA VYYCAREPRIGYYYESSGYYSLDYRGQGTLVTVSSESKYGPPCP**P**CP APE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSL**S**C**A**VK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL**V**SRLTVDKSRW QEGNVFSCSVMHEALHNHYTQKSLSLSLG (SEQ ID NO: 83)
PSMA bivalent heavy chain (clone ID 345497) + silenced IgG4 Fc hinge CH CH3, hole (S228P, F234A, L235A, T366S, L368A, Y407V, with C-terminal Lysine (K)	QVQLVESGGGVVQPGRSLRLSCAASGFSFSRYGMHWVRQAPGKGLE GVAVIWYDGSNRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTA VYYCAREPRIGYYYESSGYYSLDYRGQGTLVTVSSGGGGSGGGGSQV QLVESGGGVVQPGRSLRLSCAASGFSFSRYGMHWVRQAPGKGLEGV AVIWYDGSNRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVY YCAREPRIGYYYESSGYYSLDYRGQGTLVTVSSESKYGPPCP**P**CPAPE **AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSL**S**C**A**VKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL**V**SRLTVDKSRWQEG NVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 64)

PSMA bivalent heavy chain (clone ID 345497) + silenced IgG4 Fc hinge CH CH3, hole (S228P, F234A, L235A, T366S, L368A, Y407V, without C-terminal Lysine (K)	QVQLVESGGGVVQPGRSLRLSCAASGFSFSRYGMHWVRQAPGKGLE GVAVIWYDGSNRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTA VYYCAREPRIGYYYESSGYYSLDYRGQGTLVTVSSGGGGSGGGGSQV QLVESGGGVVQPGRSLRLSCAASGFSFSRYGMHWVRQAPGKGLEGV AVIWYDGSNRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVY YCAREPRIGYYYESSGYYSLDYRGQGTLVTVSSESKYGPPCP**P**CPAPE **AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSL**S**C**A**VKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL**V**SRLTVDKSRWQEG NVFSCSVMHEALHNHYTQKSLSLSLG (SEQ ID NO: 84)
PSMA bivalent heavy chain (clone ID 346181 x clone ID 345497) + silenced IgG4 Fc, hole (S228P, F234A, L235A, T366S, L368A, Y407V, with C-terminal Lysine (K)	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSNYFWGWIRQSPGKGLE WIGSIDYSGYTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYN CARHKAATADFDYRGQGTLVTVSSGGGGSGGGGSQVQLVESGGGVV QPGRSLRLSCAASGFSFSRYGMHWVRQAPGKGLEGVAVIWYDGSNR YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPRIGYY YESSGYYSLDYRGQGTLVTVSSESKYGPPCP**P**CPAPE**AA**GGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS KAKGQPREPQVYTLPPSQEEMTKNQVSL**S**C**A**VKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFL**V**SRLTVDKSRWQEGNVFSCSVMH EALHNHYTQKSLSLSLGK (SEQ ID NO: 65)
PSMA bivalent heavy chain (clone ID 346181 x clone ID 345497) + silenced IgG4 Fc, hole (S228P, F234A, L235A, T366S, L368A, Y407V, without C-terminal Lysine (K)	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSNYFWGWIRQSPGKGLE WIGSIDYSGYTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYN CARHKAATADFDYRGQGTLVTVSSGGGGSGGGGSQVQLVESGGGVV QPGRSLRLSCAASGFSFSRYGMHWVRQAPGKGLEGVAVIWYDGSNR YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPRIGYY YESSGYYSLDYRGQGTLVTVSSESKYGPPCP**P**CPAPE**AA**GGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS KAKGQPREPQVYTLPPSQEEMTKNQVSL**S**C**A**VKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFL**V**SRLTVDKSRWQEGNVFSCSVMH EALHNHYTQKSLSLSLG (SEQ ID NO: 85)

PSMA bivalent heavy chain (clone ID 345497 x clone ID 346181) + silenced IgG4 Fc, hole (S228P, F234A, L235A, T366S, L368A, Y407V, with C-terminal Lysine (K)	QVQLVESGGGVVQPGRSLRLSCAASGFSFSRYGMHWVRQAPGKGLE GVAVIWYDGSNRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTA VYYCAREPRIGYYYESSGYYSLDYRGQGTLVTVSSGGGGSGGGGSQL QLQESGPGLVKPSETLSLTCTVSGGSISSSNYFWGWIRQSPGKGLEWIG SIDYSGYTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR HKAATADFDYRGQGTLVTVSSESKYGPPCP**P**CPAPE**AA**GGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS KAKGQPREPQVYTLPPSQEEMTKNQVSL**S**C**A**VKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFL**V**SRLTVDKSRWQEGNVFSCSVMH EALHNHYTQKSLSLSLGK (SEQ ID NO: 66)
PSMA bivalent heavy chain (clone ID 345497 x clone ID 346181) + silenced IgG4 Fc, hole (S228P, F234A, L235A, T366S, L368A, Y407V, without C-terminal Lysine (K)	QVQLVESGGGVVQPGRSLRLSCAASGFSFSRYGMHWVRQAPGKGLE GVAVIWYDGSNRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTA VYYCAREPRIGYYYESSGYYSLDYRGQGTLVTVSSGGGGSGGGGSQL QLQESGPGLVKPSETLSLTCTVSGGSISSSNYFWGWIRQSPGKGLEWIG SIDYSGYTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR HKAATADFDYRGQGTLVTVSSESKYGPPCP**P**CPAPE**AA**GGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS KAKGQPREPQVYTLPPSQEEMTKNQVSL**S**C**A**VKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFL**V**SRLTVDKSRWQEGNVFSCSVMH EALHNHYTQKSLSLSLG (SEQ ID NO: 86)
CD19 monovalent heavy chain + silenced IgG4 Fc hinge CH CH3, hole (S228P, F234A, L235A, T366S, L368A, Y407V, with C-terminal Lysine (K)	EVQLVESGGGLVQPGGSLRLSCAASGFSFSDFWMSWVRQAPGKGLE WVATISQAGSEKDYVDSVKGRFTISRDNAKKSLYLQMNSLRAEDTAV YYCASGVYSFDYRGQGTLVTVSSESKYGPPCP**P**CPAPE**AA**GGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSL**S**C**A**VKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFL**V**SRLTVDKSRWQEGNVFSCSVMH EALHNHYTQKSLSLSLGK (SEQ ID NO: 67)

CD19 monovalent heavy chain + silenced IgG4 Fc hinge CH CH3, hole (S228P, F234A, L235A, T366S, L368A, Y407V, without C-terminal Lysine (K)	EVQLVESGGGLVQPGGSLRLSCAASGFSFSDFWMSWVRQAPGKGLE WVATISQAGSEKDYVDSVKGRFTISRDNAKKSLYLQMNSLRAEDTAV YYCASGVYSFDYRGQGTLVTVSSESKYGPPCP**P**CPAPE**AA**GGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSL**S**C**A**VKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFL**V**SRLTVDKSRWQEGNVFSCSVMH EALHNHYTQKSLSLSLG (SEQ ID NO: 78)
CD19 bivalent GS1 heavy chain + silenced IgG4 Fc hinge CH CH3, hole (S228P, F234A, L235A, T366S, L368A, Y407V, with C-terminal Lysine (K)	EVQLVESGGGLVQPGGSLRLSCAASGFSFSDFWMSWVRQAPGKGLE WVATISQAGSEKDYVDSVKGRFTISRDNAKKSLYLQMNSLRAEDTAV YYCASGVYSFDYRGQGTLVTVSSGGGGSEVQLVESGGGLVQPGGSLR LSCAASGFSFSDFWMSWVRQAPGKGLEWVATISQAGSEKDYVDSVK GRFTISRDNAKKSLYLQMNSLRAEDTAVYYCASGVYSFDYRGQGTLV TVSSESKYGPPCP**P**CPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQE EMTKNQVSL**S**C**A**VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFL**V**SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 68)
CD19 bivalent GS1 heavy chain + silenced IgG4 Fc hinge CH CH3, hole (S228P, F234A, L235A, T366S, L368A, Y407V, without C-terminal Lysine (K)	EVQLVESGGGLVQPGGSLRLSCAASGFSFSDFWMSWVRQAPGKGLE WVATISQAGSEKDYVDSVKGRFTISRDNAKKSLYLQMNSLRAEDTAV YYCASGVYSFDYRGQGTLVTVSSGGGGSEVQLVESGGGLVQPGGSLR LSCAASGFSFSDFWMSWVRQAPGKGLEWVATISQAGSEKDYVDSVK GRFTISRDNAKKSLYLQMNSLRAEDTAVYYCASGVYSFDYRGQGTLV TVSSESKYGPPCP**P**CPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQE EMTKNQVSL**S**C**A**VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFL**V**SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG (SEQ ID NO: 79)

CD19 bivalent GS2 heavy chain + silenced IgG4 Fc hinge CH CH3, hole (S228P, F234A, L235A, T366S, L368A, Y407V, with C-terminal Lysine (K)	EVQLVESGGGLVQPGGSLRLSCAASGFSFSDFWMSWVRQAPGKGLE WVATISQAGSEKDYVDSVKGRFTISRDNAKKSLYLQMNSLRAEDTAV YYCASGVYSFDYRGQGTLVTVSSGGGGSGGGGSEVQLVESGGGLVQ PGGSLRLSCAASGFSFSDFWMSWVRQAPGKGLEWVATISQAGSEKDY VDSVKGRFTISRDNAKKSLYLQMNSLRAEDTAVYYCASGVYSFDYR GQGTLVTVSSESKYGPPCP**P**CPAPE**AA**GGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSL**S**C**A**VKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFL**V**SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL SLSLGK (SEQ ID NO: 69)
CD19 bivalent GS2 heavy chain + silenced IgG4 Fc hinge CH CH3, hole (S228P, F234A, L235A, T366S, L368A, Y407V, without C-terminal Lysine (K)	EVQLVESGGGLVQPGGSLRLSCAASGFSFSDFWMSWVRQAPGKGLE WVATISQAGSEKDYVDSVKGRFTISRDNAKKSLYLQMNSLRAEDTAV YYCASGVYSFDYRGQGTLVTVSSGGGGSGGGGSEVQLVESGGGLVQ PGGSLRLSCAASGFSFSDFWMSWVRQAPGKGLEWVATISQAGSEKDY VDSVKGRFTISRDNAKKSLYLQMNSLRAEDTAVYYCASGVYSFDYR GQGTLVTVSSESKYGPPCP**P**CPAPE**AA**GGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSL**S**C**A**VKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFL**V**SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL SLSLG (SEQ ID NO: 80)

[000214] In some embodiments, bispecific or multi-specific antibodies are provided, which may have any of the configurations discussed herein, including, without limitation, a bispecific three-chain antibody like molecule. In some embodiments, a bispecific antibody can comprise at least one heavy chain variable region having binding specificity for BCMA, PSMA, or CD19, and at least one heavy chain variable region having binding specificity for a different protein, e.g., CD3. In some embodiments, a bispecific antibody can comprise a heavy chain/light chain pair that has binding specificity for a first antigen, and a heavy chain from a heavy chain-only antibody, comprising an Fc portion comprising CH2 and/or CH3 and/or CH4 domains, in the absence of a CH1 domain, and an antigen binding domain that binds an epitope of a second antigen or a different epitope of the first antigen, in a monovalent or bivalent configuration. In one particular embodiment, a bispecific antibody comprises a heavy chain/light chain pair that has binding specificity for an antigen on an effector cell (e.g., a CD3 protein on a T-cell), and a heavy chain from a heavy chain-only antibody comprising an antigen-binding domain that has binding specificity for BCMA, PSMA, or CD19, in a monovalent or bivalent configuration.

[000215] In some embodiments, where an antibody of the invention is a bispecific antibody, one arm of the antibody (one binding moiety, or one binding unit) is specific for human BCMA, human PSMA, or human CD19, while the other arm may be specific for target cells, tumor-associated antigens, targeting antigens, e.g., integrins, etc., pathogen antigens, checkpoint proteins, and the like. Target cells specifically include cancer cells, including, without limitation, cells from solid tumors, e.g., prostate tumors, as discussed below. In some embodiments, one arm of the antibody (one binding moiety, or one binding unit) is specific for human BCMA, human PSMA, or human CD19, while the other arm is specific for CD3.

[000216] In some embodiments, an antibody comprises an anti-CD3 light chain polypeptide comprising the sequence of SEQ ID NO: 43 linked to the sequence of SEQ ID NO: 48, an anti-CD3 heavy chain polypeptide comprising the sequence of any one of SEQ ID NOs: 44, 45, 46, 47, 50, 51, 52, 53, 56 or 57, and an anti-BCMA heavy chain polypeptide comprising the sequence of any one of SEQ ID NOs: 58, 59 or 60. In one preferred embodiment, an antibody is a TCA comprising a first polypeptide comprising SEQ ID NO: 49, a second polypeptide comprising SEQ ID NO: 56, and a third polypeptide comprising SEQ ID NO: 58, 59 or 60. In one preferred embodiment, an antibody is a TCA comprising a first polypeptide comprising SEQ ID NO: 49, a second polypeptide comprising SEQ ID NO: 56, and a third polypeptide comprising SEQ ID NO: 58. In one preferred embodiment, an antibody is a TCA consisting of a first polypeptide consisting of SEQ ID NO: 49, a second polypeptide consisting of SEQ ID NO: 56, and a third polypeptide consisting of SEQ ID NO: 58. In one preferred embodiment, an antibody is a TCA comprising a first polypeptide comprising SEQ ID NO: 49, a second polypeptide comprising SEQ ID NO: 56, and a third polypeptide comprising SEQ ID NO: 59. In one preferred embodiment, an antibody is a TCA consisting of a first polypeptide consisting of SEQ ID NO: 49, a second polypeptide consisting of SEQ ID NO: 56, and a third polypeptide consisting of SEQ ID NO: 59. In one preferred embodiment, an antibody is a TCA comprising a first polypeptide comprising SEQ ID NO: 49, a second polypeptide comprising SEQ ID NO: 56, and a third polypeptide comprising SEQ ID NO: 60. In one preferred embodiment, an antibody is a TCA consisting of a first polypeptide consisting of SEQ ID NO: 49, a second polypeptide consisting of SEQ ID NO: 56, and a third polypeptide consisting of SEQ ID NO: 60.

[000217] In some embodiments, an antibody comprises an anti-CD3 light chain polypeptide comprising the sequence of SEQ ID NO: 43 linked to the sequence of SEQ ID NO: 48, an anti-CD3 heavy chain polypeptide comprising the sequence of any one of SEQ ID NOs: 44, 45, 46, 47, 50, 51, 52, 53, 56 or 57, and an anti-PSMA heavy chain polypeptide comprising the sequence of any one of SEQ ID NOs: 61, 62, 63, 64, 65 or 66. In one preferred embodiment, an antibody is a TCA comprising a first polypeptide comprising SEQ ID NO: 49, a second polypeptide comprising SEQ ID NO: 56, and a third polypeptide comprising SEQ ID NO: 61. In one preferred embodiment, an antibody is a TCA consisting of a first polypeptide consisting of SEQ ID NO: 49, a second polypeptide consisting of SEQ ID NO: 56, and a third

polypeptide consisting of SEQ ID NO: 61. In one preferred embodiment, an antibody is a TCA comprising a first polypeptide comprising SEQ ID NO: 49, a second polypeptide comprising SEQ ID NO: 56, and a third polypeptide comprising SEQ ID NO: 62. In one preferred embodiment, an antibody is a TCA consisting of a first polypeptide consisting of SEQ ID NO: 49, a second polypeptide consisting of SEQ ID NO: 56, and a third polypeptide consisting of SEQ ID NO: 62. In one preferred embodiment, an antibody is a TCA comprising a first polypeptide comprising SEQ ID NO: 49, a second polypeptide comprising SEQ ID NO: 56, and a third polypeptide comprising SEQ ID NO: 63. In one preferred embodiment, an antibody is a TCA consisting of a first polypeptide consisting of SEQ ID NO: 49, a second polypeptide consisting of SEQ ID NO: 56, and a third polypeptide consisting of SEQ ID NO: 63. In one preferred embodiment, an antibody is a TCA comprising a first polypeptide comprising SEQ ID NO: 49, a second polypeptide comprising SEQ ID NO: 56, and a third polypeptide comprising SEQ ID NO: 64. In one preferred embodiment, an antibody is a TCA consisting of a first polypeptide consisting of SEQ ID NO: 49, a second polypeptide consisting of SEQ ID NO: 56, and a third polypeptide consisting of SEQ ID NO: 64. In one preferred embodiment, an antibody is a TCA comprising a first polypeptide comprising SEQ ID NO: 49, a second polypeptide comprising SEQ ID NO: 56, and a third polypeptide comprising SEQ ID NO: 65. In one preferred embodiment, an antibody is a TCA consisting of a first polypeptide consisting of SEQ ID NO: 49, a second polypeptide consisting of SEQ ID NO: 56, and a third polypeptide consisting of SEQ ID NO: 65. In one preferred embodiment, an antibody is a TCA comprising a first polypeptide comprising SEQ ID NO: 49, a second polypeptide comprising SEQ ID NO: 56, and a third polypeptide comprising SEQ ID NO: 66. In one preferred embodiment, an antibody is a TCA consisting of a first polypeptide consisting of SEQ ID NO: 49, a second polypeptide consisting of SEQ ID NO: 56, and a third polypeptide consisting of SEQ ID NO: 66.

[000218] In some embodiments, an antibody comprises an anti-CD3 light chain polypeptide comprising the sequence of SEQ ID NO: 43 linked to the sequence of SEQ ID NO: 48, an anti-CD3 heavy chain polypeptide comprising the sequence of any one of SEQ ID NOs: 44, 45, 46, 47, 50, 51, 52, 53, 56 or 57, and an anti-CD19 heavy chain polypeptide comprising the sequence of any one of SEQ ID NOs: 67, 68 or 69. In one preferred embodiment, an antibody is a TCA comprising a first polypeptide comprising SEQ ID NO: 49, a second polypeptide comprising SEQ ID NO: 56, and a third polypeptide comprising SEQ ID NO: 67. In one preferred embodiment, an antibody is a TCA consisting of a first polypeptide consisting of SEQ ID NO: 49, a second polypeptide consisting of SEQ ID NO: 56, and a third polypeptide consisting of SEQ ID NO: 67. In one preferred embodiment, an antibody is a TCA comprising a first polypeptide comprising SEQ ID NO: 49, a second polypeptide comprising SEQ ID NO: 56, and a third polypeptide comprising SEQ ID NO: 68. In one preferred embodiment, an antibody is a TCA consisting of a first polypeptide consisting of SEQ ID NO: 49, a second polypeptide consisting of SEQ ID NO: 56, and a third

polypeptide consisting of SEQ ID NO: 68. In one preferred embodiment, an antibody is a TCA comprising a first polypeptide comprising SEQ ID NO: 49, a second polypeptide comprising SEQ ID NO: 56, and a third polypeptide comprising SEQ ID NO: 69. In one preferred embodiment, an antibody is a TCA consisting of a first polypeptide consisting of SEQ ID NO: 49, a second polypeptide consisting of SEQ ID NO: 56, and a third polypeptide consisting of SEQ ID NO: 69.

[000219] Various formats of multi-specific antibodies are within the ambit of the invention, including, without limitation, single chain polypeptides, two chain polypeptides, three chain polypeptides, four chain polypeptides, and multiples thereof. The multi-specific antibodies herein specifically include T-cell multi-specific (e.g., bispecific) antibodies binding to BCMA, PSMA, or 19, and CD3 (anti-BCMA x anti-CD3 antibodies, anti-PSMA x anti-CD3 antibodies, anti-CD19 x anti-CD3 antibodies), and which contain a variant human IgG4 Fc domain comprising a first heavy chain constant region sequence comprising an S228P mutation, an F234A mutation, an L235A mutation, and a T366W mutation (knob), and a second heavy chain constant region sequence comprising an S228P mutation, an F234A mutation, an L235A mutation, a T366S mutation, an L368A mutation, and a Y407V mutation (hole). This variant, or modified, IgG4 Fc domain prevents unwanted Fab exchange, reduces effector function of the antibody, and also facilitates heterodimerization of the heavy chain polypeptide subunits to form the bispecific antibody. Such antibodies induce potent T-cell mediated killing of cells expressing BCMA, PSMA, or CD19, respectively.

Preparation of antibodies

[000220] The multispecific antibodies of the present invention can be prepared by methods known in the art. In a preferred embodiment, the heavy chain antibodies herein are produced by transgenic animals, including transgenic mice and rats, preferably rats, in which the endogenous immunoglobulin genes are knocked out or disabled. In a preferred embodiment, the heavy chain antibodies herein are produced in UniRat™. UniRat™ have their endogenous immunoglobulin genes silenced and use a human immunoglobulin heavy-chain translocus to express a diverse, naturally optimized repertoire of fully human HCAbs. While endogenous immunoglobulin loci in rats can be knocked out or silenced using a variety of technologies, in UniRat™ the zinc-finger (endo)nuclease (ZNF) technology was used to inactivate the endogenous rat heavy chain J-locus, light chain Cκ locus and light chain Cλ locus. ZNF constructs for microinjection into oocytes can produce IgH and IgL knock out (KO) lines. For details see, e.g., Geurts et al., 2009, Science 325:433. Characterization of Ig heavy chain knockout rats has been reported by Menoret et al., 2010, Eur. J. Immunol. 40:2932-2941. Advantages of the ZNF technology are that non-homologous end joining to silence a gene or locus via deletions up to several kb can also provide a target site for homologous integration (Cui et al., 2011, Nat Biotechnol 29:64-67). Human heavy chain antibodies produced in UniRat™ are called UniAbs™ and can bind epitopes that cannot be attacked with conventional antibodies. Their high specificity, affinity, and small size make them ideal for mono- and poly-specific applications.

2022259766 26 Oct 2022

[000221] In addition to UniAbs™, specifically included herein are heavy chain-only antibodies lacking the camelid VHH framework and mutations, and their functional VH regions. Such heavy chain-only antibodies can, for example, be produced in transgenic rats or mice which comprise fully human heavy chain-only gene loci as described, e.g., in WO2006/008548, but other transgenic mammals, such as rabbit, guinea pig, rat can also be used, rats and mice being preferred. Heavy chain-only antibodies, including their VHH or VH functional fragments, can also be produced by recombinant DNA technology, by expression of the encoding nucleic acid in a suitable eukaryotic or prokaryotic host, including, for example, mammalian cells (e.g., CHO cells), E. coli or yeast.

[000222] Domains of heavy chain-only antibodies combine advantages of antibodies and small molecule drugs: can be mono- or multi-valent; have low toxicity; and are cost-effective to manufacture. Due to their small size, these domains are easy to administer, including oral or topical administration, are characterized by high stability, including gastrointestinal stability; and their half-life can be tailored to the desired use or indication. In addition, VH and VHH domains of HCAbs can be manufactured in a cost effective manner.

[000223] In a particular embodiment, the heavy chain antibodies of the present invention, including UniAbs™, have the native amino acid residue at the first position of the FR4 region (amino acid position 101 according to the Kabat numbering system), substituted by another amino acid residue, which is capable of disrupting a surface-exposed hydrophobic patch comprising or associated with the native amino acid residue at that position. Such hydrophobic patches are normally buried in the interface with the antibody light chain constant region but become surface exposed in HCAbs and are, at least partially, for the unwanted aggregation and light chain association of HCAbs. The substituted amino acid residue preferably is charged, and more preferably is positively charged, such as lysine (Lys, K), arginine (Arg, R) or histidine (His, H), preferably arginine (R). In a preferred embodiment the heavy chain-only antibodies derived from the transgenic animals contain a Trp to Arg mutation at position 101. The resultant HCAbs preferably have high antigen-binding affinity and solubility under physiological conditions in the absence of aggregation.

[000224] As part of the present invention, human heavy chain antibodies with unique sequences from UniRat™ animals (UniAb™) were identified that bind human CD3, BCMA, PSMA, or CD19 in ELISA protein and cell-binding assays. The identified heavy chain variable region (VH) sequences (see, e.g., Tables 1 and 2) are positive for protein binding and/or for binding to cells expressing the target protein (e.g., CD3, BCMA, PSMA, or CD19), and are all negative for binding to cells that do not express the target protein.

[000225] Heavy chain antibodies binding to non-overlapping epitopes on a target protein, e.g., UniAbs™ can be identified by competition binding assays, such as enzyme-linked immunoassays (ELISA assays) or flow cytometric competitive binding assays. For example, one can use competition between known antibodies binding to the target antigen and the antibody of interest. By using this approach, one can divide

a set of antibodies into those that compete with the reference antibody and those that do not. The non-competing antibodies are identified as binding to a distinct epitope that does not overlap with the epitope bound by the reference antibody. Often, one antibody is immobilized, the antigen is bound, and a second, labeled (e.g., biotinylated) antibody is tested in an ELISA assay for ability to bind the captured antigen. This can be performed also by using surface plasmon resonance (SPR) platforms, including ProteOn XPR36 (BioRad, Inc), Biacore 2000 and Biacore T200 (GE Healthcare Life Sciences), and MX96 SPR imager (Ibis technologies B.V.), as well as on biolayer interferometry platforms, such as Octet Red384 and Octet HTX (ForteBio, Pall Inc). For further details see the examples herein.

[000226] Typically, an antibody "competes" with a reference antibody if it causes about 15-100% reduction in the binding of the reference antibody to the target antigen, as determined by standard techniques, such as by the competition binding assays described above. In various embodiments, the relative inhibition is at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50% at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95% or higher.

Pharmaceutical Compositions, Uses and Methods of Treatment

[000227] It is another aspect of the present invention to provide pharmaceutical compositions comprising one or more multispecific binding compounds of the present invention in admixture with a suitable pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers as used herein are exemplified, but not limited to, adjuvants, solid carriers, water, buffers, or other carriers used in the art to hold therapeutic components, or combinations thereof.

[000228] In one embodiment, a pharmaceutical composition comprises a heavy chain antibody (e.g., UniAb^{TM}) that binds to a target protein (e.g., CD3, BCMA, PSMA, or CD19). In another embodiment, a pharmaceutical composition comprises a multi-specific (including bispecific) heavy chain antibody (e.g., UniAb^{TM}) with binding specificity for two or more non-overlapping epitopes on a target protein (e.g., CD3, BCMA, PSMA, or CD19). In a preferred embodiment, a pharmaceutical composition comprises a multi-specific (including bispecific) heavy chain antibody (e.g., UniAb^{TM}) with binding specificity to a target protein (e.g., BCMA, PSMA, or CD19) and with binding specificity to a binding target on an effector cell (e.g., a binding target on a T-cell, such as, e.g., a CD3 protein on a T-cell).

[000229] Pharmaceutical compositions of the antibodies used in accordance with the present invention are prepared for storage by mixing proteins having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers (see, e.g. Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), such as in the form of lyophilized formulations or aqueous solutions. Acceptable

carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as 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 dextrins; 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).

[000230] Pharmaceutical compositions for parenteral administration are preferably sterile and substantially isotonic and manufactured under Good Manufacturing Practice (GMP) conditions. Pharmaceutical compositions can be provided in unit dosage form (i.e., the dosage for a single administration). The formulation depends on the route of administration chosen. The antibodies herein can be administered by intravenous injection or infusion or subcutaneously. For injection administration, the antibodies herein can be formulated in aqueous solutions, preferably in physiologically-compatible buffers to reduce discomfort at the site of injection. The solution can contain carriers, excipients, or stabilizers as discussed above. Alternatively, antibodies can be in lyophilized form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[000231] Antibody formulations are disclosed, for example, in U.S. Patent No. 9,034,324. Similar formulations can be used for the heavy chain antibodies, including UniAbs™, of the present invention. Subcutaneous antibody formulations are described, for example, in US20160355591 and US20160166689.

Methods of Use

[000232] The heavy chain-only antibodies, multi-specific antibodies, and pharmaceutical compositions described herein can be used for the treatment of diseases and conditions characterized by the expression of a target protein (e.g., CD3, BCMA, PSMA, or CD19), including, without limitation, the conditions and diseases described further herein.

[000233] The pharmaceutical compositions herein comprising anti-BCMA antibodies can be used for the treatment of B-cell related disorders, including B-cell and plasma cell malignancies and autoimmune disorders characterized by the expression or overexpression of BCMA.

[000234] Such B-cell related disorders include B-cell and plasma cell malignancies and autoimmune disorders, including, without limitation, plasmacytoma, Hodgkins' lymphoma, follicular lymphomas, small non-cleaved cell lymphomas, endemic Burkitt's lymphoma, sporadic Burkitt's lymphoma, marginal zone lymphoma, extranodal mucosa-associated lymphoid tissue lymphoma, nodal monocytoid B-cell lymphoma, splenic lymphoma, mantle cell lymphoma, large cell lymphoma, diffuse mixed cell lymphoma, immunoblastic lymphoma, primary mediastinal B-cell lymphoma, pulmonary B-cell angiocentric lymphoma, small lymphocytic lymphoma, B-cell proliferations of uncertain malignant potential, lymphomatoid granulomatosis, post-transplant lymphoproliferative disorder, an immunoregulatory disorder, rheumatoid arthritis, myasthenia gravis, idiopathic thrombocytopenia purpura, anti-phospholipid syndrome, Chagas' disease, Grave's disease, Wegener's granulomatosis, poly-arteritis nodosa, Sjogren's syndrome, pemphigus vulgaris, scleroderma, multiple sclerosis, anti-phospholipid syndrome, ANCA associated vasculitis, Goodpasture's disease, Kawasaki disease, autoimmune hemolytic anemia, and rapidly progressive glomerulonephritis, heavy-chain disease, primary or immunocyte-associated amyloidosis, or monoclonal gammopathy.

[000235] The plasma cell disorders characterized by the expression of BCMA include Multiple Myeloma (MM). MM is a B-cell malignancy characterized by a monoclonal expansion and accumulation of abnormal plasma cells in the bone marrow compartment. Current therapies for MM often cause remissions, but nearly all patients eventually relapse and die. There is substantial evidence of an immune-mediated elimination of myeloma cells in the setting of allogeneic hematopoietic stem cell transplantation; however, the toxicity of this approach is high, and few patients are cured. Although some monoclonal antibodies have shown promise for treating MM in preclinical studies and early clinical trials, consistent clinical efficacy of any monoclonal antibody therapy for MM has not been conclusively demonstrated. There is therefore a great need for new therapies, including immunotherapies for MM (see, e.g., Carpenter et al., Clin Cancer Res 2013, 19(8):2048-2060).

[000236] Overexpression or activation of BCMA by its proliferation-inducing ligand, APRIL it known to promote human Multiple Myeloma (MM) progression in vivo. BCMA has also been shown to promote in vivo growth of xenografted MM cells harboring p53 mutation in mice. Since activity of the APRIL/BCMA pathway plays a central role in MM pathogenesis and drug resistance via bidirectional interactions between tumor cells and their supporting bone marrow microenvironment, BCMA has been identified as a target for the treatment of MM. For further details see, e.g., Yu-Tsu Tai et al., Blood 2016; 127(25):3225-3236.

[000237] Another B-cell disorder involving plasma cells i.e. expressing BCMA is systemic lupus erythematosus (SLE), also known as lupus. SLE is a systemic, autoimmune disease that can affect any part of the body and is represented with the immune system attacking the body's own cells and tissue, resulting in chronic inflammation and tissue damage. It is a Type III hypersensitivity reaction in which antibody-

2022259766 26 Oct 2022

immune complexes precipitate and cause a further immune response (Inaki & Lee, Nat Rev Rheumatol 2010; 6: 326-337).

[000238] The anti-BCMA heavy chain-only antibodies (UniAb) of the present invention can be used to develop therapeutic agents for the treatment of MM, SLE, and other B-cell disorders or plasma cell disorders characterized by the expression of BCMA, such as those listed above. In particular, the anti-BCMA heavy chain-only antibodies (UniAb) of the present invention are candidates for the treatment of MM, alone or in combination with other MM treatments.

[000239] PSMA is a type II transmembrane protein that is expressed on prostate epithelium tissue and is upregulated in prostate cancer and the neovasculature of solid tumors. It is also expressed at low levels in healthy tissues such as the brain, kidney, and salivary glands but its overexpression in malignant prostate tissue makes it an attractive target for the therapeutic treatment of prostate cancer. It may also be relevant for therapy or imaging of solid tumors, given its high expression in malignant neovasculature. Monoclonal antibodies, antibody drug conjugates and chimeric antigen receptor T-cells targeting PSMA have been described for treatment of metastatic prostate cancer (Hernandez-Hoyos et al., 2016, PMID: 27406985, DiPippo et al., 2014, PMID: 25327986, Serganova et al., 2016, PMID: 28345023). In addition, radionuclide conjugates specific to PSMA are being investigated for imaging and treatment of prostate cancer (e.g., Hofman et al., 2018 PMID: 29752180).

[000240] In one aspect, the PSMA heavy chain antibodies (e.g., UniAbs^{TM}) and pharmaceutical compositions herein can be used to treat disorders characterized by the expression of PSMA, including, without limitation, prostate cancer and solid tumors.

[000241] CD19 is a cell surface receptor that is expressed on all human B-cells, but is not found on plasma cells. It has a relatively large, 240 amino acid, cytoplasmic tail. The extracellular Ig-like domains are divided by a potential disulfide linked non-Ig-like domain and N-linked carbohydrate addition sites. The cytoplasmic tail contains at least nine tyrosine residues near the C-terminus, some of which have been shown to be phosphorylated. Along with CD20 and CD22, the restricted expression of CD19 to the B-cell lineage makes it an attractive target for the therapeutic treatment of B-cell malignancies. Due to its observed expression in a number of hematological malignancies, CD19 is a promising target for antibody-based therapeutics.

[000242] In one aspect, the CD19 heavy chain antibodies (e.g., UniAbs^{TM}) and pharmaceutical compositions herein can be used to treat hematological malignancies characterized by the expression of CD19, including, without limitation, diffuse large B-cell lymphoma (DLBCL), non-Hodgkin's lymphoma, B-cell chronic lymphocylic leukemia (CLL), and B-cell acute lymphoblastic leukemia (ALL).

[000243] Diffuse large B-cell lymphoma (DLBCL or DLBL) is the most common form of non-Hodgkin's lymphoma among adults (Blood 1997 89 (11): 3909-18), with an estimated annual incidence of 7 to 8 cases

per 100,000 people per year in the US and the UK. It is characterized as an aggressive cancer that can arise in virtually any part of the body. The causes of DLBCL are not well understood, and it can arise from normal B-cells as well as malignant transformation of other types of lymphoma or leukemia cells. Treatment approaches generally involve chemotherapy and radiation, and have resulted in an overall five-year survival rate average of approximately 58% for adults. Although some monoclonal antibodies have shown promise for treating DLBCL, consistent clinical efficacy has not yet been conclusively demonstrated. There is therefore a great need for new therapies, including immunotherapies, for DLBCL.

[000244] In another aspect, the CD19 heavy chain antibodies (e.g., UniAbs^{TM}) and pharmaceutical compositions herein can be used to treat autoimmune disorders characterized by pathogenic B-cells that express CD19, including, without limitation, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and multiple sclerosis (MS).

[000245] Effective doses of the compositions of the present invention for the treatment of disease vary depending upon many different factors, including means of administration, target site, physiological state of the patient, whether the patient is human or an animal, other medications administered, and whether treatment is prophylactic or therapeutic. Usually, the patient is a human, but nonhuman mammals may also be treated, e.g., companion animals such as dogs, cats, horses, etc., laboratory mammals such as rabbits, mice, rats, etc., and the like. Treatment dosages can be titrated to optimize safety and efficacy.

[000246] Dosage levels can be readily determined by the ordinarily skilled clinician, and can be modified as required, e.g., as required to modify a subject's response to therapy. The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form varies depending upon the host treated and the particular mode of administration. Dosage unit forms generally contain between from about 1 mg to about 500 mg of an active ingredient.

[000247] In some embodiments, the therapeutic dosage the agent may range from about 0.0001 to 100 mg/kg, and more usually 0.01 to 5 mg/kg, of the host body weight. For example dosages can be 1 mg/kg body weight or 10 mg/kg body weight or within the range of 1-10 mg/kg. An exemplary treatment regime entails administration once every two weeks or once a month or once every 3 to 6 months. Therapeutic entities of the present invention are usually administered on multiple occasions. Intervals between single dosages can be weekly, monthly or yearly. Intervals can also be irregular as indicated by measuring blood levels of the therapeutic entity in the patient. Alternatively, therapeutic entities of the present invention can be administered as a sustained release formulation, in which case less frequent administration is required. Dosage and frequency vary depending on the half-life of the polypeptide in the patient.

[000248] Typically, compositions are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection can also be prepared. The pharmaceutical compositions herein are suitable for intravenous or subcutaneous administration, directly

2022259766 26 Oct 2022

or after reconstitution of solid (e.g., lyophilized) compositions. The preparation also can be emulsified or encapsulated in liposomes or micro particles such as polylactide, polyglycolide, or copolymer for enhanced adjuvant effect, as discussed above. Langer, Science 249: 1527, 1990 and Hanes, Advanced Drug Delivery Reviews 28: 97-119, 1997. The agents of this invention can be administered in the form of a depot injection or implant preparation which can be formulated in such a manner as to permit a sustained or pulsatile release of the active ingredient. The pharmaceutical compositions are generally formulated as sterile, substantially isotonic and in full compliance with all Good Manufacturing Practice (GMP) regulations of the U.S. Food and Drug Administration.

[000249] Toxicity of the antibodies and antibody structures described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., by determining the LD50 (the dose lethal to 50% of the population) or the LD100 (the dose lethal to 100% of the population). The dose ratio between toxic and therapeutic effect is the therapeutic index. The data obtained from these cell culture assays and animal studies can be used in formulating a dosage range that is not toxic for use in humans. The dosage of the antibodies described herein lies preferably within a range of circulating concentrations that include the effective dose with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition.

[000250] The compositions for administration will commonly comprise an antibody or other agent (e.g., another ablative agent) dissolved in a pharmaceutically acceptable carrier, preferably an aqueous carrier. A variety of aqueous carriers can be used, e.g., buffered saline and the like. These solutions are sterile and generally free of undesirable matter. These compositions may be sterilized by conventional, well known sterilization techniques. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, toxicity adjusting agents and the like, e.g., sodium acetate, sodium chloride, potassium chloride, calcium chloride, sodium lactate and the like. The concentration of active agent in these formulations can vary widely, and will be selected primarily based on fluid volumes, viscosities, body weight and the like in accordance with the particular mode of administration selected and the patient's needs (e.g., Remington's Pharmaceutical Science (15th ed., 1980) and Goodman & Gillman, The Pharmacological Basis of Therapeutics (Hardman et al., eds., 1996)).

[000251] Also within the scope of the invention are kits comprising the active agents and formulations thereof, of the invention and instructions for use. The kit can further contain a least one additional reagent, e.g., a chemotherapeutic drug, etc. Kits typically include a label indicating the intended use of the contents of the kit. The term "label" as used herein includes any writing, or recorded material supplied on or with a kit, or which otherwise accompanies a kit.

2022259766 26 Oct 2022

[000252] The invention now being fully described, it will be apparent to one of ordinary skill in the art that various changes and modifications can be made without departing from the spirit or scope of the invention.

EXAMPLES

Example 1: Heterodimer formation

[000253] Heterodimer formation was analyzed by non-reducing and reducing SDS-PAGE analyses to determine whether antibodies in accordance with embodiments of the invention, comprising various mutations in their hinge and Fc regions, as well as knobs-in-holes mutations, could be successfully expressed and assembled into desired heterodimer combinations. To test this, antibody constructs were expressed in recombinant CHO cell cultures. Harvested cell culture fluid was then purified via protein A affinity chromatography to analyze the different antibody fragments produced. The Protein A elution pools were then analyzed on reducing and non-reducing gels to visualize the different species.

[000254] The results of these analyses are shown in FIG. 2, panels A and B, in FIG. 3, panels A and B, and in FIG. 24, and demonstrate that the percentage of heterodimer formation for the antibody species that include knobs-in-holes mutations is superior, even when effector function silencing mutations (F234A, L235A) and Fab arm exchange-preventing mutations (S228P) are also present in the heavy chain sequences. As provided in FIG. 25, purified CD19 constructs were evaluated to analyze the percentage of high molecular weight (HMW) and low molecular weight (LMW) species, as well as the percentage of monomers.

Example 2: Fc gamma receptor binding by Biolayer Interferometry (BLI)

[000255] Fc gamma receptor-IgG interactions were analyzed on the Octet platform using an Ni-NTA biosensor (ForteBio). Ni-NTA biosensors have QIAGEN's Tris-NTA charged with nickel (Ni^{2+}) pre-immobilized onto the tip. Ni-NTA will bind to a HIS-tag attached to recombinant proteins. In this format, the Fc gamma receptor protein is loaded onto the biosensor as the ligand, followed by association with IgG. Antibodies in accordance with embodiments of the invention were investigated to analyze the extent of interactions between their Fc regions and the Fc gamma receptor proteins immobilized on the biosensor.

[000256] Here, the Fc gamma receptor was human Fc gamma receptor I/CD64 (Acro Biosystems). Antibody concentrations tested included a 2x serial diluation from 100 nM to 1.6 nM. The results of these studies are shown in FIG. 4, panels A-D, FIG. 5, panels A-E, FIG. 6, panels A-D, FIG. 7, panels A-E, and FIG. 26, panels A-D, and demonstrate that binding of the silenced Fc receptor antibodies to human Fc gamma R1 is suppressed significantly, even when knobs-in-holes mutations and Fab arm exchange mutations are also present in the Fc region.

[000257] Specifically, FIG. 4, panel A shows the results from a bispecific CD3 x BCMA (monovalent) IgG1 antibody that does not comprise KiH mutations or silencing mutations. The data demonstrate that the antibody interacts with the Fc gamma receptor immobilized on the biosensor. FIG. 4, panel B shows the results from the same bispecific antibody used in panel A, but now including silencing mutations in the CH2 domain. These results demonstrate that interaction between the antibody and the Fc gamma receptor on the biosensor is significantly reduced due to the presence of the silencing mutations. FIG. 4, panel C shows the results from a bispecific CD3 x BCMA (monovalent) IgG1 antibody that does include KiH mutations, but does not include silencing mutations. These data demonstrate that the antibody interacts with the Fc gamma receptor immobilized on the biosensor in a manner that is very similar to what was observed with the antibody in panel A. FIG. 4, panel D shows the results from the same bispecific antibody used in panel C, but now including silencing mutations in the CH2 domain. These results demonstrate that interaction between the antibody and the Fc gamma receptor on the biosensor is significantly reduced due to the presence of the silencing mutations, even when the KiH mutations are included.

[000258] FIG. 5, panel A shows the results from a bispecific CD3 x BCMA (monovalent) IgG4 antibody that does not comprise KiH mutations or silencing mutations, but that does include an S228P mutation to prevent Fab arm exchange. The data demonstrate that the antibody interacts with the Fc gamma receptor immobilized on the biosensor. FIG. 5, panel B shows the results from the same bispecific antibody used in panel A, but now including silencing mutations in the CH2 domain (F234A, L235A). These results demonstrate that interaction between the antibody and the Fc gamma receptor on the biosensor is significantly reduced due to the presence of the silencing mutations, even when the S228P mutation is present. FIG. 5, panel C shows the results from a bispecific CD3 x BCMA (monovalent) IgG4 antibody that does include KiH mutations and the S228P mutation, but does not include silencing mutations. These data demonstrate that the antibody interacts with the Fc gamma receptor immobilized on the biosensor in a manner that is very similar to what was observed with the antibody in panel A. FIG. 5, panel D shows the results from the same bispecific antibody used in panel C, but now including silencing mutations in the CH2 domain (F234A, L235A), in addition to the S228P and KiH mutations. These results demonstrate that interaction between the antibody and the Fc gamma receptor on the biosensor is significantly reduced due to the presence of the silencing mutations, even when the S228P and KiH mutations are included. Panel E shows the results from a bispecific CD3 x BCMA (bivalent) IgG4 antibody that inludes the S228P mutation, the silencing mutations F234A and L235A, as well as the KiH mutations in the CH3 domain. These data demonstrate that interaction between this antibody and the Fc gamma receptor immobilized on the biosensor was significantly reduced, even with S228P and the KiH mutations present.

[000259] FIG. 6, panel A shows the results from a bispecific CD3 x PSMA (monovalent) IgG1 antibody that does not comprise KiH mutations or silencing mutations. The data demonstrate that the antibody interacts

with the Fc gamma receptor immobilized on the biosensor. FIG. 6, panel B shows the results from the same bispecific antibody used in panel A, but now including silencing mutations in the CH2 domain. These results demonstrate that interaction between the antibody and the Fc gamma receptor on the biosensor is significantly reduced due to the presence of the silencing mutations. FIG. 6, panel C shows the results from a bispecific CD3 x PSMA (monovalent) IgG1 antibody that does include KiH mutations, but does not include silencing mutations. These data demonstrate that the antibody interacts with the Fc gamma receptor immobilized on the biosensor in a manner that is very similar to what was observed with the antibody in panel A. FIG. 6, panel D shows the results from the same bispecific antibody used in panel C, but now including silencing mutations in the CH2 domain. These results demonstrate that interaction between the antibody and the Fc gamma receptor on the biosensor is significantly reduced due to the presence of the silencing mutations, even when the KiH mutations are included.

[000260] FIG. 7, panel A shows the results from a bispecific CD3 x PSMA (monovalent) IgG4 antibody that does not comprise KiH mutations or silencing mutations, but that does include an S228P mutation to prevent Fab arm exchange. The data demonstrate that the antibody interacts with the Fc gamma receptor immobilized on the biosensor. FIG. 7, panel B shows the results from the same bispecific antibody used in panel A, but now including silencing mutations in the CH2 domain (F234A, L235A). These results demonstrate that interaction between the antibody and the Fc gamma receptor on the biosensor is significantly reduced due to the presence of the silencing mutations, even when the S228P mutation is present. FIG. 7, panel C shows the results from a bispecific CD3 x PSMA (monovalent) IgG4 antibody that does include KiH mutations and the S228P mutation, but does not include silencing mutations. These data demonstrate that the antibody interacts with the Fc gamma receptor immobilized on the biosensor in a manner that is very similar to what was observed with the antibody in panel A. FIG. 7, panel D shows the results from the same bispecific antibody used in panel C, but now including silencing mutations in the CH2 domain (F234A, L235A), in addition to the S228P and KiH mutations. These results demonstrate that interaction between the antibody and the Fc gamma receptor on the biosensor is significantly reduced due to the presence of the silencing mutations, even when the S228P and KiH mutations are included. Panel E shows the results from a bispecific CD3 x PSMA (bivalent) IgG4 antibody that inludes the S228P mutation, the silencing mutations F234A and L235A, as well as the KiH mutations in the CH3 domain. These data demonstrate that interaction between this antibody and the Fc gamma receptor immobilized on the biosensor was significantly reduced, even with S228P and the KiH mutations present.

[000261] FIG. 26, panel A, shows the results from a bispecific CD3 x CD19 (monovalent) IgG4 antibody that does not comprise KiH mutations or silencing mutations, but that does include an S228P mutation to prevent Fab arm exchange. The data demonstrate that the antibody interacts with the Fc gamma receptor immobilized on the biosensor. FIG. 26, panel B, shows the results from the same bispecific antibody used

in panel A, but now including silencing mutations in the CH2 domain (F234A, L235A). These results demonstrate that interaction between the antibody and the Fc gamma receptor on the biosensor is significantly reduced due to the presence of the silencing mutations, even when the S228P mutation is present. FIG. 26, panel C, shows the results from a bispecific CD3 x CD19 (monovalent) IgG4 antibody that does include KiH mutations and the S228P mutation, but does not include silencing mutations. These data demonstrate that the antibody interacts with the Fc gamma receptor immobilized on the biosensor in a manner that is very similar to what was observed with the antibody in panel A. FIG. 26, panel D, shows the results from the same bispecific antibody used in panel C, but now including silencing mutations in the CH2 domain (F234A, L235A), in addition to the S228P and KiH mutations. These results demonstrate that interaction between the antibody and the Fc gamma receptor on the biosensor is significantly reduced due to the presence of the silencing mutations, even when the S228P and KiH mutations are included.

[000262] Together, the data provided in FIGS. 4, 5, 6, 7, and 26 demonstrate that the VH region sequence of a bispecific antibody has no impact on the functional properties of the IgG4 Fc mutations described herein. As such, the IgG4 Fc modifications described herein (S228P; F234A, L235A; T366W, T366S, L368A, and Y407V) can be implemented in antibodies having different VH sequences (i.e., different binding targets) to achieve reduced Fab arm exchange (S228P), reduced effector function activity (F234A, L235A), and proper heterodimerization (T366W; T366S, L368A, and Y407V).

Example 3: Flow cytometry analysis of binding to PSMA positive and negative cells by anti-PSMA UniAbs™

[000263] Binding to PSMA-positive cells was assessed by flow cytometry (Guava easyCyte 8HT, EMD Millipore) using the LNCaP cell line (ATCC: CRL-1740), 22Rv1 cell line (ATCC CRL-2505), a PC3 cell line (ATCC CRL-1435) stably transfected to express human PSMA, or the DU-145 cell line (ATCC HTB-81). Briefly, 50,000 target cells were stained with a dilution series of purified UniAbs™ for 30 minutes at 4°C. Following incubation, the cells were washed twice with flow cytometry buffer (1X PBS, 1% BSA, 0.1% NaN_3) and stained with goat $F(ab')_2$ anti-human IgG conjugated to R-phycoerythrin (PE) (Southern Biotech, cat. #2042-09) to detect cell-bound antibodies. After a 20-minute incubation at 4°C, the cells were washed twice with flow cytometry buffer and the mean fluorescence intensity (MFI) was measured by flow cytometry. The MFI of cells stained with secondary antibody alone were used for determination of background signal and binding of each antibody was converted to fold over background. Binding to cynomolgus PSMA positive cells was determined using the same protocol with the following modifications: the target cells were from Freestyle 293-F cells (ThermoFisher R79007) transiently transfected to express the extracellular domain of cynomolgus PSMA. In some experiments EC50 values were calculated using GraphPad Prism 7.

2022259766 26 Oct 2022

[000264] Table 8 summarizes target binding activity of the anti-PSMA heavy-chain antibodies (HCAb) described herein. Column 1 indicates the clone ID of the HCAb. Column 2 indicates binding to LNCaP cells measured as fold over the background MFI signal.

Table 8: Binding to PSMA-expressing cell line

Column 1: CLONE_ID	Column 2: LNCaP
325920	282
346181	264
346165	243
346172	216
326109	25
325867	210
325742	200
325748	193
325940	169
325836	163
326027	138
326087	129
326084	125
326028	117
345497	112
326029	109
345461	102
345493	101
345436	87
345443	84
345490	80
345482	80
345485	71
345463	68
325932	64
345505	59
345508	55
345480	47
326116	38
345509	37
345444	23
345421	22
345447	14
345510	13
345438	13

2022259766 26 Oct 2022

[000265] The differences in binding to cynomolgus PSMA, as shown in FIG. 8, panels A and B, supports the difference in human PSMA epitope recognized by HCAbs 346181 and 345497.

Example 4: Composition of biparatopic and bivalent anti-PSMA antibodies

[000266] As shown in Table 9, anti-PSMA clone ID 350123 is composed of clone ID 346181 sequence linked to clone ID 345497 sequence with the bridging sequence GGGGSGGGGS (SEQ ID NO: 71). Clone ID 350122 is composed of two repeats of clone ID 346181 joined by the same linker sequence. Clone ID 350123 is biparatopic as it is composed of two anti-PSMA domains recognizing different epitopes on PSMA. Clone ID 350122 is bivalent but not biparatopic, as it is composed of the same anti-PSMA domain in tandem. Schematic illustrations of various three-chain antibody-like molecules (TCAs) are depicted in FIG. 1, panels A-C.

Table 9: Description of amino acid sequence of biparatopic and bivalent anti-PSMA antibodies

Clone ID	Sequence 1	Linker sequence	Sequence 2
350123	346181	GGGGSGGGGS (SEQ ID NO: 71)	345497
350122	346181	GGGGSGGGGS (SEQ ID NO: 71)	346181

Example 5: Multi-specific antibody mediated killing of PSMA positive prostate tumor cells through T-cell redirection

Assays using resting T-cells

[000267] Target cells were seeded at 15,000 cells per well in a 96-well plate and grown overnight at 37°C. Following incubation, increasing amounts of multi-specific antibody were added together with resting human T-cells at a 10:1 effector to target cell ratio and incubated for an additional 48 or 72 hours at 37°C (48 hours for assays with LNCaP, MDA-PCa-2b and PC3-PSMA cells and 72 hours for assays with 22Rv1 cells). Cell death was measured using either the cell proliferation reagent WST-1 (Sigma Cat No.: 11644807001) or flow cytometry. In some experiments, a small sample of each supernatant was collected after incubation but prior to analysis of target cell viability and saved for analysis of cytokine production. When cell viability was analyzed with WST-1 reagent, the reagent stock was added to each well at a 1:10 dilution and incubated for 90 minutes at 37°C. The absorbance was then measured at 450 nm (reference 690 nm), and the percent specific lysis was calculated.

2022259766 26 Oct 2022

[000268] If target cell viability was analyzed by flow cytometry, then the target cells were labeled before initiating the assay with the membrane dye DiR (ThermoFisher D12731). After incubation with T-cells and antibody, the supernatants were either saved for cytokine analysis or disposed of. Wells were then washed once to collect dead tumor cells and T-cells, which were transferred to a flow cytometry plate. The remaining attached tumor cells were trypsinized and then added to the corresponding wells in the flow cytometry plate. Annexin-V reagent was used to stain dead cells and flow cytometry was conducted (BD FACSCelesta) to quantitate the percent of dead tumor cells in each sample, gated by DiR staining. Wells containing untreated target cells were used to normalize for spontaneous cell death. In some experiments, a negative control antibody was used, consisting of the same CD3-targeting arm as in the PSMAxCD3 multi-specific molecules, but replacing the tumor-targeting arm with a VH specific to the HIV protein gp120.

[000269] FIG. 9 shows T-cell mediated lysis of PSMA positive cells using unstimulated T-cells. Unstimulated human T-cells were incubated with PSMA-expressing cells (LNCaP) and different concentrations of multi-specific antibodies. The biparatopic anti-PSMAxCD3 antibody (350123xCD3) outperformed the monoparatopic PSMAxCD3 antibody (346181xCD3).

Assays using pre-activated T-cells

[000270] Human pan T-cells were pre-activated with plate-bound OKT3 and IL-2 for three days, followed by an additional day of incubation in fresh IL-2. Target cells were trypsinized, loaded with Calcein-AM (ThermoFisher C3100MP), mixed with activated T-cells to an E:T ratio of 20:1, and added to the wells of a 96-well plate. Dilution series of different multi-specific antibodies were added, followed by incubation for 4 hours at 37°C. Supernatants were then transferred to black 96-well plates and absorbance was measured at 480 nm/520 nm ex/em to quantify release of calcein. Target cells incubated without T-cells were used to normalize for spontaneous calcein release of intact tumor cells. Addition of 2% Triton-X to control wells containing target cells allowed for calculation of the calcein signal corresponding to maximum cell lysis. Using this value, each experimental well was reported as percent of maximum cell lysis. Data analysis was conducted using GraphPad prism 7.

[000271] FIG. 10 shows T-cell mediated lysis of PSMA positive cells using pre-activated T-cells. Pre-activated human T-cells were incubated with human PSMA-expressing cells (LNCaP) and different concentrations of multi-specific antibodies. Tumor cell death was measured by calcein release and normalized to spontaneous release of tumor cells in the absence of T-cells. The biparatopic anti-PSMAxCD3 antibody (350123xCD3) outperformed both monoparatopic PSMAxCD3 antibodies.

2022259766 26 Oct 2022

[000272] FIG. 11 shows that multi-specific antibodies do not lyse PSMA-negative cells. Pre-activated human T-cells were incubated with PSMA-negative prostate cancer cells (DU145) and different concentrations of multi-specific antibodies. No lysis of these cells occurred by any of the antibodies tested.

[000273] FIG. 12 shows binding of PSMAxCD3 multi-specific antibodies to PSMA positive and negative cells. Multi-specific anti-PSMA x anti-CD3 antibodies show binding to PSMA positive prostate tumor cells (22Rv1), but no binding to PSMA negative prostate tumor cells (DU145). The biparatopic molecule (350123) showed the strongest on-target cell binding.

[000274] FIG. 13 depicts T-cell mediated lysis of PSMA positive cells. The data in FIG. 13 demonstrates that binding to PSMA via two different epitopes results in increased cell killing as compared to a bivalent but monospecific version of the antibody.

Example 6: A monoparatopic PSMAxCD3 bispecific antibody induces less cytokine production than a biparatopic PSMAxCD3 multi-specific antibody

[000275] Cytokine production was analyzed in tumor cytotoxicity assays with resting T-cells. The design of these assays is detailed elsewhere. Supernatants were collected upon completion of the assays (after 72 hours of incubation for assays using 22Rv1 cells, 48 hours for all other cell lines). ELISA kits were used for detection of IL-2 (Biolegend 431804) and IFNγ (Biolegend 430104) according to the manufacturer's protocol. Experimental supernatants were diluted before analysis in the ELISAs such that the levels of cytokines would fall within the linear portion of the standard curve supplied with each kit. In some cases, no cytokines could be detected in the experiment wells, and values were reported as less than or equal to the lower limit of quantification for the assay.

[000276] FIG. 14 (Panels A, B, and C) shows T-cell mediated lysis of PSMA positive cells and comparison with cytokine production. Multi-ispecific PSMAxCD3 antibodies induce T-cell mediated lysis of the PSMA positive prostate cancer cell line LNCaP. The biparatopic molecule (350123) stimulated more potent tumor cell killing as compared to the monoparatopic molecule (346181), but also caused production of higher levels of the cytokines interferon gamma (IFNγ) and interleukin 2 (IL-2), as exemplified by FIG. 14, panels B and C.

[000277] Table 10 shows T-cell mediated lysis and cytokine production against four PSMA positive prostate tumor cell lines. The PSMAxCD3 multi-specific antibodies were tested in *in vitro* tumor cell cytotoxicity assays using unstimulated T-cells and a dose series of antibody against a panel of four PSMA positive tumor cell lines. After 72 hours (22Rv1) or 48 hours (MDA-PCa-2b, LNCAP, PC3-PSMA) the percent of tumor cell death was calculated and reported by EC50 as well as the highest percent killing achieved. Supernatants from these experiment wells were collected and analyzed by ELISA for the cytokines interferon-gamma (IFNγ) or interleukin-2 (IL-2). The monoparatopic molecule (3461881) induced

2022259766 26 Oct 2022

approximately equivalent levels of tumor cytotoxicity against all four cell lines tested as compared to the biparatopic molecule, but had higher EC50s for cytokine production and in most cases stimulated lower levels of maximum cytokine production.

Table 10: T-cell mediated lysis and cytokine production against four PSMA positive prostate tumor cell lines.

Cell line	Antibody	Cell binding EC50 (nM)	Max Cytoxicity (% lysis)	Kill EC50 (nM)	Max IFNγ (pg/mL)	IFNγ EC50 (nM)	Max IL-2 (pg/ml)	IL-2 EC50 (nM)
22Rv1	346181xCD3	58	45	52.8	21,150	173.8	≤LLOQ	NA
	350123xCD3	3	53	0.42	73,031	380.2	≤LLOQ	NA
MDA-PCa-2b	346181xCD3	28	26	23.6	14,309	116.5	524	38.5
	350123xCD3	2	29	0.41	12,026	0.90	1111	1.11
LNCAP	346181xCD3	17	79	14.6	32,237	63.0	183	575
	350123xCD3	2	75	0.84	60,397	3.29	1057	3.73
PC3-PSMA	346181xCD3	30	42	3.7	7,340	10.1	1569	4.1
	350123xCD3	6	51	0.40	10,136	1.01	3480	1.1

Example 7: PSMAxCD3 multi-specific antibodies induce T-cell proliferation

[000278] PSMA positive tumor cells were seeded at 25,000 cells per well in a 96-well plate and grown overnight at 37°C. Human pan T-cells isolated from resting PBMCs (Miltenyi 130-096-535) were labeled with the lineage tracing dye CFSE according to manufacturer's instructions (ThermoFisher C34554). 100,000 labeled pan T-cells were then added to the wells containing the tumor cells, followed by a dilution series of antibodies, and incubated at 37°C, 8% CO_2. After 5 days of incubation, the cells were mixed gently and transferred to a flow cytometry plate. The cells were pelleted, and the supernatant removed, followed by staining with anti-CD8 conjugated to APC (Biolegend 301049) and anti-CD4 conjugated to PE (Biolegend 317410) for 20 minutes on ice. The cells were then washed and resuspending in flow cytometry buffer for analysis (BD FACSCelesta). Cells were gated on forward and side scatter, and CD4 or CD8 expression. The percent of T-cells that had proliferated, as indicated by CD4 or CD8 positive staining and low or negative CFSE signal, was calculated for the entire T-cell population, as well as the CD4 and CD8 subsets. Flow cytometry data was analyzed using FlowJo and plotted in GraphPad Prism 7.

[000279] FIG. 15 (Panels A, B, C, and D) shows that PSMAxCD3 multi-specific antibodies stimulated T-cell proliferation in the presence of PSMA positive tumor cells, and that monoparatopic PSMA bispecfic antibodies preferentially activate CD3 T-cells. Multi-specific antibodies were incubated together with PSMA expressing tumor cells and T-cells labeled with the lineage tracing dye CFSE. After 5 days of incubation, T-cell proliferation and the composition of proliferated T-cells (CD8+ versus CD4+) were analyzed by flow cytometry. Panels A and B show total T-cell proliferation, while panels C and D indicate

2022259766 26 Oct 2022

the ratio of CD8+ to CD4+ T-cells in the proliferated wells. A dashed horizontal line indicates that CD8:CD4 ratio of the unstimulated T-cells and is approximately 1:2 (actual value = 0.64). The monoparatopic PSMAxCD3 bispecific antibody (346181) preferentially activates CD8 T-cells (CD8:CD4 ratio after expansion of approximately 2:1) whereas the biparatopic PSMAxCD3 multi-specific antibody (350123) less preferentially activates CD8+ T-cells (CD8:CD4 ratio of about 1:1).

Example 8: A multi-specific antibody causes suppression of prostate tumor growth in a xenograft model

[000280] 5-6 week old male immune-deficient CIEA-NOG mice (Taconic) were implanted with 10 million 22Rv1 cells subcutaneously into their lower right flanks, followed by addition of 10 million human PBMCs via tail vein injection one day following tumor implantation. The animals received treatment with 100 μg of multi-specific antibody or vehicle by tail vein injection starting one day after tumor implantation on days 1, 5, 9 and 13. Tumor volume was quantified using calipers and was recorded for 25 days.

[000281] FIG. 16 shows the results of the 22Rv1 tumor xenograft model. The biparatopic PSMAxCD3 molecule (350123) showed inhibition of 22Rv1 tumor growth in a tumor xenograft model. Three mice were tested for each treatment group, and the change in tumor volume for each animal was plotted in millimeters cubed. Animals received PBMCs on day 1 post tumor implantation and were treated with antibody on days 1, 5, 9, and 13. Two out of the three animals treated with multispecific antibody showed delay in tumor progression.

Example 9: Analysis of T-cell Activation

[000282] CD69 is a cell surface marker on T-cells that is upregulated upon stimulation, thereby serving as an indicator of T-cell activation. In this experiment, CD69 activation was evaluated under 3 different conditions: 1) total peripheral blood mononuclear cells (PBMCs) without BCMA coating; 2) Pan T-cells with BCMA coating; and 3) Pan T-cells without BCMA coating. PBMCs were isolated from buffy coats using Ficoll (1.077 g/ml density) and cryopreserved PBMCs were thawed and rested for 24 hours at $2x10^6$ cells/mL in RPMI1640 supplemented with 10% FBS at 37°C. On day 2, pan T cells were isolated from the rested PBMCs using a Miltenyi negative selection kit, and the isolated cells were used in the 2nd and 3rd assay conditions. For the first assay condition, PBMCs were counted and plated in the assay plates.

[000283] For cells that were evaluated under antigen coating conditions, 96-well plates were coated with recombinant BCMA protein at a concentration of 1 μg/mL (Human BCMA Protein, Fc Tag, Acro Biosystems, Catalog No – BC7-H5254), recombinant PSMA protein at a concentration of 1 μg/mL (Recombinant Human PSMA/FOLH1 Protein, from RND systems, Catalog No – 4234-ZN-0101)), or recombinant CD19 protein at a concentration of 10 μg/mL (Human CD19 Protein, His Tag, Acro

2022259766 26 Oct 2022

Biosystems, Catalog No – CD9-H52H2).Bispecific antibodies were analyzed using a 12-point dose curve with 3-fold dilutions, the highest dose being 300 nM. Bispecific antibodies and T-cells were resuspended in RPMI1640 supplemented with 10% FBS and incubated for 18 hours. Pan T-cells were the effector cells and were plated at 100K cells/well.

[000284] For cells that were evaluated without antigen coating conditions, bispecific antibodies were incubated with the cells using a 12-point dose curve with 3-fold dilutions. 300 nM of bispecific antibody was the highest concentration tested in this assay. Samples were incubated for 18 hours in RPMI1640 supplemented with 10% FBS at 37 °C. Pan T-cells isolated from PBMCs were the effector cells that were plated at 100K cells/well.

[000285] For all experimental conditions, cells were washed and labeled with cell surface T-cell antibodies. The following antibodies were used to label (1) CD4 positive T-cells (FITC anti-human CD4 antibody), (2) CD8 positive T-cells (PE anti-human CD8a antibody), (3) CD69 activation (Alexa Fluor 647 anti-human CD69 antibody) (Biolegend). Cells were then analyzed on a BD Celesta using the appropriate templates to measure CD69 activation.

[000286] Results of T-cell activation studies are shown in the following figures: FIGS. 17-18, FIG. 27, panels A-B (without BCMA antigen coating, using PBMCs); FIG. 30, panels A-B (without PSMA coating); and FIG. 33, panels A-B (without CD19 coating).

[000287] FIG. 17 is a graph showing %CD4+CD69+ T-cells as a function of bispecific antibody concentration for the bispecific antibody constructs shown in the legend. In general, the bispecific antibodies containing IgG1 Fc sequences exhibited CD4+ T-cell activation at lower concentrations of bispecific antibody. The bispecific antibodies containing IgG4 Fc sequences exhibited CD4+ T-cell activation at higher concentrations of bispecific antibody. Notably, CD4+ T-cell activation achieved by the IgG4 Fc bispecific antibodies that contained the PAA and KiH mutations was low, demonstrating that the introduction of the PAA and KiH mutations reduces the BCMA independent activation of the T-cells by these bispecific antibodies.

[000288] FIG. 18 is a graph showing %CD8+CD69+ T-cells as a function of bispecific antibody concentration for the bispecific antibody constructs shown in the legend. As was the case for CD4+ T-cells, the bispecific antibodies containing IgG1 Fc sequences exhibited CD8+ T-cell activation at lower concentrations of bispecific antibody. The bispecific antibodies containing IgG4 Fc sequences exhibited CD8+ T-cell activation at higher concentrations of bispecific antibody. Notably, CD8+ T-cell activation achieved by the IgG4 Fc bispecific antibodies that contained the PAA and KiH mutations was low, demonstrating that the introduction of the PAA and KiH mutations reduces the BCMA independent activation of the T-cells by these bispecific antibodies.

[000289] FIG. 27, panel A, is a graph showing %CD4+CD69+ T-cells as a function of bispecific antibody concentration for the bispecific antibody constructs shown in the legend. CD4+ T-cell activation achieved by the IgG4 Fc bispecific antibodies that contained the PAA and KiH mutations was similar to the negative control (gp120, CD3 (F2B)), demonstrating that the introduction of the PAA and KiH mutations reduces the BCMA-independent activation of the T-cells by these bispecific antibodies. FIG. 27, panel B, is a graph showing %CD8+CD69+ T-cells as a function of bispecific antibody concentration for the bispecific antibody constructs shown in the legend. As was the case for CD4+ T-cells, CD8+ T-cell activation achieved by the IgG4 Fc bispecific antibodies that contained the PAA and KiH mutations was similar to the negative control, demonstrating that the introduction of the PAA and KiH mutations reduces the BCMA-independent activation of the T-cells by these bispecific antibodies.

[000290] FIG. 30, panel A, is a graph showing %CD4+CD69+ T-cells as a function of bispecific antibody concentration for the bispecific antibody constructs shown in the legend. CD4+ T-cell activation achieved by the IgG4 Fc bispecific antibodies that contained the PAA and KiH mutations was similar to the negative control (gp120, CD3 (F2B)), demonstrating that the introduction of the PAA and KiH mutations reduces the PSMA-independent activation of the T-cells by these bispecific antibodies. FIG. 30, panel B, is a graph showing %CD8+CD69+ T-cells as a function of bispecific antibody concentration for the bispecific antibody constructs shown in the legend. As was the case for CD4+ T-cells, CD8+ T-cell activation achieved by the IgG4 Fc bispecific antibodies that contained the PAA and KiH mutations was similar to the negative control, demonstrating that the introduction of the PAA and KiH mutations reduces the PSMA-independent activation of the T-cells by these bispecific antibodies.

[000291] FIG. 33, panel A, is a graph showing %CD4+CD69+ T-cells as a function of bispecific antibody concentration for the bispecific antibody constructs shown in the legend. CD4+ T-cell activation achieved by the IgG4 Fc bispecific antibodies that contained the PAA and KiH mutations was much lower than what was observed from other antibody constructs that did not contain the PAA and KiH mutations, demonstrating that the introduction of the PAA and KiH mutations reduces the CD19-independent activation of the T-cells by these bispecific antibodies. FIG. 33, panel B, is a graph showing %CD8+CD69+ T-cells as a function of bispecific antibody concentration for the bispecific antibody constructs shown in the legend. As was the case for CD4+ T-cells, CD8+ T-cell activation achieved by the IgG4 Fc bispecific antibodies that contained the PAA and KiH mutations was much lower than what was observed from other antibody constructs that did not contain the PAA and KiH mutations, demonstrating that the introduction of the PAA and KiH mutations reduces the CD19-independent activation of the T-cells by these bispecific antibodies.

[000292] Results of CD8+ T-cell activation with antigen coating using pan T-cells isolated from resting PBMCs are provided in FIG. 19, FIG. 28, panel B, FIG. 31, panel B, and FIG. 34, panel B. Results of CD4+

2022259766 26 Oct 2022

T-cell activation with antigen coating using pan T-cells isolated from resting PBMCs are provided in FIG. 28, panel A, FIG. 31, panel A, and FIG. 34, panel A. The antigen coating concentration for BCMA and PSMA was 1 μg/mL, whereas the antigen coating concentration for CD19 was 10 μg/mL.

[000293] FIG. 19 is a graph showing %CD8+CD69+ T-cells as a function of bispecific antibody concentration for the bispecific antibody constructs shown in the legend. Unlike the case for the experiments without BCMA coating, all the bispecific antibodies exhibited CD8+ T-cell activation at similar concentrations of bispecific antibody for the antigen coated cells. Notably, CD8+ T-cell activation was achieved by the IgG4 Fc bispecific antibodies that contained the PAA and KiH mutations, demonstrating that the introduction of the PAA and KiH mutations did not eliminate the CD8+ T-cell activation activity of these molecules.

[000294] FIG. 28, panel B, is a graph showing %CD8+CD69+ T-cells as a function of bispecific antibody concentration for the bispecific antibody constructs shown in the legend. Unlike the case for the experiments without BCMA coating, all the bispecific antibodies exhibited CD8+ T-cell activation at similar concentrations of bispecific antibody for the antigen coated cells. Notably, CD8+ T-cell activation was achieved by the IgG4 Fc bispecific antibodies that contained the PAA and KiH mutations, demonstrating that the introduction of the PAA and KiH mutations did not eliminate the CD8+ T-cell activation activity of these molecules.

[000295] FIG. 31, panel B, is a graph showing %CD8+CD69+ T-cells as a function of bispecific antibody concentration for the bispecific antibody constructs shown in the legend. Unlike the case for the experiments without PSMA coating, all the bispecific antibodies exhibited CD8+ T-cell activation at similar concentrations of bispecific antibody for the antigen coated cells. Notably, CD8+ T-cell activation was achieved by the IgG4 Fc bispecific antibodies that contained the PAA and KiH mutations, demonstrating that the introduction of the PAA and KiH mutations did not eliminate the CD8+ T-cell activation activity of these molecules.

[000296] FIG. 34, panel B, is a graph showing %CD8+CD69+ T-cells as a function of bispecific antibody concentration for the bispecific antibody constructs shown in the legend. Unlike the case for the experiments without CD19 coating, all the bispecific antibodies exhibited CD8+ T-cell activation at similar concentrations of bispecific antibody for the antigen coated cells. Notably, CD8+ T-cell activation was achieved by the IgG4 Fc bispecific antibodies that contained the PAA and KiH mutations, demonstrating that the introduction of the PAA and KiH mutations did not eliminate the CD8+ T-cell activation activity of these molecules.

[000297] FIG. 28, panel A, is a graph showing %CD4+CD69+ T-cells as a function of bispecific antibody concentration for the bispecific antibody constructs shown in the legend. Unlike the case for the experiments without BCMA coating, all the bispecific antibodies exhibited CD4+ T-cell activation at

2022259766 26 Oct 2022

similar concentrations of bispecific antibody for the antigen coated cells. Notably, CD4+ T-cell activation was achieved by the IgG4 Fc bispecific antibodies that contained the PAA and KiH mutations, demonstrating that the introduction of the PAA and KiH mutations did not eliminate the CD4+ T-cell activation activity of these molecules.

[000298] FIG. 31, panel A, is a graph showing %CD4+CD69+ T-cells as a function of bispecific antibody concentration for the bispecific antibody constructs shown in the legend. Unlike the case for the experiments without PSMA coating, all the bispecific antibodies exhibited CD4+ T-cell activation at similar concentrations of bispecific antibody for the antigen coated cells. Notably, CD4+ T-cell activation was achieved by the IgG4 Fc bispecific antibodies that contained the PAA and KiH mutations, demonstrating that the introduction of the PAA and KiH mutations did not eliminate the CD4+ T-cell activation activity of these molecules.

[000299] FIG. 34, panel A, is a graph showing %CD4+CD69+ T-cells as a function of bispecific antibody concentration for the bispecific antibody constructs shown in the legend. Unlike the case for the experiments without CD19 coating, all the bispecific antibodies exhibited CD4+ T-cell activation at similar concentrations of bispecific antibody for the antigen coated cells. Notably, CD4+ T-cell activation was achieved by the IgG4 Fc bispecific antibodies that contained the PAA and KiH mutations, demonstrating that the introduction of the PAA and KiH mutations did not eliminate the CD4+ T-cell activation activity of these molecules.

[000300] Results of CD8+ T-cell activation without antigen coating using pan T-cells isolated from resting PBMCs are provided in FIG. 20, FIG. 29, panel B, FIG. 32, panel B, and FIG. 35, panel B. Results of CD4+ T-cell activation without antigen coating using pan T-cells isolated from resting PBMCs are provided in FIG. 29, panel A, FIG. 32, panel A, and FIG. 35, panel A.

[000301] FIG. 20 is a graph showing %CD8+CD69+ T-cells as a function of bispecific antibody concentration for the bispecific antibody constructs shown in the legend. These results demonstrate that CD69 activation in CD8+ T-cells is BCMA dependent for all the bispecific antibody molecules tested.

[000302] FIG. 29, panels A and B, are graphs showing %CD4+CD69+ and %CD8+CD69+ T-cells, respectively, as a function of bispecific antibody concentration for the bispecific antibody constructs shown in the legend. These results demonstrate that CD69 activation in CD4+ and CD8+ T-cells is BCMA dependent for all the bispecific antibody molecules tested. CD69 activation was slightly increased in both CD4+ and CD8+ T-cells at higher concentrations of the bispecific antibody constructs that did not include silencing mutations.

[000303] FIG. 32, panels A and B, are graphs showing %CD4+CD69+ and %CD8+CD69+ T-cells, respectively, as a function of bispecific antibody concentration for the bispecific antibody constructs shown

2022259766 26 Oct 2022

in the legend. These results demonstrate that CD69 activation in CD4+ and CD8+ T-cells is PSMA dependent for all the bispecific antibody molecules tested.

[000304] FIG. 35, panels A and B, are graphs showing %CD4+CD69+ and %CD8+CD69+ T-cells, respectively, as a function of bispecific antibody concentration for the bispecific antibody constructs shown in the legend. These results demonstrate that CD69 activation in CD4+ and CD8+ T-cells is CD19 dependent for all the bispecific antibody molecules tested. CD69 activation was slightly increased in both CD4+ and CD8+ T-cells at higher concentrations of the bispecific antibody constructs that did not include silencing mutations.

Example 10: Lysis of Tumor Cells

[000305] Anti-CD3 x anti-BCMA bispecific antibodies were assayed for the ability to kill three different BCMA+ tumor cells and one BCMA-negative cell line through redirection of activated primary T-cells. In this experiment, tumor cells were mixed with activated pan T-cells in a 10:1 E:T ratio along with the addition of bispecific antibody. The results are shown in FIG. 21, Panels A-D. Panel A shows killing of RPMI-8226 cells, panel B shows killing of NCI-H929 cells, panel C shows killing of U-266 cells, and panel D shows killing of K562 cells, a negative control. The x-axis shows the concentration of antibody used and the y-axis shows the % lysis of tumor cells 6 hours after addition of antibody.

[000306] The level of IL-2 cytokine release was measured after resting human T-cells were cultured with various tumor cell lines and increasing doses of anti-CD3 x anti-BCMA bispecific antibody. FIG. 22, panel A shows IL-2 release stimulated by RPMI-8226 cells, FIG. 22, panel B shows IL-2 release stimulated by NCI-H929 cells. FIG. 22, panel C shows IL-2 release stimulated by U-266 cells, and FIG. 22, panel D shows IL-2 release stimulated by K562 cells, a negative control.

[000307] The level of IFN-γ cytokine release was measured after resting human T-cells were cultured with various tumor cell lines and increasing doses of anti-CD3 x anti-BCMA bispecific antibody. FIG. 23, panel A shows IFN-γ release stimulated by RPMI-8226 cells, FIG. 23, panel B shows IFN-γ release stimulated by NCI-H929 cells, FIG. 23, panel C shows IFN-γ release stimulated by U-266 cells, and FIG. 23, panel D shows IFN-γ release stimulated by K562 cells, a negative control.

[000308] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

2022259766 26 Oct 2022

EMBODIMENTS

1. An isolated multispecific antibody comprising:

a first heavy chain polypeptide subunit comprising a mutated human IgG4 constant region comprising mutations S228P, F234A, L235A, and T366W; and

a second heavy chain polypeptide subunit comprising a mutated human IgG4 constant region comprising mutations S228P, F234A, L235A, T366S, L368A, and Y407V.

2. The isolated multispecific antibody of embodiment 1, wherein the mutated human IgG4 constant region of the first heavy chain polypeptide subunit or the mutated human IgG4 constant region of second heavy chain polypeptide subunit lacks a CH1 domain.

3. The isolated multispecific antibody of embodiment 1 or 2, wherein the mutated human IgG4 constant region of the first heavy chain polypeptide subunit comprises a sequence of SEQ ID NO: 73 or 55, and the mutated human IgG4 constant region of the second heavy chain polypeptide subunit comprises a sequence of SEQ ID NO: 72 or 54.

4. The isolated multispecific antibody of any one of embodiments 1-3, further comprising a first binding moiety that has binding specificity for CD3, comprising:

a heavy chain variable domain comprising a CDR1 sequence comprising a sequence of SEQ ID NO: 36, a CDR2 sequence comprising a sequence of SEQ ID NO: 37, and a CDR3 sequence comprising a sequence of SEQ ID NO: 38; and

a light chain variable domain comprising a CDR1 sequence comprising a sequence of SEQ ID NO: 39, a CDR2 sequence comprising a sequence of SEQ ID NO: 40, and a CDR3 sequence comprising a sequence of SEQ ID NO: 41.

5. The isolated multispecific antibody of embodiment 4, wherein:

the CDR1, CDR2 and CDR3 sequences in the heavy chain variable domain of the first binding moiety are present in a human VH framework; and

the CDR1, CDR2 and CDR3 sequences in the light chain variable domain of the first binding moiety are present in a human Vkappa framework.

6. The isolated multispecific antibody of embodiment 5, wherein:

2022259766 26 Oct 2022

the heavy chain variable domain of the first binding moiety comprises a sequence having at least 95% identity to SEQ ID NO: 42; and

the light chain variable domain of the first binding moiety comprises a sequence having at least 95% identity to SEQ ID NO: 43.

7. The isolated multispecific antibody of embodiment 6, wherein:

the heavy chain variable domain of the first binding moiety comprises the sequence of SEQ ID NO: 42; and

the light chain variable domain of the first binding moiety comprises the sequence of SEQ ID NO: 43.

8. The isolated multispecific antibody of any one of embodiments 1-7, further comprising a second binding moiety having binding specificity to a protein other than CD3.

9. The isolated multispecific antibody of embodiment 8, wherein the second binding moiety comprises a single heavy chain variable region, in a monovalent or bivalent configuration.

10. The isolated multispecific antibody of embodiment 9, wherein the first binding moiety comprises a light chain polypeptide subunit and a heavy chain polypeptide subunit, and wherein the second binding moiety comprises a heavy chain polypeptide subunit.

11. The isolated multispecific antibody of embodiment 10, wherein the light chain polypeptide subunit of the first binding moiety comprises a light chain constant domain.

12. The isolated multispecific antibody of any one of embodiments 8-11, wherein the protein other than CD3 is a tumor-associated antigen (TAA) or a tumor-specific antigen (TSA).

13. The isolated multispecific antibody of embodiment 12, wherein the TAA is B-cell maturation antigen (BCMA).

14. The isolated multispecific antibody of embodiment 12, wherein the TAA is CD19.

15. The isolated multispecific antibody of embodiment 12, wherein the TAA is prostate specific membrane antigen (PSMA).

2022259766 26 Oct 2022

16. A pharmaceutical composition comprising a multispecific antibody according to any one of embodiments 1-15.

17. A polynucleotide encoding a multispecific antibody according to any one of embodiments 1-15.

18. A vector comprising a polynucleotide according to embodiment 17.

19. A cell comprising a vector according to embodiment 18.

20. A method of producing a multispecific antibody according to any one of embodiments 1-15, comprising growing a cell according to embodiment 19 under conditions permissive for expression of the multispecific antibody, and isolating the multispecific antibody from the cell.

21. A method of treatment, comprising administering to an individual in need an effective dose of the multispecific antibody of any one of embodiments 1-15, or the pharmaceutical composition of embodiment 16.

22. Use of a multispecific antibody of any one of embodiments 1-15 in the preparation of a medicament for the treatment of a disease or disorder in an individual in need.

23. The multispecific antibody of any one of embodiments 1-15, or the pharmaceutical composition of embodiment 16, for use in therapy in an individual in need.

24. A method for treating a disease or condition characterized by expression of BCMA, comprising administering to an individual in need an effective dose of the multispecific antibody according to embodiment 13, or a pharmaceutical composition comprising the multispecific antibody of embodiment 13.

25. The method of embodiment 24, wherein the disease is an autoimmune disease.

26. The method of embodiment 24, wherein the disease is a cancer.

27. The method of embodiment 26, wherein the cancer is a myeloma.

2022259766 26 Oct 2022

28. The method of embodiment 27, wherein the myeloma is multiple myeloma.

29. A method for treating a disease or condition characterized by expression of PSMA, comprising administering to an individual in need an effective dose of the multispecific antibody according to embodiment 15, or a pharmaceutical composition comprising the multispecific antibody of embodiment 15.

30. The method of embodiment 29, wherein the disease is a cancer.

31. The method of embodiment 29, wherein the cancer is prostate cancer.

32. A method for treating a disease or condition characterized by expression of CD19, comprising administering to an individual in need an effective dose of the multispecific antibody according to embodiment 14, or a pharmaceutical composition comprising the multispecific antibody of embodiment 14.

33. The method of embodiment 32, wherein the disorder is diffuse large B-cell lymphoma (DLBCL).

34. The method of embodiment 32, wherein the disorder is acute lymphoblastic leukemia (ALL).

35. The method of embodiment 32, wherein the disorder is non-Hodgkin's lymphoma (NHL).

36. The method of embodiment 32, wherein the disorder is systemic lupus erythematosus (SLE).

37. The method of embodiment 32, wherein the disorder is rheumatoid arthritis (RA).

38. The method of embodiment 32, wherein the disorder is multiple sclerosis (MS).

39. A kit for treating a disease or disorder in an individual in need, comprising a multispecific antibody of any one of embodiments 1-15, or the pharmaceutical composition of embodiment 16, and instructions for use.

40. The kit of embodiment 39, further comprising at least one additional reagent.

2022259766 26 Oct 2022

41. The kit of embodiment 40, wherein the at least one additional reagent comprises a chemotherapeutic drug.

42. A bispecific three-chain antibody like molecule comprising:

a first polypeptide subunit comprising:

a light chain variable domain (VL) comprising a sequence of SEQ ID NO: 43; and

a light chain constant domain (CL);

a second polypeptide subunit comprising:

a heavy chain variable domain (VH) comprising a sequence of SEQ ID NO: 42; and

a heavy chain constant domain (CH) comprising a sequence of SEQ ID NO: 72 or 73;

wherein the light chain variable domain and the heavy chain variable domain together form a first binding moiety that binds to CD3; and

a third polypeptide subunit comprising:

a heavy chain-only variable region, in a monovalent or bivalent configuration, that binds to a protein other than CD3; and

a heavy chain constant domain (CH) comprising a sequence of SEQ ID NO: 54 or 55.

43. The bispecific three-chain antibody like molecule of embodiment 42, wherein the third polypeptide subunit comprises a heavy chain-only variable region in a bivalent configuration that binds to BCMA.

44. The bispecific three-chain antibody like molecule of embodiment 43, comprising:

a first polypeptide subunit comprising a sequence of SEQ ID NO: 49;

a second polypeptide subunit comprising a sequence of SEQ ID NO: 56; and

a third polypeptide subunit comprising a sequence of SEQ ID NO: 58.

45. A pharmaceutical composition comprising the bispecific three-chain antibody like molecule of any one of embodiments 42-44.

46. A polynucleotide encoding a bispecific three-chain antibody like molecule according to any one of embodiments 42-44.

47. A vector comprising a polynucleotide according to embodiment 46.

48. A cell comprising a vector according to embodiment 47.

49. A method of producing a bispecific three-chain antibody like molecule according to any one of embodiments 42-44, comprising growing a cell according to embodiment 48 under conditions permissive for expression of the bispecific three-chain antibody like molecule, and isolating the bispecific three-chain antibody like molecule from the cell.

50. A method of treatment, comprising administering to an individual in need an effective dose of the bispecific three-chain antibody like molecule of any one of embodiments 42-44, or the pharmaceutical composition of embodiment 45.

51. Use of a bispecific three-chain antibody like molecule of any one of embodiments 42-44 in the preparation of a medicament for the treatment of a disease or disorder in an individual in need.

52. The bispecific three-chain antibody like molecule of any one of embodiments 42-44, or the pharmaceutical composition of embodiment 45, for use in therapy in an individual in need.

53. A method for treating a disease or condition characterized by expression of BCMA, comprising administering to an individual in need an effective dose of the bispecific three-chain antibody like molecule according to any one of embodiments 42-44, or the pharmaceutical composition of embodiment 45.

54. The method of embodiment 53, wherein the disease is an autoimmune disease.

55. The method of embodiment 53, wherein the disease is a cancer.

56. The method of embodiment 55, wherein the cancer is a myeloma.

57. The method of embodiment 56, wherein the myeloma is multiple myeloma.

58. A kit for treating a disease or disorder in an individual in need, comprising a bispecific three-chain antibody like molecule of any one of embodiments 42-44, or the pharmaceutical composition of embodiment 45, and instructions for use.

59. The kit of embodiment 58, further comprising at least one additional reagent.

2022259766 26 Oct 2022

60. The kit of embodiment 59, wherein the at least one additional reagent comprises a chemotherapeutic drug.

2022259766 16 Jun 2023

CLAIMS

1. A bispecific monoclonal antibody that binds to human CD3 and human BCMA, comprising:
   (i) a first polypeptide subunit comprising the amino acid sequence of SEQ ID NO:49;
   (ii) a second polypeptide subunit comprising the amino acid sequence of SEQ ID NO:56,
   wherein the first and second polypeptide subunits together form a first binding moiety that binds to human CD3; and
   (iii) a third polypeptide subunit that binds to human BCMA, comprising the amino acid sequence of SEQ ID NO:58.

2. The bispecific monoclonal antibody of claim 1, wherein the first polypeptide subunit comprises a light chain.

3. The bispecific monoclonal antibody of claim 1, wherein the second polypeptide subunit comprises a heavy chain.

4. The bispecific monoclonal antibody of claim 1, wherein the third polypeptide subunit comprises a bivalent heavy chain.

5. The bispecific monoclonal antibody of claim 4, wherein the bivalent heavy chain comprises a heavy chain-only variable region in a bivalent configuration.

6. The bispecific monoclonal antibody of claim 4, wherein the bivalent heavy chain lacks a CH1 domain.

7. A bispecific monoclonal antibody that binds to human CD3 and human BCMA, comprising:
   (i) a first polypeptide subunit comprising the amino acid sequence of SEQ ID NO:49;
   (ii) a second polypeptide subunit comprising the amino acid sequence of SEQ ID NO:75,

2022259766 16 Jun 2023

wherein the first and second polypeptide subunits together form a first binding moiety that binds to human CD3; and

(iii) a third polypeptide subunit that binds to human BCMA, comprising the amino acid sequence of SEQ ID NO:76.

8. The bispecific monoclonal antibody of claim 7, wherein the first polypeptide subunit comprises a light chain.

9. The bispecific monoclonal antibody of claim 7, wherein the second polypeptide subunit comprises a heavy chain.

10. The bispecific monoclonal antibody of claim 7, wherein the third polypeptide subunit comprises a bivalent heavy chain.

11. The bispecific monoclonal antibody of claim 10, wherein the bivalent heavy chain comprises a heavy chain-only variable region in a bivalent configuration.

12. The bispecific monoclonal antibody of claim 10, wherein the bivalent heavy chain lacks a CH1 domain.

13. A human, monoclonal IgG4 bispecific antibody comprising:

(i) a first binding arm that binds to human CD3; and

(ii) a second binding arm that binds to human BCMA,

wherein the first binding arm comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO:56 and a light chain comprising the amino acid sequence of SEQ ID NO:49; and

wherein the second binding arm comprises a bivalent second heavy chain comprising the amino acid sequence of SEQ ID NO:58.

14. The human, monoclonal IgG4 bispecific antibody of claim 13, wherein the second binding arm does not comprise a light chain.

15. The human, monoclonal IgG4 bispecific antibody of claim 13, wherein the bivalent second heavy chain comprises a heavy chain-only variable region in a bivalent configuration.

2022259766 16 Jun 2023

16. The human, monoclonal IgG4 bispecific antibody of claim 13, wherein the bivalent second heavy chain lacks a CH1 domain.

17. A human, monoclonal IgG4 bispecific antibody comprising:
(i) a first binding arm that binds to human CD3; and
(ii) a second binding arm that binds to human BCMA,
wherein the first binding arm comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO:75 and a light chain comprising the amino acid sequence of SEQ ID NO:49; and
wherein the second binding arm comprises a bivalent second heavy chain comprising the amino acid sequence of SEQ ID NO:76.

18. The human, monoclonal IgG4 bispecific antibody of claim 17, wherein the second binding arm does not comprise a light chain.

19. The human, monoclonal IgG4 bispecific antibody of claim 17, wherein the bivalent second heavy chain comprises a heavy chain-only variable region in a bivalent configuration.

20. The human, monoclonal IgG4 bispecific antibody of claim 17, wherein the bivalent second heavy chain lacks a CH1 domain.

21. A pharmaceutical composition comprising the bispecific antibody of any one of claims 1 to 20, and a pharmaceutically acceptable carrier.

22. One or more polynucleotides encoding the bispecific antibody of any one of claims 1 to 20.

23. One or more vectors comprising the one or more polynucleotides of claim 22.

24. An isolated or non-human cell comprising the one or more vectors of claim 23.

25. A method of producing a bispecific antibody, comprising growing the cell of claim 24 under conditions permissive for expression of the bispecific antibody, and isolating the bispecific antibody from the cell.

2022259766 16 Jun 2023

26. A kit comprising the bispecific antibody of any one of claims 1 to 20, and instructions for use.

27. A method for treating a BCMA-expressing cancer in a human subject in need thereof, comprising administering to the subject a therapeutically effective amount of the bispecific antibody of any one of claims 1 to 20.

28. Use of the bispecific antibody of any one of claims 1 to 20 in the manufacture of a medicament for treating a BCMA-expressing cancer in a human subject in need thereof.

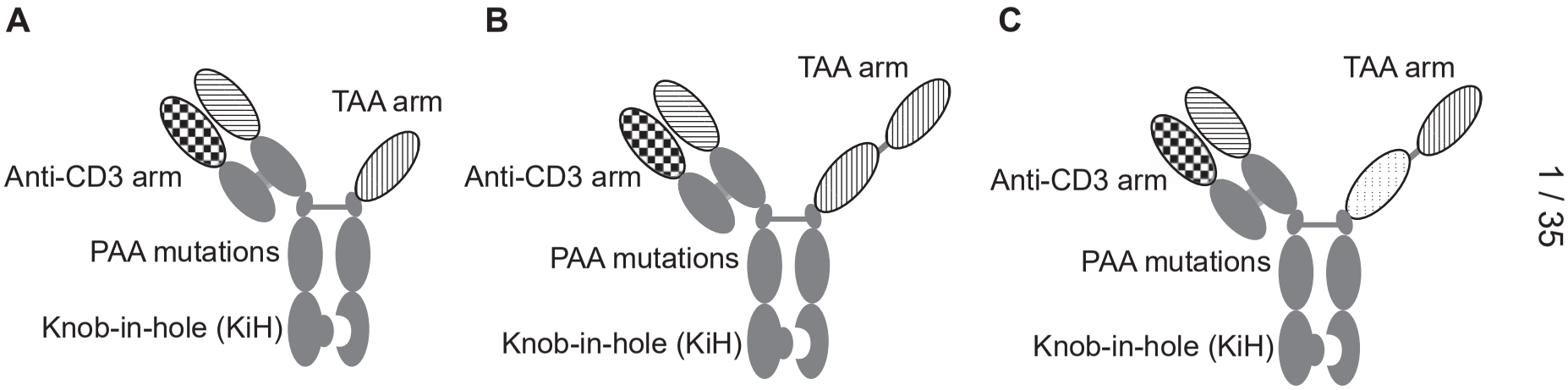

A
TAA arm
Anti-CD3 arm
PAA mutations
Knob-in-hole (KiH)
B
TAA arm
Anti-CD3 arm
PAA mutations
Knob-in-hole (KiH)
C
TAA arm
Anti-CD3 arm
PAA mutations
Knob-in-hole (KiH)

FIG. 1

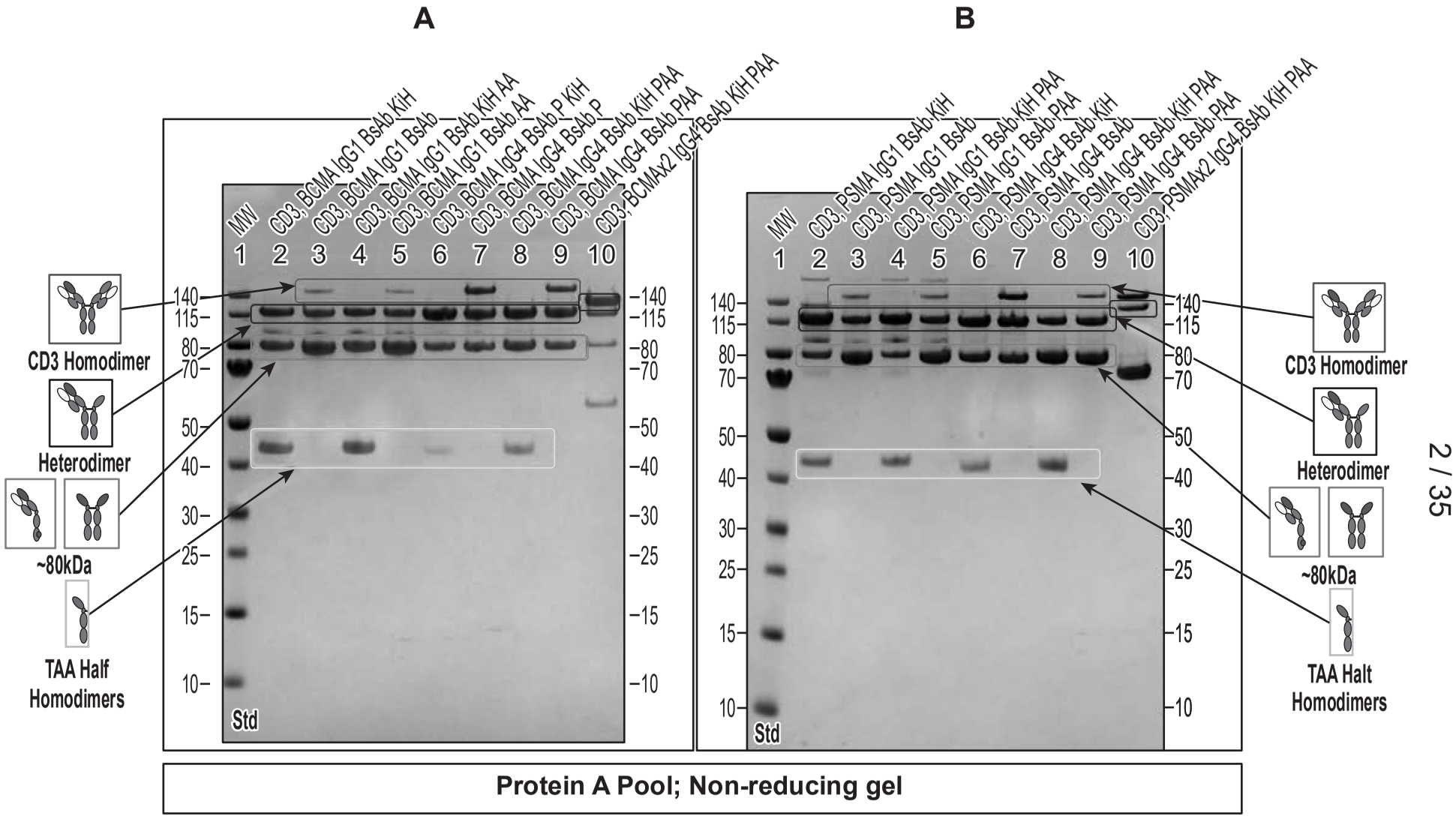

A
B
MW
1
2
3
4
5
6
7
8
9
10
CD3, BCMA IgG1 BsAb KiH
CD3, BCMA IgG1 BsAb
CD3, BCMA IgG1 BsAb KiH AA
CD3, BCMA IgG1 BsAb AA
CD3, BCMA IgG4 BsAb P KiH
CD3, BCMA IgG4 BsAb P
CD3, BCMA IgG4 BsAb KiH PAA
CD3, BCMA IgG4 BsAb PAA
CD3, BCMAx2 IgG4 BsAb KiH PAA
CD3, PSMA IgG1 BsAb KiH
CD3, PSMA IgG1 BsAb
CD3, PSMA IgG1 BsAb KiH PAA
CD3, PSMA IgG1 BsAb PAA
CD3, PSMA IgG4 BsAb KiH
CD3, PSMA IgG4 BsAb
CD3, PSMA IgG4 BsAb KiH PAA
CD3, PSMA IgG4 BsAb PAA
CD3, PSMAx2 IgG4 BsAb KiH PAA
140
115
80
70
50
40
30
25
15
10
Std
CD3 Homodimer
Heterodimer
~80kDa
TAA Half Homodimers
TAA Halt Homodimers
Protein A Pool; Non-reducing gel

FIG. 2

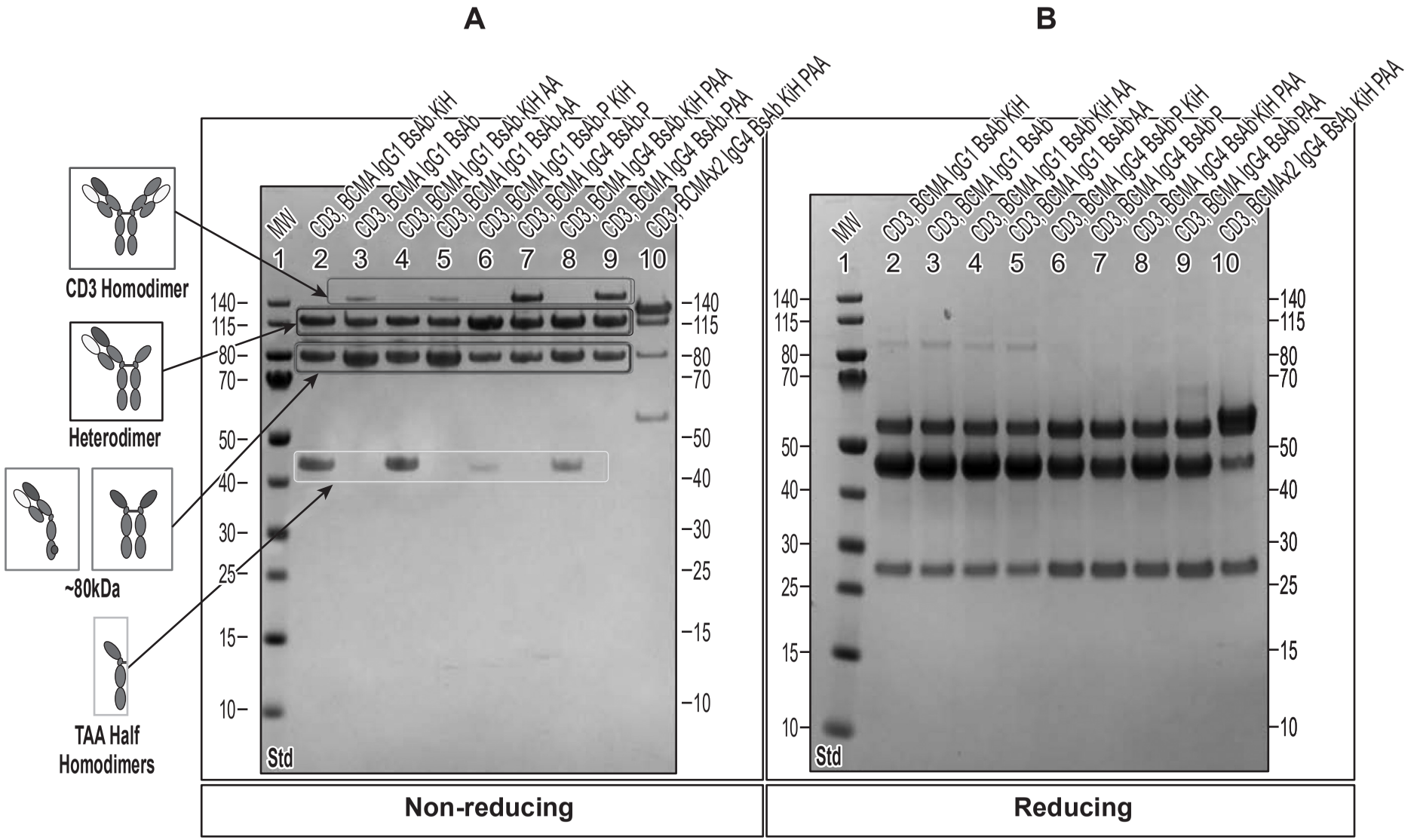

A
B
MW
1
2
3
4
5
6
7
8
9
10
CD3, BCMA IgG1 BsAb KiH
CD3, BCMA IgG1 BsAb
CD3, BCMA IgG1 BsAb KiH AA
CD3, BCMA IgG1 BsAb AA
CD3, BCMA IgG1 BsAb P KiH
CD3, BCMA IgG4 BsAb P
CD3, BCMA IgG4 BsAb KiH PAA
CD3, BCMA IgG4 BsAb PAA
CD3, BCMAx2 IgG4 BsAb KiH PAA
140
115
80
70
50
40
30
25
15
10
Std
CD3 Homodimer
Heterodimer
~80kDa
TAA Half Homodimers
Non-reducing
Reducing

FIG. 3

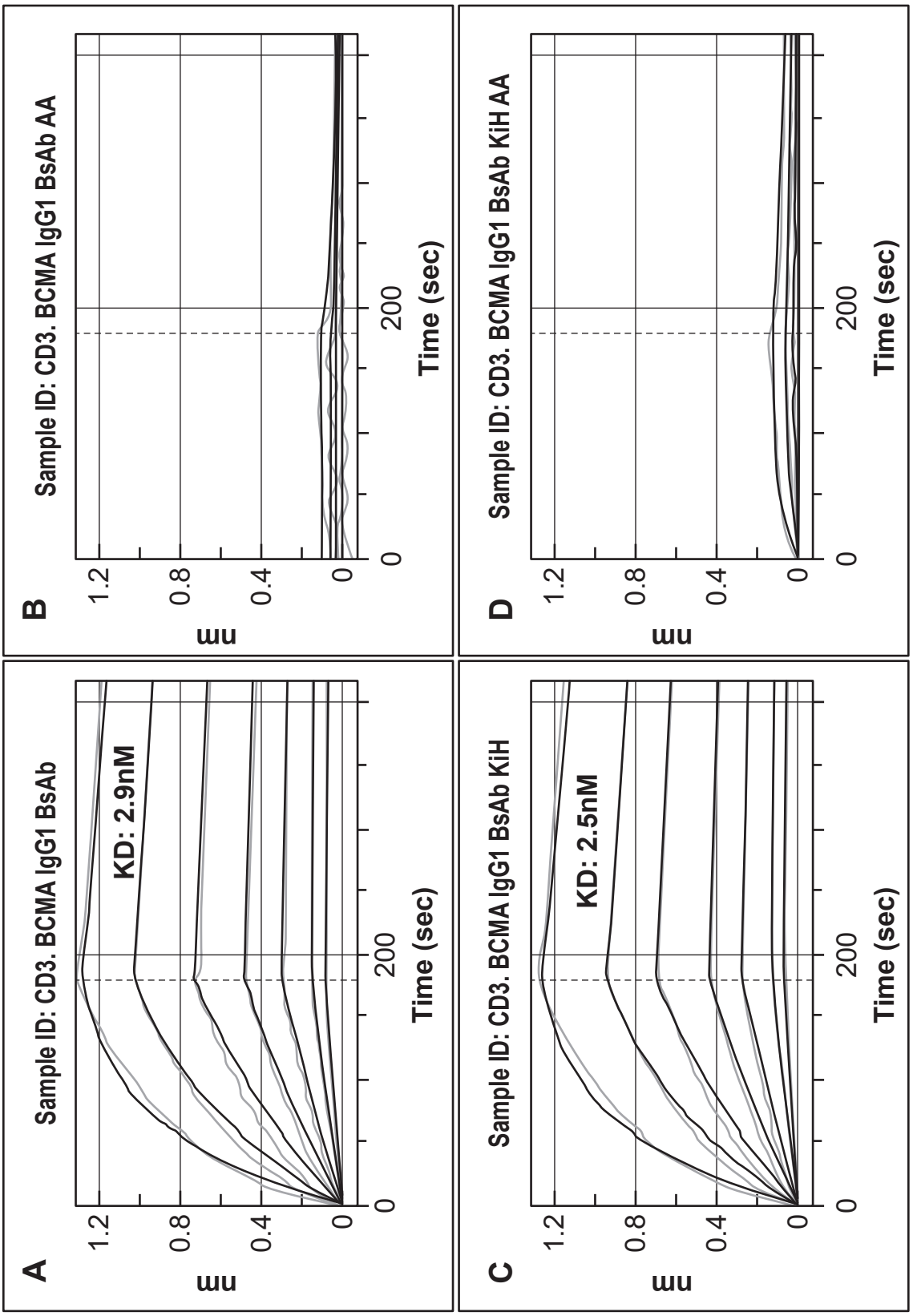

A
Sample ID: CD3. BCMA IgG1 BsAb
KD: 2.9nM
nm
1.2
0.8
0.4
0
0
200
Time (sec)
B
Sample ID: CD3. BCMA IgG1 BsAb AA
nm
1.2
0.8
0.4
0
0
200
Time (sec)
C
Sample ID: CD3. BCMA IgG1 BsAb KiH
KD: 2.5nM
nm
1.2
0.8
0.4
0
0
200
Time (sec)
D
Sample ID: CD3. BCMA IgG1 BsAb KiH AA
nm
1.2
0.8
0.4
0
0
200
Time (sec)

FIG. 4

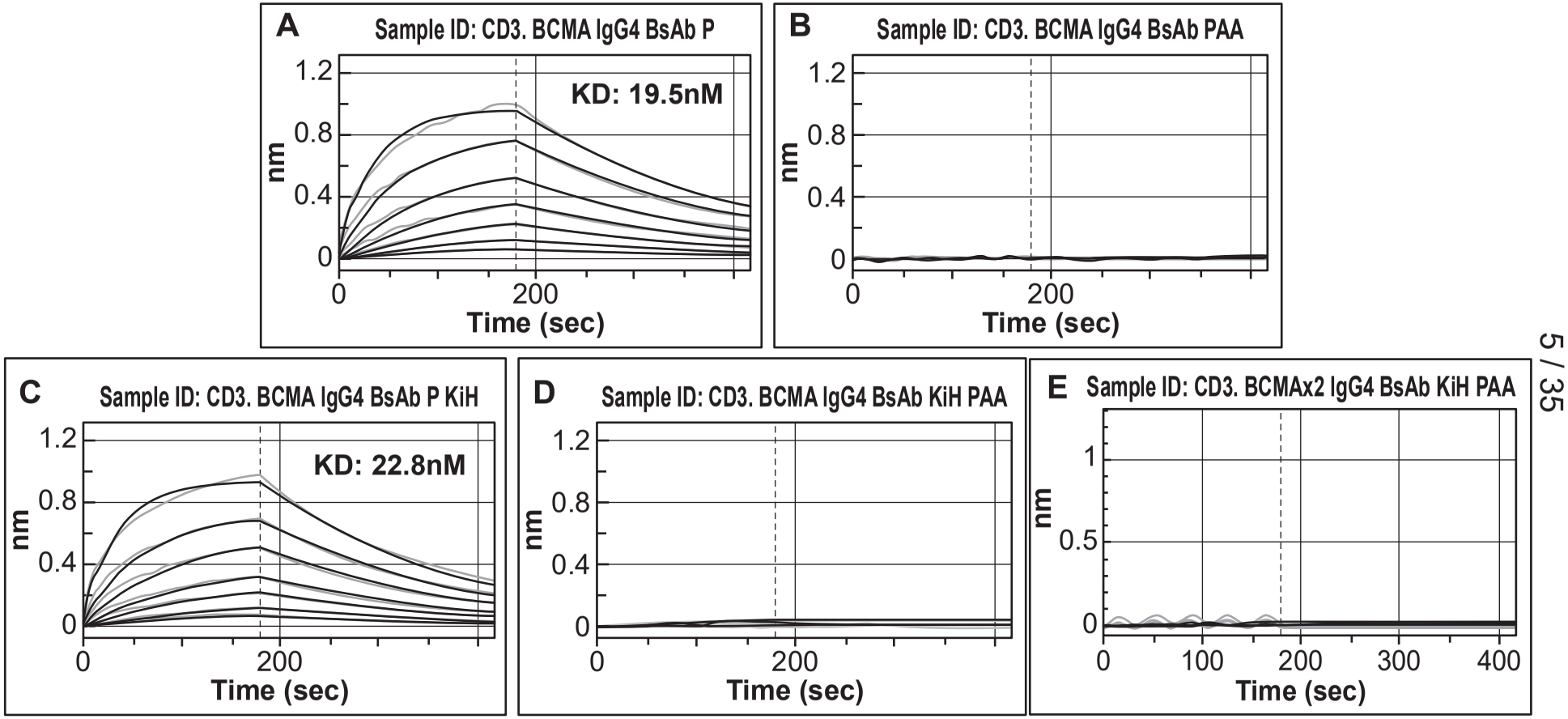

A
Sample ID: CD3. BCMA IgG4 BsAb P
KD: 19.5nM
nm
1.2
0.8
0.4
0
0
200
Time (sec)
B
Sample ID: CD3. BCMA IgG4 BsAb PAA
nm
1.2
0.8
0.4
0
0
200
Time (sec)
C
Sample ID: CD3. BCMA IgG4 BsAb P KiH
KD: 22.8nM
nm
1.2
0.8
0.4
0
0
200
Time (sec)
D
Sample ID: CD3. BCMA IgG4 BsAb KiH PAA
nm
1.2
0.8
0.4
0
0
200
Time (sec)
E
Sample ID: CD3. BCMAx2 IgG4 BsAb KiH PAA
nm
1
0.5
0
0
100
200
300
400
Time (sec)

FIG. 5

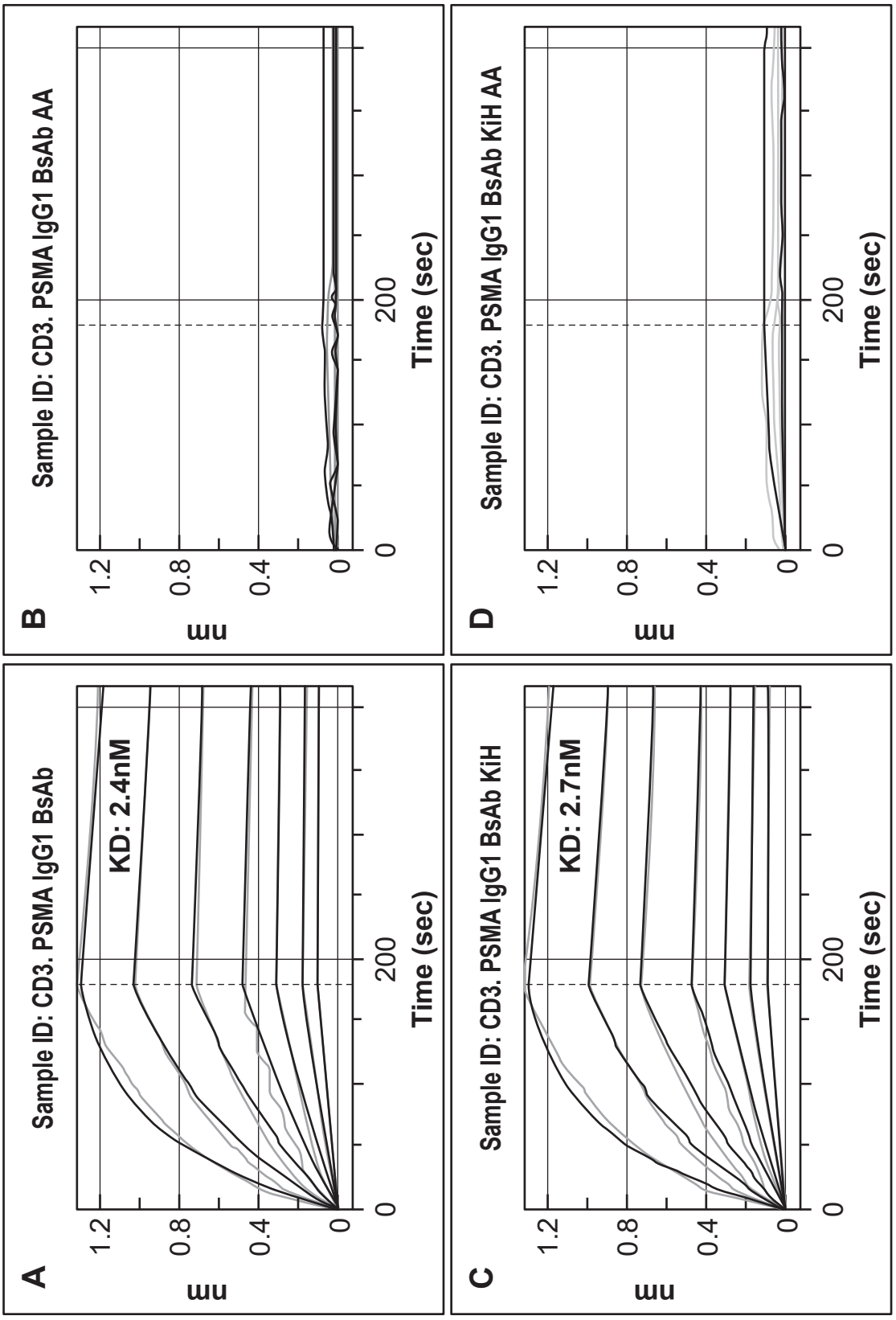

A
Sample ID: CD3. PSMA IgG1 BsAb
KD: 2.4nM
nm
1.2
0.8
0.4
0
0
200
Time (sec)
B
Sample ID: CD3. PSMA IgG1 BsAb AA
nm
1.2
0.8
0.4
0
0
200
Time (sec)
C
Sample ID: CD3. PSMA IgG1 BsAb KiH
KD: 2.7nM
nm
1.2
0.8
0.4
0
0
200
Time (sec)
D
Sample ID: CD3. PSMA IgG1 BsAb KiH AA
nm
1.2
0.8
0.4
0
0
200
Time (sec)

FIG. 6

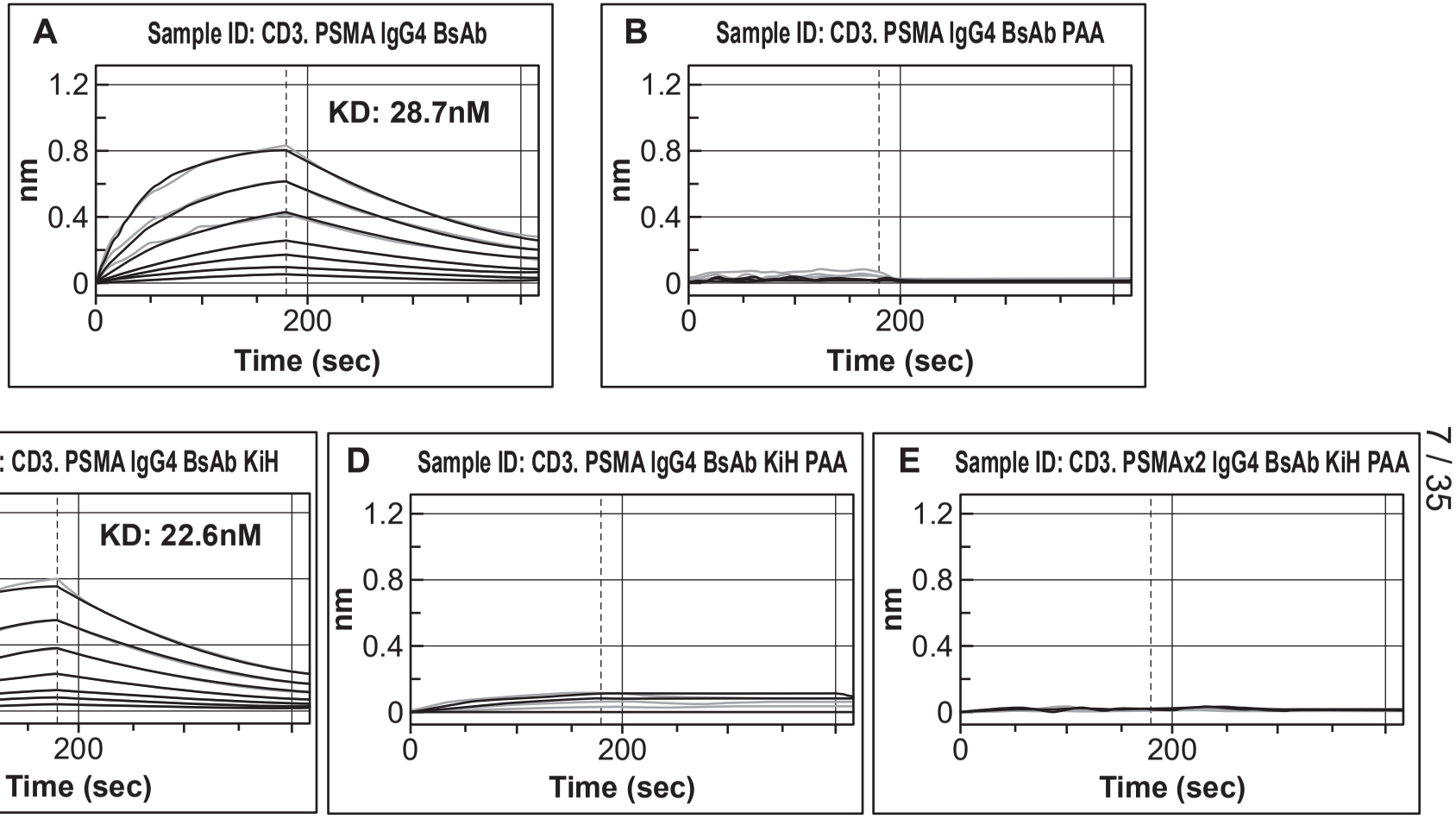

A
Sample ID: CD3. PSMA IgG4 BsAb
KD: 28.7nM
nm
1.2
0.8
0.4
0
0
200
Time (sec)
B
Sample ID: CD3. PSMA IgG4 BsAb PAA
nm
1.2
0.8
0.4
0
0
200
Time (sec)
C
Sample ID: CD3. PSMA IgG4 BsAb KiH
KD: 22.6nM
nm
1.2
0.8
0.4
0
0
200
Time (sec)
D
Sample ID: CD3. PSMA IgG4 BsAb KiH PAA
nm
1.2
0.8
0.4
0
0
200
Time (sec)
E
Sample ID: CD3. PSMAx2 IgG4 BsAb KiH PAA
nm
1.2
0.8
0.4
0
0
200
Time (sec)

FIG. 7

2022259766 26 Oct 2022

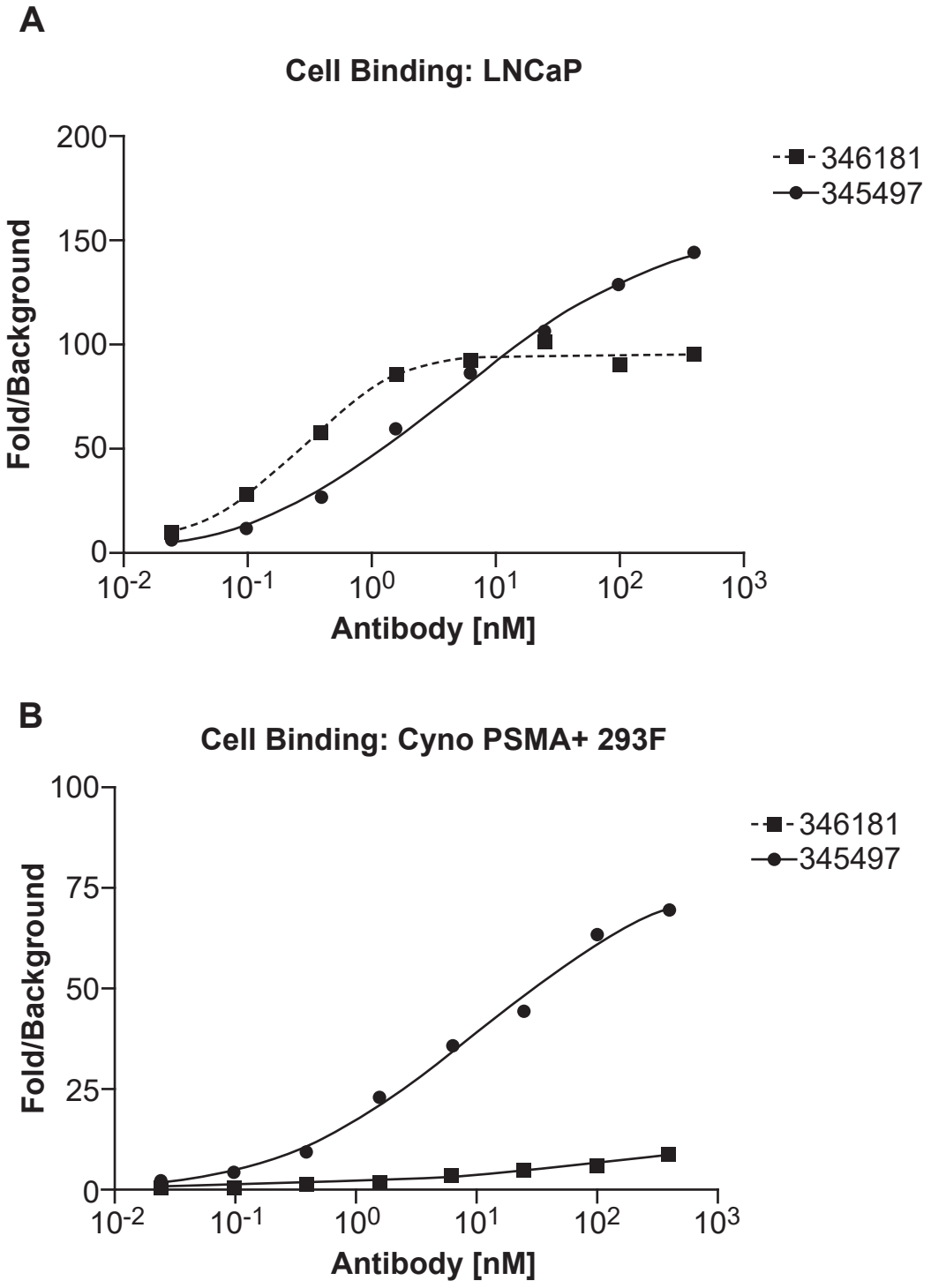


FIG. 8

2022259766 26 Oct 2022

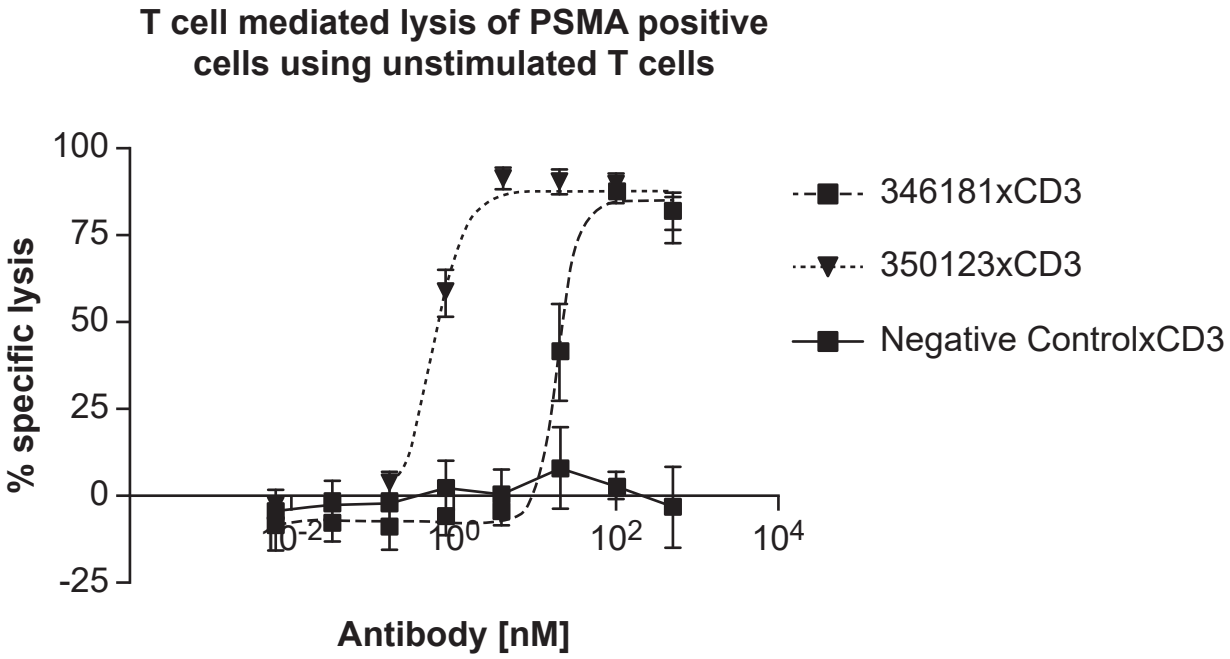


FIG. 9

2022259766 26 Oct 2022

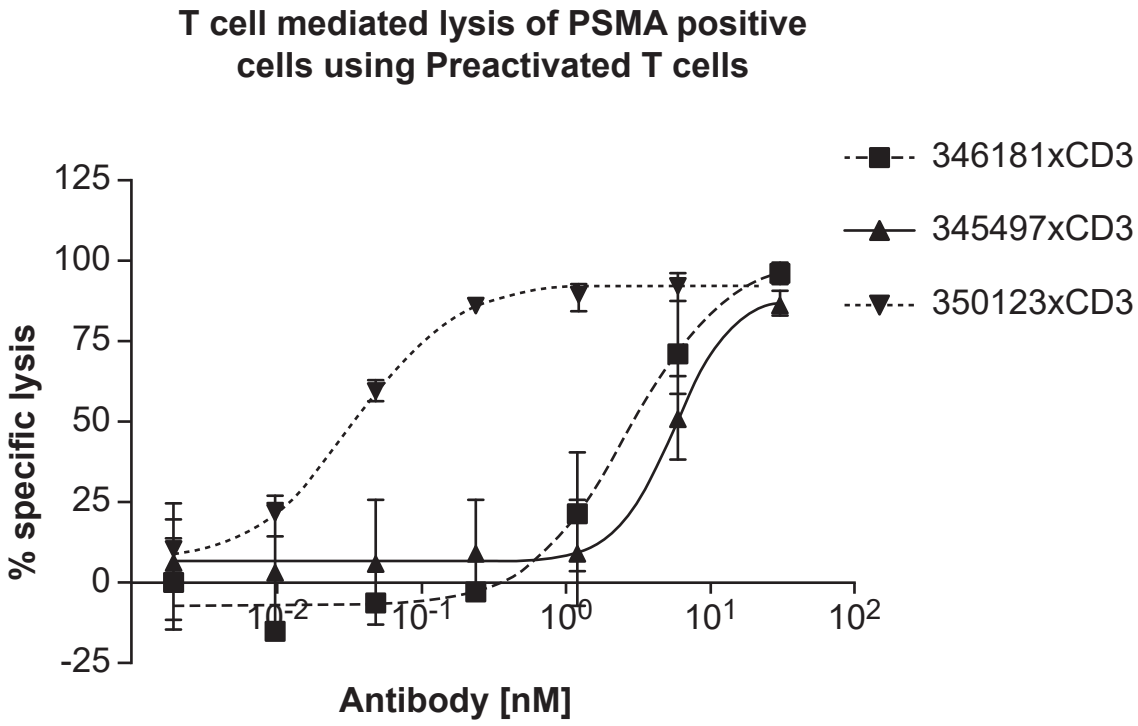


FIG. 10

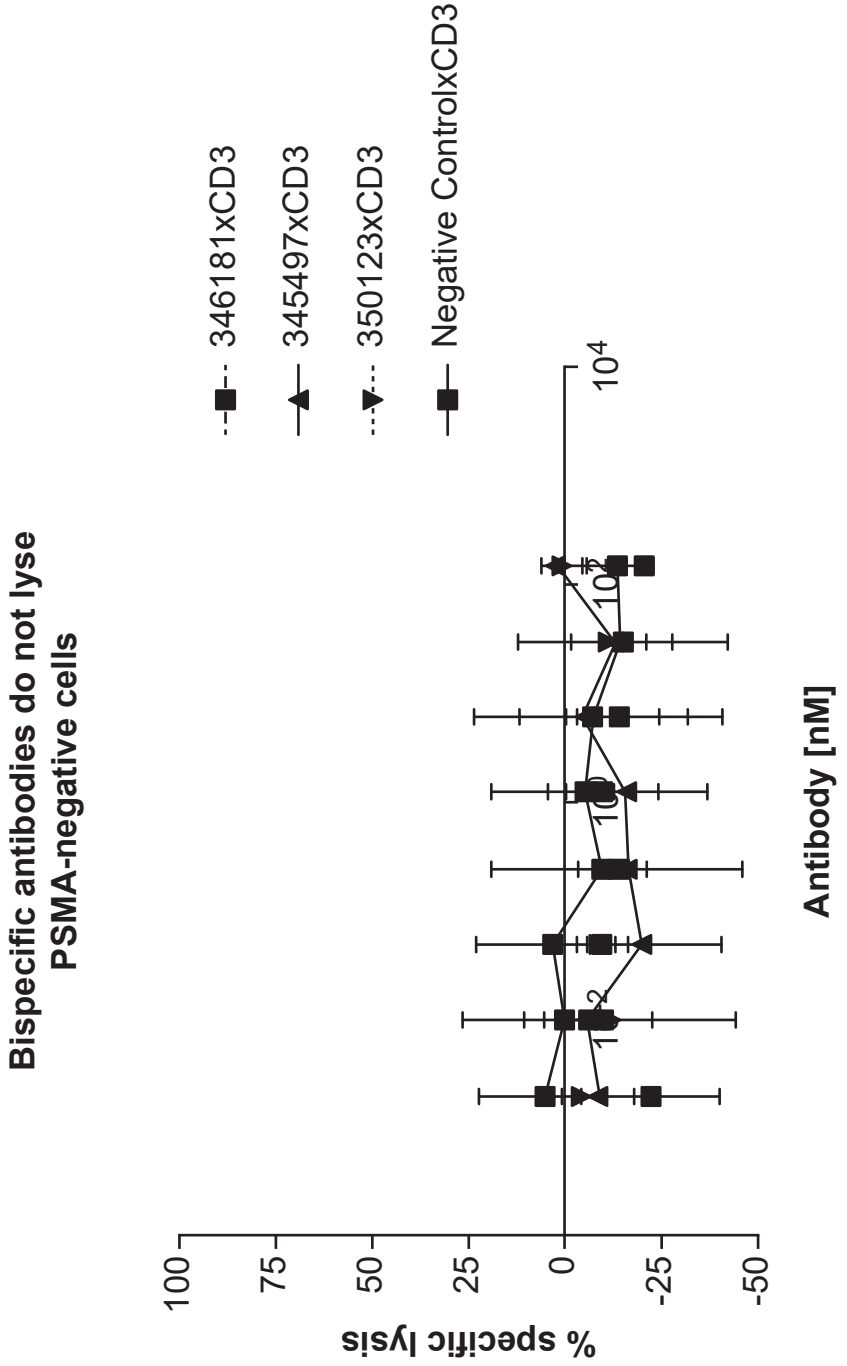

Bispecific antibodies do not lyse PSMA-negative cells
346181xCD3
345497xCD3
350123xCD3
Negative ControlxCD3
% specific lysis
100
75
50
25
0
-25
-50
Antibody [nM]

FIG. 11

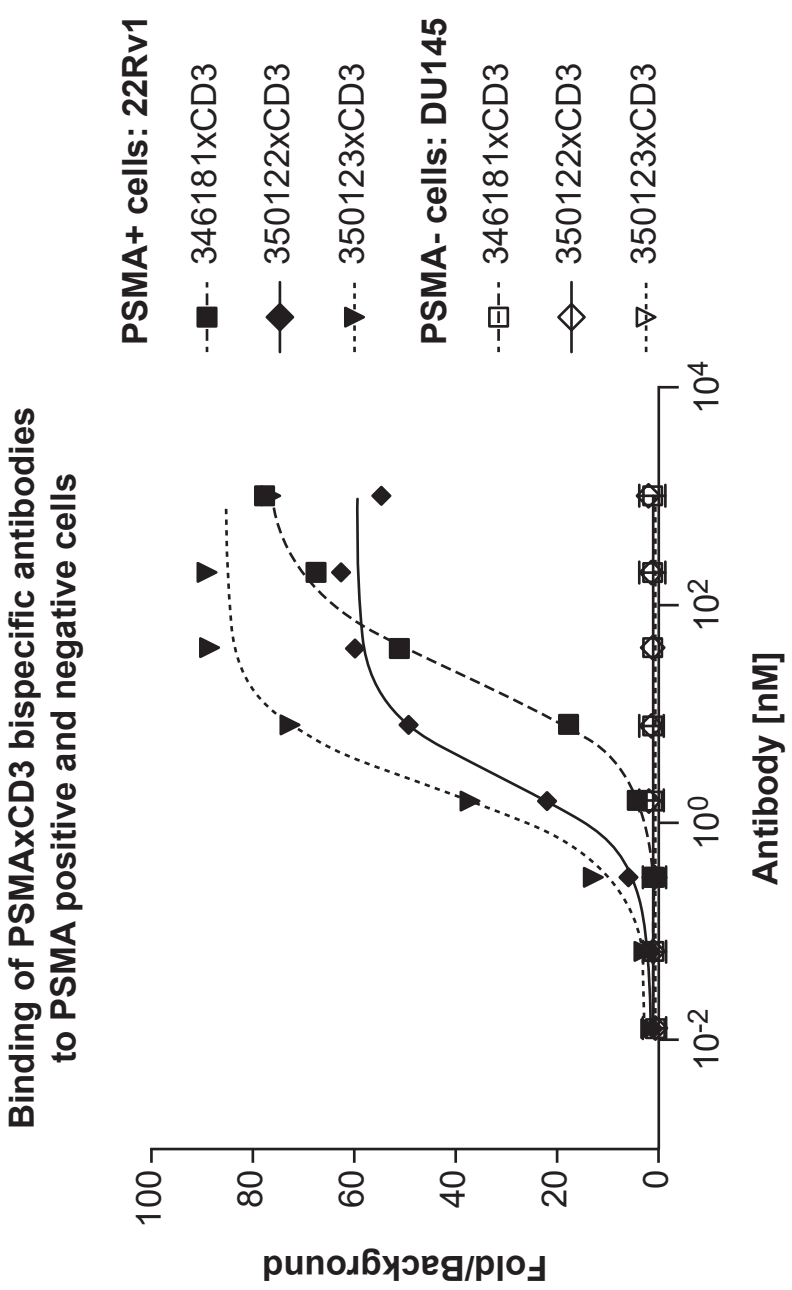

Binding of PSMAxCD3 bispecific antibodies to PSMA positive and negative cells
PSMA+ cells: 22Rv1
346181xCD3
350122xCD3
350123xCD3
PSMA- cells: DU145
346181xCD3
350122xCD3
350123xCD3
Fold/Background
100
80
60
40
20
0
10^{-2}
10^{0}
10^{2}
10^{4}
Antibody [nM]

FIG. 12

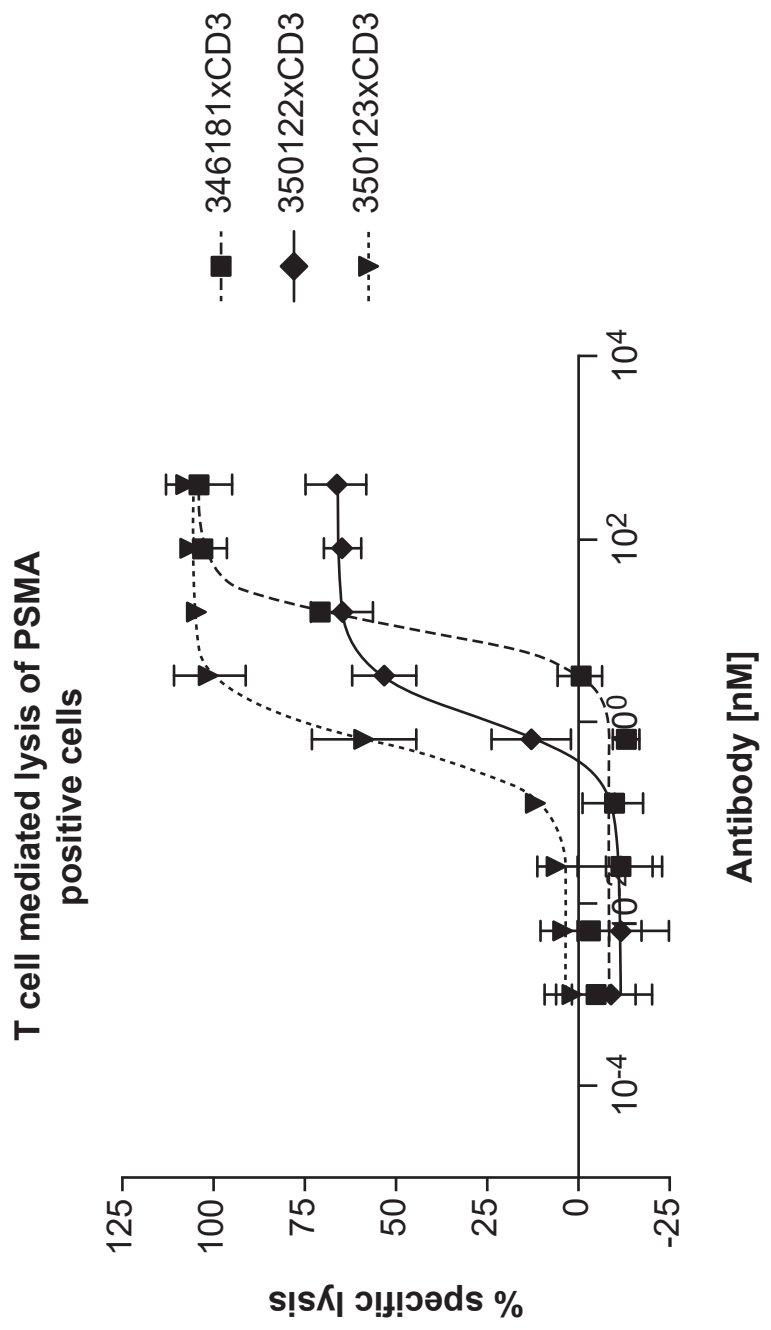

T cell mediated lysis of PSMA positive cells
% specific lysis
125
100
75
50
25
0
-25
10-4
10-2
100
102
104
Antibody [nM]
346181xCD3
350122xCD3
350123xCD3

FIG. 13

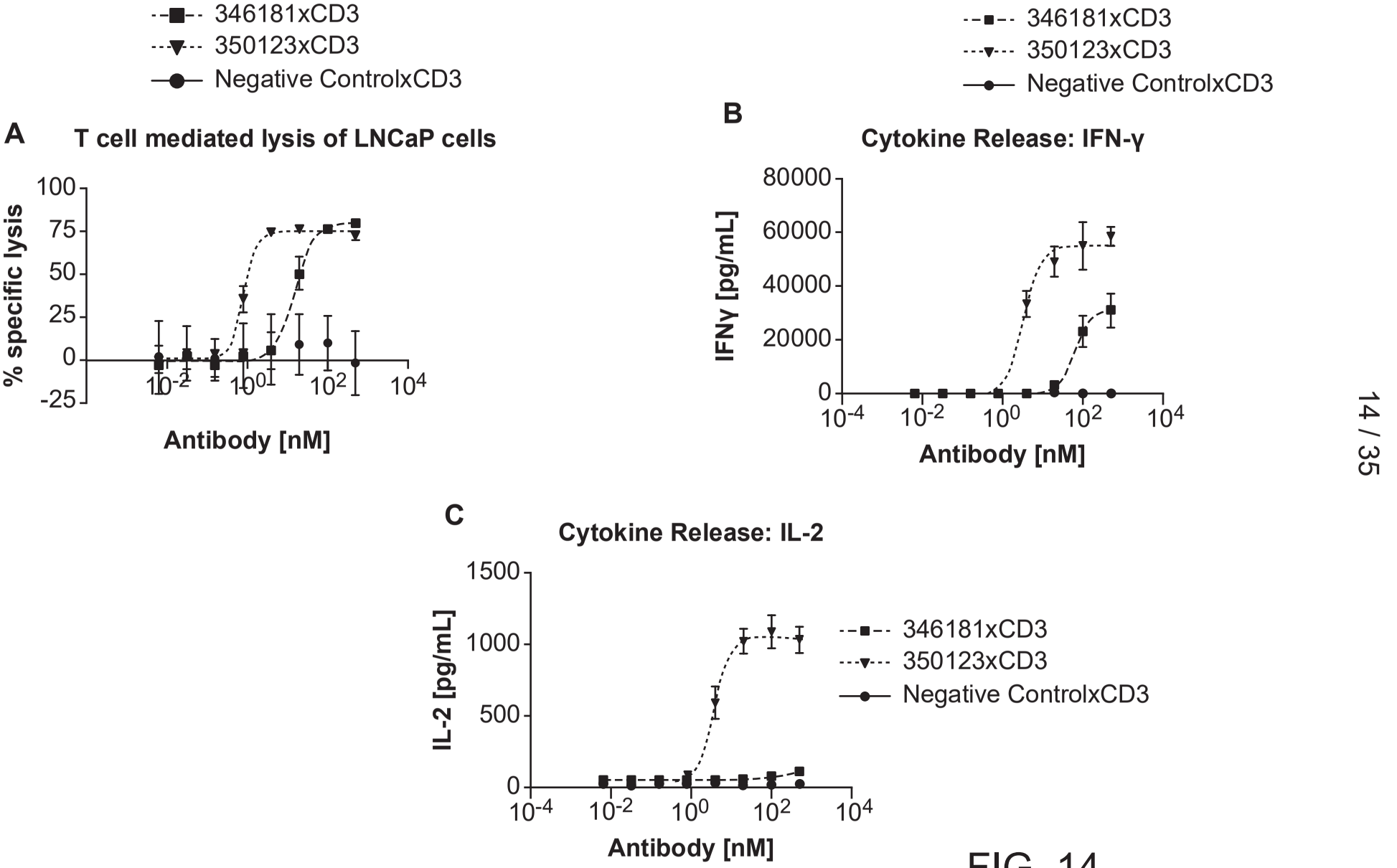

346181xCD3
350123xCD3
Negative ControlxCD3
A
T cell mediated lysis of LNCaP cells
% specific lysis
100
75
50
25
0
-25
10-2
100
102
104
Antibody [nM]
B
Cytokine Release: IFN-γ
IFNγ [pg/mL]
80000
60000
40000
20000
0
10-4
10-2
100
102
104
Antibody [nM]
C
Cytokine Release: IL-2
IL-2 [pg/mL]
1500
1000
500
0
10-4
10-2
100
102
104
Antibody [nM]

FIG. 14

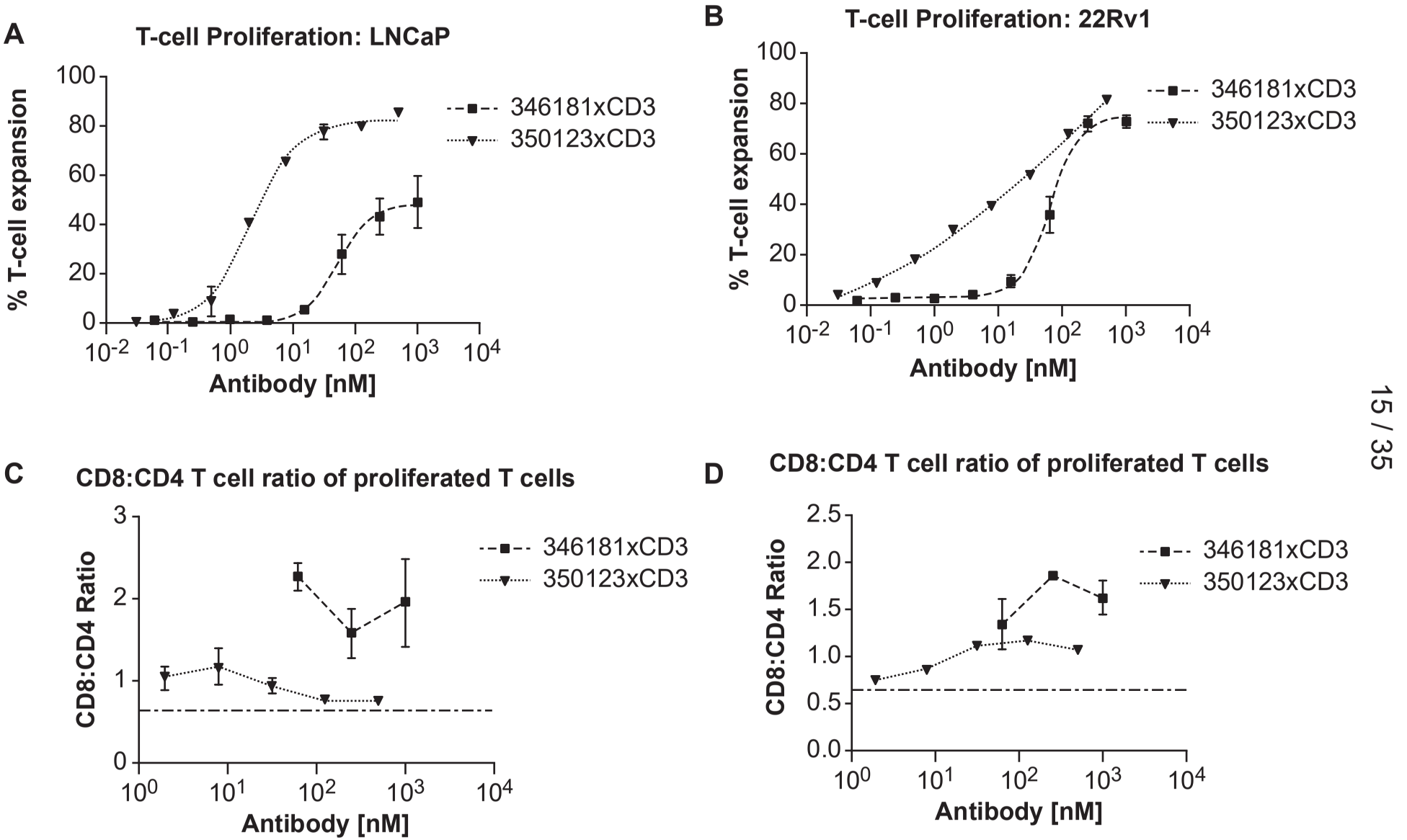

A
T-cell Proliferation: LNCaP
% T-cell expansion
Antibody [nM]
346181xCD3
350123xCD3
B
T-cell Proliferation: 22Rv1
% T-cell expansion
Antibody [nM]
346181xCD3
350123xCD3
C
CD8:CD4 T cell ratio of proliferated T cells
CD8:CD4 Ratio
Antibody [nM]
346181xCD3
350123xCD3
D
CD8:CD4 T cell ratio of proliferated T cells
CD8:CD4 Ratio
Antibody [nM]
346181xCD3
350123xCD3

FIG. 15

2022259766 26 Oct 2022

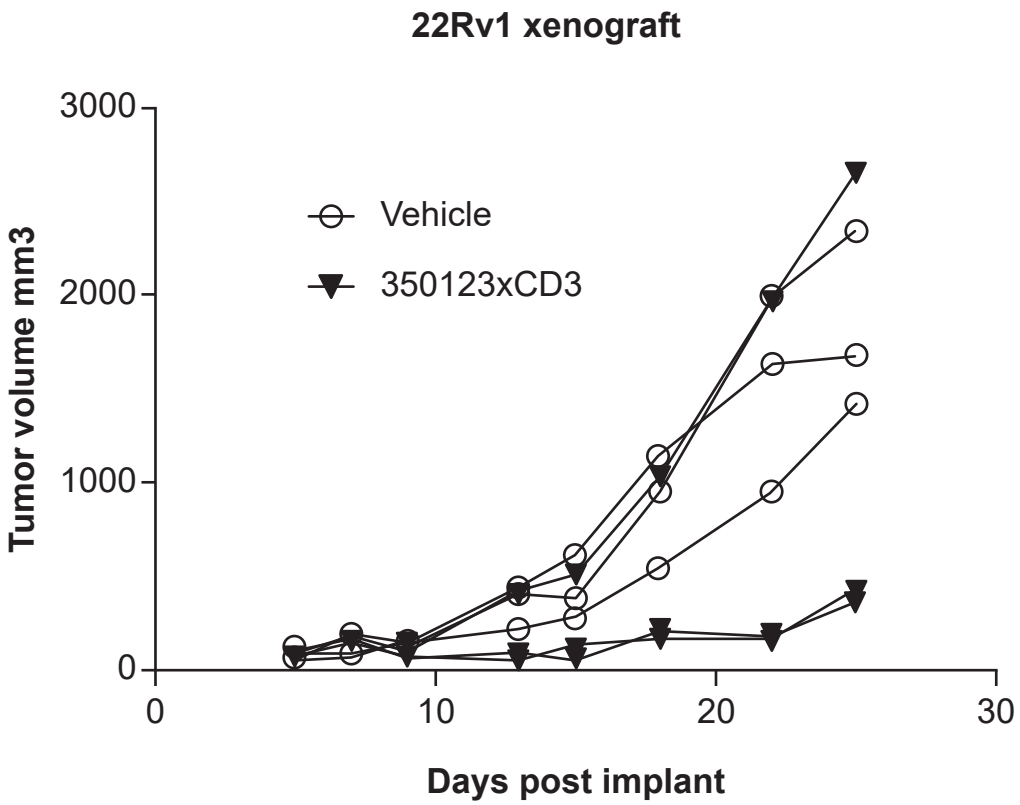


FIG. 16

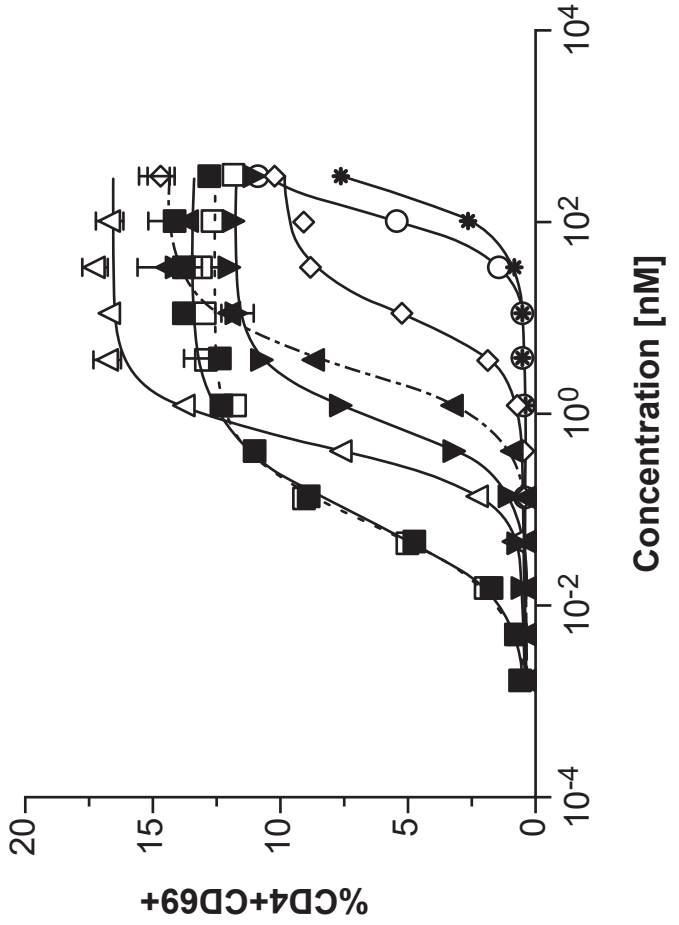

CD3, BCMA IgG1 BsAb KiH
CD3, BCMA IgG1 BsAb
CD3, BCMA IgG1 BsAb KiH AA
CD3, BCMA IgG1 BsAb AA
CD3, BCMA IgG4 BsAb P KiH
CD3, BCMA IgG4 BsAb P
CD3, BCMA IgG4 BsAb PAA
CD3, BCMAx2 IgG4 BsAb KiH PAA
%CD4+CD69+
20
15
10
5
0
10-4
10-2
100
102
104
Concentration [nM]

FIG. 17

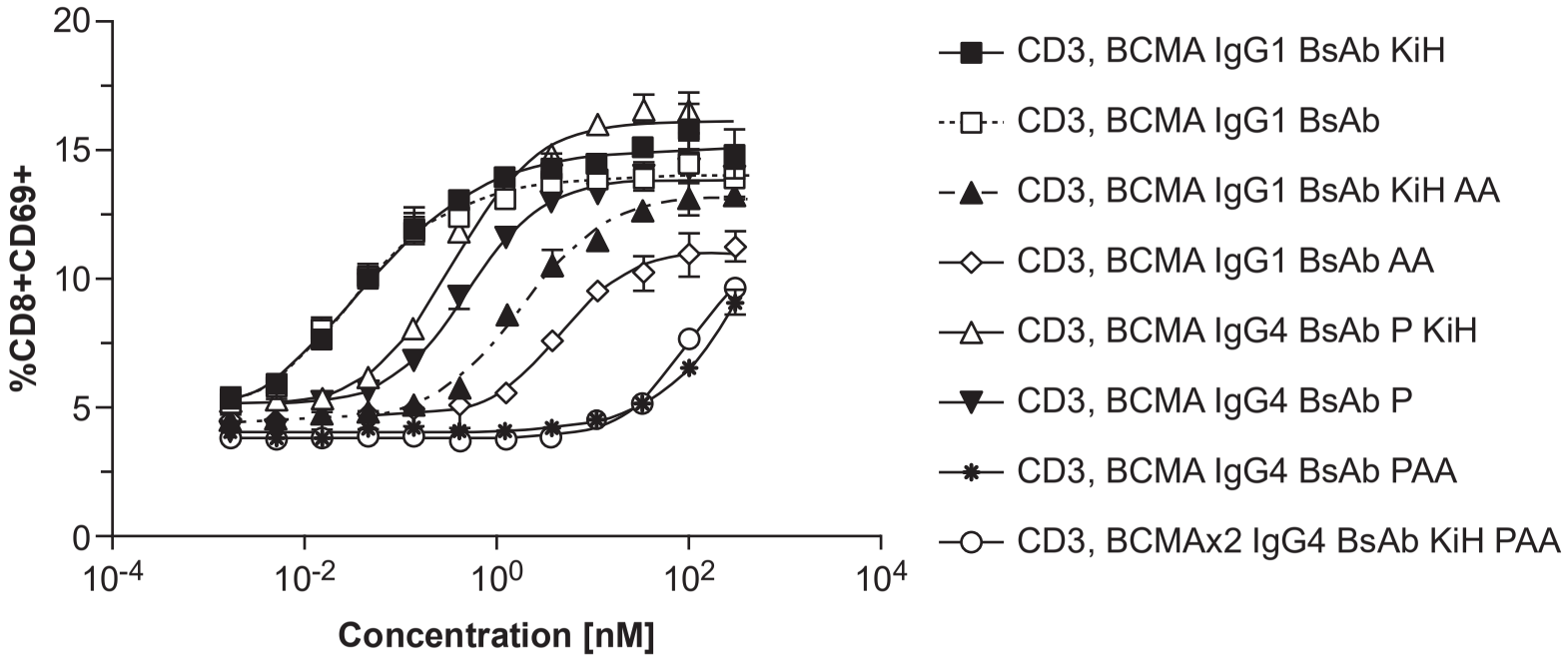

%CD8+CD69+
20
15
10
5
0
10-4
10-2
100
102
104
Concentration [nM]
CD3, BCMA IgG1 BsAb KiH
CD3, BCMA IgG1 BsAb
CD3, BCMA IgG1 BsAb KiH AA
CD3, BCMA IgG1 BsAb AA
CD3, BCMA IgG4 BsAb P KiH
CD3, BCMA IgG4 BsAb P
CD3, BCMA IgG4 BsAb PAA
CD3, BCMAx2 IgG4 BsAb KiH PAA

FIG. 18

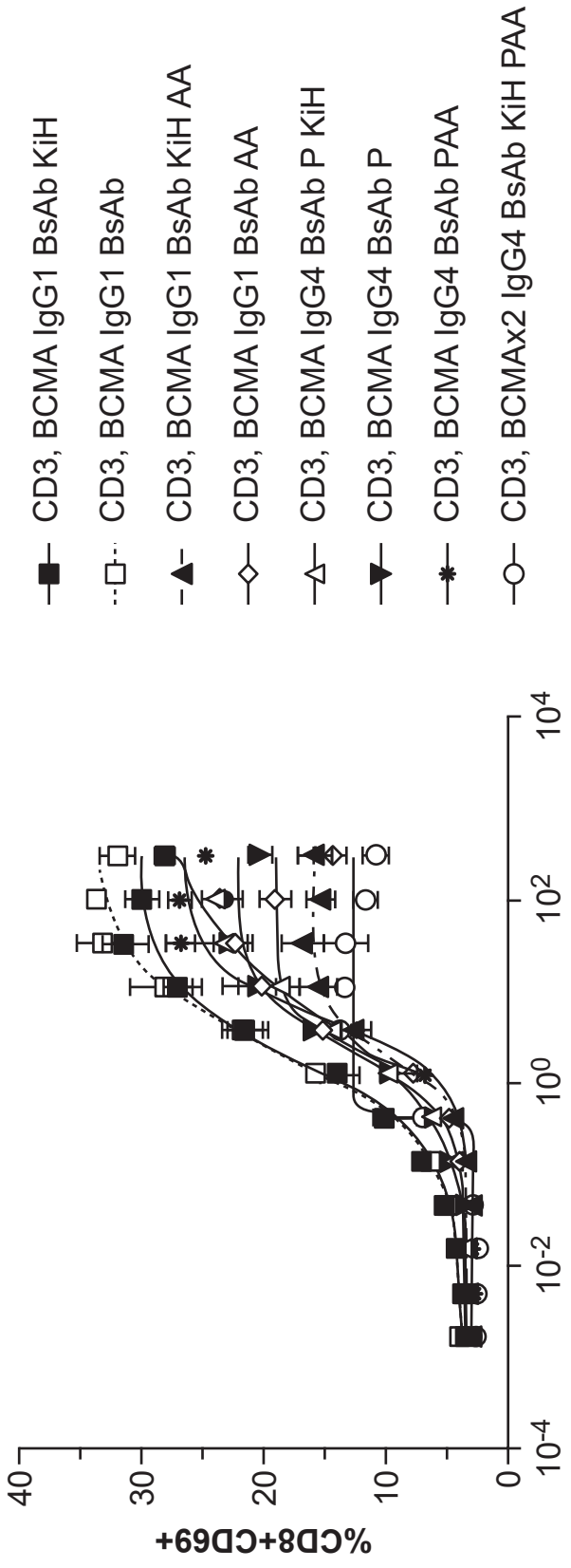

CD3, BCMA IgG1 BsAb KiH
CD3, BCMA IgG1 BsAb
CD3, BCMA IgG1 BsAb KiH AA
CD3, BCMA IgG1 BsAb AA
CD3, BCMA IgG4 BsAb P KiH
CD3, BCMA IgG4 BsAb P
CD3, BCMA IgG4 BsAb PAA
CD3, BCMAx2 IgG4 BsAb KiH PAA
%CD8+CD69+
0
10
20
30
40
10-4
10-2
100
102
104
Concentration [nM]

FIG. 19

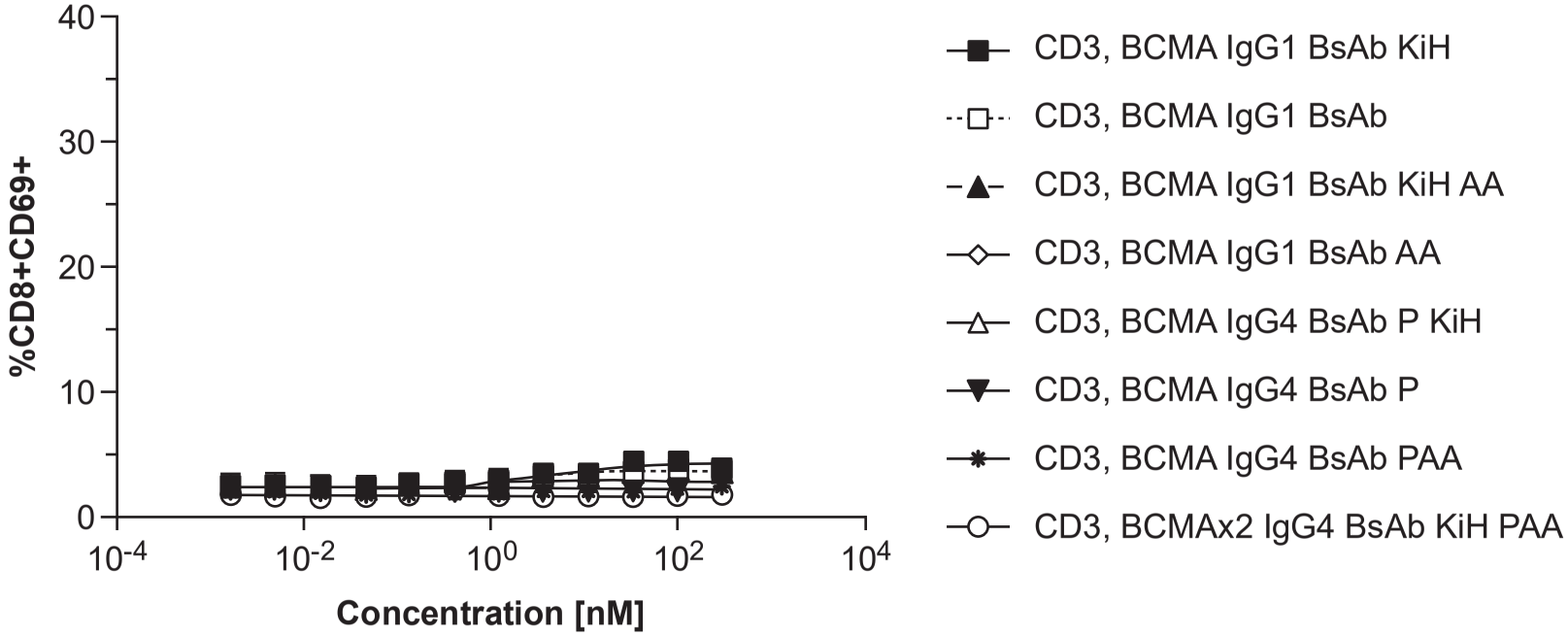

40
30
20
10
0
%CD8+CD69+
10-4
10-2
100
102
104
Concentration [nM]
CD3, BCMA IgG1 BsAb KiH
CD3, BCMA IgG1 BsAb
CD3, BCMA IgG1 BsAb KiH AA
CD3, BCMA IgG1 BsAb AA
CD3, BCMA IgG4 BsAb P KiH
CD3, BCMA IgG4 BsAb P
CD3, BCMA IgG4 BsAb PAA
CD3, BCMAx2 IgG4 BsAb KiH PAA

FIG. 20

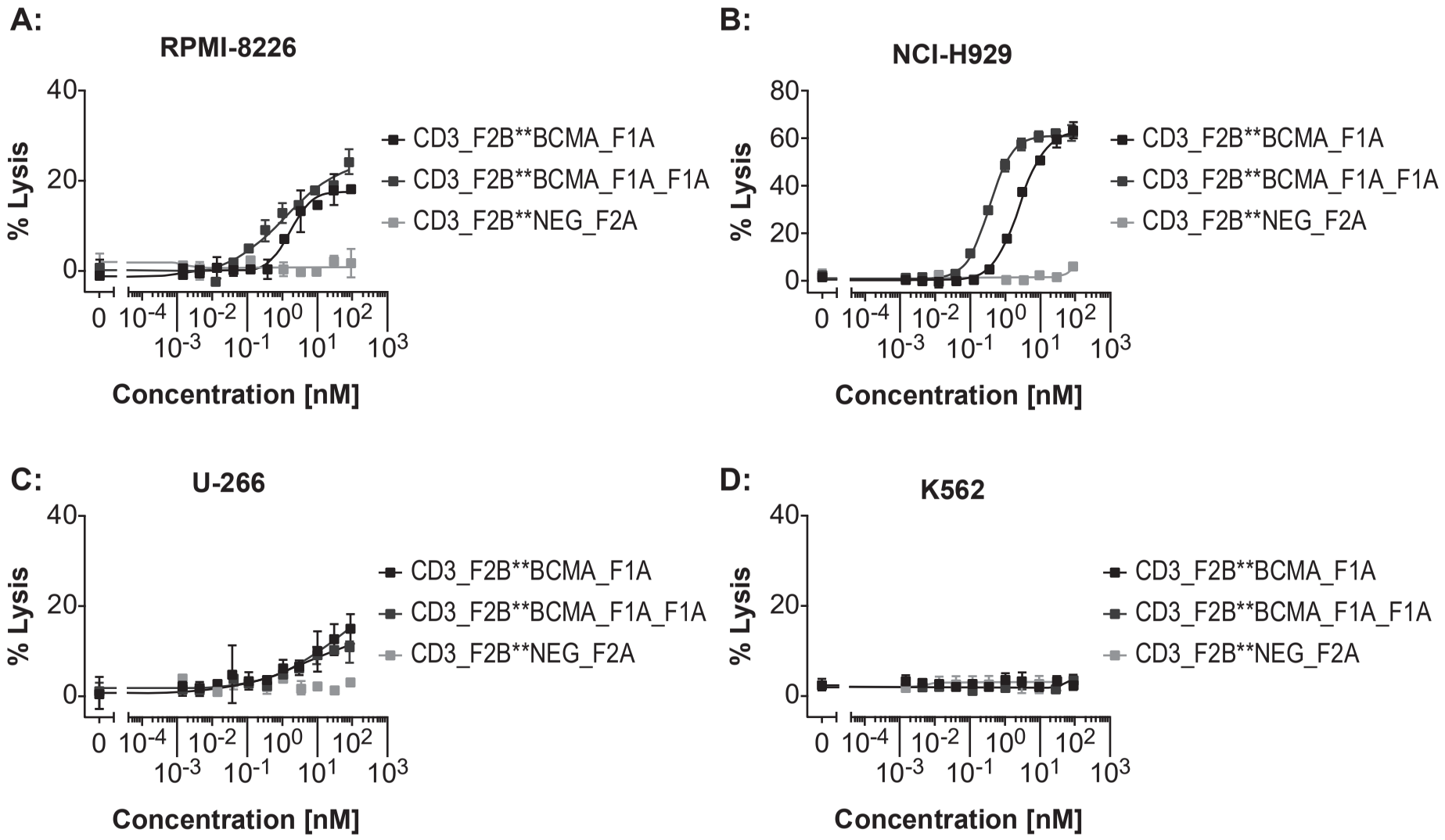

A:
RPMI-8226
% Lysis
Concentration [nM]
CD3_F2B**BCMA_F1A
CD3_F2B**BCMA_F1A_F1A
CD3_F2B**NEG_F2A
B:
NCI-H929
% Lysis
Concentration [nM]
CD3_F2B**BCMA_F1A
CD3_F2B**BCMA_F1A_F1A
CD3_F2B**NEG_F2A
C:
U-266
% Lysis
Concentration [nM]
CD3_F2B**BCMA_F1A
CD3_F2B**BCMA_F1A_F1A
CD3_F2B**NEG_F2A
D:
K562
% Lysis
Concentration [nM]
CD3_F2B**BCMA_F1A
CD3_F2B**BCMA_F1A_F1A
CD3_F2B**NEG_F2A

FIG. 21

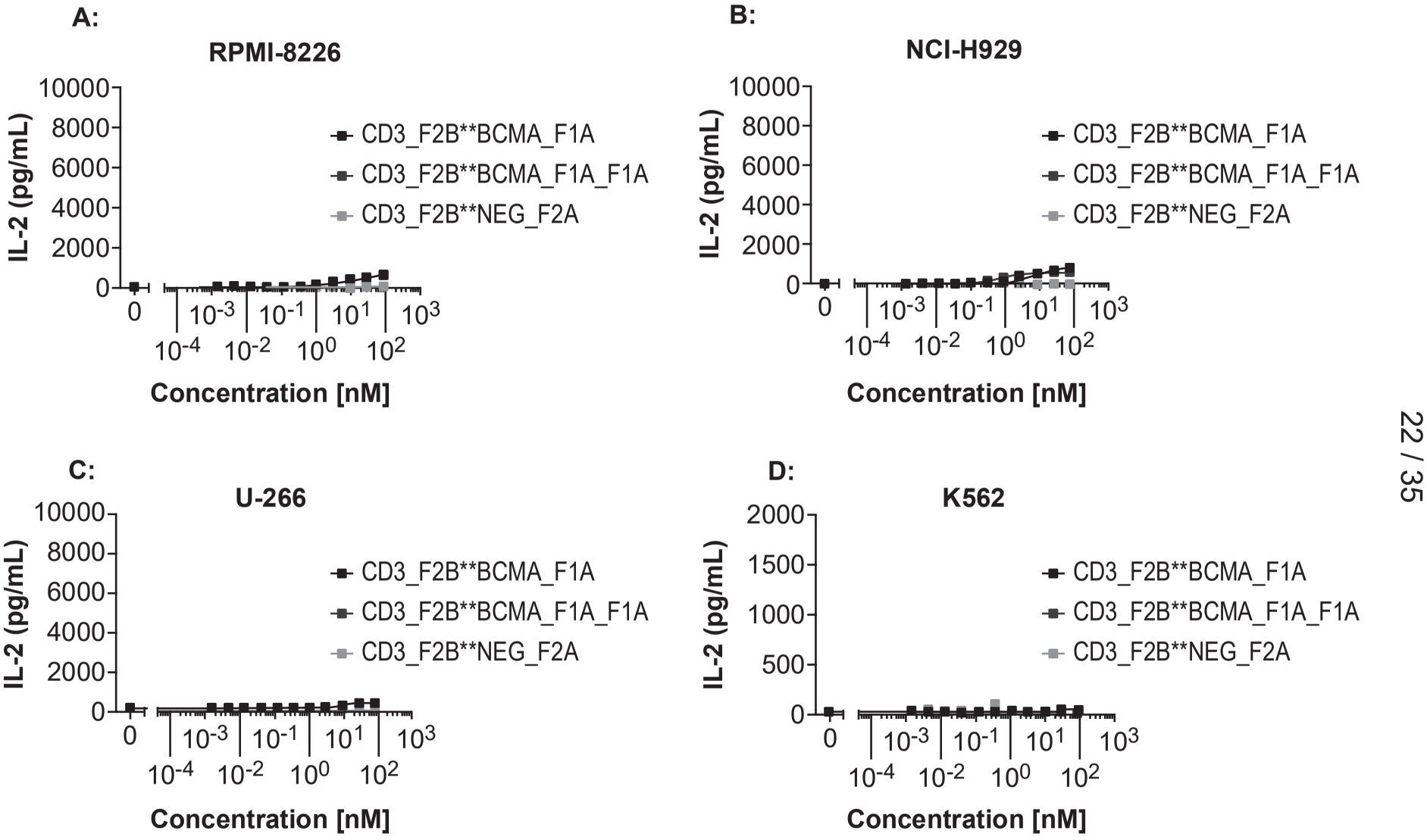

A:
RPMI-8226
IL-2 (pg/mL)
10000
8000
6000
4000
2000
0
CD3_F2B**BCMA_F1A
CD3_F2B**BCMA_F1A_F1A
CD3_F2B**NEG_F2A
0
10-4
10-3
10-2
10-1
100
101
102
103
Concentration [nM]
B:
NCI-H929
IL-2 (pg/mL)
10000
8000
6000
4000
2000
0
CD3_F2B**BCMA_F1A
CD3_F2B**BCMA_F1A_F1A
CD3_F2B**NEG_F2A
0
10-4
10-3
10-2
10-1
100
101
102
103
Concentration [nM]
C:
U-266
IL-2 (pg/mL)
10000
8000
6000
4000
2000
0
CD3_F2B**BCMA_F1A
CD3_F2B**BCMA_F1A_F1A
CD3_F2B**NEG_F2A
0
10-4
10-3
10-2
10-1
100
101
102
103
Concentration [nM]
D:
K562
IL-2 (pg/mL)
2000
1500
1000
500
0
CD3_F2B**BCMA_F1A
CD3_F2B**BCMA_F1A_F1A
CD3_F2B**NEG_F2A
0
10-4
10-3
10-2
10-1
100
101
102
103
Concentration [nM]

FIG. 22

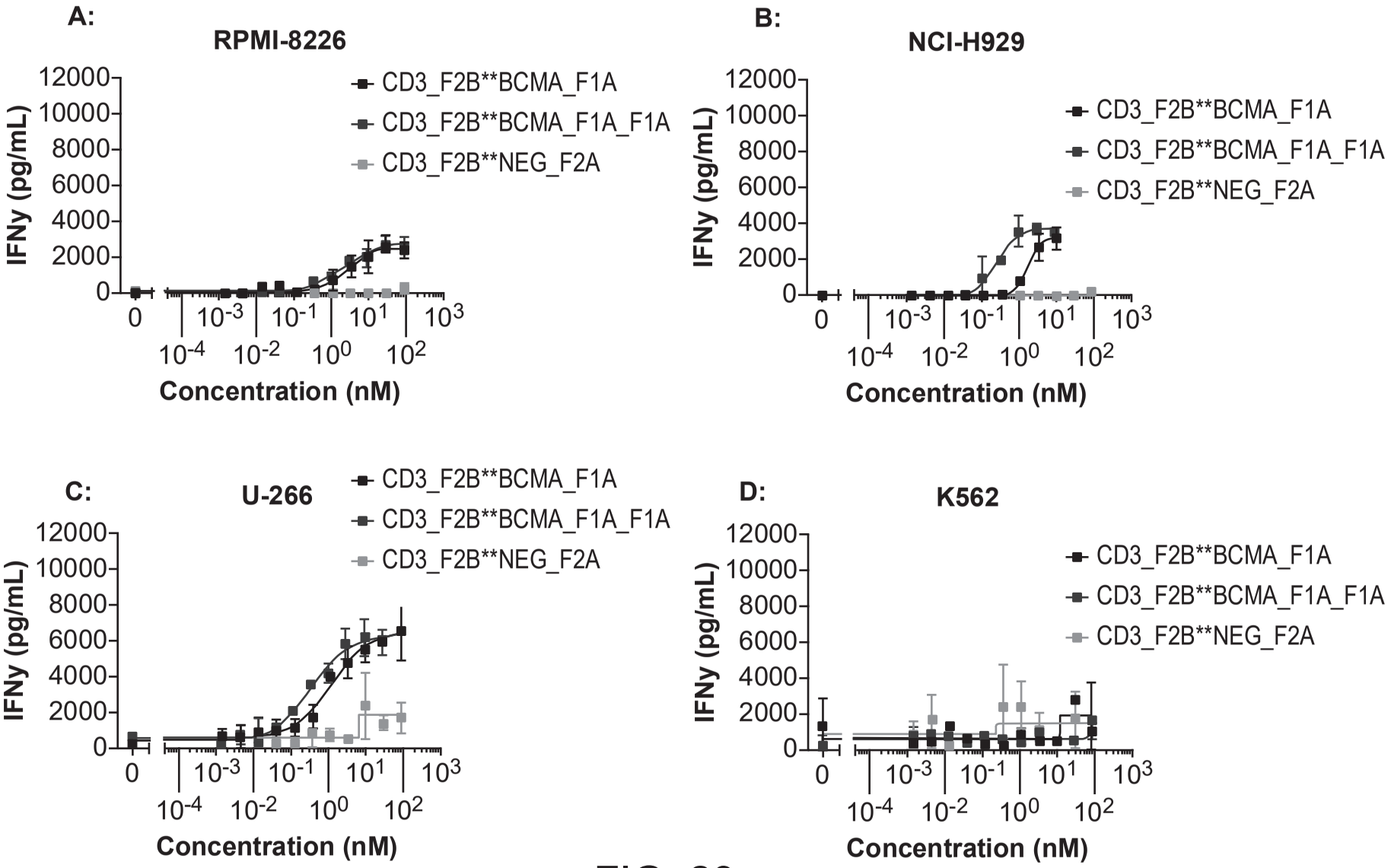

A:
RPMI-8226
B:
NCI-H929
C:
U-266
D:
K562
CD3_F2B**BCMA_F1A
CD3_F2B**BCMA_F1A_F1A
CD3_F2B**NEG_F2A
IFNy (pg/mL)
Concentration (nM)
0
10-4
10-3
10-2
10-1
100
101
102
103
2000
4000
6000
8000
10000
12000

FIG. 23

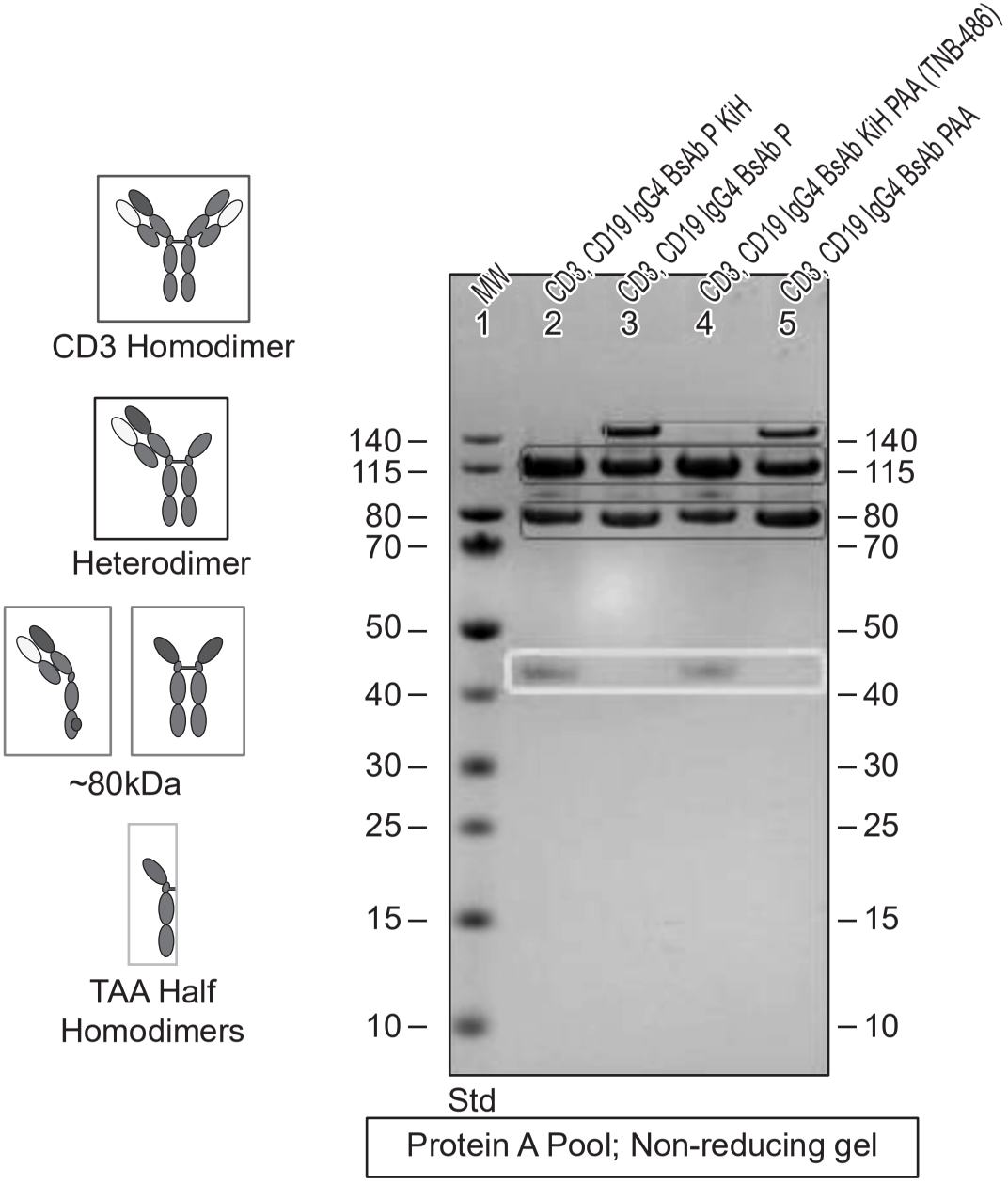

CD3 Homodimer
Heterodimer
~80kDa
TAA Half Homodimers
MW
1
CD3, CD19 IgG4 BsAb P KiH
2
CD3, CD19 IgG4 BsAb P
3
CD3, CD19 IgG4 BsAb KiH PAA (TNB-486)
4
CD3, CD19 IgG4 BsAb PAA
5
140
115
80
70
50
40
30
25
15
10
Std
Protein A Pool; Non-reducing gel

FIG. 24

expression ID	Format	% HMW	% Monomers	% LMW
385171_394399_312325	CD3, CD19 IgG4 BsAb P KiH	0.10	99.9	0.0
385173_394256_312325	CD3, CD19 IgG4 BsAb P	2.33	97.7	0.0
318390_338683_312325	CD3, CD19 IgG4 BsAb KiH PAA (TNB-486)	0.05	99.9	0.07
316220_394259_312325	CD3, CD19 IgG4 BsAb PAA	2.09	97.9	0.0

FIG. 25

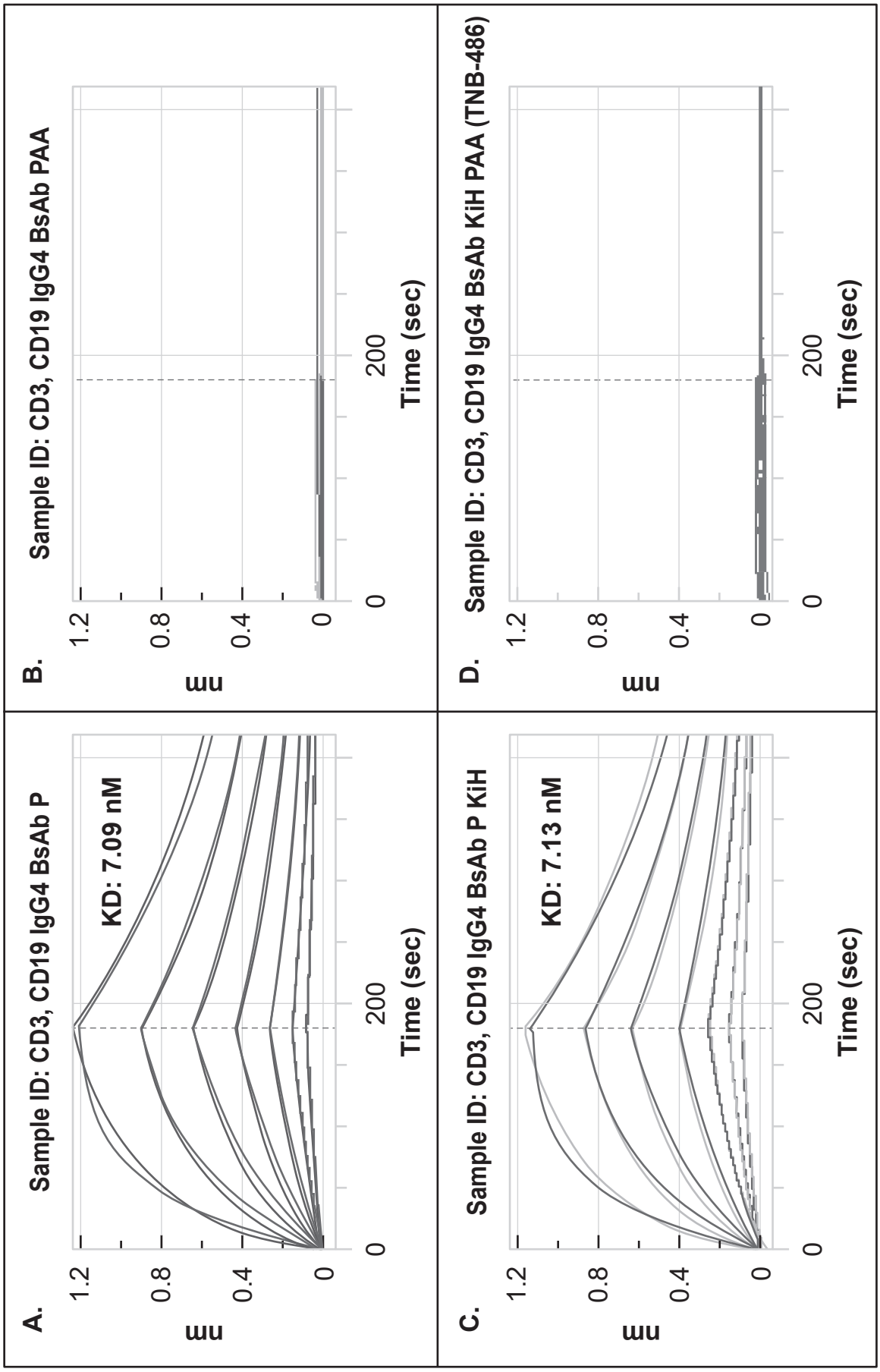

A.
Sample ID: CD3, CD19 IgG4 BsAb P
KD: 7.09 nM
nm
1.2
0.8
0.4
0
0
200
Time (sec)
B.
Sample ID: CD3, CD19 IgG4 BsAb PAA
nm
1.2
0.8
0.4
0
0
200
Time (sec)
C.
Sample ID: CD3, CD19 IgG4 BsAb P KiH
KD: 7.13 nM
nm
1.2
0.8
0.4
0
0
200
Time (sec)
D.
Sample ID: CD3, CD19 IgG4 BsAb KiH PAA (TNB-486)
nm
1.2
0.8
0.4
0
0
200
Time (sec)

FIG. 26

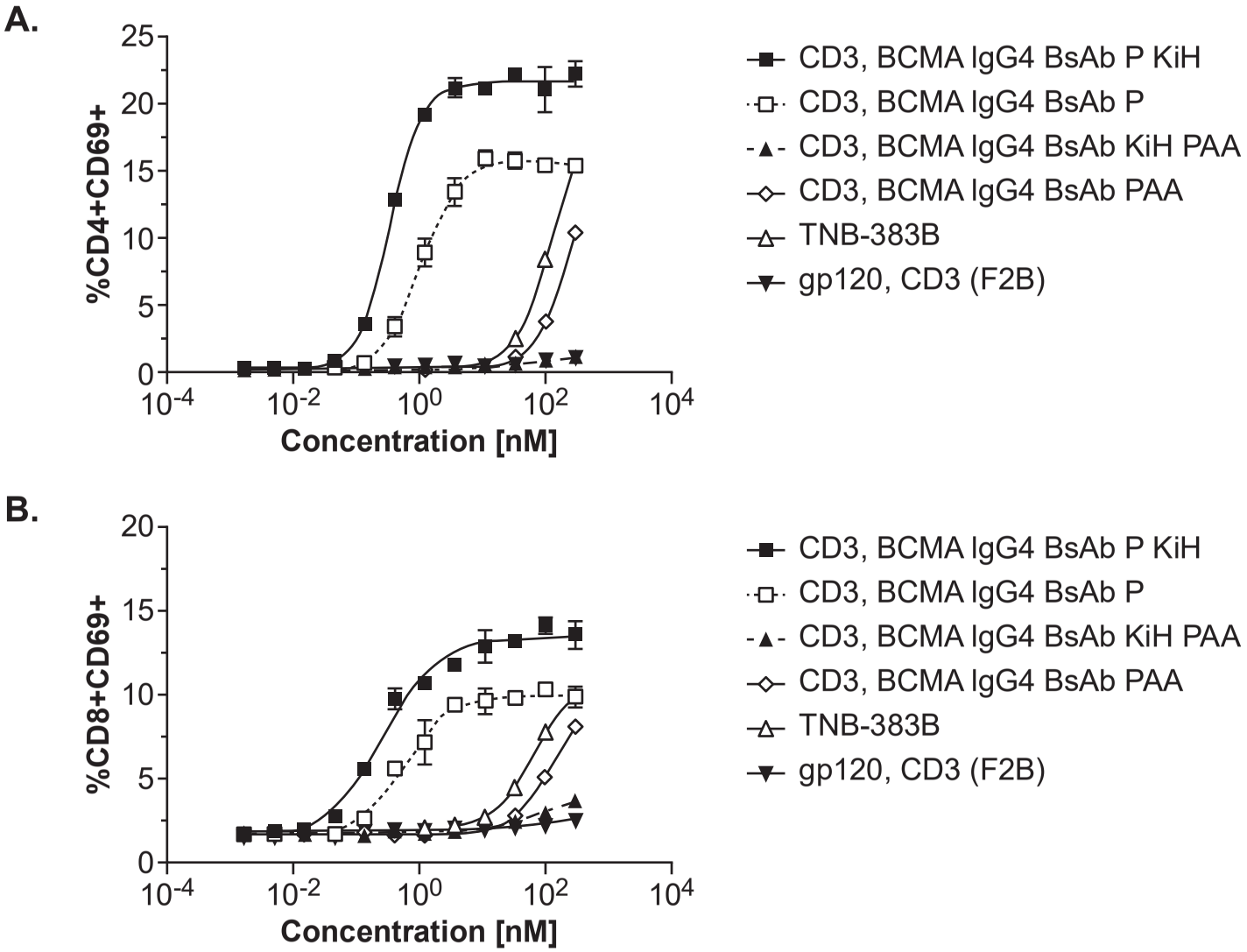

A.
%CD4+CD69+
25
20
15
10
5
0
10-4
10-2
100
102
104
Concentration [nM]
CD3, BCMA IgG4 BsAb P KiH
CD3, BCMA IgG4 BsAb P
CD3, BCMA IgG4 BsAb KiH PAA
CD3, BCMA IgG4 BsAb PAA
TNB-383B
gp120, CD3 (F2B)
B.
%CD8+CD69+
20
15
10
5
0
10-4
10-2
100
102
104
Concentration [nM]
CD3, BCMA IgG4 BsAb P KiH
CD3, BCMA IgG4 BsAb P
CD3, BCMA IgG4 BsAb KiH PAA
CD3, BCMA IgG4 BsAb PAA
TNB-383B
gp120, CD3 (F2B)

FIG. 27

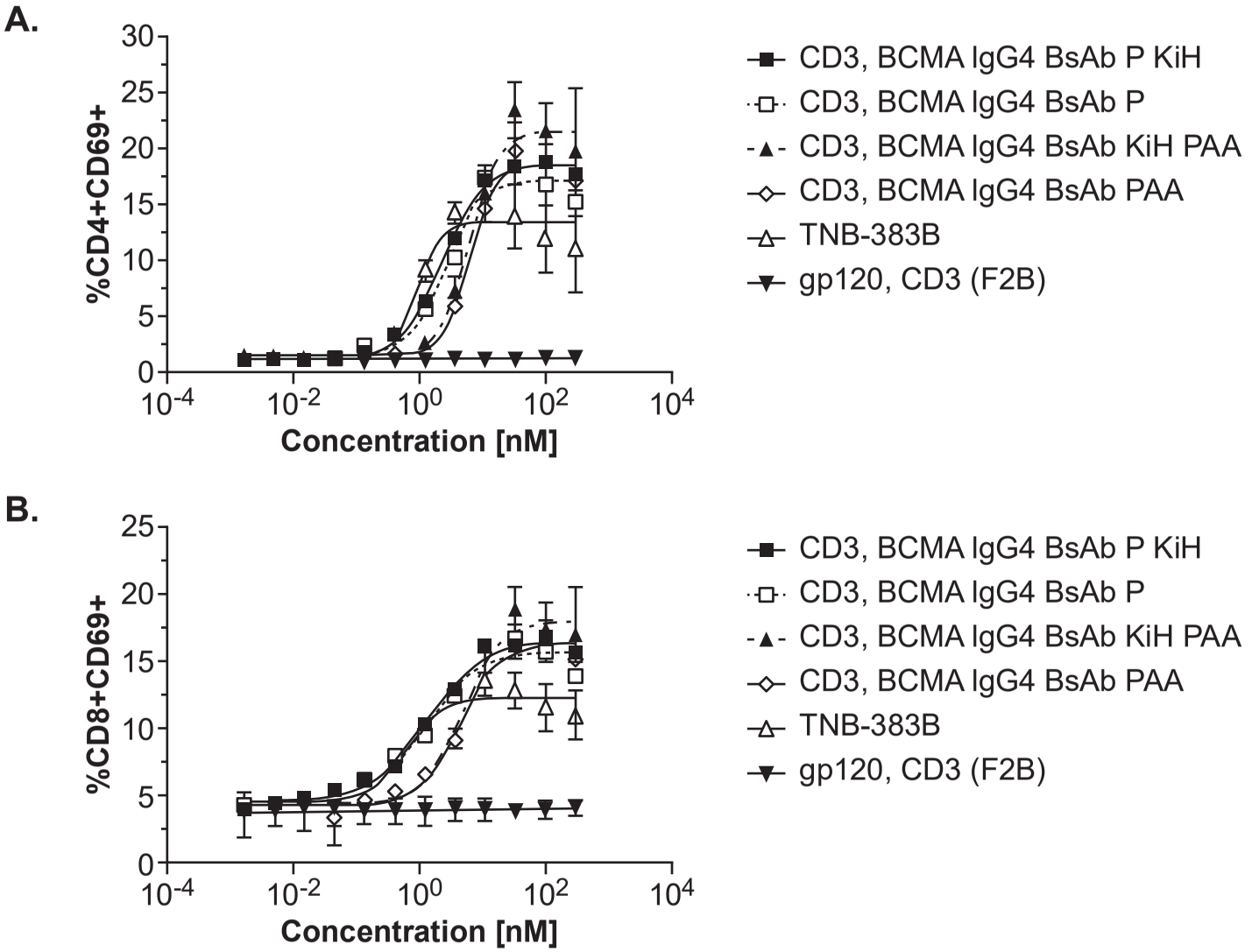

A.
%CD4+CD69+
30
25
20
15
10
5
0
10-4
10-2
100
102
104
Concentration [nM]
CD3, BCMA IgG4 BsAb P KiH
CD3, BCMA IgG4 BsAb P
CD3, BCMA IgG4 BsAb KiH PAA
CD3, BCMA IgG4 BsAb PAA
TNB-383B
gp120, CD3 (F2B)
B.
%CD8+CD69+
25
20
15
10
5
0
10-4
10-2
100
102
104
Concentration [nM]
CD3, BCMA IgG4 BsAb P KiH
CD3, BCMA IgG4 BsAb P
CD3, BCMA IgG4 BsAb KiH PAA
CD3, BCMA IgG4 BsAb PAA
TNB-383B
gp120, CD3 (F2B)

FIG. 28

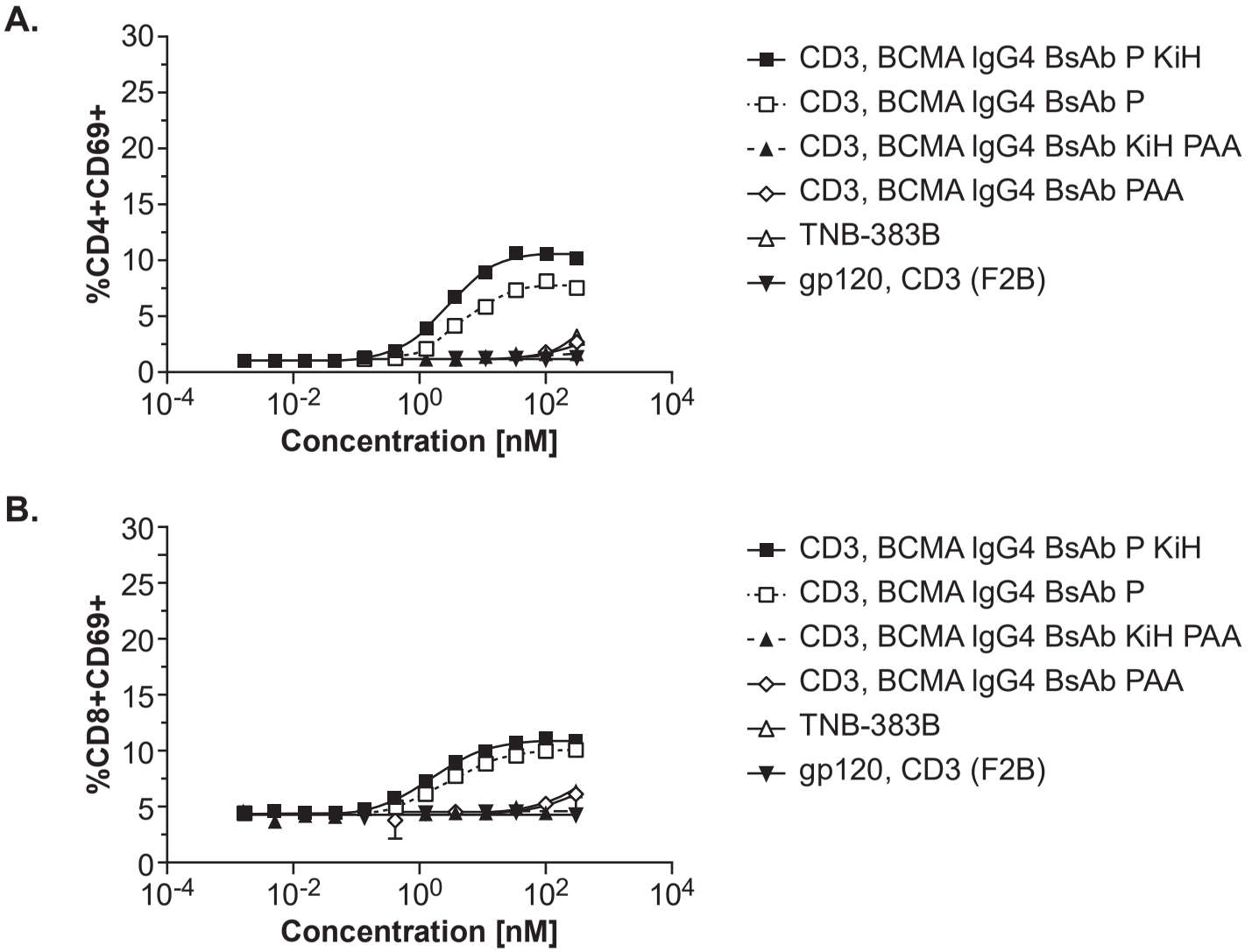

A.
%CD4+CD69+
30
25
20
15
10
5
0
10-4
10-2
100
102
104
Concentration [nM]
CD3, BCMA IgG4 BsAb P KiH
CD3, BCMA IgG4 BsAb P
CD3, BCMA IgG4 BsAb KiH PAA
CD3, BCMA IgG4 BsAb PAA
TNB-383B
gp120, CD3 (F2B)
B.
%CD8+CD69+
30
25
20
15
10
5
0
10-4
10-2
100
102
104
Concentration [nM]
CD3, BCMA IgG4 BsAb P KiH
CD3, BCMA IgG4 BsAb P
CD3, BCMA IgG4 BsAb KiH PAA
CD3, BCMA IgG4 BsAb PAA
TNB-383B
gp120, CD3 (F2B)

FIG. 29

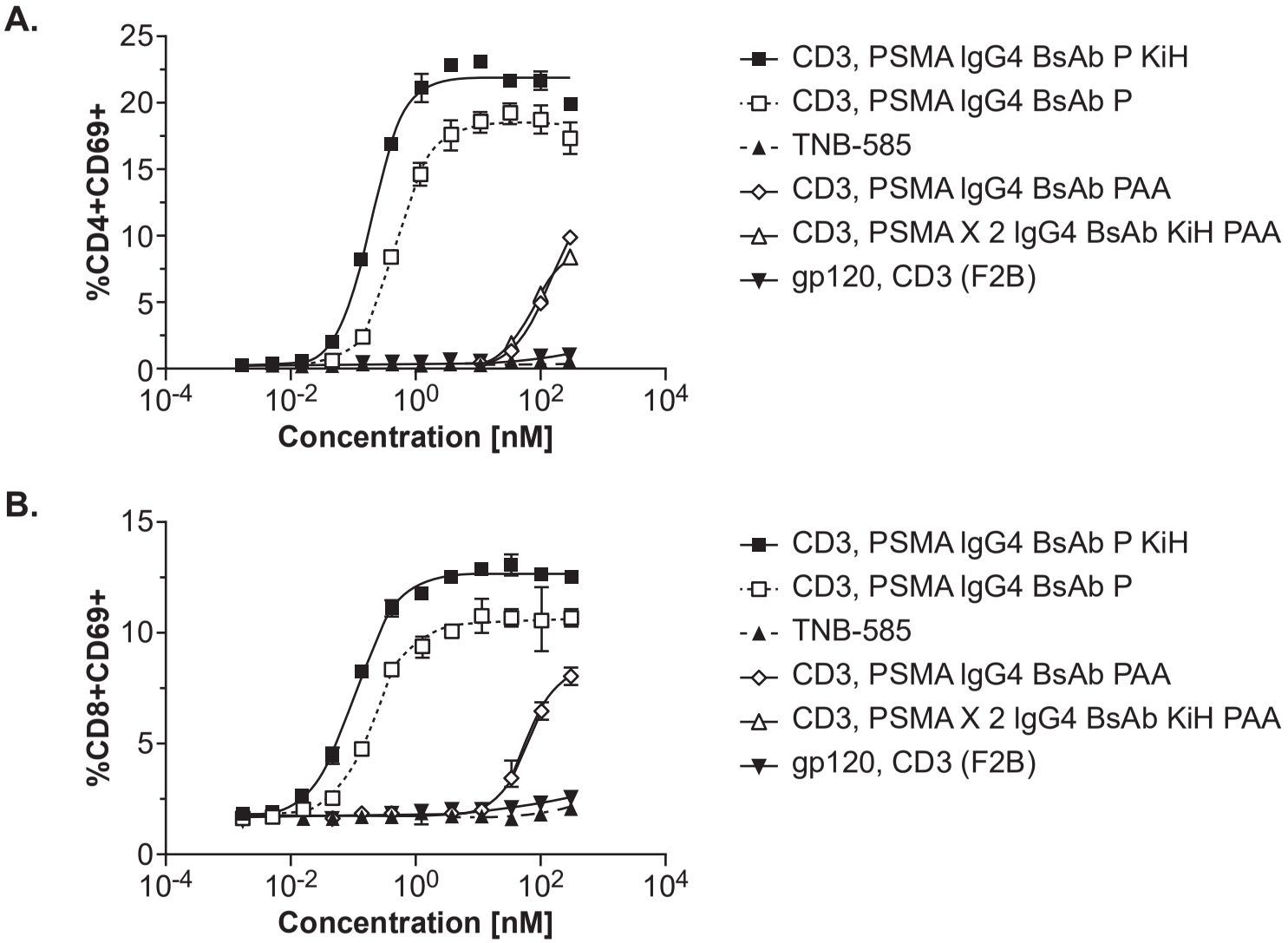

A.
%CD4+CD69+
25
20
15
10
5
0
10-4
10-2
100
102
104
Concentration [nM]
CD3, PSMA IgG4 BsAb P KiH
CD3, PSMA IgG4 BsAb P
TNB-585
CD3, PSMA IgG4 BsAb PAA
CD3, PSMA X 2 IgG4 BsAb KiH PAA
gp120, CD3 (F2B)
B.
%CD8+CD69+
15
10
5
0
10-4
10-2
100
102
104
Concentration [nM]
CD3, PSMA IgG4 BsAb P KiH
CD3, PSMA IgG4 BsAb P
TNB-585
CD3, PSMA IgG4 BsAb PAA
CD3, PSMA X 2 IgG4 BsAb KiH PAA
gp120, CD3 (F2B)

FIG. 30

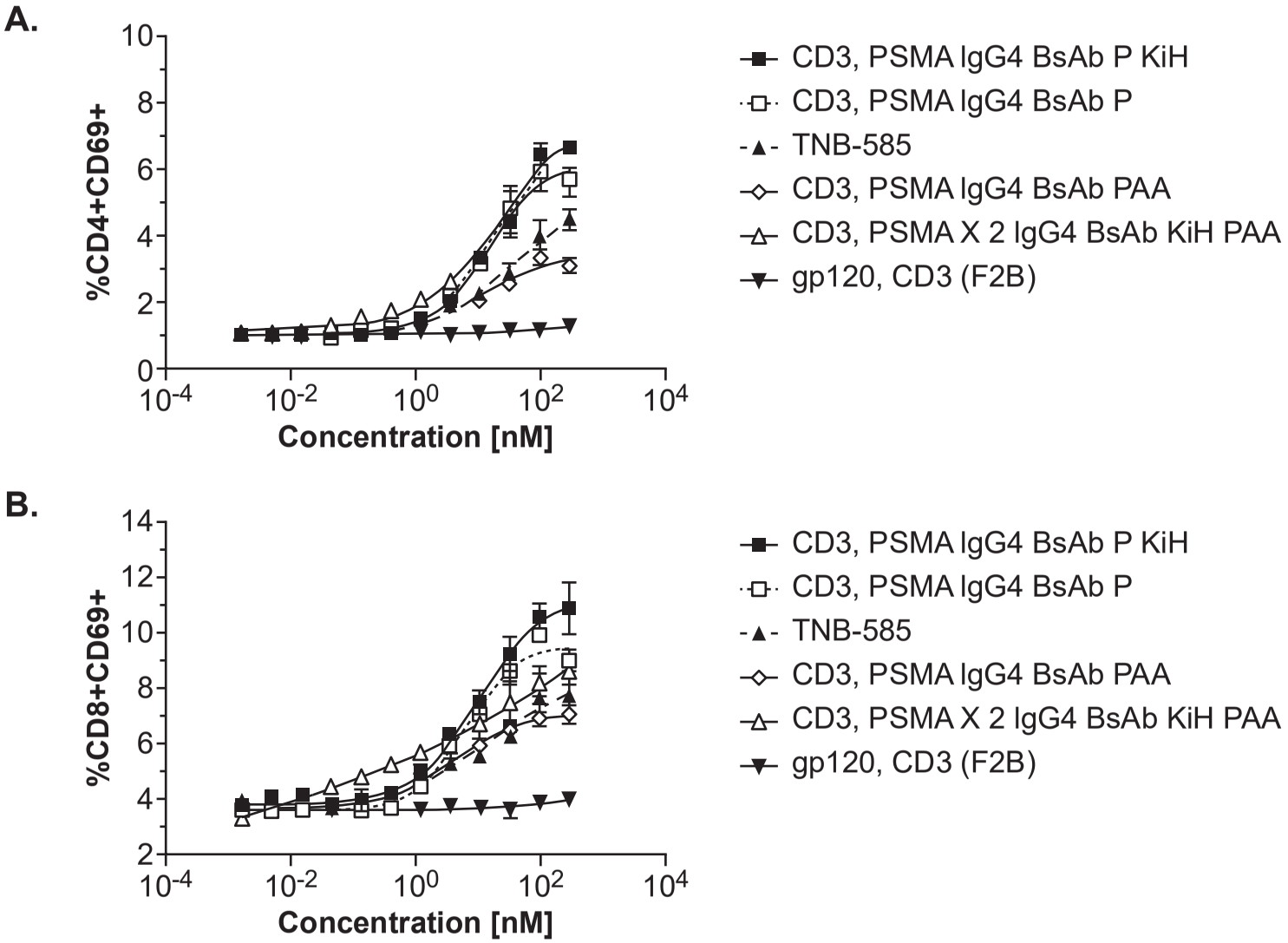

A.
%CD4+CD69+
Concentration [nM]
B.
%CD8+CD69+
Concentration [nM]
CD3, PSMA IgG4 BsAb P KiH
CD3, PSMA IgG4 BsAb P
TNB-585
CD3, PSMA IgG4 BsAb PAA
CD3, PSMA X 2 IgG4 BsAb KiH PAA
gp120, CD3 (F2B)

FIG. 31

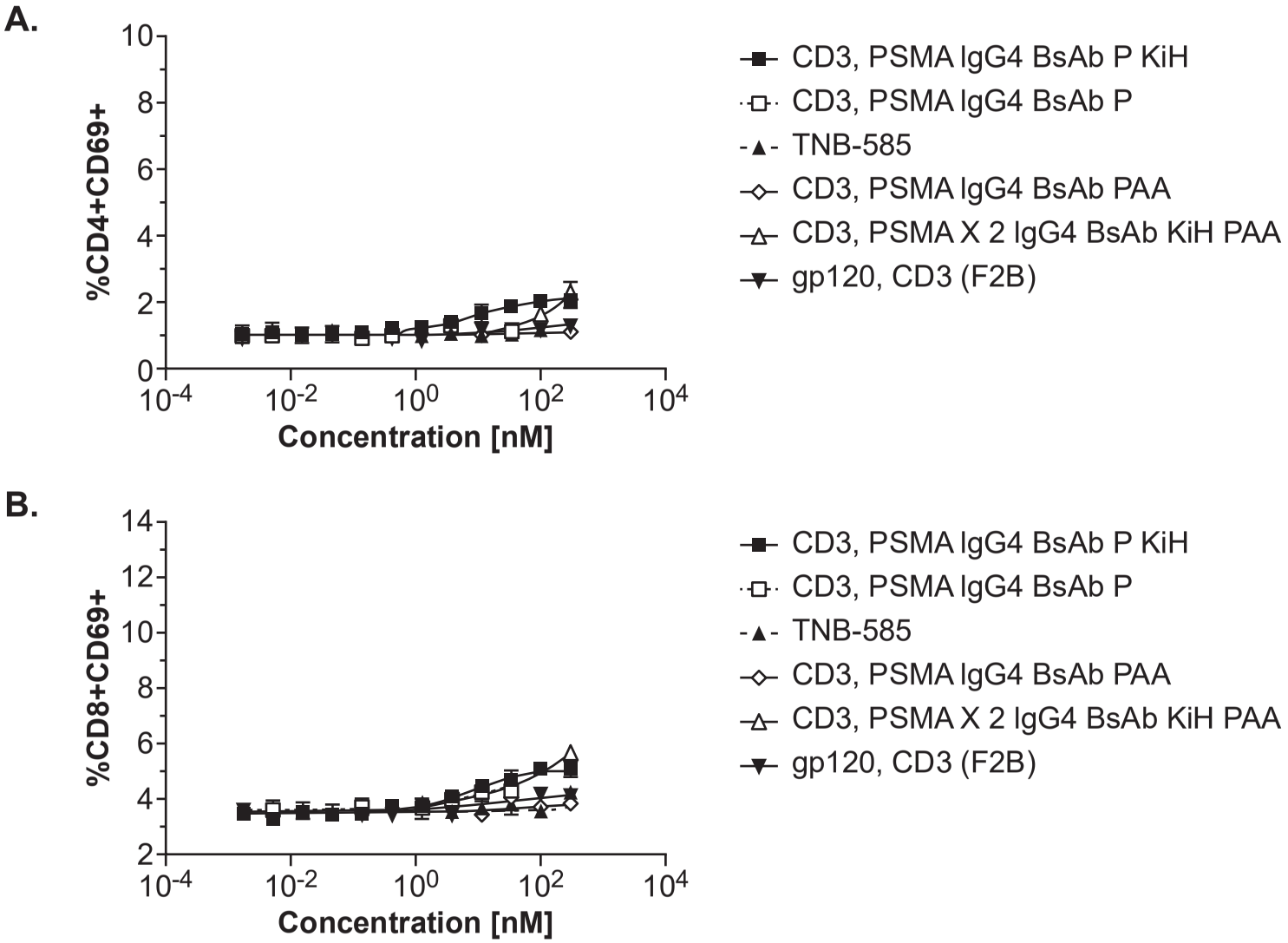

A.
%CD4+CD69+
10
8
6
4
2
0
10-4
10-2
100
102
104
Concentration [nM]
CD3, PSMA IgG4 BsAb P KiH
CD3, PSMA IgG4 BsAb P
TNB-585
CD3, PSMA IgG4 BsAb PAA
CD3, PSMA X 2 IgG4 BsAb KiH PAA
gp120, CD3 (F2B)
B.
%CD8+CD69+
14
12
10
8
6
4
2
10-4
10-2
100
102
104
Concentration [nM]
CD3, PSMA IgG4 BsAb P KiH
CD3, PSMA IgG4 BsAb P
TNB-585
CD3, PSMA IgG4 BsAb PAA
CD3, PSMA X 2 IgG4 BsAb KiH PAA
gp120, CD3 (F2B)

FIG. 32

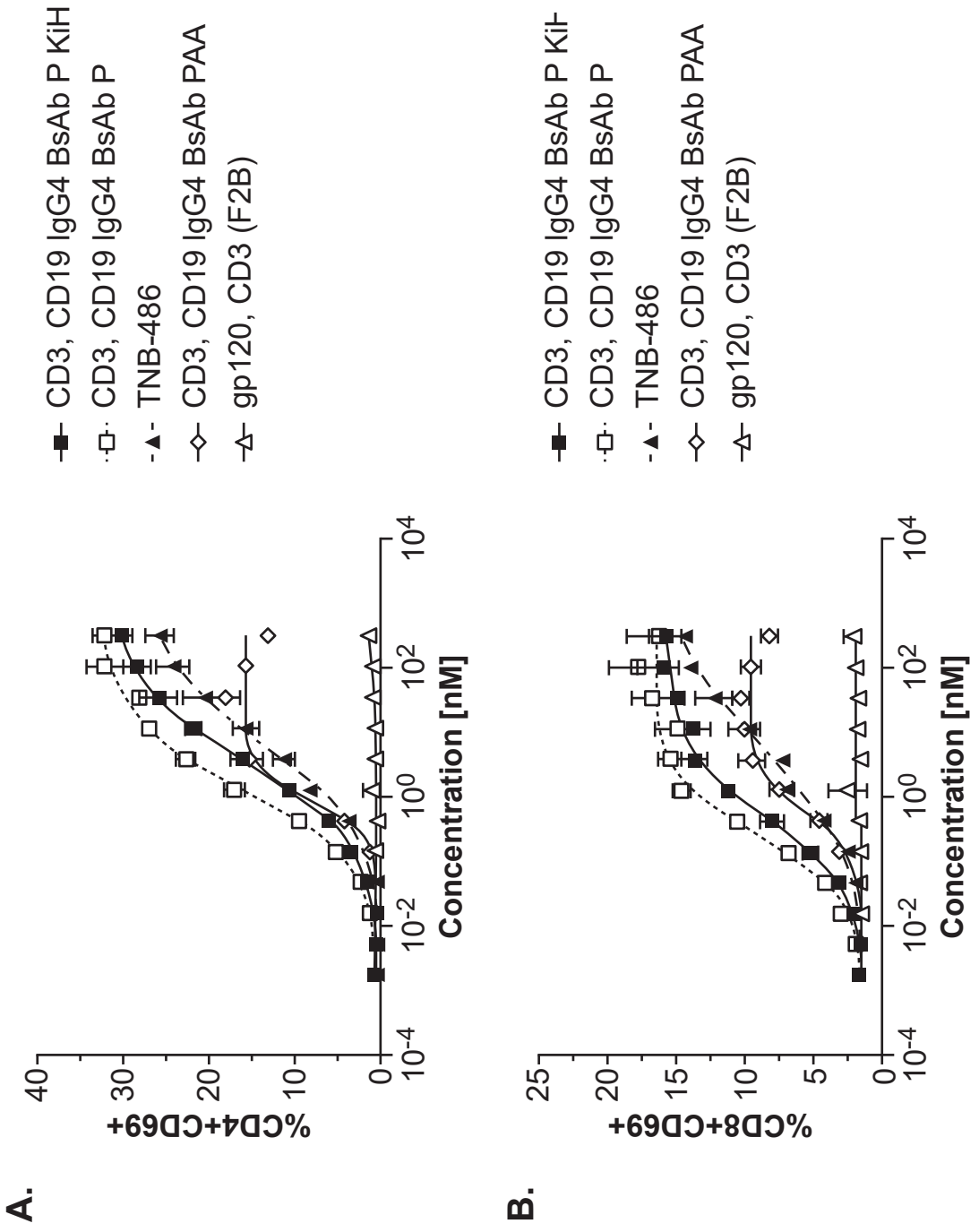

A.
%CD4+CD69+
Concentration [nM]
CD3, CD19 IgG4 BsAb P KiH
CD3, CD19 IgG4 BsAb P
TNB-486
CD3, CD19 IgG4 BsAb PAA
gp120, CD3 (F2B)
B.
%CD8+CD69+
Concentration [nM]
CD3, CD19 IgG4 BsAb P KiH
CD3, CD19 IgG4 BsAb P
TNB-486
CD3, CD19 IgG4 BsAb PAA
gp120, CD3 (F2B)

FIG. 33

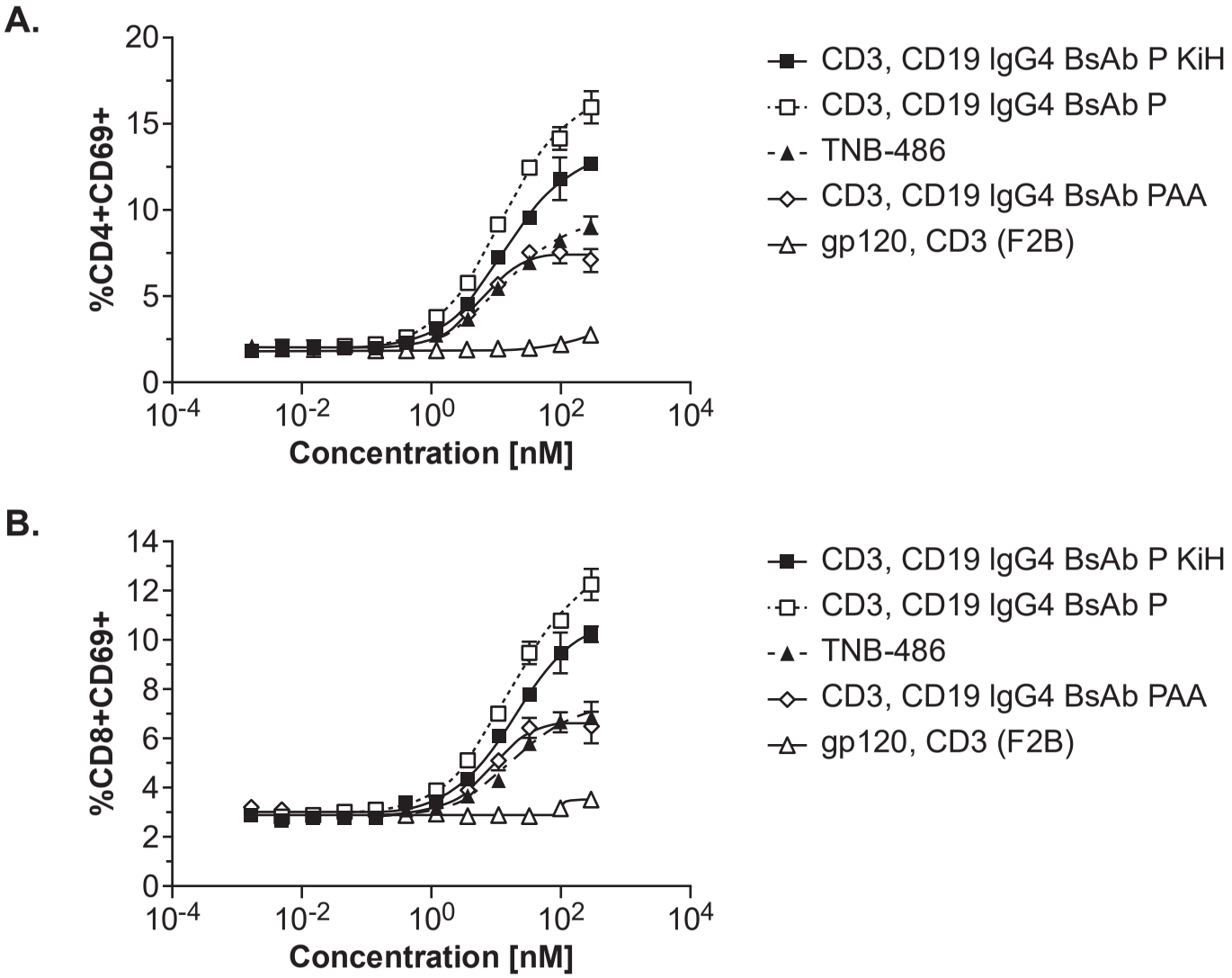

A.
%CD4+CD69+
20
15
10
5
0
10-4
10-2
100
102
104
Concentration [nM]
CD3, CD19 IgG4 BsAb P KiH
CD3, CD19 IgG4 BsAb P
TNB-486
CD3, CD19 IgG4 BsAb PAA
gp120, CD3 (F2B)
B.
%CD8+CD69+
14
12
10
8
6
4
2
0
10-4
10-2
100
102
104
Concentration [nM]
CD3, CD19 IgG4 BsAb P KiH
CD3, CD19 IgG4 BsAb P
TNB-486
CD3, CD19 IgG4 BsAb PAA
gp120, CD3 (F2B)

FIG. 34

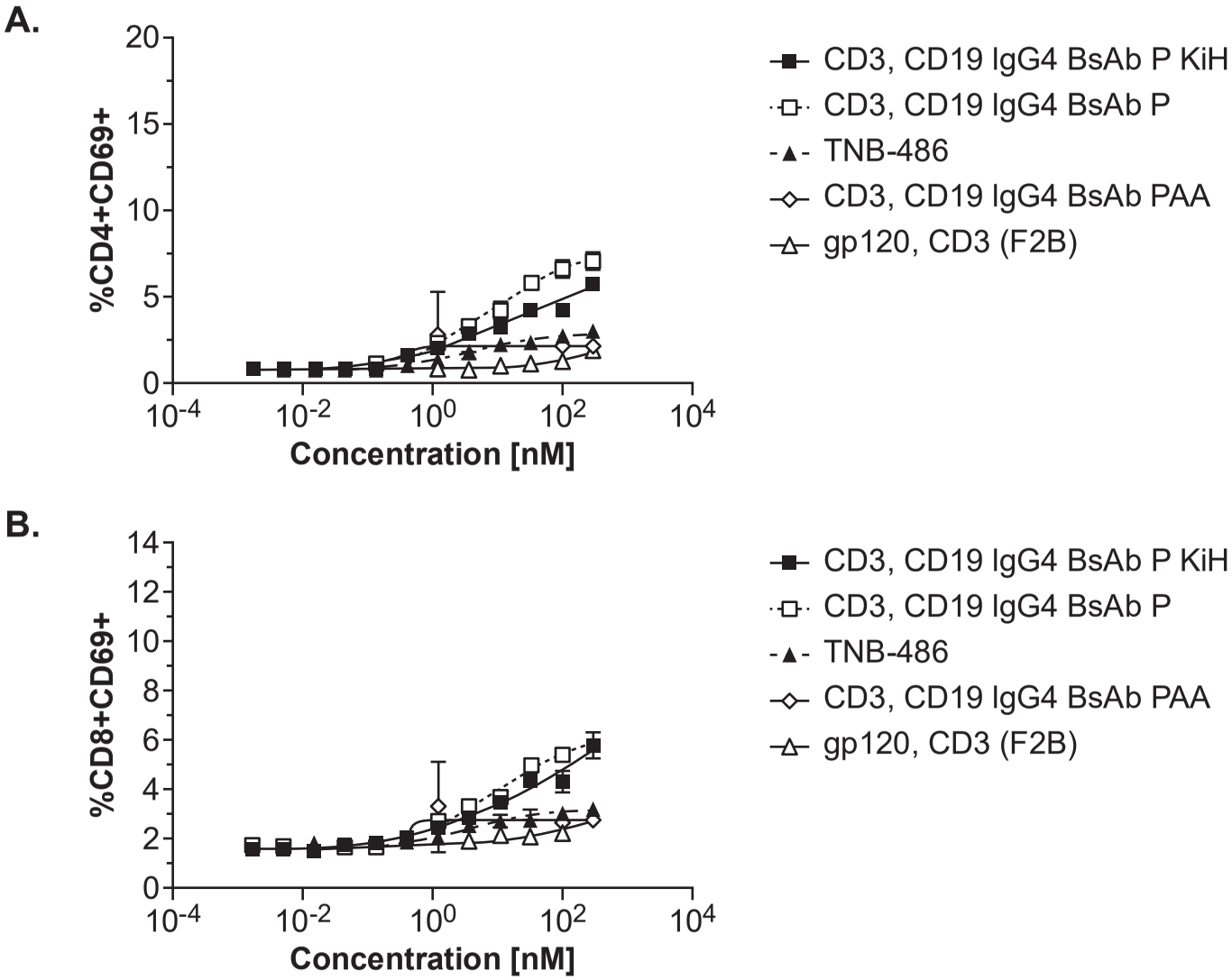

A.
%CD4+CD69+
20
15
10
5
0
10-4
10-2
100
102
104
Concentration [nM]
CD3, CD19 IgG4 BsAb P KiH
CD3, CD19 IgG4 BsAb P
TNB-486
CD3, CD19 IgG4 BsAb PAA
gp120, CD3 (F2B)
B.
%CD8+CD69+
14
12
10
8
6
4
2
0
10-4
10-2
100
102
104
Concentration [nM]
CD3, CD19 IgG4 BsAb P KiH
CD3, CD19 IgG4 BsAb P
TNB-486
CD3, CD19 IgG4 BsAb PAA
gp120, CD3 (F2B)

FIG. 35

2022259766 26 Oct 2022

```
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"ST26SequenceListing_V1_3.dtd">
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softwareName="WIPO Sequence" softwareVersion="2.1.2"
productionDate="2022-09-14">
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                <IPOfficeCode>US</IPOfficeCode>

<ApplicationNumberText>PCT/US2021/029909</ApplicationNumberText>
                <FilingDate>2021-04-29</FilingDate>
        </ApplicationIdentification>
        <ApplicantFileReference>TNO-0018-WO
(60792.00035WO01)</ApplicantFileReference>
        <EarliestPriorityApplicationIdentification>
                <IPOfficeCode>US</IPOfficeCode>
                <ApplicationNumberText>63/017589</ApplicationNumberText>
                <FilingDate>2020-04-29</FilingDate>
        </EarliestPriorityApplicationIdentification>
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        <InventorName languageCode="en">Katherine Harris</InventorName>
        <InventionTitle languageCode="en">MULTISPECIFIC HEAVY CHAIN ANTIBODIES
WITH MODIFIED HEAVY CHAIN CONSTANT REGIONS</InventionTitle>
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                        <INSDSeq_moltype>AA</INSDSeq_moltype>
                        <INSDSeq_division>PAT</INSDSeq_division>
                        <INSDSeq_feature-table>
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Syntheticpolypeptide&amp;quot;</INSDQualifier_value>
                                                </INSDQualifier>
                                        </INSDFeature_quals>
                                </INSDFeature>
                                <INSDFeature>

<INSDFeature_key>source</INSDFeature_key>

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<INSDQualifier_name>mol_type</INSDQualifier_name>
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2022259766 26 Oct 2022

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<INSDQualifier_value>protein</INSDQualifier_value>
                                                </INSDQualifier>
                                                <INSDQualifier id="q1">

<INSDQualifier_name>organism</INSDQualifier_name>

<INSDQualifier_value>synthetic construct</INSDQualifier_value>
                                                </INSDQualifier>
                                        </INSDFeature_quals>
                                </INSDFeature>
                        </INSDSeq_feature-table>

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NPSLQSRVTISVDTSKNQFSLKLSSVTAADTAVYNCARHKAATADFDYRGQGTLVTVSS</INSDSeq_sequence>
                </INSDSeq>
        </SequenceData>
        <SequenceData sequenceIDNumber="2">
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                        <INSDSeq_length>120</INSDSeq_length>
                        <INSDSeq_moltype>AA</INSDSeq_moltype>
                        <INSDSeq_division>PAT</INSDSeq_division>
                        <INSDSeq_feature-table>
                                <INSDFeature>

<INSDFeature_key>REGION</INSDFeature_key>

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                                        <INSDFeature_quals>
                                                <INSDQualifier id="q4">

<INSDQualifier_name>note</INSDQualifier_name>

<INSDQualifier_value>source = /note=&amp;quot;Description of Artificial Sequence:
Syntheticpolypeptide&amp;quot;</INSDQualifier_value>
                                                </INSDQualifier>
                                        </INSDFeature_quals>
                                </INSDFeature>
                                <INSDFeature>

<INSDFeature_key>source</INSDFeature_key>

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2022259766 26 Oct 2022

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2022259766 26 Oct 2022


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26 Oct 2022
2022259766


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2022259766 26 Oct 2022


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2022259766 26 Oct 2022


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2022259766 26 Oct 2022


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2022259766 26 Oct 2022

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2022259766 26 Oct 2022

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2022259766 26 Oct 2022

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26 Oct 2022
2022259766

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26 Oct 2022
2022259766


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2022259766 26 Oct 2022


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2022259766 26 Oct 2022


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2022259766 26 Oct 2022

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2022259766 26 Oct 2022


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20222259766 26 Oct 2022


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2022259766 26 Oct 2022

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2022259766 26 Oct 2022

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26 Oct 2022
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2022259766 26 Oct 2022


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2022259766 26 Oct 2022

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2022259766 26 Oct 2022

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2022259766 26 Oct 2022


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20222597766 26 Oct 2022

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2022259766 26 Oct 2022

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26 Oct 2022
2022259766


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2022259766 26 Oct 2022


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2022259766 26 Oct 2022

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2022259766 26 Oct 2022

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2022259766 26 Oct 2022

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20222597766 26 Oct 2022

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20222597766 26 Oct 2022

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20222597766 26 Oct 2022

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2022259766 26 Oct 2022

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2022259766 26 Oct 2022

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2022259766 26 Oct 2022


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26 Oct 2022
2022259766

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26 Oct 2022
2022259766

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2022259766 26 Oct 2022


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2022259766 26 Oct 2022

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2022259766 26 Oct 2022


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2022259766 26 Oct 2022


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26 Oct 2022

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20222597766 26 Oct 2022


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2022259766 26 Oct 2022


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2022259766 26 Oct 2022


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2022259766 26 Oct 2022


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26 Oct 2022
2022259766

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26 Oct 2022
2022259766

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2022259766 26 Oct 2022


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26 Oct 2022
2022259766


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26 Oct 2022
2022259766

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2022259766 26 Oct 2022


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26 Oct 2022

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26 Oct 2022
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26 Oct 2022
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26 Oct 2022

2022259766


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26 Oct 2022
2022259766


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2022259766 26 Oct 2022

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2022259766 26 Oct 2022

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2022259766 26 Oct 2022

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2022259766 26 Oct 2022

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2022259766 26 Oct 2022


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2022259766 26 Oct 2022

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26 Oct 2022
2022259766

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26 Oct 2022
2022259766


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20222597766 26 Oct 2022


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26 Oct 2022
2022259766

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2022259766 26 Oct 2022


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26 Oct 2022
2022259766

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2022259766 26 Oct 2022


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26 Oct 2022
2022259766

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26 Oct 2022
2022259766


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2022259766 26 Oct 2022


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26 Oct 2022
2022259766

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2022259766 26 Oct 2022


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2022259766 26 Oct 2022

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26 Oct 2022

2022259766


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2022259766 26 Oct 2022

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2022259766 26 Oct 2022


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